Dokumentvorlage, Version vom 16.12.2021

Dossier zur Nutzenbewertung gemäß § 35a SGB V

Trastzumab-Deruxtecan (Enhertu®)

Daiichi Sankyo Deutschland GmbH

Modul 4 A Anhang 4-H

Behandlung von erwachsenen Patienten mit inoperablem oder metastasiertem HER2-positivem Brustkrebs, die bereits mindestens eine gegen HER2 gerichtete Vorbehandlung erhalten haben

Medizinischer Nutzen und
medizinischer Zusatznutzen,
Patientengruppen mit therapeutisch
bedeutsamem Zusatznutzen

Stand: 27.07.2022

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Table 4 Pre-specified Subgroups Analysis of Overall Survival (OS) - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median OS (95% CI) [a] (months)	n	No. of Events (%)	Median OS (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Age								
<65	212	24 (11.3)	NE (NE , NE)	206	47 (22.8)	NE (NE , NE)	0.4338 (0.2652 , 0.7095)	0.0135
>=65	49	9 (18.4)	NE (NE , NE)	57	6 (10.5)	NE (NE , NE)	1.7362 (0.6178 , 4.8797)	
Age								
<75	253	33 (13.0)	NE (NE , NE)	255	53 (20.8)	NE (NE , NE)	0.5687 (0.3682 , 0.8784)	0.9995
>=75	8	0	NE (NE , NE)	8	0	NE (NE , NE)		
Region								
Asia	149	19 (12.8)	NE (NE , NE)	160	38 (23.8)	NE (NE , NE)	0.4797 (0.2765 , 0.8322)	0.0857
North America	17	5 (29.4)	NE (14.6 , NE)	17	2 (11.8)	NE (NE , NE)	3.0699 (0.5884 , 16.018)	
Europe	54	5 (9.3)	NE (NE , NE)	50	4 (8.0)	NE (NE , NE)	1.0608 (0.2847 , 3.9525)	
Rest of World	41	4 (9.8)	NE (NE , NE)	36	9 (25.0)	NE (NE , NE)	0.3305 (0.1014 , 1.0771)	

Notes: OS is defined as the time from the date of randomization to the date of death due to any cause, whichever comes first. If there is no death reported for a subject before the data cutoff for OS analysis, OS will be censored at the last contact date at which the subject is known to be alive.
[a] Median OS is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 4 Pre-specified Subgroups Analysis of Overall Survival (OS) - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median OS (95% CI) [a] (months)	n	No. of Events (%)	Median OS (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Race								
White	71	11 (15.5)	NE (NE , NE)	72	12 (16.7)	NE (NE , NE)	0.8641 (0.3812 , 1.9588)	0.4288
Black or African American	10	0	NE (NE , NE)	9	1 (11.1)	NE (1.3 , NE)	0.0000 (0.0000 , NE)	
Asian	152	19 (12.5)	NE (NE , NE)	162	38 (23.5)	NE (NE , NE)	0.4785 (0.2758 , 0.8301)	
Other	28	3 (10.7)	NE (NE , NE)	20	2 (10.0)	NE (17.6 , NE)	0.8823 (0.1471 , 5.2924)	
ECOG PS								
0	154	11 (7.1)	NE (NE , NE)	175	24 (13.7)	NE (NE , NE)	0.4716 (0.2310 , 0.9629)	0.8033
1	106	22 (20.8)	NE (19.9 , NE)	87	29 (33.3)	NE (16.6 , NE)	0.5254 (0.3013 , 0.9161)	
Hormone Receptor Status								
Positive	133	17 (12.8)	NE (NE , NE)	139	26 (18.7)	NE (NE , NE)	0.6305 (0.3421 , 1.1622)	0.7399
Negative	126	16 (12.7)	NE (NE , NE)	122	26 (21.3)	NE (NE , NE)	0.5369 (0.2879 , 1.0011)	

Notes: OS is defined as the time from the date of randomization to the date of death due to any cause, whichever comes first. If there is no death reported for a subject before the data cutoff for OS analysis, OS will be censored at the last contact date at which the subject is known to be alive.
[a] Median OS is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 4 Pre-specified Subgroups Analysis of Overall Survival (OS) - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median OS (95% CI) [a] (months)	n	No. of Events (%)	Median OS (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Estrogen Receptors								
Positive	129	15 (11.6)	NE (NE , NE)	132	23 (17.4)	NE (NE , NE)	0.6136 (0.3201 , 1.1762)	0.8286
Negative	130	18 (13.8)	NE (NE , NE)	128	29 (22.7)	NE (NE , NE)	0.5497 (0.3052 , 0.9900)	
Progesterone Receptors								
Positive	81	11 (13.6)	NE (NE , NE)	92	20 (21.7)	NE (NE , NE)	0.5811 (0.2783 , 1.2133)	0.9175
Negative	177	22 (12.4)	NE (NE , NE)	168	32 (19.0)	NE (NE , NE)	0.5897 (0.3426 , 1.0151)	
Prior Treatment with Pertuzumab								
Yes	162	19 (11.7)	NE (NE , NE)	158	27 (17.1)	NE (NE , NE)	0.6137 (0.3412 , 1.1040)	0.7545
No	99	14 (14.1)	NE (NE , NE)	105	26 (24.8)	NE (NE , NE)	0.5305 (0.2769 , 1.0162)	
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	21 (11.2)	NE (NE , NE)	191	29 (15.2)	NE (NE , NE)	0.6685 (0.3812 , 1.1724)	0.3414
>= 3 lines	73	12 (16.4)	NE (NE , NE)	72	24 (33.3)	NE (17.4 , NE)	0.4405 (0.2201 , 0.8815)	

Notes: OS is defined as the time from the date of randomization to the date of death due to any cause, whichever comes first. If there is no death reported for a subject before the data cutoff for OS analysis, OS will be censored at the last contact date at which the subject is known to be alive.
[a] Median OS is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 4 Pre-specified Subgroups Analysis of Overall Survival (OS) - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median OS (95% CI) [a] (months)	n	No. of Events (%)	Median OS (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	18 (11.5)	NE (NE , NE)	152	26 (17.1)	NE (NE , NE)	0.6063 (0.3323 , 1.1061)	0.9158
>= 3 lines	6	1 (16.7)	NE (9.7 , NE)	6	1 (16.7)	NE (1.1 , NE)	0.7454 (0.0464 , 11.968)	
Renal Impairment at Baseline								
Within Normal Range	130	15 (11.5)	NE (NE , NE)	130	28 (21.5)	NE (NE , NE)	0.4471 (0.2385 , 0.8379)	0.4132
Mild Impairment	92	13 (14.1)	NE (NE , NE)	104	18 (17.3)	NE (NE , NE)	0.7956 (0.3896 , 1.6247)	
Moderate Impairment	30	4 (13.3)	NE (NE , NE)	22	6 (27.3)	NE (13.1 , NE)	0.4047 (0.1138 , 1.4388)	
Hepatic Impairment								
Within Normal Range	208	19 (9.1)	NE (NE , NE)	212	32 (15.1)	NE (NE , NE)	0.5479 (0.3105 , 0.9667)	0.9124
Mild Impairment	49	14 (28.6)	NE (19.8 , NE)	49	21 (42.9)	17.4 (11.2 , NE)	0.5486 (0.2786 , 1.0800)	
Baseline Visceral Disease								
Yes	195	29 (14.9)	NE (NE , NE)	189	44 (23.3)	NE (NE , NE)	0.5783 (0.3618 , 0.9244)	0.6655
No	66	4 (6.1)	NE (NE , NE)	74	9 (12.2)	NE (NE , NE)	0.4460 (0.1373 , 1.4486)	

Notes: OS is defined as the time from the date of randomization to the date of death due to any cause, whichever comes first. If there is no death reported for a subject before the data cutoff for OS analysis, OS will be censored at the last contact date at which the subject is known to be alive.

[a] Median OS is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 4 Pre-specified Subgroups Analysis of Overall Survival (OS) - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median OS (95% CI) [a] (months)	n	No. of Events (%)	Median OS (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Baseline CNS Metastases								
Yes	43	9 (20.9)	NE (18.2 , NE)	39	16 (41.0)	NE (12.6 , NE)	0.4360 (0.1917 , 0.9914)	0.4891
No	218	24 (11.0)	NE (NE , NE)	224	37 (16.5)	NE (NE , NE)	0.6097 (0.3647 , 1.0193)	
History of CNS Metastases								
Yes	62	15 (24.2)	NE (18.2 , NE)	52	18 (34.6)	NE (15.8 , NE)	0.6560 (0.3292 , 1.3073)	0.5408
No	199	18 (9.0)	NE (NE , NE)	211	35 (16.6)	NE (NE , NE)	0.4920 (0.2786 , 0.8690)	

Notes: OS is defined as the time from the date of randomization to the date of death due to any cause, whichever comes first. If there is no death reported for a subject before the data cutoff for OS analysis, OS will be censored at the last contact date at which the subject is known to be alive.

[a] Median OS is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 2 Pre-specified Subgroups Analysis of Progression Free Survival (PFS) - Based on BICR - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median PFS (95% CI) [a] (months)	n	No. of Events (%)	Median PFS (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Age								
<65	212	75 (35.4)	22.4 (17.9 , NE)	206	128 (62.1)	5.8 (4.2 , 7.1)	0.2862 (0.2138 , 0.3832)	0.7555
>=65	49	12 (24.5)	NE (NE , NE)	57	30 (52.6)	11.3 (5.6 , 19.5)	0.3278 (0.1673 , 0.6424)	
Age								
<75	253	85 (33.6)	NE (18.5 , NE)	255	156 (61.2)	6.8 (5.5 , 8.1)	0.3023 (0.2312 , 0.3952)	0.4898
>=75	8	2 (25.0)	NE (8.4 , NE)	8	2 (25.0)	NE (3.1 , NE)	0.3267 (0.0292 , 3.6498)	
Region								
Asia	149	54 (36.2)	NE (16.8 , NE)	160	108 (67.5)	5.6 (4.1 , 6.9)	0.2724 (0.1951 , 0.3801)	0.2702
North America	17	7 (41.2)	22.2 (8.3 , NE)	17	8 (47.1)	12.1 (2.8 , NE)	0.3778 (0.1226 , 1.1639)	
Europe	54	15 (27.8)	NE (17.7 , NE)	50	19 (38.0)	18.0 (10.0 , NE)	0.4750 (0.2402 , 0.9394)	
Rest of World	41	11 (26.8)	NE (15.1 , NE)	36	23 (63.9)	6.8 (4.2 , 9.7)	0.2391 (0.1156 , 0.4948)	

Notes: PFS is defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever comes first. See SAP for the handling of censored cases. Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median PFS is from Kaplan-Meier analysis. Confidence Interval (CI) for the median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 2 Pre-specified Subgroups Analysis of Progression Free Survival (PFS) - Based on BICR - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median PFS (95% CI) [a] (months)	n	No. of Events (%)	Median PFS (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Race								
White	71	21 (29.6)	NE (17.7 , NE)	72	34 (47.2)	10.0 (5.6 , NE)	0.4030 (0.2333 , 0.6962)	0.4729
Black or African American	10	3 (30.0)	22.2 (15.1 , 22.4)	9	6 (66.7)	8.2 (1.3 , 9.7)	0.0586 (0.0067 , 0.5129)	
Asian	152	56 (36.8)	NE (16.5 , NE)	162	110 (67.9)	5.6 (4.1 , 7.0)	0.2775 (0.1998 , 0.3853)	
Other	28	7 (25.0)	NE (15.0 , NE)	20	8 (40.0)	18.0 (5.4 , NE)	0.4004 (0.1439 , 1.1139)	
ECOG PS								
0	154	46 (29.9)	NE (22.2 , NE)	175	103 (58.9)	7.0 (5.5 , 9.7)	0.2853 (0.2007 , 0.4056)	0.7242
1	106	41 (38.7)	17.7 (15.0 , NE)	87	55 (63.2)	5.7 (4.0 , 8.2)	0.2969 (0.1956 , 0.4507)	
Hormone Receptor Status								
Positive	133	46 (34.6)	22.4 (17.7 , NE)	139	84 (60.4)	6.9 (4.2 , 9.8)	0.3191 (0.2217 , 0.4594)	0.8014
Negative	126	41 (32.5)	NE (18.0 , NE)	122	73 (59.8)	6.8 (5.4 , 8.3)	0.2965 (0.2008 , 0.4378)	

Notes: PFS is defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever comes first. See SAP for the handling of censored cases. Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median PFS is from Kaplan-Meier analysis. Confidence Interval (CI) for the median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 2 Pre-specified Subgroups Analysis of Progression Free Survival (PFS) - Based on BICR - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median PFS (95% CI) [a] (months)	n	No. of Events (%)	Median PFS (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Estrogen Receptors								
Positive	129	43 (33.3)	22.4 (17.7 , NE)	132	80 (60.6)	5.8 (4.2 , 9.8)	0.3035 (0.2084 , 0.4420)	0.9372
Negative	130	44 (33.8)	NE (18.0 , NE)	128	76 (59.4)	6.8 (5.4 , 8.3)	0.3127 (0.2143 , 0.4562)	
Progesterone Receptors								
Positive	81	31 (38.3)	22.4 (14.1 , NE)	92	56 (60.9)	5.6 (3.2 , 8.0)	0.3360 (0.2153 , 0.5244)	0.8316
Negative	177	56 (31.6)	NE (21.6 , NE)	168	100 (59.5)	7.1 (5.7 , 9.7)	0.2999 (0.2151 , 0.4181)	
Prior Treatment with Pertuzumab								
Yes	162	57 (35.2)	NE (18.5 , NE)	158	98 (62.0)	6.8 (5.4 , 8.3)	0.3050 (0.2185 , 0.4257)	0.9184
No	99	30 (30.3)	NE (16.5 , NE)	105	60 (57.1)	7.0 (4.2 , 9.7)	0.2999 (0.1924 , 0.4675)	
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	60 (31.9)	NE (21.6 , NE)	191	107 (56.0)	8.2 (6.8 , 10.0)	0.3242 (0.2354 , 0.4465)	0.3175
>= 3 lines	73	27 (37.0)	22.2 (15.4 , NE)	72	51 (70.8)	4.3 (2.9 , 5.7)	0.2531 (0.1563 , 0.4097)	

Notes: PFS is defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever comes first. See SAP for the handling of censored cases. Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median PFS is from Kaplan-Meier analysis. Confidence Interval (CI) for the median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 2 Pre-specified Subgroups Analysis of Progression Free Survival (PFS) - Based on BICR - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median PFS (95% CI) [a] (months)	n	No. of Events (%)	Median PFS (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	54 (34.6)	NE (18.5 , NE)	152	95 (62.5)	6.8 (5.4 , 8.3)	0.2975 (0.2115 , 0.4186)	0.6835
>= 3 lines	6	3 (50.0)	NE (3.0 , NE)	6	3 (50.0)	2.6 (1.1 , NE)	0.5141 (0.1019 , 2.5942)	
Renal Impairment at Baseline								
Within Normal Range	130	39 (30.0)	NE (21.6 , NE)	130	84 (64.6)	5.5 (4.2 , 8.0)	0.2178 (0.1472 , 0.3223)	0.0337
Mild Impairment	92	38 (41.3)	17.7 (14.2 , NE)	104	61 (58.7)	7.1 (5.7 , 11.1)	0.4326 (0.2875 , 0.6511)	
Moderate Impairment	30	8 (26.7)	NE (13.9 , NE)	22	10 (45.5)	15.2 (3.0 , NE)	0.3638 (0.1424 , 0.9291)	
Hepatic Impairment								
Within Normal Range	208	62 (29.8)	NE (21.6 , NE)	212	123 (58.0)	7.0 (5.7 , 9.7)	0.2722 (0.1994 , 0.3716)	0.3736
Mild Impairment	49	25 (51.0)	16.5 (9.7 , NE)	49	35 (71.4)	3.0 (1.9 , 6.8)	0.3988 (0.2373 , 0.6701)	
Baseline Visceral Disease								
Yes	195	72 (36.9)	22.2 (16.5 , NE)	189	123 (65.1)	5.7 (4.2 , 7.0)	0.2806 (0.2083 , 0.3779)	0.8593
No	66	15 (22.7)	NE (NE , NE)	74	35 (47.3)	11.3 (6.8 , NE)	0.3157 (0.1718 , 0.5804)	

Notes: PFS is defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever comes first. See SAP for the handling of censored cases. Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median PFS is from Kaplan-Meier analysis. Confidence Interval (CI) for the median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 2 Pre-specified Subgroups Analysis of Progression Free Survival (PFS) - Based on BICR - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median PFS (95% CI) [a] (months)	n	No. of Events (%)	Median PFS (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Baseline CNS Metastases								
Yes	43	22 (51.2)	15.0 (12.5 , 22.2)	39	27 (69.2)	3.0 (2.8 , 5.8)	0.2465 (0.1341 , 0.4529)	0.9743
No	218	65 (29.8)	NE (22.4 , NE)	224	131 (58.5)	7.1 (5.6 , 9.7)	0.2971 (0.2199 , 0.4014)	
History of CNS Metastases								
Yes	62	31 (50.0)	15.0 (12.6 , 22.2)	52	31 (59.6)	5.7 (2.9 , 7.1)	0.3796 (0.2267 , 0.6357)	0.1428
No	199	56 (28.1)	NE (22.4 , NE)	211	127 (60.2)	7.0 (5.5 , 9.7)	0.2665 (0.1939 , 0.3665)	

Notes: PFS is defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever comes first. See SAP for the handling of censored cases. Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median PFS is from Kaplan-Meier analysis. Confidence Interval (CI) for the median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 6 Objective Response Rate (ORR) - Based on BICR - by pre specified Subgroups - Full Analysis Set

Subgroup	T-DXd (N=261) Confirmed ORR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed ORR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	Interaction p-value [e]
Age						
<65 (n = 418)	169 (79.7) (73.7, 84.9)	69 (33.5) (27.1, 40.4)	7.80 (5.01, 12.15)	2.38 (1.94, 2.92)	0.462 (0.373, 0.551)	0.7581
>=65 (n = 106)	39 (79.6) (65.7, 89.8)	21 (36.8) (24.4, 50.7)	6.69 (2.78, 16.10)	2.16 (1.49, 3.12)	0.427 (0.240, 0.615)	
Age						
<75 (n = 508)	202 (79.8) (74.4, 84.6)	86 (33.7) (27.9, 39.9)	7.78 (5.21, 11.64)	2.37 (1.97, 2.84)	0.461 (0.381, 0.541)	0.3859
>=75 (n = 16)	6 (75.0) (34.9, 96.8)	4 (50.0) (15.7, 84.3)	3.00 (0.36, 24.92)	1.50 (0.67, 3.34)	0.250 (-0.333, 0.833)	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

Table 6 Objective Response Rate (ORR) - Based on BICR - by pre specified Subgroups - Full Analysis Set

Subgroup	T-DXd (N=261) Confirmed ORR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed ORR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	Interaction p-value [e]
Region						
Asia (n = 309)	114 (76.5) (68.9, 83.1)	50 (31.3) (24.2, 39.0)	7.17 (4.32, 11.88)	2.45 (1.91, 3.13)	0.453 (0.347, 0.558)	0.9067
North America (n = 34)	13 (76.5) (50.1, 93.2)	5 (29.4) (10.3, 56.0)	7.80 (1.69, 36.06)	2.60 (1.19, 5.68)	0.471 (0.116, 0.825)	
Europe (n = 104)	45 (83.3) (70.7, 92.1)	21 (42.0) (28.2, 56.8)	6.90 (2.78, 17.15)	1.98 (1.40, 2.81)	0.413 (0.225, 0.602)	
Rest of World (n = 77)	36 (87.8) (73.8, 95.9)	14 (38.9) (23.1, 56.5)	11.31 (3.58, 35.76)	2.26 (1.48, 3.45)	0.489 (0.275, 0.703)	
Race						
White (n = 143)	63 (88.7) (79.0, 95.0)	27 (37.5) (26.4, 49.7)	13.12 (5.46, 31.54)	2.37 (1.74, 3.22)	0.512 (0.364, 0.660)	0.4861
Black or African American (n = 19)	8 (80.0) (44.4, 97.5)	4 (44.4) (13.7, 78.8)	5.00 (0.66, 38.15)	1.80 (0.81, 3.98)	0.356 (-0.158, 0.870)	
Asian (n = 314)	116 (76.3) (68.7, 82.8)	51 (31.5) (24.4, 39.2)	7.01 (4.25, 11.56)	2.42 (1.90, 3.09)	0.448 (0.344, 0.553)	
Other (n = 48)	21 (75.0) (55.1, 89.3)	8 (40.0) (19.1, 63.9)	4.50 (1.31, 15.52)	1.88 (1.05, 3.34)	0.350 (0.039, 0.661)	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

Table 6 Objective Response Rate (ORR) - Based on BICR - by pre specified Subgroups - Full Analysis Set

Subgroup	T-DXd (N=261) Confirmed ORR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed ORR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	Interaction p-value [e]
ECOG PS						
0 (n = 329)	130 (84.4) (77.7, 89.8)	65 (37.1) (30.0, 44.8)	9.17 (5.38, 15.61)	2.27 (1.85, 2.79)	0.473 (0.375, 0.571)	0.5036
1 (n = 193)	78 (73.6) (64.1, 81.7)	25 (28.7) (19.5, 39.4)	6.91 (3.66, 13.02)	2.56 (1.80, 3.63)	0.448 (0.311, 0.586)	
Hormone Receptor Status						
Positive (n = 272)	104 (78.2) (70.2, 84.9)	43 (30.9) (23.4, 39.3)	8.01 (4.64, 13.83)	2.53 (1.94, 3.29)	0.473 (0.361, 0.584)	0.7799
Negative (n = 248)	103 (81.7) (73.9, 88.1)	47 (38.5) (29.9, 47.8)	7.15 (4.00, 12.77)	2.12 (1.67, 2.69)	0.432 (0.315, 0.550)	
Estrogen Receptors						
Positive (n = 261)	102 (79.1) (71.0, 85.7)	41 (31.1) (23.3, 39.7)	8.38 (4.78, 14.71)	2.55 (1.94, 3.33)	0.480 (0.367, 0.593)	0.6568
Negative (n = 258)	105 (80.8) (72.9, 87.2)	48 (37.5) (29.1, 46.5)	7.00 (3.98, 12.31)	2.15 (1.70, 2.73)	0.433 (0.317, 0.548)	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

Table 6 Objective Response Rate (ORR) - Based on BICR - by pre specified Subgroups - Full Analysis Set

Subgroup	T-DXd (N=261) Confirmed ORR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed ORR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	Interaction p-value [e]
Progesterone Receptors						
Positive (n = 173)	59 (72.8) (61.8, 82.1)	22 (23.9) (15.6, 33.9)	8.53 (4.30, 16.93)	3.05 (2.07, 4.49)	0.489 (0.347, 0.631)	0.6957
Negative (n = 345)	147 (83.1) (76.7, 88.3)	68 (40.5) (33.0, 48.3)	7.21 (4.37, 11.87)	2.05 (1.69, 2.49)	0.426 (0.327, 0.524)	
Prior Treatment with Pertuzumab						
Yes (n = 320)	129 (79.6) (72.6, 85.5)	52 (32.9) (25.7, 40.8)	7.97 (4.80, 13.22)	2.42 (1.91, 3.06)	0.467 (0.365, 0.569)	0.7444
No (n = 204)	79 (79.8) (70.5, 87.2)	38 (36.2) (27.0, 46.1)	6.96 (3.70, 13.10)	2.20 (1.68, 2.90)	0.436 (0.305, 0.567)	
Lines of Prior Systemic Therapy Not Including Hormone Therapy						
< 3 lines (n = 379)	151 (80.3) (73.9, 85.7)	70 (36.6) (29.8, 43.9)	7.05 (4.43, 11.23)	2.19 (1.80, 2.68)	0.437 (0.343, 0.531)	0.5480
>= 3 lines (n = 145)	57 (78.1) (66.9, 86.9)	20 (27.8) (17.9, 39.6)	9.26 (4.34, 19.75)	2.81 (1.90, 4.16)	0.503 (0.349, 0.657)	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

Table 6 Objective Response Rate (ORR) - Based on BICR - by pre specified Subgroups - Full Analysis Set

Subgroup	T-DXd (N=261) Confirmed ORR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed ORR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	Interaction p-value [e]
Lines of Systemic Therapy Prior to Pertuzumab Treatment						
< 3 lines (n = 308)	124 (79.5) (72.3, 85.5)	51 (33.6) (26.1, 41.7)	7.67 (4.59, 12.83)	2.37 (1.87, 3.00)	0.459 (0.355, 0.564)	0.4523
>= 3 lines (n = 12)	5 (83.3) (35.9, 99.6)	1 (16.7) (0.4, 64.1)	24.99 (1.20, 520.48)	5.00 (0.81, 31.00)	0.667 (0.078, 1.000)	
Renal Impairment at Baseline						
Within Normal Range (n = 260)	110 (84.6) (77.2, 90.3)	38 (29.2) (21.6, 37.8)	13.31 (7.25, 24.45)	2.89 (2.19, 3.82)	0.554 (0.446, 0.661)	0.0489
Mild Impairment (n = 196)	69 (75.0) (64.9, 83.4)	41 (39.4) (30.0, 49.5)	4.61 (2.49, 8.52)	1.90 (1.46, 2.48)	0.356 (0.216, 0.495)	
Moderate Impairment (n = 52)	26 (86.7) (69.3, 96.2)	8 (36.4) (17.2, 59.3)	11.37 (2.91, 44.53)	2.38 (1.35, 4.22)	0.503 (0.229, 0.777)	
Hepatic Impairment						
Within Normal Range (n = 420)	171 (82.2) (76.3, 87.2)	78 (36.8) (30.3, 43.7)	7.94 (5.05, 12.47)	2.23 (1.85, 2.70)	0.454 (0.366, 0.542)	0.7306
Mild Impairment (n = 98)	37 (75.5) (61.1, 86.7)	12 (24.5) (13.3, 38.9)	9.51 (3.79, 23.87)	3.08 (1.84, 5.17)	0.510 (0.320, 0.701)	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

Table 6 Objective Response Rate (ORR) - Based on BICR - by pre specified Subgroups - Full Analysis Set

Subgroup	T-DXd (N=261) Confirmed ORR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed ORR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	Interaction p-value [e]
Baseline Visceral Disease						
Yes (n = 384)	151 (77.4) (70.9, 83.1)	55 (29.1) (22.7, 36.1)	8.36 (5.28, 13.24)	2.66 (2.10, 3.37)	0.483 (0.391, 0.576)	0.7271
No (n = 140)	57 (86.4) (75.7, 93.6)	35 (47.3) (35.6, 59.3)	7.06 (3.05, 16.31)	1.83 (1.41, 2.37)	0.391 (0.236, 0.546)	
Baseline CNS Metastases						
Yes (n = 82)	29 (67.4) (51.5, 80.9)	8 (20.5) (9.3, 36.5)	8.03 (2.94, 21.94)	3.29 (1.71, 6.31)	0.469 (0.256, 0.683)	0.9859
No (n = 442)	179 (82.1) (76.4, 87.0)	82 (36.6) (30.3, 43.3)	7.95 (5.12, 12.34)	2.24 (1.87, 2.69)	0.455 (0.369, 0.541)	
History of CNS Metastases						
Yes (n = 114)	45 (72.6) (59.8, 83.1)	10 (19.2) (9.6, 32.5)	11.12 (4.58, 26.99)	3.77 (2.12, 6.73)	0.533 (0.362, 0.705)	0.4259
No (n = 410)	163 (81.9) (75.8, 87.0)	80 (37.9) (31.3, 44.8)	7.41 (4.70, 11.69)	2.16 (1.80, 2.60)	0.440 (0.351, 0.529)	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

Table 9 Clinical Benefit Rate (CBR) by pre-specified subgroup - Based on BICR

Subgroup	T-DXd (N=261) Confirmed DCR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed DCR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	T-DXd vs T-DM1 p-value [e]	Interaction P-value [f]
Age							
<65 (n = 418)	187 (88.2) (83.1, 92.2)	90 (43.7) (36.8, 50.8)	9.64 (5.85, 15.90)	2.02 (1.72, 2.38)	0.445 (0.360, 0.530)	<0.0001	0.6087
>=65 (n = 106)	46 (93.9) (83.1, 98.7)	30 (52.6) (39.0, 66.0)	13.80 (3.84, 49.55)	1.78 (1.38, 2.31)	0.412 (0.248, 0.577)	<0.0001	
Age							
<75 (n = 508)	226 (89.3) (84.9, 92.8)	115 (45.1) (38.9, 51.4)	10.19 (6.37, 16.29)	1.98 (1.72, 2.28)	0.442 (0.366, 0.518)	<0.0001	0.5008
>=75 (n = 16)	7 (87.5) (47.3, 99.7)	5 (62.5) (24.5, 91.5)	4.20 (0.33, 53.12)	1.40 (0.77, 2.54)	0.250 (-0.281, 0.781)	0.2636	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value derived from Cochran- Mantel-Haenszel test
[f] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 9 Clinical Benefit Rate (CBR) by pre-specified subgroup - Based on BICR

Subgroup	T-DXd (N=261) Confirmed DCR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed DCR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	T-DXd vs T-DM1 p-value [e]	Interaction P-value [f]
Region							
Asia (n = 309)	129 (86.6) (80.0, 91.6)	64 (40.0) (32.3, 48.0)	9.67 (5.49, 17.06)	2.16 (1.77, 2.64)	0.466 (0.366, 0.566)	<0.0001	0.8393
North America (n = 34)	15 (88.2) (63.6, 98.5)	8 (47.1) (23.0, 72.2)	8.44 (1.46, 48.85)	1.88 (1.10, 3.20)	0.412 (0.071, 0.753)	0.0115	
Europe (n = 104)	50 (92.6) (82.1, 97.9)	30 (60.0) (45.2, 73.6)	8.33 (2.60, 26.72)	1.54 (1.22, 1.96)	0.326 (0.154, 0.498)	<0.0001	
Rest of World (n = 77)	39 (95.1) (83.5, 99.4)	18 (50.0) (32.9, 67.1)	19.50 (4.08, 93.14)	1.90 (1.36, 2.66)	0.451 (0.249, 0.653)	<0.0001	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value derived from Cochran- Mantel-Haenszel test
[f] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 9 Clinical Benefit Rate (CBR) by pre-specified subgroup - Based on BICR

Subgroup	T-DXd (N=261) Confirmed DCR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed DCR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	T-DXd vs T-DM1 p-value [e]	Interaction P-value [f]
Race							
White (n = 143)	67 (94.4) (86.2, 98.4)	36 (50.0) (38.0, 62.0)	16.75 (5.52, 50.80)	1.89 (1.49, 2.39)	0.444 (0.302, 0.585)	<0.0001	0.5769
Black or African American (n = 19)	10 (100.0) (69.2, 100.0)	5 (55.6) (21.2, 86.3)	NE (NE, NE)	1.80 (1.00, 3.23)	0.444 (0.014, 0.875)	0.0209	
Asian (n = 314)	131 (86.2) (79.7, 91.2)	66 (40.7) (33.1, 48.7)	9.07 (5.20, 15.84)	2.12 (1.74, 2.57)	0.454 (0.355, 0.554)	<0.0001	
Other (n = 48)	25 (89.3) (71.8, 97.7)	13 (65.0) (40.8, 84.6)	4.49 (0.99, 20.30)	1.37 (0.97, 1.94)	0.243 (-0.038, 0.524)	0.0433	
ECOG PS							
0 (n = 329)	142 (92.2) (86.8, 95.9)	86 (49.1) (41.5, 56.8)	12.25 (6.33, 23.68)	1.88 (1.60, 2.20)	0.431 (0.339, 0.522)	<0.0001	0.5972
1 (n = 193)	91 (85.8) (77.7, 91.9)	34 (39.1) (28.8, 50.1)	9.46 (4.72, 18.95)	2.20 (1.67, 2.89)	0.468 (0.335, 0.600)	<0.0001	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value derived from Cochran- Mantel-Haenszel test
[f] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 9 Clinical Benefit Rate (CBR) by pre-specified subgroup - Based on BICR

Subgroup	T-DXd (N=261) Confirmed DCR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed DCR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	T-DXd vs T-DM1 p-value [e]	Interaction P-value [f]
Hormone Receptor Status							
Positive (n = 272)	124 (93.2) (87.5, 96.9)	62 (44.6) (36.2, 53.3)	17.11 (8.04, 36.39)	2.09 (1.73, 2.53)	0.486 (0.386, 0.587)	<0.0001	0.0556
Negative (n = 248)	108 (85.7) (78.4, 91.3)	58 (47.5) (38.4, 56.8)	6.62 (3.59, 12.21)	1.80 (1.48, 2.20)	0.382 (0.266, 0.497)	<0.0001	
Estrogen Receptors							
Positive (n = 261)	121 (93.8) (88.1, 97.3)	59 (44.7) (36.0, 53.6)	18.71 (8.46, 41.37)	2.10 (1.73, 2.55)	0.491 (0.389, 0.593)	<0.0001	0.0404
Negative (n = 258)	111 (85.4) (78.1, 91.0)	60 (46.9) (38.0, 55.9)	6.62 (3.64, 12.04)	1.82 (1.49, 2.22)	0.385 (0.272, 0.498)	<0.0001	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value derived from Cochran- Mantel-Haenszel test
[f] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 9 Clinical Benefit Rate (CBR) by pre-specified subgroup - Based on BICR

Subgroup	T-DXd (N=261) Confirmed DCR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed DCR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	T-DXd vs T-DM1 p-value [e]	Interaction P-value [f]
Progesterone Receptors							
Positive (n = 173)	73 (90.1) (81.5, 95.6)	32 (34.8) (25.1, 45.4)	17.11 (7.34, 39.90)	2.59 (1.94, 3.46)	0.553 (0.425, 0.682)	<0.0001	0.1156
Negative (n = 345)	158 (89.3) (83.7, 93.4)	88 (52.4) (44.5, 60.1)	7.56 (4.30, 13.29)	1.70 (1.46, 1.99)	0.369 (0.275, 0.463)	<0.0001	
Prior Treatment with Pertuzumab							
Yes (n = 320)	145 (89.5) (83.7, 93.8)	74 (46.8) (38.9, 54.9)	9.68 (5.36, 17.50)	1.91 (1.61, 2.27)	0.427 (0.329, 0.524)	<0.0001	0.9041
No (n = 204)	88 (88.9) (81.0, 94.3)	46 (43.8) (34.1, 53.8)	10.26 (4.92, 21.42)	2.03 (1.62, 2.55)	0.451 (0.328, 0.574)	<0.0001	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value derived from Cochran- Mantel-Haenszel test
[f] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 9 Clinical Benefit Rate (CBR) by pre-specified subgroup - Based on BICR

Subgroup	T-DXd (N=261) Confirmed DCR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed DCR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	T-DXd vs T-DM1 p-value [e]	Interaction P-value [f]
Lines of Prior Systemic Therapy Not Including Hormone Therapy							
< 3 lines (n = 379)	171 (91.0) (85.9, 94.6)	96 (50.3) (43.0, 57.6)	9.95 (5.61, 17.66)	1.81 (1.56, 2.10)	0.407 (0.320, 0.494)	<0.0001	0.8055
>= 3 lines (n = 145)	62 (84.9) (74.6, 92.2)	24 (33.3) (22.7, 45.4)	11.27 (5.03, 25.26)	2.55 (1.81, 3.58)	0.516 (0.366, 0.666)	<0.0001	
Lines of Systemic Therapy Prior to Pertuzumab Treatment							
< 3 lines (n = 308)	140 (89.7) (83.9, 94.0)	72 (47.4) (39.2, 55.6)	9.72 (5.30, 17.85)	1.89 (1.59, 2.26)	0.424 (0.325, 0.523)	<0.0001	0.9843
>= 3 lines (n = 12)	5 (83.3) (35.9, 99.6)	2 (33.3) (4.3, 77.7)	10.00 (0.65, 154.37)	2.50 (0.76, 8.19)	0.500 (-0.147, 1.000)	0.0926	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value derived from Cochran- Mantel-Haenszel test
[f] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 9 Clinical Benefit Rate (CBR) by pre-specified subgroup - Based on BICR

Subgroup	T-DXd (N=261) Confirmed DCR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed DCR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	T-DXd vs T-DM1 p-value [e]	Interaction P-value [f]
Renal Impairment at Baseline							
Within Normal Range (n = 260)	119 (91.5) (85.4, 95.7)	51 (39.2) (30.8, 48.2)	16.76 (8.23, 34.12)	2.33 (1.87, 2.91)	0.523 (0.419, 0.627)	<0.0001	0.1357
Mild Impairment (n = 196)	81 (88.0) (79.6, 93.9)	55 (52.9) (42.8, 62.8)	6.56 (3.14, 13.72)	1.66 (1.37, 2.03)	0.352 (0.225, 0.478)	<0.0001	
Moderate Impairment (n = 52)	29 (96.7) (82.8, 99.9)	11 (50.0) (28.2, 71.8)	29.00 (3.34, 251.86)	1.93 (1.27, 2.95)	0.467 (0.209, 0.725)	<0.0001	
Hepatic Impairment							
Within Normal Range (n = 420)	191 (91.8) (87.2, 95.2)	104 (49.1) (42.1, 56.0)	11.67 (6.64, 20.52)	1.87 (1.62, 2.16)	0.428 (0.346, 0.509)	<0.0001	0.9198
Mild Impairment (n = 98)	42 (85.7) (72.8, 94.1)	16 (32.7) (19.9, 47.5)	12.37 (4.56, 33.58)	2.63 (1.73, 3.99)	0.531 (0.346, 0.715)	<0.0001	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value derived from Cochran- Mantel-Haenszel test
[f] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 9 Clinical Benefit Rate (CBR) by pre-specified subgroup - Based on BICR

Subgroup	T-DXd (N=261) Confirmed DCR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed DCR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	T-DXd vs T-DM1 p-value [e]	Interaction P-value [f]
Baseline Visceral Disease							
Yes (n = 384)	172 (88.2) (82.8, 92.4)	77 (40.7) (33.7, 48.1)	10.88 (6.45, 18.35)	2.17 (1.81, 2.59)	0.475 (0.386, 0.563)	<0.0001	0.7168
No (n = 140)	61 (92.4) (83.2, 97.5)	43 (58.1) (46.1, 69.5)	8.80 (3.17, 24.44)	1.59 (1.30, 1.95)	0.343 (0.200, 0.487)	<0.0001	
Baseline CNS Metastases							
Yes (n = 82)	37 (86.0) (72.1, 94.7)	10 (25.6) (13.0, 42.1)	17.88 (5.82, 54.96)	3.36 (1.94, 5.80)	0.604 (0.408, 0.800)	<0.0001	0.2938
No (n = 442)	196 (89.9) (85.1, 93.6)	110 (49.1) (42.4, 55.9)	9.23 (5.53, 15.42)	1.83 (1.59, 2.11)	0.408 (0.327, 0.489)	<0.0001	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value derived from Cochran- Mantel-Haenszel test
[f] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 9 Clinical Benefit Rate (CBR) by pre-specified subgroup - Based on BICR

Subgroup	T-DXd (N=261) Confirmed DCR n (%) (95% CI)[a]	T-DM1 (N=263) Confirmed DCR n (%) (95% CI)[a]	T-DXd vs T-DM1 OR[b] (95% CI)	T-DXd vs T-DM1 RR[c] (95% CI)	T-DXd vs T-DM1 ARR[d] (95% CI)	T-DXd vs T-DM1 p-value [e]	Interaction P-value [f]
History of CNS Metastases							
Yes (n = 114)	52 (83.9) (72.3, 92.0)	18 (34.6) (22.0, 49.1)	9.82 (4.05, 23.81)	2.42 (1.64, 3.58)	0.493 (0.316, 0.669)	<0.0001	0.8662
No (n = 410)	181 (91.0) (86.1, 94.6)	102 (48.3) (41.4, 55.3)	10.75 (6.17, 18.71)	1.88 (1.63, 2.18)	0.426 (0.343, 0.509)	<0.0001	

Notes: BICR: blinded independent central review.
[a] Based on Clopper-Pearson method for single proportion
[b] OR and 95% CI obtained from unadjusted logistic regression models
[c] derived using the Cochran-Mantel-Haenszel method
[d] Derived from the difference of two proportions with continuity correction. ARR presented on the risk scale.
[e] P-value derived from Cochran- Mantel-Haenszel test
[f] P-value for interaction is obtained by including a treatment times subgroup variable interaction term in the logistic regression model. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 8 Duration of Response - Based on BICR - by pre specified Subgroups - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median DoR (95% CI) [a] (months)	n	No. of Events (%)	Median DoR (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Age								
<65	169	50 (29.6)	NE (16.6 , NE)	69	26 (37.7)	NE (8.2 , NE)	0.6111 (0.3794 , 0.9842)	0.4802
>=65	39	8 (20.5)	NE (NE , NE)	21	5 (23.8)	NE (11.0 , NE)	0.9269 (0.3019 , 2.8454)	
Age								
<75	202	57 (28.2)	NE (20.3 , NE)	86	31 (36.0)	NE (11.1 , NE)	0.6674 (0.4305 , 1.0347)	0.2973
>=75	6	1 (16.7)	NE (13.0 , NE)	4	0	NE (NE , NE)	NE (NE , NE)	
Region								
Asia	114	34 (29.8)	NE (20.3 , NE)	50	19 (38.0)	13.8 (8.2 , NE)	0.6111 (0.3473 , 1.0751)	0.2308
North America	13	4 (30.8)	16.6 (9.8 , NE)	5	0	NE (NE , NE)	NE (NE , NE)	
Europe	45	11 (24.4)	NE (16.2 , NE)	21	5 (23.8)	NE (12.6 , NE)	1.0364 (0.3588 , 2.9936)	
Rest of World	36	9 (25.0)	NE (12.3 , NE)	14	7 (50.0)	NE (4.1 , NE)	0.4291 (0.1592 , 1.1567)	

Notes: Duration of response (DoR) is defined as the time from date of initial response (CR or PR) to the date of disease progression or death due to any cause for subjects with a confirmed CR or PR. See SAP for the handling of censored cases. Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median DoR is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 8 Duration of Response - Based on BICR - by pre specified Subgroups - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median DoR (95% CI) [a] (months)	n	No. of Events (%)	Median DoR (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Race								
White	63	16 (25.4)	NE (16.2 , NE)	27	5 (18.5)	NE (NE , NE)	1.4260 (0.5220 , 3.8953)	0.1675
Black or African American	8	2 (25.0)	16.6 (12.3 , NE)	4	2 (50.0)	6.9 (5.6 , NE)	0.1283 (0.0113 , 1.4604)	
Asian	116	36 (31.0)	NE (15.4 , NE)	51	20 (39.2)	13.8 (8.2 , NE)	0.6171 (0.3559 , 1.0698)	
Other	21	4 (19.0)	NE (14.0 , NE)	8	4 (50.0)	9.8 (2.8 , 15.2)	0.2922 (0.0715 , 1.1932)	
ECOG PS								
0	130	33 (25.4)	NE (NE , NE)	65	21 (32.3)	NE (12.6 , NE)	0.6378 (0.3684 , 1.1042)	0.9044
1	78	25 (32.1)	20.3 (13.8 , NE)	25	10 (40.0)	9.8 (6.9 , NE)	0.6617 (0.3146 , 1.3919)	
Hormone Receptor Status								
Positive	104	30 (28.8)	NE (16.2 , NE)	43	10 (23.3)	NE (15.2 , NE)	1.2482 (0.6098 , 2.5549)	0.0168
Negative	103	28 (27.2)	NE (20.3 , NE)	47	21 (44.7)	11.1 (5.8 , NE)	0.4390 (0.2481 , 0.7768)	
Estrogen Receptors								
Positive	102	29 (28.4)	NE (16.2 , NE)	41	9 (22.0)	NE (NE , NE)	1.2790 (0.6050 , 2.7039)	0.0232
Negative	105	29 (27.6)	NE (20.3 , NE)	48	21 (43.8)	11.1 (5.8 , NE)	0.4644 (0.2638 , 0.8176)	

Notes: Duration of response (DoR) is defined as the time from date of initial response (CR or PR) to the date of disease progression or death due to any cause for subjects with a confirmed CR or PR. See SAP for the handling of censored cases. Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median DoR is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 8 Duration of Response - Based on BICR - by pre specified Subgroups - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median DoR (95% CI) [a] (months)	n	No. of Events (%)	Median DoR (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Progesterone Receptors								
Positive	59	16 (27.1)	NE (13.9 , NE)	22	3 (13.6)	NE (15.2 , NE)	2.1662 (0.6311 , 7.4354)	0.0221
Negative	147	42 (28.6)	NE (16.6 , NE)	68	28 (41.2)	13.8 (8.2 , NE)	0.5419 (0.3349 , 0.8766)	
Prior Treatment with Pertuzumab								
Yes	129	37 (28.7)	NE (20.3 , NE)	52	20 (38.5)	NE (8.2 , NE)	0.5552 (0.3208 , 0.9608)	0.2136
No	79	21 (26.6)	NE (13.8 , NE)	38	11 (28.9)	NE (13.8 , NE)	0.9552 (0.4600 , 1.9833)	
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	151	40 (26.5)	NE (20.3 , NE)	70	24 (34.3)	NE (11.1 , NE)	0.6475 (0.3893 , 1.0769)	0.6628
>= 3 lines	57	18 (31.6)	16.6 (13.8 , NE)	20	7 (35.0)	NE (5.7 , NE)	0.8266 (0.3439 , 1.9867)	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	124	35 (28.2)	NE (20.3 , NE)	51	20 (39.2)	NE (8.2 , NE)	0.5310 (0.3050 , 0.9245)	0.2399
>= 3 lines	5	2 (40.0)	NE (6.9 , NE)	1	0	NE (NE , NE)	NE (NE , NE)	

Notes: Duration of response (DoR) is defined as the time from date of initial response (CR or PR) to the date of disease progression or death due to any cause for subjects with a confirmed CR or PR. See SAP for the handling of censored cases. Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median DoR is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 8 Duration of Response - Based on BICR - by pre specified Subgroups - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median DoR (95% CI) [a] (months)	n	No. of Events (%)	Median DoR (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	110	26 (23.6)	NE (20.3 , NE)	38	14 (36.8)	NE (7.0 , NE)	0.4449 (0.2290 , 0.8645)	0.1948
Mild Impairment	69	25 (36.2)	16.2 (12.9 , NE)	41	14 (34.1)	NE (9.8 , NE)	1.0014 (0.5194 , 1.9308)	
Moderate Impairment	26	6 (23.1)	NE (9.9 , NE)	8	2 (25.0)	NE (4.2 , NE)	0.9736 (0.1948 , 4.8650)	
Hepatic Impairment								
Within Normal Range	171	42 (24.6)	NE (20.3 , NE)	78	27 (34.6)	NE (11.1 , NE)	0.5573 (0.3424 , 0.9073)	0.0745
Mild Impairment	37	16 (43.2)	13.9 (7.9 , NE)	12	4 (33.3)	NE (5.5 , NE)	1.5238 (0.5038 , 4.6092)	
Baseline Visceral Disease								
Yes	151	46 (30.5)	NE (15.4 , NE)	55	21 (38.2)	NE (8.2 , NE)	0.6649 (0.3962 , 1.1160)	0.8771
No	57	12 (21.1)	NE (16.6 , NE)	35	10 (28.6)	NE (11.1 , NE)	0.5971 (0.2568 , 1.3881)	
Baseline CNS Metastases								
Yes	29	15 (51.7)	12.9 (8.5 , NE)	8	4 (50.0)	7.2 (2.8 , NE)	0.4522 (0.1339 , 1.5277)	0.9933
No	179	43 (24.0)	NE (20.3 , NE)	82	27 (32.9)	NE (12.6 , NE)	0.6304 (0.3892 , 1.0212)	

Notes: Duration of response (DoR) is defined as the time from date of initial response (CR or PR) to the date of disease progression or death due to any cause for subjects with a confirmed CR or PR. See SAP for the handling of censored cases. Subgroup values are as defined at baseline. BICR: blinded independent central review.
[a] Median DoR is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 8 Duration of Response - Based on BICR - by pre specified Subgroups - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median DoR (95% CI) [a] (months)	n	No. of Events (%)	Median DoR (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
History of CNS Metastases								
Yes	45	21 (46.7)	13.8 (9.8 , NE)	10	3 (30.0)	NE (2.8 , NE)	1.0129 (0.2933 , 3.4985)	0.2712
No	163	37 (22.7)	NE (20.3 , NE)	80	28 (35.0)	NE (11.1 , NE)	0.5426 (0.3317 , 0.8877)	

Notes: Duration of response (DoR) is defined as the time from date of initial response (CR or PR) to the date of disease progression or death due to any cause for subjects with a confirmed CR or PR. See SAP for the handling of censored cases. Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median DoR is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 11 Time to response (TTR) based on BICR by pre-specified subgroups - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	p-value [c]
Age								
<65	212	169 (79.7)	2.7 (1.9 , 2.8)	206	69 (33.5)	NE (7.4 , NE)	2.6933 (2.0344 , 3.5655) <0.0001	0.9383
>=65	49	39 (79.6)	2.6 (1.5 , 2.8)	57	21 (36.8)	NE (2.8 , NE)	2.5860 (1.5176 , 4.4064) 0.0003	
Age								
<75	253	202 (79.8)	2.7 (2.1 , 2.8)	255	86 (33.7)	NE (8.1 , NE)	2.7243 (2.1155 , 3.5083) <0.0001	0.7727
>=75	8	6 (75.0)	1.6 (1.1 , 2.8)	8	4 (50.0)	1.9 (1.2 , NE)	2.1656 (0.6087 , 7.7042) 0.2214	

Notes: Time to response (TTR) is defined as the time from randomization to initial response (CR or PR). Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median TTR is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate. P-value obtained from an unstratified log-rank test

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 11 Time to response (TTR) based on BICR by pre-specified subgroups - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	p-value [c]
Region								
Asia	149	114 (76.5)	2.6 (1.6 , 2.8)	160	50 (31.3)	NE (7.4 , NE)	2.8608 (2.0502 , 3.9920) <0.0001	0.8122
North America	17	13 (76.5)	4.0 (2.7 , 5.3)	17	5 (29.4)	NE (2.9 , NE)	2.3229 (0.8202 , 6.5784) 0.0993	
Europe	54	45 (83.3)	2.7 (1.6 , 3.0)	50	21 (42.0)	9.5 (2.6 , NE)	2.0977 (1.2449 , 3.5346) 0.0045	
Rest of World	41	36 (87.8)	2.8 (1.5 , 2.9)	36	14 (38.9)	NE (2.8 , NE)	2.8794 (1.5428 , 5.3740) 0.0005	

Notes: Time to response (TTR) is defined as the time from randomization to initial response (CR or PR). Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median TTR is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate. P-value obtained from an unstratified log-rank test

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 11 Time to response (TTR) based on BICR by pre-specified subgroups - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	p-value [c]
Race								
White	71	63 (88.7)	2.8 (1.6 , 2.8)	72	27 (37.5)	NE (2.9 , NE)	2.8219 (1.7921 , 4.4436) <0.0001	0.6455
Black or African American	10	8 (80.0)	3.0 (1.4 , 5.7)	9	4 (44.4)	4.2 (1.3 , NE)	1.3794 (0.4137 , 4.5999) 0.5951	
Asian	152	116 (76.3)	2.6 (1.6 , 2.8)	162	51 (31.5)	NE (8.1 , NE)	2.8644 (2.0592 , 3.9844) <0.0001	
Other	28	21 (75.0)	3.0 (1.5 , 13.9)	20	8 (40.0)	9.5 (2.8 , NE)	1.8110 (0.7886 , 4.1588) 0.1546	
ECOG PS								
0	154	130 (84.4)	2.6 (1.6 , 2.7)	175	65 (37.1)	NE (7.1 , NE)	2.6211 (1.9437 , 3.5345) <0.0001	0.7135
1	106	78 (73.6)	2.8 (2.6 , 3.2)	87	25 (28.7)	NE (6.8 , NE)	2.9624 (1.8864 , 4.6519) <0.0001	

Notes: Time to response (TTR) is defined as the time from randomization to initial response (CR or PR). Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median TTR is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate. P-value obtained from an unstratified log-rank test

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 11 Time to response (TTR) based on BICR by pre-specified subgroups - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	p-value [c]
Hormone Receptor Status								
Positive	133	104 (78.2)	2.9 (2.7 , 3.4)	139	43 (30.9)	NE (8.1 , NE)	2.6872 (1.8826 , 3.8355) <0.0001	0.8538
Negative	126	103 (81.7)	1.6 (1.4 , 2.6)	122	47 (38.5)	NE (4.0 , NE)	2.6858 (1.8986 , 3.7995) <0.0001	
Estrogen Receptors								
Positive	129	102 (79.1)	2.9 (2.7 , 3.2)	132	41 (31.1)	NE (8.1 , NE)	2.7580 (1.9182 , 3.9653) <0.0001	0.9657
Negative	130	105 (80.8)	1.6 (1.4 , 2.7)	128	48 (37.5)	NE (4.2 , NE)	2.6619 (1.8892 , 3.7507) <0.0001	

Notes: Time to response (TTR) is defined as the time from randomization to initial response (CR or PR). Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median TTR is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate. P-value obtained from an unstratified log-rank test

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 11 Time to response (TTR) based on BICR by pre-specified subgroups - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	p-value [c]
Progesterone Receptors								
Positive	81	59 (72.8)	3.0 (2.8 , 4.2)	92	22 (23.9)	NE (9.5 , NE)	3.1513 (1.9307 , 5.1436) <0.0001	0.4790
Negative	177	147 (83.1)	1.7 (1.5 , 2.7)	168	68 (40.5)	8.1 (4.2 , NE)	2.4923 (1.8674 , 3.3262) <0.0001	
Prior Treatment with Pertuzumab								
Yes	162	129 (79.6)	2.6 (1.6 , 2.8)	158	52 (32.9)	NE (8.1 , NE)	3.0433 (2.2033 , 4.2035) <0.0001	0.1768
No	99	79 (79.8)	2.8 (2.6 , 3.1)	105	38 (36.2)	NE (5.8 , NE)	2.2165 (1.5040 , 3.2666) <0.0001	

Notes: Time to response (TTR) is defined as the time from randomization to initial response (CR or PR). Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median TTR is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate. P-value obtained from an unstratified log-rank test

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 11 Time to response (TTR) based on BICR by pre-specified subgroups - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	151 (80.3)	2.6 (1.6 , 2.8)	191	70 (36.6)	NE (6.8 , NE)	2.5987 (1.9562 , 3.4522) <0.0001	0.6168
>= 3 lines	73	57 (78.1)	2.8 (2.7 , 4.0)	72	20 (27.8)	NE (NE , NE)	3.0458 (1.8239 , 5.0861) <0.0001	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	124 (79.5)	2.6 (1.5 , 2.7)	152	51 (33.6)	NE (8.1 , NE)	2.9990 (2.1626 , 4.1590) <0.0001	0.6970
>= 3 lines	6	5 (83.3)	2.8 (1.7 , NE)	6	1 (16.7)	NE (1.8 , NE)	4.3485 (0.5001 , 37.813) 0.1519	

Notes: Time to response (TTR) is defined as the time from randomization to initial response (CR or PR). Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median TTR is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate. P-value obtained from an unstratified log-rank test

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 11 Time to response (TTR) based on BICR by pre-specified subgroups - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	110 (84.6)	2.7 (1.9 , 2.9)	130	38 (29.2)	NE (8.1 , NE)	3.5752 (2.4678 , 5.1795) <0.0001	0.1819
Mild Impairment	92	69 (75.0)	2.8 (1.6 , 3.0)	104	41 (39.4)	NE (4.0 , NE)	2.1174 (1.4381 , 3.1176) <0.0001	
Moderate Impairment	30	26 (86.7)	2.2 (1.4 , 2.8)	22	8 (36.4)	NE (1.4 , NE)	2.3139 (1.0420 , 5.1382) 0.0331	
Hepatic Impairment								
Within Normal Range	208	171 (82.2)	2.7 (1.6 , 2.8)	212	78 (36.8)	NE (7.4 , NE)	2.6799 (2.0484 , 3.5060) <0.0001	0.8767
Mild Impairment	49	37 (75.5)	2.8 (2.6 , 5.6)	49	12 (24.5)	NE (4.2 , NE)	2.7254 (1.4163 , 5.2444) 0.0018	

Notes: Time to response (TTR) is defined as the time from randomization to initial response (CR or PR). Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median TTR is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate. P-value obtained from an unstratified log-rank test

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 11 Time to response (TTR) based on BICR by pre-specified subgroups - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	p-value [c]
Baseline Visceral Disease								
Yes	195	151 (77.4)	2.8 (2.6 , 2.8)	189	55 (29.1)	NE (NE , NE)	3.1823 (2.3353 , 4.3366) <0.0001	0.0956
No	66	57 (86.4)	1.6 (1.4 , 2.8)	74	35 (47.3)	6.8 (2.8 , NE)	1.9481 (1.2757 , 2.9750) 0.0014	
Baseline CNS Metastases								
Yes	43	29 (67.4)	2.8 (2.0 , 5.9)	39	8 (20.5)	NE (8.1 , NE)	3.6968 (1.6873 , 8.0996) 0.0005	0.4256
No	218	179 (82.1)	2.7 (1.6 , 2.8)	224	82 (36.6)	NE (6.8 , NE)	2.6144 (2.0115 , 3.3981) <0.0001	

Notes: Time to response (TTR) is defined as the time from randomization to initial response (CR or PR). Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median TTR is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate. P-value obtained from an unstratified log-rank test

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 11 Time to response (TTR) based on BICR by pre-specified subgroups - Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	n	No. of Events (%)	Median TTR (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	p-value [c]
History of CNS Metastases								
Yes	62	45 (72.6)	2.8 (2.0 , 4.4)	52	10 (19.2)	NE (NE , NE)	4.6818 (2.3578 , 9.2963) <0.0001	0.0744
No	199	163 (81.9)	2.7 (1.6 , 2.8)	211	80 (37.9)	9.5 (6.8 , NE)	2.4558 (1.8776 , 3.2120) <0.0001	

Notes: Time to response (TTR) is defined as the time from randomization to initial response (CR or PR). Subgroup values are as defined at baseline. BICR: blinded independent central review.

[a] Median TTR is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate. P-value obtained from an unstratified log-rank test

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 14 Change of Sum of Diameters from baseline to post-baseline minimum per pre-specified subgroups - Based on BICR – Full Analysis Set

	T-DXd			T-DM1			T-DXd vs T-DM1	Interaction
Subgroup	n	Mean (SD)	Median (min, max)	n	Mean (SD)	Median (min, max)	Coefficient (95% CI)[a]	p-value[b]
Age								
<65	198	-67.5 (30.26)	-70.5 (-100, 24)	178	-30.2 (44.03)	-27.5 (-100, 97)	-37.29 (-44.79, -29.79)	0.5572
>=65	47	-67.8 (29.75)	-69.0 (-100, -10)	50	-36.0 (39.45)	-21.5 (-100, 39)	-32.65 (-46.27, -19.04)	
Age								
<75	238	-67.6 (30.17)	-70.5 (-100, 24)	221	-30.8 (43.07)	-27.0 (-100, 97)	-37.03 (-43.72, -30.35)	0.1646
>=75	7	-66.7 (29.89)	-69.0 (-100, -17)	7	-54.7 (38.11)	-55.0 (-100, -11)	-4.86 (-37.06, 27.34)	
Region								
Asia	139	-65.6 (30.92)	-69.0 (-100, 24)	140	-25.9 (42.00)	-17.0 (-100, 76)	-39.80 (-48.39, -31.21)	0.1913
North America	17	-57.2 (30.29)	-53.0 (-100, -6)	15	-34.1 (35.85)	-41.0 (-100, 15)	-23.14 (-45.06, -1.22)	
Europe	49	-71.7 (29.18)	-78.0 (-100, 2)	41	-49.0 (38.17)	-50.0 (-100, 15)	-24.44 (-37.90, -10.99)	
Rest of World	40	-73.8 (27.17)	-80.5 (-100, -17)	32	-32.2 (51.49)	-29.0 (-100, 97)	-41.26 (-59.89, -22.64)	

Notes: BICR: blinded independent central review.
[a] Coefficient and p-value obtained from a linear model considering treatment arm and baseline value as covariates.
[b] P-value for interaction obtained by addind treatment times subgroup interaction to [a]. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

Table 14 Change of Sum of Diameters from baseline to post-baseline minimum per pre-specified subgroups - Based on BICR – Full Analysis Set

	T-DXd			T-DM1			T-DXd vs T-DM1	Interaction
Subgroup	n	Mean (SD)	Median (min, max)	n	Mean (SD)	Median (min, max)	Coefficient (95% CI)[a]	p-value[b]
Race								
White	71	-71.9 (27.36)	-77.0 (-100, -17)	62	-36.4 (46.29)	-34.0 (-100, 97)	-35.50 (-47.97, -23.03)	0.2176
Black or African American	9	-65.8 (29.65)	-70.0 (-100, -6)	7	-45.0 (36.78)	-42.0 (-100, 15)	-21.71 (-55.60, 12.18)	
Asian	141	-66.0 (30.87)	-69.0 (-100, 24)	141	-26.4 (42.31)	-17.0 (-100, 76)	-39.66 (-48.23, -31.10)	
Other	24	-64.8 (33.79)	-66.5 (-100, 2)	18	-48.7 (33.84)	-47.5 (-100, 0)	-17.91 (-38.05, 2.23)	
ECOG PS								
0	149	-69.8 (29.33)	-71.0 (-100, 9)	157	-30.9 (43.64)	-23.0 (-100, 97)	-38.86 (-47.16, -30.56)	0.2877
1	96	-64.2 (31.11)	-69.0 (-100, 24)	71	-32.8 (42.00)	-29.0 (-100, 57)	-31.34 (-42.23, -20.46)	
Hormone Receptor Status								
Positive	127	-66.3 (29.60)	-68.0 (-100, 2)	124	-30.1 (43.66)	-20.5 (-100, 97)	-35.77 (-44.80, -26.73)	0.9262
Negative	117	-68.8 (30.78)	-75.0 (-100, 24)	103	-34.1 (41.33)	-33.0 (-100, 57)	-35.10 (-44.59, -25.62)	

Notes: BICR: blinded independent central review.
[a] Coefficient and p-value obtained from a linear model considering treatment arm and baseline value as covariates.
[b] P-value for interaction obtained by addind treatment times subgroup interaction to [a]. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

Table 14 Change of Sum of Diameters from baseline to post-baseline minimum per pre-specified subgroups - Based on BICR – Full Analysis Set

	T-DXd			T-DM1			T-DXd vs T-DM1	Interaction
Subgroup	n	Mean (SD)	Median (min, max)	n	Mean (SD)	Median (min, max)	Coefficient (95% CI)[a]	p-value[b]
Estrogen Receptors								
Positive	123	-67.0 (28.83)	-68.0 (-100, 2)	118	-30.4 (43.89)	-22.0 (-100, 97)	-36.05 (-45.17, -26.93)	0.8866
Negative	121	-68.0 (31.53)	-74.0 (-100, 24)	108	-33.5 (41.41)	-31.0 (-100, 57)	-35.03 (-44.45, -25.61)	
Progesterone Receptors								
Positive	77	-61.9 (30.92)	-62.0 (-100, 2)	82	-21.7 (42.39)	-11.5 (-100, 97)	-40.21 (-51.67, -28.75)	0.2513
Negative	166	-70.1 (29.60)	-75.5 (-100, 24)	144	-38.1 (41.65)	-39.0 (-100, 57)	-32.19 (-40.06, -24.32)	
Prior Treatment with Pertuzumab								
Yes	154	-66.9 (31.60)	-71.0 (-100, 24)	137	-30.1 (39.71)	-27.0 (-100, 57)	-36.74 (-44.71, -28.77)	0.8684
No	91	-68.6 (27.51)	-69.0 (-100, 0)	91	-33.5 (47.80)	-27.0 (-100, 97)	-35.35 (-46.68, -24.03)	

Notes: BICR: blinded independent central review.
[a] Coefficient and p-value obtained from a linear model considering treatment arm and baseline value as covariates.
[b] P-value for interaction obtained by addind treatment times subgroup interaction to [a]. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

Table 14 Change of Sum of Diameters from baseline to post-baseline minimum per pre-specified subgroups - Based on BICR – Full Analysis Set

	T-DXd			T-DM1			T-DXd vs T-DM1	Interaction
Subgroup	n	Mean (SD)	Median (min, max)	n	Mean (SD)	Median (min, max)	Coefficient (95% CI)[a]	p-value[b]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	177	-68.9 (30.85)	-75.0 (-100, 24)	163	-31.7 (44.92)	-28.0 (-100, 97)	-36.82 (-44.79, -28.85)	0.7271
>= 3 lines	68	-64.1 (27.97)	-64.0 (-100, 0)	65	-30.9 (38.29)	-23.0 (-100, 28)	-33.43 (-44.87, -21.99)	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	148	-66.5 (31.81)	-71.0 (-100, 24)	134	-30.5 (39.84)	-27.5 (-100, 57)	-36.01 (-44.16, -27.87)	0.3205
>= 3 lines	6	-77.2 (26.13)	-82.0 (-100, -41)	3	-15.3 (36.50)	0.0 (-57, 11)	-60.53 (-102.79, -18.26)	
Renal Impairment at Baseline								
Within Normal Range	123	-69.6 (29.51)	-73.0 (-100, 6)	111	-24.3 (41.74)	-20.0 (-100, 76)	-45.18 (-54.31, -36.06)	0.0203
Mild Impairment	88	-63.9 (30.56)	-65.5 (-100, 24)	92	-38.5 (41.65)	-34.0 (-100, 57)	-25.54 (-36.08, -15.01)	
Moderate Impairment	29	-70.4 (30.91)	-77.0 (-100, 2)	20	-28.2 (50.54)	-18.0 (-100, 97)	-42.72 (-65.76, -19.68)	

Notes: BICR: blinded independent central review.
[a] Coefficient and p-value obtained from a linear model considering treatment arm and baseline value as covariates.
[b] P-value for interaction obtained by addind treatment times subgroup interaction to [a]. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

Table 14 Change of Sum of Diameters from baseline to post-baseline minimum per pre-specified subgroups - Based on BICR – Full Analysis Set

	T-DXd			T-DM1			T-DXd vs T-DM1	Interaction
Subgroup	n	Mean (SD)	Median (min, max)	n	Mean (SD)	Median (min, max)	Coefficient (95% CI)[a]	p-value[b]
Hepatic Impairment								
Within Normal Range	197	-70.4 (30.30)	-77.0 (-100, 24)	186	-34.3 (40.84)	-28.0 (-100, 74)	-35.93 (-43.06, -28.81)	0.8291
Mild Impairment	48	-55.8 (26.46)	-54.5 (-100, 2)	42	-19.2 (50.46)	-20.0 (-100, 97)	-37.50 (-53.94, -21.07)	
Baseline Visceral Disease								
Yes	184	-64.5 (30.54)	-67.5 (-100, 24)	164	-27.6 (41.40)	-20.0 (-100, 97)	-37.39 (-44.93, -29.84)	0.6419
No	61	-76.7 (26.96)	-86.0 (-100, -4)	64	-41.5 (45.85)	-46.5 (-100, 74)	-32.98 (-46.12, -19.84)	
Baseline CNS Metastases								
Yes	39	-60.9 (33.25)	-67.0 (-100, 24)	33	-24.0 (38.93)	-14.0 (-100, 57)	-37.59 (-54.27, -20.91)	0.8361
No	206	-68.8 (29.38)	-71.5 (-100, 6)	195	-32.7 (43.68)	-30.0 (-100, 97)	-36.00 (-43.15, -28.84)	

Notes: BICR: blinded independent central review.
[a] Coefficient and p-value obtained from a linear model considering treatment arm and baseline value as covariates.
[b] P-value for interaction obtained by addind treatment times subgroup interaction to [a]. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

Table 14 Change of Sum of Diameters from baseline to post-baseline minimum per pre-specified subgroups - Based on BICR – Full Analysis Set

	T-DXd			T-DM1			T-DXd vs T-DM1	Interaction
Subgroup	n	Mean (SD)	Median (min, max)	n	Mean (SD)	Median (min, max)	Coefficient (95% CI)[a]	p-value[b]
History of CNS Metastases								
Yes	57	-63.7 (33.76)	-71.0 (-100, 24)	40	-26.6 (40.99)	-16.5 (-100, 57)	-37.12 (-51.82, -22.42)	0.9198
No	188	-68.8 (28.89)	-69.0 (-100, 6)	188	-32.5 (43.51)	-29.0 (-100, 97)	-36.27 (-43.66, -28.88)	

Notes: BICR: blinded independent central review.
[a] Coefficient and p-value obtained from a linear model considering treatment arm and baseline value as covariates.
[b] P-value for interaction obtained by addind treatment times subgroup interaction to [a]. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

Table 77 Analysis of the time to first hospitalization by pre-specified Subgroup– Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Age								
<65	212	10 (4.7)	NE (NE , NE)	206	11 (5.3)	NE (NE , NE)	0.6330 (0.2634 , 1.5208)	0.4227
>=65	49	8 (16.3)	23.8 (16.8 , NE)	57	8 (14.0)	NE (NE , NE)	0.8812 (0.3283 , 2.3656)	
Age								
<75	253	16 (6.3)	NE (NE , NE)	255	18 (7.1)	NE (NE , NE)	0.5780 (0.2901 , 1.1518)	0.3501
>=75	8	2 (25.0)	NE (0.7 , NE)	8	1 (12.5)	NE (1.8 , NE)	2.3066 (0.2084 , 25.531)	
Region								
Asia	149	8 (5.4)	NE (NE , NE)	160	12 (7.5)	NE (NE , NE)	0.4701 (0.1883 , 1.1736)	0.7406
North America	17	1 (5.9)	NE (NE , NE)	17	1 (5.9)	NE (NE , NE)	0.8044 (0.0495 , 13.073)	
Europe	54	4 (7.4)	23.8 (23.8 , NE)	50	3 (6.0)	NE (NE , NE)	0.8208 (0.1647 , 4.0913)	
Rest of World	41	5 (12.2)	NE (NE , NE)	36	3 (8.3)	NE (13.1 , NE)	0.9568 (0.2241 , 4.0849)	

Notes: Time to first hospitalization is defined as the time from randomization to date of first hospital admission

[a] Median time to first hospitalization is from Kaplan-Meier analysis. Confidence Interval (CI) for the median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 77 Analysis of the time to first hospitalization by pre-specified Subgroup– Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Race								
White	71	7 (9.9)	NE (NE , NE)	72	6 (8.3)	NE (NE , NE)	0.8420 (0.2783 , 2.5472)	0.7027
Black or African American	10	0	NE (NE , NE)	9	0	NE (NE , NE)		
Asian	152	8 (5.3)	NE (NE , NE)	162	12 (7.4)	NE (NE , NE)	0.4715 (0.1889 , 1.1769)	
Other	28	3 (10.7)	23.8 (23.8 , NE)	20	1 (5.0)	NE (NE , NE)	1.2792 (0.1154 , 14.178)	
ECOG PS								
0	154	12 (7.8)	NE (NE , NE)	175	12 (6.9)	NE (NE , NE)	0.7787 (0.3443 , 1.7614)	0.5348
1	106	6 (5.7)	NE (23.8 , NE)	87	7 (8.0)	NE (NE , NE)	0.4269 (0.1335 , 1.3653)	
Hormone Receptor Status								
Positive	133	8 (6.0)	NE (NE , NE)	139	10 (7.2)	NE (NE , NE)	0.6293 (0.2457 , 1.6120)	0.7092
Negative	126	10 (7.9)	NE (23.8 , NE)	122	9 (7.4)	NE (NE , NE)	0.6338 (0.2492 , 1.6116)	

Notes: Time to first hospitalization is defined as the time from randomization to date of first hospital admission

[a] Median time to first hospitalization is from Kaplan-Meier analysis. Confidence Interval (CI) for the median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 77 Analysis of the time to first hospitalization by pre-specified Subgroup– Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Estrogen Receptors								
Positive	129	8 (6.2)	NE (NE , NE)	132	10 (7.6)	NE (NE , NE)	0.6158 (0.2402 , 1.5786)	0.6711
Negative	130	10 (7.7)	NE (23.8 , NE)	128	9 (7.0)	NE (NE , NE)	0.6384 (0.2510 , 1.6236)	
Progesterone Receptors								
Positive	81	5 (6.2)	NE (NE , NE)	92	6 (6.5)	NE (NE , NE)	0.7860 (0.2380 , 2.5964)	0.9766
Negative	177	13 (7.3)	NE (NE , NE)	168	13 (7.7)	NE (NE , NE)	0.5788 (0.2624 , 1.2766)	
Prior Treatment with Pertuzumab								
Yes	162	14 (8.6)	NE (NE , NE)	158	12 (7.6)	NE (NE , NE)	0.7169 (0.3201 , 1.6059)	0.4935
No	99	4 (4.0)	NE (NE , NE)	105	7 (6.7)	NE (NE , NE)	0.4062 (0.1169 , 1.4119)	
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	13 (6.9)	NE (NE , NE)	191	14 (7.3)	NE (NE , NE)	0.6465 (0.2979 , 1.4028)	0.9922
>= 3 lines	73	5 (6.8)	NE (NE , NE)	72	5 (6.9)	NE (NE , NE)	0.5330 (0.1455 , 1.9517)	

Notes: Time to first hospitalization is defined as the time from randomization to date of first hospital admission

[a] Median time to first hospitalization is from Kaplan-Meier analysis. Confidence Interval (CI) for the median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 77 Analysis of the time to first hospitalization by pre-specified Subgroup– Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	13 (8.3)	NE (NE , NE)	152	12 (7.9)	NE (NE , NE)	0.6724 (0.2952 , 1.5315)	0.2665
>= 3 lines	6	1 (16.7)	NE (9.4 , NE)	6	0	NE (NE , NE)		
Renal Impairment at Baseline								
Within Normal Range	130	8 (6.2)	NE (NE , NE)	130	4 (3.1)	NE (NE , NE)	1.0612 (0.3022 , 3.7257)	0.5269
Mild Impairment	92	6 (6.5)	NE (NE , NE)	104	10 (9.6)	NE (NE , NE)	0.5442 (0.1963 , 1.5086)	
Moderate Impairment	30	4 (13.3)	23.8 (16.8 , 23.8)	22	4 (18.2)	NE (13.1 , NE)	0.6214 (0.1497 , 2.5806)	
Hepatic Impairment								
Within Normal Range	208	14 (6.7)	NE (NE , NE)	212	16 (7.5)	NE (NE , NE)	0.5500 (0.2620 , 1.1545)	0.6003
Mild Impairment	49	4 (8.2)	NE (NE , NE)	49	3 (6.1)	NE (NE , NE)	1.0565 (0.2327 , 4.7977)	
Baseline Visceral Disease								
Yes	195	13 (6.7)	NE (NE , NE)	189	12 (6.3)	NE (NE , NE)	0.7689 (0.3458 , 1.7099)	0.6928
No	66	5 (7.6)	NE (23.8 , NE)	74	7 (9.5)	NE (NE , NE)	0.4441 (0.1358 , 1.4518)	

Notes: Time to first hospitalization is defined as the time from randomization to date of first hospital admission

[a] Median time to first hospitalization is from Kaplan-Meier analysis. Confidence Interval (CI) for the median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 77 Analysis of the time to first hospitalization by pre-specified Subgroup– Full Analysis Set

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) [b]	p-value [c]
Baseline CNS Metastases								
Yes	43	4 (9.3)	NE (NE , NE)	39	4 (10.3)	NE (NE , NE)	0.4751 (0.1070 , 2.1090)	0.7779
No	218	14 (6.4)	NE (NE , NE)	224	15 (6.7)	NE (NE , NE)	0.6572 (0.3127 , 1.3814)	
History of CNS Metastases								
Yes	62	8 (12.9)	NE (NE , NE)	52	4 (7.7)	NE (NE , NE)	0.9241 (0.2593 , 3.2935)	0.2682
No	199	10 (5.0)	NE (NE , NE)	211	15 (7.1)	NE (NE , NE)	0.4844 (0.2142 , 1.0958)	

Notes: Time to first hospitalization is defined as the time from randomization to date of first hospital admission

[a] Median time to first hospitalization is from Kaplan-Meier analysis. Confidence Interval (CI) for the median was computed using the Brookmeyer-Crowley method

[b] Hazard ratio stems from unstratified Cox proportional hazards model with treatment as the only covariate.

[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 46 - Analysis of time to first deterioration of EQ-5D-5L-VAS by pre-specified Subgroup – Threshold 15
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
EQ-5D-5L Score VAS									
Age	<65	212	72 (34.0)	NE (19.5,NE)	206	68 (33.0)	14.4 (12.0,NE)	0.7765 (0.5541,1.0882) [0.1398]	0.7815
	>=65	49	19 (38.8)	19.4 (7.7,NE)	57	25 (43.9)	9.7 (7.0,NE)	0.7661 (0.4206,1.3954) [0.3856]	
Age	<75	253	86 (34.0)	NE (19.5,NE)	255	90 (35.3)	14.4 (12.0,NE)	0.7254 (0.5374,0.9791) [0.0348]	0.0643
	>=75	8	5 (62.5)	3.8 (0.8,NE)	8	3 (37.5)	NE (4.0,NE)	2.6388 (0.5823,11.9583) [0.1916]	
Region	Asia	149	51 (34.2)	NE (17.9,NE)	160	66 (41.3)	12.4 (9.7,15.2)	0.5548 (0.3805,0.8088) [0.0019]	0.0668
	Europe	54	19 (35.2)	NE (14.0,NE)	50	15 (30.0)	NE (7.9,NE)	0.9805 (0.4949,1.9428) [0.9556]	
	North America	17	8 (47.1)	12.2 (1.7,NE)	17	3 (17.6)	NE (3.0,NE)	2.6421 (0.6981,10.0002) [0.1372]	
	Rest of World	41	13 (31.7)	NE (12.5,NE)	36	9 (25.0)	NE (11.7,NE)	1.1997 (0.5120,2.8111) [0.6787]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 46 - Analysis of time to first deterioration of EQ-5D-5L-VAS by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
EQ-5D-5L Score VAS									
Race	Asian	152	51 (33.6)	NE (17.9,NE)	162	66 (40.7)	13.8 (9.8,15.2)	0.5574 (0.3823,0.8126) [0.0021]	0.0067
	Black Or African American	10	4 (40.0)	NE (2.7,NE)	9	0 (0.0)	NE (NE,NE)	NE	
	Other	28	7 (25.0)	NE (15.1,NE)	20	6 (30.0)	NE (3.5,NE)	0.6866 (0.2275,2.0720) [0.5023]	
	White	71	29 (40.8)	19.4 (11.3,NE)	72	21 (29.2)	NE (8.8,NE)	1.2924 (0.7356,2.2706) [0.3735]	
ECOG PS	0	154	55 (35.7)	NE (19.5,NE)	175	62 (35.4)	15.2 (11.7,NE)	0.7766 (0.5371,1.1228) [0.1770]	0.7904
	1	106	36 (34.0)	19.4 (17.9,NE)	87	31 (35.6)	14.4 (9.8,NE)	0.7258 (0.4463,1.1802) [0.1951]	
Hormone Receptor Status	Negative	126	51 (40.5)	24.6 (12.2,NE)	122	41 (33.6)	14.4 (11.1,NE)	0.9527 (0.6289,1.4433) [0.8194]	0.1205
	Positive	133	40 (30.1)	NE (19.4,NE)	139	51 (36.7)	14.3 (10.3,NE)	0.6026 (0.3940,0.9214) [0.0181]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 46 - Analysis of time to first deterioration of EQ-5D-5L-VAS by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
EQ-5D-5L Score VAS									
Estrogen Receptors	Negative	130	52 (40.0)	24.6 (12.2,NE)	128	42 (32.8)	NE (11.1,NE)	0.9742 (0.6459,1.4692) [0.8990]	0.0789
	Positive	129	39 (30.2)	NE (19.4,NE)	132	50 (37.9)	14.3 (9.8,NE)	0.5678 (0.3686,0.8744) [0.0093]	
Progesterone Receptors	Negative	177	64 (36.2)	NE (24.6,NE)	168	62 (36.9)	14.3 (11.1,NE)	0.7401 (0.5191,1.0551) [0.0948]	0.6869
	Positive	81	27 (33.3)	19.5 (17.9,NE)	92	30 (32.6)	15.2 (9.7,NE)	0.8104 (0.4773,1.3760) [0.4345]	
Prior Treatment with Pertuzumab	No	99	28 (28.3)	NE (17.9,NE)	105	37 (35.2)	14.1 (9.8,NE)	0.6281 (0.3822,1.0323) [0.0642]	0.3772
	Yes	162	63 (38.9)	24.6 (15.1,NE)	158	56 (35.4)	20.5 (10.8,NE)	0.8398 (0.5828,1.2101) [0.3458]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 46 - Analysis of time to first deterioration of EQ-5D-5L-VAS by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
EQ-5D-5L Score VAS									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	66 (35.1)	24.6 (19.4,NE)	191	74 (38.7)	14.1 (10.7,NE)	0.6852 (0.4889,0.9603) [0.0268]	0.2424
	>= 3	73	25 (34.2)	NE (14.0,NE)	72	19 (26.4)	NE (11.7,NE)	1.0188 (0.5559,1.8670) [0.9505]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	61 (39.1)	24.6 (15.1,NE)	152	56 (36.8)	20.5 (10.7,NE)	0.8234 (0.5699,1.1898) [0.2976]	0.1374
	>= 3	6	2 (33.3)	NE (4.4,NE)	6	0 (0.0)	NE (NE,NE)	NE	
Renal Impairment at Baseline	Mild	92	32 (34.8)	NE (14.8,NE)	104	36 (34.6)	20.5 (10.8,NE)	0.8700 (0.5390,1.4042) [0.5633]	0.6206
	Moderate	30	13 (43.3)	19.4 (6.9,NE)	22	11 (50.0)	7.2 (2.8,NE)	0.5542 (0.2414,1.2722) [0.1595]	
	Normal	130	45 (34.6)	24.6 (19.5,NE)	130	46 (35.4)	14.1 (11.1,NE)	0.6650 (0.4347,1.0173) [0.0578]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 46 - Analysis of time to first deterioration of EQ-5D-5L-VAS by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
EQ-5D-5L Score VAS									
Hepatic Impairment	Mild	49	14 (28.6)	NE (10.3,NE)	49	14 (28.6)	NE (6.6,NE)	0.7637 (0.3624,1.6094) [0.4781]	0.8051
	Normal	208	77 (37.0)	24.6 (17.9,NE)	212	79 (37.3)	14.4 (11.1,NE)	0.7559 (0.5493,1.0402) [0.0838]	
Baseline Visceral Disease	No	66	25 (37.9)	NE (10.7,NE)	74	29 (39.2)	14.3 (9.7,NE)	0.7488 (0.4366,1.2842) [0.2920]	0.8335
	Yes	195	66 (33.8)	24.6 (17.9,NE)	189	64 (33.9)	14.4 (12.0,NE)	0.7620 (0.5366,1.0821) [0.1270]	
Baseline CNS Metastases	No	218	81 (37.2)	24.6 (17.9,NE)	224	80 (35.7)	15.2 (12.0,NE)	0.8194 (0.5992,1.1207) [0.2109]	0.2000
	Yes	43	10 (23.3)	NE (NE,NE)	39	13 (33.3)	14.4 (8.3,NE)	0.4434 (0.1883,1.0438) [0.0566]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 46 - Analysis of time to first deterioration of EQ-5D-5L-VAS by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
EQ-5D-5L Score VAS									
History of CNS Metastases	No	199	73 (36.7)	24.6 (17.9,NE)	211	73 (34.6)	15.2 (12.0,NE)	0.8206 (0.5906,1.1402) [0.2381]	0.3008
	Yes	62	18 (29.0)	NE (NE,NE)	52	20 (38.5)	14.1 (8.3,NE)	0.5362 (0.2778,1.0352) [0.0586]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Global Health Status									
Age	<65	212	114 (53.8)	9.7 (4.4,14.5)	206	98 (47.6)	8.4 (6.1,11.3)	1.0195 (0.7766,1.3383) [0.9029]	0.9626
	>=65	49	32 (65.3)	4.4 (2.1,8.5)	57	37 (64.9)	7.0 (2.8,9.0)	1.0489 (0.6489,1.6954) [0.8503]	
Age	<75	253	141 (55.7)	7.3 (4.4,11.3)	255	129 (50.6)	7.6 (6.3,10.6)	1.0019 (0.7879,1.2741) [0.9932]	0.5033
	>=75	8	5 (62.5)	3.9 (0.8,NE)	8	6 (75.0)	1.4 (0.9,4.8)	0.5937 (0.1751,2.0129) [0.4094]	
Region	Asia	149	86 (57.7)	7.3 (4.7,10.4)	160	95 (59.4)	6.9 (4.4,8.4)	0.7804 (0.5804,1.0494) [0.0952]	0.0651
	Europe	54	29 (53.7)	3.6 (1.5,NE)	50	19 (38.0)	NE (4.2,NE)	1.5781 (0.8836,2.8185) [0.1203]	
	North America	17	10 (58.8)	3.1 (0.9,NE)	17	5 (29.4)	NE (1.9,NE)	2.2629 (0.7724,6.6290) [0.1215]	
	Rest of World	41	21 (51.2)	11.7 (3.0,NE)	36	16 (44.4)	7.2 (4.8,NE)	1.1207 (0.5839,2.1509) [0.7297]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Global Health Status									
Race	Asian	152	87 (57.2)	7.3 (4.7,10.4)	162	96 (59.3)	6.5 (4.5,8.4)	0.7842 (0.5842,1.0527) [0.0998]	0.0920
	Black Or African American	10	5 (50.0)	13.8 (1.6,NE)	9	2 (22.2)	NE (4.2,NE)	2.4660 (0.4746,12.8129) [0.2673]	
	Other	28	15 (53.6)	9.9 (1.5,NE)	20	6 (30.0)	NE (2.9,NE)	1.7427 (0.6729,4.5133) [0.2535]	
	White	71	39 (54.9)	3.7 (2.1,14.8)	72	31 (43.1)	11.1 (4.8,NE)	1.3902 (0.8671,2.2291) [0.1683]	
ECOG PS	0	154	98 (63.6)	4.7 (2.9,9.4)	175	89 (50.9)	7.6 (5.6,11.6)	1.1997 (0.8986,1.6017) [0.2227]	0.0341
	1	106	48 (45.3)	NE (5.5,NE)	87	46 (52.9)	7.0 (4.8,10.3)	0.7288 (0.4854,1.0943) [0.1212]	
Hormone Receptor Status	Negative	126	75 (59.5)	7.3 (4.4,9.9)	122	59 (48.4)	8.3 (6.3,12.3)	1.0972 (0.7789,1.5457) [0.6061]	0.3543
	Positive	133	71 (53.4)	5.7 (3.1,NE)	139	75 (54.0)	7.0 (4.8,10.6)	0.9332 (0.6732,1.2937) [0.6702]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Global Health Status									
Estrogen Receptors	Negative	130	77 (59.2)	7.3 (4.4,9.9)	128	63 (49.2)	7.6 (6.1,11.3)	1.0816 (0.7740,1.5114) [0.6613]	0.3635
	Positive	129	69 (53.5)	5.7 (3.1,NE)	132	71 (53.8)	7.1 (4.5,10.6)	0.9236 (0.6615,1.2895) [0.6342]	
Progesterone Receptors	Negative	177	106 (59.9)	6.1 (3.4,9.7)	168	86 (51.2)	7.6 (6.1,11.3)	1.0885 (0.8175,1.4494) [0.5725]	0.2534
	Positive	81	39 (48.1)	14.7 (3.6,NE)	92	47 (51.1)	7.2 (4.2,11.1)	0.8433 (0.5502,1.2923) [0.4311]	
Prior Treatment with Pertuzumab	No	99	50 (50.5)	9.8 (5.6,NE)	105	56 (53.3)	6.9 (4.2,7.3)	0.7628 (0.5181,1.1231) [0.1597]	0.1144
	Yes	162	96 (59.3)	5.7 (3.0,9.7)	158	79 (50.0)	10.0 (6.1,12.3)	1.1513 (0.8537,1.5527) [0.3631]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Global Health Status									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	107 (56.9)	6.0 (3.0,11.7)	191	101 (52.9)	7.0 (5.1,10.3)	0.9578 (0.7281,1.2599) [0.7433]	0.5744
	>= 3	73	39 (53.4)	7.3 (4.4,NE)	72	34 (47.2)	9.0 (6.1,17.1)	1.1002 (0.6927,1.7473) [0.6888]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	92 (59.0)	5.7 (3.0,9.8)	152	76 (50.0)	10.0 (6.1,12.3)	1.1529 (0.8495,1.5647) [0.3673]	0.9708
	>= 3	6	4 (66.7)	5.7 (0.8,NE)	6	3 (50.0)	10.8 (0.8,NE)	1.5861 (0.2885,8.7190) [0.5925]	
Renal Impairment at Baseline	Mild	92	52 (56.5)	6.8 (2.9,11.7)	104	62 (59.6)	7.0 (4.8,11.1)	0.9676 (0.6686,1.4004) [0.8392]	0.3368
	Moderate	30	17 (56.7)	8.5 (2.1,NE)	22	13 (59.1)	2.0 (1.4,7.0)	0.5855 (0.2821,1.2150) [0.1466]	
	Normal	130	75 (57.7)	6.2 (3.1,14.7)	130	59 (45.4)	8.5 (6.1,17.1)	1.1050 (0.7816,1.5622) [0.5819]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Global Health Status									
Hepatic Impairment	Mild	49	23 (46.9)	9.8 (5.3,NE)	49	19 (38.8)	9.0 (5.3,NE)	1.0069 (0.5469,1.8538) [0.9810]	0.9640
	Normal	208	123 (59.1)	5.7 (3.6,9.9)	212	116 (54.7)	7.1 (5.6,10.3)	0.9984 (0.7733,1.2890) [0.9746]	
Baseline Visceral Disease	No	66	41 (62.1)	4.2 (1.6,9.7)	74	41 (55.4)	5.6 (2.9,12.3)	1.0422 (0.6754,1.6081) [0.8586]	0.9836
	Yes	195	105 (53.8)	8.7 (5.3,14.5)	189	94 (49.7)	8.4 (6.5,10.6)	0.9773 (0.7381,1.2940) [0.8613]	
Baseline CNS Metastases	No	218	125 (57.3)	6.0 (4.2,9.9)	224	115 (51.3)	7.3 (5.6,10.6)	1.0357 (0.8031,1.3358) [0.7985]	0.4775
	Yes	43	21 (48.8)	10.4 (3.0,NE)	39	20 (51.3)	7.0 (4.5,11.6)	0.7332 (0.3906,1.3763) [0.3271]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Global Health Status									
History of CNS Metastases	No	199	115 (57.8)	5.7 (3.7,9.8)	211	111 (52.6)	7.0 (5.3,10.3)	1.0023 (0.7713,1.3024) [0.9945]	0.9306
	Yes	62	31 (50.0)	10.4 (3.4,NE)	52	24 (46.2)	8.4 (6.1,11.6)	0.9269 (0.5373,1.5991) [0.7675]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale Subgroup			T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Functioning	Scales/Physical									
Age		<65	212	61 (28.8)	NE (20.0,NE)	206	48 (23.3)	NE (17.2,NE)	0.9510 (0.6481,1.3955) [0.7991]	0.7678
		>=65	49	18 (36.7)	16.1 (10.7,NE)	57	18 (31.6)	NE (9.0,NE)	0.9863 (0.5102,1.9065) [0.9572]	
Age		<75	253	77 (30.4)	NE (20.0,NE)	255	65 (25.5)	NE (17.2,NE)	0.9312 (0.6668,1.3005) [0.6756]	0.5457
		>=75	8	2 (25.0)	16.1 (1.4,NE)	8	1 (12.5)	NE (5.3,NE)	1.4142 (0.0848,23.5730) [0.8084]	
Region		Asia	149	47 (31.5)	NE (18.0,NE)	160	39 (24.4)	NE (13.9,NE)	0.9174 (0.5942,1.4163) [0.6963]	0.0995
		Europe	54	10 (18.5)	NE (NE,NE)	50	10 (20.0)	NE (NE,NE)	0.8027 (0.3333,1.9334) [0.6251]	
		North America	17	8 (47.1)	NE (1.4,NE)	17	2 (11.8)	NE (NE,NE)	4.0185 (0.8526,18.9413) [0.0576]	
		Rest of World	41	14 (34.1)	NE (7.4,NE)	36	15 (41.7)	16.6 (3.0,NE)	0.6211 (0.2993,1.2888) [0.1962]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale	Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Functioning	Scales/Physical									
Race		Asian	152	47 (30.9)	NE (18.0,NE)	162	40 (24.7)	NE (13.9,NE)	0.8916 (0.5791,1.3728) [0.6005]	0.3838
		Black Or African American	10	6 (60.0)	7.4 (2.7,NE)	9	3 (33.3)	NE (1.4,NE)	1.3125 (0.3277,5.2568) [0.7000]	
		Other	28	3 (10.7)	NE (NE,NE)	20	5 (25.0)	NE (7.1,NE)	0.3692 (0.0881,1.5469) [0.1556]	
		White	71	23 (32.4)	NE (16.1,NE)	72	18 (25.0)	NE (16.6,NE)	1.1641 (0.6275,2.1596) [0.6331]	
ECOG PS		0	154	48 (31.2)	NE (19.5,NE)	175	38 (21.7)	NE (17.2,NE)	1.0916 (0.7087,1.6815) [0.6898]	0.1615
		1	106	31 (29.2)	NE (NE,NE)	87	28 (32.2)	NE (9.9,NE)	0.7178 (0.4285,1.2023) [0.2007]	
Hormone Receptor Status		Negative	126	47 (37.3)	NE (14.5,NE)	122	34 (27.9)	NE (13.9,NE)	1.0702 (0.6853,1.6714) [0.7724]	0.4327
		Positive	133	32 (24.1)	NE (20.0,NE)	139	31 (22.3)	NE (16.6,NE)	0.8404 (0.5096,1.3860) [0.4954]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	 No. of Events (%)	 Median (95% CI) [a] (months)	T-DM1 (N=263) n	 No. of Events (%)	 Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Physical Functioning									
Estrogen Receptors	Negative	130	47 (36.2)	NE (14.8,NE)	128	35 (27.3)	NE (16.6,NE)	1.0496 (0.6746,1.6333) [0.8379]	0.4700
	Positive	129	32 (24.8)	NE (20.0,NE)	132	30 (22.7)	NE (NE,NE)	0.8517 (0.5140,1.4115) [0.5332]	
Progesterone Receptors	Negative	177	59 (33.3)	NE (18.0,NE)	168	46 (27.4)	NE (17.2,NE)	0.9378 (0.6343,1.3864) [0.7456]	0.7867
	Positive	81	20 (24.7)	NE (19.5,NE)	92	18 (19.6)	NE (16.6,NE)	1.0561 (0.5565,2.0041) [0.8682]	
Prior Treatment with Pertuzumab	No	99	28 (28.3)	NE (20.0,NE)	105	30 (28.6)	NE (12.0,NE)	0.7970 (0.4741,1.3397) [0.3890]	0.4618
	Yes	162	51 (31.5)	NE (19.5,NE)	158	36 (22.8)	NE (NE,NE)	1.0715 (0.6945,1.6532) [0.7538]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Physical Functioning									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	47 (25.0)	NE (20.0,NE)	191	44 (23.0)	NE (17.2,NE)	0.8136 (0.5354,1.2362) [0.3327]	0.1946
	>= 3	73	32 (43.8)	15.0 (7.4,NE)	72	22 (30.6)	16.6 (9.1,NE)	1.2182 (0.7043,2.1071) [0.4831]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	48 (30.8)	NE (19.5,NE)	152	34 (22.4)	NE (NE,NE)	1.0890 (0.6967,1.7023) [0.7071]	0.6008
	>= 3	6	3 (50.0)	15.0 (2.2,NE)	6	2 (33.3)	NE (0.7,NE)	0.7043 (0.1163,4.2647) [0.7015]	
Renal Impairment at Baseline	Mild	92	33 (35.9)	NE (14.6,NE)	104	30 (28.8)	NE (13.9,NE)	1.0683 (0.6485,1.7600) [0.7960]	0.7313
	Moderate	30	8 (26.7)	NE (15.0,NE)	22	6 (27.3)	17.2 (5.3,NE)	0.7000 (0.2417,2.0272) [0.5090]	
	Normal	130	38 (29.2)	NE (20.0,NE)	130	30 (23.1)	NE (16.6,NE)	0.8983 (0.5493,1.4691) [0.6704]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Physical Functioning									
Hepatic Impairment	Mild	49	15 (30.6)	NE (14.3,NE)	49	12 (24.5)	16.6 (9.0,NE)	0.8646 (0.4014,1.8624) [0.7081]	0.8604
	Normal	208	64 (30.8)	NE (20.0,NE)	212	54 (25.5)	NE (17.2,NE)	0.9594 (0.6645,1.3851) [0.8236]	
Baseline Visceral Disease	No	66	19 (28.8)	NE (18.0,NE)	74	24 (32.4)	NE (13.9,NE)	0.6806 (0.3715,1.2469) [0.2111]	0.1572
	Yes	195	60 (30.8)	NE (19.5,NE)	189	42 (22.2)	NE (16.6,NE)	1.0810 (0.7243,1.6132) [0.7058]	
Baseline CNS Metastases	No	218	68 (31.2)	NE (20.0,NE)	224	57 (25.4)	NE (17.2,NE)	0.9648 (0.6759,1.3771) [0.8408]	0.8201
	Yes	43	11 (25.6)	NE (14.8,NE)	39	9 (23.1)	NE (8.4,NE)	0.8137 (0.3292,2.0111) [0.6545]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	No. of Events (%)	Median (95% CI) [a] (months)	T-DM1 (N=263) n	No. of Events (%)	Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Physical Functioning									
History of CNS Metastases	No	199	62 (31.2)	NE (19.5,NE)	211	55 (26.1)	NE (17.2,NE)	0.9346 (0.6475,1.3490) [0.7141]	0.8335
	Yes	62	17 (27.4)	NE (14.8,NE)	52	11 (21.2)	NE (NE,NE)	0.9915 (0.4554,2.1589) [0.9814]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Role Functioning									
Age	<65	212	102 (48.1)	13.6 (6.1,NE)	206	106 (51.5)	6.3 (4.3,8.9)	0.7166 (0.5441,0.9439) [0.0168]	0.3664
	>=65	49	28 (57.1)	9.4 (4.1,16.4)	57	32 (56.1)	6.9 (3.3,15.2)	0.9228 (0.5550,1.5344) [0.7612]	
Age	<75	253	125 (49.4)	11.7 (6.2,NE)	255	133 (52.2)	6.3 (4.7,9.9)	0.7393 (0.5776,0.9463) [0.0157]	0.6535
	>=75	8	5 (62.5)	4.5 (1.8,NE)	8	5 (62.5)	6.9 (0.9,NE)	0.9216 (0.2402,3.5360) [0.9050]	
Region	Asia	149	85 (57.0)	7.3 (4.4,13.6)	160	86 (53.8)	6.3 (4.7,9.9)	0.8521 (0.6286,1.1552) [0.2970]	<.0001
	Europe	54	23 (42.6)	16.4 (4.2,NE)	50	27 (54.0)	4.3 (2.8,16.7)	0.6520 (0.3732,1.1391) [0.1284]	
	North America	17	10 (58.8)	4.3 (1.4,NE)	17	2 (11.8)	NE (NE,NE)	5.6404 (1.2318,25.8272) [0.0122]	
	Rest of World	41	12 (29.3)	NE (11.7,NE)	36	23 (63.9)	4.1 (1.4,8.4)	0.2459 (0.1209,0.5004) [<.0001]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Role Functioning									
Race	Asian	152	85 (55.9)	8.3 (4.5,13.7)	162	87 (53.7)	6.3 (4.7,9.9)	0.8386 (0.6191,1.1359) [0.2496]	0.3593
	Black Or African American	10	5 (50.0)	6.9 (1.4,NE)	9	3 (33.3)	NE (1.4,NE)	1.2755 (0.3037,5.3570) [0.7390]	
	Other	28	10 (35.7)	NE (4.9,NE)	20	10 (50.0)	7.1 (1.4,NE)	0.5006 (0.2068,1.2120) [0.1193]	
	White	71	30 (42.3)	NE (5.9,NE)	72	38 (52.8)	4.2 (2.9,13.9)	0.6099 (0.3764,0.9885) [0.0423]	
ECOG PS	0	154	75 (48.7)	12.1 (6.2,NE)	175	89 (50.9)	7.1 (4.8,11.8)	0.7635 (0.5597,1.0414) [0.0862]	0.7158
	1	106	55 (51.9)	11.5 (4.3,16.4)	87	49 (56.3)	4.8 (2.9,8.9)	0.6785 (0.4592,1.0026) [0.0503]	
Hormone Receptor Status	Negative	126	69 (54.8)	7.3 (5.6,13.4)	122	69 (56.6)	4.7 (3.5,8.1)	0.7719 (0.5514,1.0804) [0.1288]	0.7180
	Positive	133	61 (45.9)	16.4 (7.1,NE)	139	69 (49.6)	8.3 (5.6,11.3)	0.7169 (0.5057,1.0163) [0.0597]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Role Functioning									
Estrogen Receptors	Negative	130	70 (53.8)	9.4 (5.6,13.7)	128	69 (53.9)	5.3 (4.2,10.0)	0.8026 (0.5742,1.1218) [0.1953]	0.4662
	Positive	129	60 (46.5)	16.4 (5.6,NE)	132	69 (52.3)	7.1 (4.8,10.2)	0.6780 (0.4771,0.9634) [0.0287]	
Progesterone Receptors	Negative	177	93 (52.5)	10.7 (5.9,16.4)	168	93 (55.4)	5.8 (4.2,8.4)	0.7302 (0.5458,0.9769) [0.0330]	0.8737
	Positive	81	37 (45.7)	NE (4.3,NE)	92	44 (47.8)	8.4 (4.2,11.8)	0.7994 (0.5151,1.2406) [0.3152]	
Prior Treatment with Pertuzumab	No	99	38 (38.4)	23.7 (13.4,NE)	105	58 (55.2)	5.6 (4.1,8.4)	0.4541 (0.2985,0.6908) [0.0002]	0.0085
	Yes	162	92 (56.8)	5.6 (4.2,11.5)	158	80 (50.6)	8.1 (4.3,12.5)	0.9616 (0.7112,1.3002) [0.7968]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Role Functioning									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	93 (49.5)	12.1 (6.9,NE)	191	103 (53.9)	5.4 (4.2,8.9)	0.6920 (0.5207,0.9195) [0.0104]	0.3657
	>= 3	73	37 (50.7)	7.3 (4.3,NE)	72	35 (48.6)	7.0 (5.5,13.9)	0.8929 (0.5610,1.4211) [0.6348]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	89 (57.1)	5.6 (4.2,11.5)	152	77 (50.7)	8.3 (4.3,12.5)	0.9794 (0.7204,1.3315) [0.8926]	0.5023
	>= 3	6	3 (50.0)	8.3 (1.4,NE)	6	3 (50.0)	5.1 (0.8,NE)	0.5413 (0.1078,2.7178) [0.4491]	
Renal Impairment at Baseline	Mild	92	57 (62.0)	5.6 (4.1,11.5)	104	59 (56.7)	5.8 (4.2,11.8)	1.0172 (0.7065,1.4646) [0.9265]	0.1445
	Moderate	30	16 (53.3)	9.4 (3.0,NE)	22	13 (59.1)	4.2 (1.4,13.9)	0.6123 (0.2942,1.2744) [0.1867]	
	Normal	130	56 (43.1)	23.7 (10.4,NE)	130	63 (48.5)	7.0 (4.4,10.3)	0.6504 (0.4501,0.9398) [0.0201]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Role Functioning									
Hepatic Impairment	Mild	49	21 (42.9)	13.7 (5.6,NE)	49	20 (40.8)	6.9 (3.1,NE)	0.7102 (0.3833,1.3159) [0.2760]	0.8167
	Normal	208	109 (52.4)	11.5 (5.6,16.4)	212	118 (55.7)	6.3 (4.3,8.9)	0.7496 (0.5758,0.9759) [0.0310]	
Baseline Visceral Disease	No	66	35 (53.0)	10.4 (4.3,NE)	74	44 (59.5)	6.9 (3.0,10.2)	0.6667 (0.4265,1.0422) [0.0727]	0.6010
	Yes	195	95 (48.7)	11.7 (6.2,NE)	189	94 (49.7)	6.0 (4.7,10.3)	0.7846 (0.5878,1.0472) [0.0979]	
Baseline CNS Metastases	No	218	104 (47.7)	14.5 (7.3,NE)	224	121 (54.0)	6.0 (4.2,8.5)	0.6773 (0.5197,0.8827) [0.0036]	0.0659
	Yes	43	26 (60.5)	5.6 (3.1,11.6)	39	17 (43.6)	7.0 (4.4,NE)	1.2030 (0.6436,2.2489) [0.5649]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Role Functioning									
History of CNS Metastases	No	199	96 (48.2)	13.7 (6.9,NE)	211	114 (54.0)	5.8 (4.2,8.5)	0.6911 (0.5254,0.9091) [0.0078]	0.1949
	Yes	62	34 (54.8)	6.2 (4.4,14.5)	52	24 (46.2)	7.0 (4.7,NE)	0.9484 (0.5550,1.6206) [0.8408]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale Subgroup			T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Functioning	Scales/Emotional									
Age		<65	212	94 (44.3)	17.1 (14.1,21.7)	206	83 (40.3)	12.7 (8.5,15.2)	0.7504 (0.5544,1.0158) [0.0620]	0.4484
		>=65	49	22 (44.9)	11.7 (7.6,NE)	57	24 (42.1)	8.6 (7.0,NE)	0.8698 (0.4857,1.5576) [0.6347]	
Age		<75	253	113 (44.7)	17.1 (13.0,21.7)	255	104 (40.8)	11.1 (8.4,15.2)	0.7839 (0.5979,1.0277) [0.0771]	0.6940
		>=75	8	3 (37.5)	7.6 (2.9,NE)	8	3 (37.5)	NE (1.5,NE)	1.2079 (0.2397,6.0864) [0.8186]	
Region		Asia	149	68 (45.6)	17.1 (12.5,21.7)	160	60 (37.5)	13.8 (8.9,NE)	0.8599 (0.6036,1.2250) [0.4034]	0.3900
		Europe	54	21 (38.9)	15.8 (11.7,NE)	50	20 (40.0)	15.2 (5.6,NE)	0.7148 (0.3834,1.3327) [0.2858]	
		North America	17	11 (64.7)	9.0 (1.4,NE)	17	8 (47.1)	7.0 (2.8,NE)	1.2473 (0.4972,3.1289) [0.6420]	
		Rest of World	41	16 (39.0)	NE (8.7,NE)	36	19 (52.8)	7.9 (2.9,NE)	0.4968 (0.2536,0.9733) [0.0379]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Emotional Functioning									
Race	Asian	152	70 (46.1)	16.7 (12.5,21.7)	162	62 (38.3)	12.7 (8.5,NE)	0.8529 (0.6018,1.2087) [0.3706]	0.4263
	Black Or African American	10	7 (70.0)	4.4 (1.4,NE)	9	4 (44.4)	10.1 (1.5,NE)	1.5093 (0.4407,5.1695) [0.4946]	
	Other	28	11 (39.3)	19.4 (11.7,NE)	20	8 (40.0)	NE (2.9,NE)	0.6150 (0.2404,1.5732) [0.3031]	
	White	71	28 (39.4)	NE (9.4,NE)	72	33 (45.8)	7.9 (4.2,NE)	0.6277 (0.3770,1.0452) [0.0712]	
ECOG PS	0	154	63 (40.9)	18.5 (15.8,NE)	175	74 (42.3)	10.5 (8.1,NE)	0.6824 (0.4848,0.9605) [0.0270]	0.2318
	1	106	53 (50.0)	12.8 (7.6,NE)	87	33 (37.9)	11.1 (8.4,NE)	0.9550 (0.6135,1.4865) [0.8429]	
Hormone Receptor Status	Negative	126	62 (49.2)	14.1 (10.4,18.5)	122	48 (39.3)	12.7 (8.3,NE)	0.9522 (0.6488,1.3974) [0.7972]	0.1400
	Positive	133	54 (40.6)	18.8 (15.0,NE)	139	58 (41.7)	9.8 (7.6,NE)	0.6715 (0.4610,0.9782) [0.0367]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Emotional Functioning									
Estrogen Receptors	Negative	130	65 (50.0)	14.1 (8.7,18.5)	128	50 (39.1)	11.1 (8.4,NE)	0.9796 (0.6732,1.4256) [0.9092]	0.0643
	Positive	129	51 (39.5)	18.8 (15.8,NE)	132	56 (42.4)	9.8 (6.9,NE)	0.6318 (0.4296,0.9293) [0.0186]	
Progesterone Receptors	Negative	177	81 (45.8)	16.7 (11.8,21.7)	168	71 (42.3)	10.5 (8.4,15.2)	0.8005 (0.5790,1.1068) [0.1763]	0.9804
	Positive	81	35 (43.2)	16.5 (10.8,NE)	92	35 (38.0)	15.2 (7.6,NE)	0.7837 (0.4871,1.2610) [0.3134]	
Prior Treatment with Pertuzumab	No	99	40 (40.4)	17.3 (12.5,NE)	105	45 (42.9)	9.0 (5.6,NE)	0.7221 (0.4688,1.1123) [0.1368]	0.3468
	Yes	162	76 (46.9)	15.8 (11.8,21.7)	158	62 (39.2)	14.3 (8.3,NE)	0.8426 (0.5988,1.1858) [0.3264]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Emotional Functioning									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	76 (40.4)	18.8 (15.0,NE)	191	79 (41.4)	11.1 (8.3,NE)	0.6612 (0.4800,0.9108) [0.0109]	0.0553
	>= 3	73	40 (54.8)	10.4 (3.2,18.5)	72	28 (38.9)	12.7 (7.9,NE)	1.1981 (0.7346,1.9541) [0.4767]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	73 (46.8)	15.8 (11.8,21.7)	152	62 (40.8)	11.1 (8.1,NE)	0.8038 (0.5690,1.1355) [0.2154]	0.0450
	>= 3	6	3 (50.0)	8.5 (1.5,NE)	6	0 (0.0)	NE (NE,NE)	NE	
Renal Impairment at Baseline	Mild	92	41 (44.6)	15.0 (10.7,NE)	104	48 (46.2)	9.8 (6.9,NE)	0.7869 (0.5170,1.1977) [0.2629]	0.1503
	Moderate	30	18 (60.0)	9.4 (5.7,15.8)	22	6 (27.3)	13.8 (5.3,NE)	1.5746 (0.6231,3.9787) [0.3346]	
	Normal	130	56 (43.1)	18.8 (16.5,NE)	130	51 (39.2)	11.1 (7.9,NE)	0.6959 (0.4691,1.0323) [0.0697]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Emotional Functioning									
Hepatic Impairment	Mild	49	20 (40.8)	16.7 (7.3,NE)	49	18 (36.7)	8.7 (5.6,NE)	0.7202 (0.3765,1.3778) [0.3202]	0.6588
	Normal	208	96 (46.2)	16.5 (12.5,21.7)	212	89 (42.0)	12.7 (8.4,NE)	0.8071 (0.6022,1.0817) [0.1505]	
Baseline Visceral Disease	No	66	31 (47.0)	14.1 (9.2,NE)	74	35 (47.3)	10.5 (7.2,15.2)	0.7315 (0.4486,1.1927) [0.2074]	0.7223
	Yes	195	85 (43.6)	17.1 (12.9,19.4)	189	72 (38.1)	12.7 (8.4,NE)	0.8317 (0.6045,1.1443) [0.2580]	
Baseline CNS Metastases	No	218	100 (45.9)	16.7 (12.5,21.7)	224	89 (39.7)	13.8 (8.6,NE)	0.8567 (0.6414,1.1443) [0.2929]	0.1100
	Yes	43	16 (37.2)	19.4 (10.4,NE)	39	18 (46.2)	8.3 (2.9,NE)	0.4896 (0.2417,0.9917) [0.0444]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	 No. of Events (%)	 Median (95% CI) [a] (months)	T-DM1 (N=263) n	 No. of Events (%)	 Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Emotional Functioning									
History of CNS Metastases	No	199	89 (44.7)	17.3 (13.0,NE)	211	85 (40.3)	13.8 (8.5,NE)	0.8137 (0.6022,1.0995) [0.1783]	0.7290
	Yes	62	27 (43.5)	14.5 (10.4,NE)	52	22 (42.3)	10.1 (4.8,NE)	0.6571 (0.3641,1.1858) [0.1611]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale	Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Cognitive Functioning										
Age		<65	212	110 (51.9)	10.6 (8.6,15.3)	206	105 (51.0)	8.3 (4.8,10.5)	0.7373 (0.5619,0.9673) [0.0274]	0.4668
		>=65	49	28 (57.1)	9.9 (5.6,15.3)	57	30 (52.6)	8.3 (3.3,20.5)	0.8982 (0.5347,1.5086) [0.6822]	
Age		<75	253	134 (53.0)	10.3 (8.6,14.5)	255	130 (51.0)	8.3 (4.8,10.5)	0.7684 (0.6018,0.9811) [0.0343]	0.8846
		>=75	8	4 (50.0)	6.6 (1.4,NE)	8	5 (62.5)	2.8 (0.9,NE)	0.5397 (0.1273,2.2878) [0.3956]	
Region		Asia	149	84 (56.4)	10.3 (6.9,14.1)	160	80 (50.0)	8.4 (4.8,14.1)	0.8707 (0.6378,1.1888) [0.3828]	0.3325
		Europe	54	26 (48.1)	9.9 (7.4,NE)	50	29 (58.0)	4.2 (1.4,9.8)	0.5558 (0.3252,0.9498) [0.0294]	
		North America	17	7 (41.2)	19.6 (1.5,NE)	17	6 (35.3)	NE (4.4,NE)	1.0746 (0.3461,3.3364) [0.9090]	
		Rest of World	41	21 (51.2)	12.0 (6.0,NE)	36	20 (55.6)	7.2 (2.1,10.5)	0.5677 (0.3059,1.0534) [0.0702]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale	Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Functioning	Scales/Cognitive									
Race		Asian	152	84 (55.3)	10.3 (6.9,14.1)	162	80 (49.4)	8.4 (4.8,14.1)	0.8739 (0.6401,1.1930) [0.3952]	0.0123
		Black Or African American	10	9 (90.0)	4.9 (1.4,6.9)	9	4 (44.4)	9.6 (1.5,NE)	5.4230 (1.1259,26.1209) [0.0192]	
		Other	28	13 (46.4)	19.4 (5.8,NE)	20	12 (60.0)	1.5 (0.9,NE)	0.3301 (0.1423,0.7658) [0.0073]	
		White	71	32 (45.1)	15.3 (7.7,NE)	72	39 (54.2)	5.6 (2.8,10.5)	0.5885 (0.3663,0.9454) [0.0264]	
ECOG PS		0	154	81 (52.6)	10.6 (8.6,16.4)	175	86 (49.1)	8.7 (4.8,12.9)	0.8094 (0.5958,1.0997) [0.1735]	0.3755
		1	106	57 (53.8)	10.3 (5.6,14.8)	87	49 (56.3)	5.3 (2.8,10.3)	0.6625 (0.4486,0.9783) [0.0376]	
Hormone Receptor Status		Negative	126	76 (60.3)	6.9 (4.7,10.3)	122	59 (48.4)	8.3 (4.2,20.7)	1.0384 (0.7368,1.4635) [0.8212]	0.0240
		Positive	133	62 (46.6)	14.1 (10.1,NE)	139	75 (54.0)	7.2 (4.5,10.3)	0.5824 (0.4138,0.8198) [0.0017]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	No. of Events (%)	Median (95% CI) [a] (months)	T-DM1 (N=263) n	No. of Events (%)	Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Cognitive Functioning									
Estrogen Receptors	Negative	130	78 (60.0)	7.4 (5.6,10.3)	128	64 (50.0)	8.3 (4.2,14.1)	1.0015 (0.7174,1.3980) [0.9885]	0.0433
	Positive	129	60 (46.5)	14.1 (10.1,NE)	132	69 (52.3)	8.4 (4.8,11.1)	0.5981 (0.4208,0.8502) [0.0037]	
Progesterone Receptors	Negative	177	102 (57.6)	8.6 (5.8,12.4)	168	84 (50.0)	8.4 (4.3,12.9)	0.9245 (0.6906,1.2376) [0.6046]	0.0628
	Positive	81	36 (44.4)	16.4 (9.9,NE)	92	49 (53.3)	5.7 (4.4,11.1)	0.5356 (0.3458,0.8297) [0.0045]	
Prior Treatment with Pertuzumab	No	99	50 (50.5)	12.0 (6.9,16.4)	105	54 (51.4)	8.4 (4.2,14.1)	0.7113 (0.4818,1.0501) [0.0843]	0.7017
	Yes	162	88 (54.3)	9.9 (7.7,14.1)	158	81 (51.3)	8.3 (4.4,11.1)	0.8032 (0.5914,1.0908) [0.1601]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Cognitive Functioning									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	97 (51.6)	12.4 (8.6,15.3)	191	102 (53.4)	8.3 (4.2,9.8)	0.6790 (0.5119,0.9006) [0.0069]	0.1808
	>= 3	73	41 (56.2)	7.7 (4.7,12.5)	72	33 (45.8)	9.0 (4.5,NE)	1.0274 (0.6479,1.6293) [0.9041]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	86 (55.1)	9.7 (7.4,14.1)	152	78 (51.3)	8.3 (4.4,11.1)	0.8365 (0.6130,1.1415) [0.2600]	0.1825
	>= 3	6	2 (33.3)	NE (5.8,NE)	6	3 (50.0)	3.8 (0.8,NE)	0.2680 (0.0437,1.6426) [0.1284]	
Renal Impairment at Baseline	Mild	92	50 (54.3)	10.7 (5.6,16.4)	104	62 (59.6)	5.6 (3.0,9.7)	0.6919 (0.4738,1.0104) [0.0561]	0.7375
	Moderate	30	18 (60.0)	9.9 (6.9,12.4)	22	10 (45.5)	5.3 (1.5,NE)	0.9465 (0.4290,2.0883) [0.8935]	
	Normal	130	68 (52.3)	12.0 (7.0,19.6)	130	62 (47.7)	8.7 (4.5,14.1)	0.7931 (0.5579,1.1275) [0.1943]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	No. of Events (%)	Median (95% CI) [a] (months)	T-DM1 (N=263) n	No. of Events (%)	Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Cognitive Functioning									
Hepatic Impairment	Mild	49	22 (44.9)	10.3 (6.0,NE)	49	19 (38.8)	9.8 (4.2,NE)	0.7839 (0.4214,1.4583) [0.4473]	0.9811
	Normal	208	116 (55.8)	10.3 (8.2,14.1)	212	116 (54.7)	7.2 (4.5,10.3)	0.7668 (0.5908,0.9952) [0.0451]	
Baseline Visceral Disease	No	66	29 (43.9)	NE (9.0,NE)	74	41 (55.4)	5.0 (3.0,12.9)	0.4943 (0.3050,0.8013) [0.0036]	0.0397
	Yes	195	109 (55.9)	8.8 (6.0,13.6)	189	94 (49.7)	8.4 (4.8,11.1)	0.8824 (0.6673,1.1669) [0.3795]	
Baseline CNS Metastases	No	218	113 (51.8)	11.1 (8.6,15.3)	224	116 (51.8)	8.3 (4.5,9.8)	0.7239 (0.5570,0.9409) [0.0152]	0.2521
	Yes	43	25 (58.1)	7.7 (2.9,14.8)	39	19 (48.7)	8.3 (3.5,NE)	1.0298 (0.5602,1.8930) [0.9199]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	No. of Events (%)	Median (95% CI) [a] (months)	T-DM1 (N=263) n	No. of Events (%)	Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Cognitive Functioning									
History of CNS Metastases	No	199	106 (53.3)	10.3 (8.6,15.3)	211	109 (51.7)	7.2 (4.3,10.5)	0.7429 (0.5670,0.9732) [0.0304]	0.6226
	Yes	62	32 (51.6)	9.7 (3.0,19.4)	52	26 (50.0)	9.6 (4.2,14.1)	0.8412 (0.4939,1.4325) [0.5254]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Social Functioning									
Age	<65	212	117 (55.2)	8.3 (5.6,13.6)	206	99 (48.1)	7.1 (5.6,11.7)	0.9556 (0.7295,1.2517) [0.7375]	0.1610
	>=65	49	30 (61.2)	5.8 (2.8,10.7)	57	27 (47.4)	11.3 (5.8,NE)	1.4208 (0.8435,2.3934) [0.1868]	
Age	<75	253	143 (56.5)	7.3 (5.7,11.9)	255	122 (47.8)	8.4 (5.7,11.7)	1.0300 (0.8080,1.3131) [0.8169]	0.6580
	>=75	8	4 (50.0)	7.4 (1.4,NE)	8	4 (50.0)	6.9 (1.5,NE)	1.3938 (0.3375,5.7558) [0.6450]	
Region	Asia	149	87 (58.4)	7.3 (4.9,11.8)	160	79 (49.4)	7.1 (5.6,12.0)	1.0109 (0.7438,1.3739) [0.9440]	0.6232
	Europe	54	29 (53.7)	5.6 (2.8,17.5)	50	25 (50.0)	8.6 (4.2,16.7)	1.0845 (0.6332,1.8572) [0.7842]	
	North America	17	12 (70.6)	3.0 (1.4,16.8)	17	6 (35.3)	NE (1.9,NE)	1.8330 (0.6835,4.9162) [0.2137]	
	Rest of World	41	19 (46.3)	13.6 (6.4,NE)	36	16 (44.4)	11.7 (3.0,NE)	0.8880 (0.4561,1.7288) [0.7192]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Social Functioning									
Race	Asian	152	87 (57.2)	8.3 (5.5,11.8)	162	80 (49.4)	7.1 (5.6,12.0)	0.9915 (0.7303,1.3462) [0.9576]	0.8452
	Black Or African American	10	8 (80.0)	6.2 (1.4,8.3)	9	4 (44.4)	NE (0.8,NE)	1.5039 (0.4504,5.0217) [0.4848]	
	Other	28	16 (57.1)	4.5 (1.5,NE)	20	10 (50.0)	9.8 (1.5,NE)	1.1329 (0.5063,2.5349) [0.7788]	
	White	71	36 (50.7)	13.1 (5.6,17.5)	72	32 (44.4)	8.4 (5.3,NE)	1.0005 (0.6195,1.6156) [0.9893]	
ECOG PS	0	154	84 (54.5)	9.9 (6.4,14.5)	175	84 (48.0)	8.4 (5.6,16.6)	0.9312 (0.6868,1.2626) [0.6438]	0.3228
	1	106	63 (59.4)	5.6 (3.0,10.4)	87	42 (48.3)	8.4 (5.6,16.7)	1.1877 (0.8016,1.7598) [0.3986]	
Hormone Receptor Status	Negative	126	73 (57.9)	7.0 (5.5,13.4)	122	57 (46.7)	7.9 (5.3,NE)	1.1219 (0.7926,1.5880) [0.5153]	0.6068
	Positive	133	74 (55.6)	8.6 (4.5,13.6)	139	68 (48.9)	8.4 (5.6,11.3)	0.9830 (0.7052,1.3701) [0.9056]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Social Functioning									
Estrogen Receptors	Negative	130	75 (57.7)	6.9 (5.5,13.4)	128	61 (47.7)	7.9 (5.3,16.7)	1.0987 (0.7829,1.5419) [0.5841]	0.7521
	Positive	129	72 (55.8)	8.6 (4.5,13.6)	132	63 (47.7)	8.4 (5.7,11.7)	1.0111 (0.7189,1.4221) [0.9644]	
Progesterone Receptors	Negative	177	101 (57.1)	7.0 (5.6,11.8)	168	80 (47.6)	8.4 (5.6,16.7)	1.0928 (0.8142,1.4668) [0.5584]	0.8470
	Positive	81	46 (56.8)	8.3 (3.3,13.6)	92	44 (47.8)	8.4 (5.6,11.7)	1.0039 (0.6612,1.5242) [0.9887]	
Prior Treatment with Pertuzumab	No	99	54 (54.5)	6.9 (3.2,18.2)	105	54 (51.4)	7.1 (4.8,11.7)	1.0101 (0.6920,1.4743) [0.9774]	0.7741
	Yes	162	93 (57.4)	8.5 (5.8,13.4)	158	72 (45.6)	10.2 (5.8,NE)	1.0565 (0.7749,1.4404) [0.7259]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Social Functioning									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	99 (52.7)	11.5 (6.9,16.8)	191	98 (51.3)	6.2 (5.6,10.3)	0.8194 (0.6180,1.0864) [0.1633]	0.0021
	>= 3	73	48 (65.8)	4.3 (2.9,6.9)	72	28 (38.9)	12.0 (7.1,NE)	1.9046 (1.1942,3.0376) [0.0060]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	90 (57.7)	8.5 (5.7,13.4)	152	71 (46.7)	9.8 (5.8,20.5)	1.0482 (0.7660,1.4345) [0.7666]	0.6076
	>= 3	6	3 (50.0)	9.9 (1.5,NE)	6	1 (16.7)	NE (0.8,NE)	1.8191 (0.1887,17.5373) [0.5994]	
Renal Impairment at Baseline	Mild	92	62 (67.4)	5.6 (3.1,8.5)	104	55 (52.9)	7.6 (4.8,16.7)	1.2698 (0.8824,1.8273) [0.1954]	0.1886
	Moderate	30	19 (63.3)	6.9 (2.9,14.5)	22	9 (40.9)	11.3 (5.3,NE)	1.5022 (0.6750,3.3430) [0.3130]	
	Normal	130	64 (49.2)	13.4 (5.9,NE)	130	60 (46.2)	8.4 (5.6,NE)	0.8853 (0.6198,1.2645) [0.4934]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Social Functioning									
Hepatic Impairment	Mild	49	30 (61.2)	4.5 (2.9,8.5)	49	18 (36.7)	9.0 (4.8,NE)	1.4638 (0.8155,2.6274) [0.1972]	0.1812
	Normal	208	117 (56.3)	8.6 (5.8,13.4)	212	108 (50.9)	7.6 (5.6,12.0)	0.9608 (0.7382,1.2506) [0.7590]	
Baseline Visceral Disease	No	66	38 (57.6)	6.9 (4.2,13.4)	74	36 (48.6)	8.6 (5.6,NE)	1.0908 (0.6904,1.7235) [0.7168]	0.8191
	Yes	195	109 (55.9)	8.2 (5.6,13.1)	189	90 (47.6)	8.4 (5.6,12.0)	1.0111 (0.7633,1.3395) [0.9446]	
Baseline CNS Metastases	No	218	122 (56.0)	8.3 (5.7,12.2)	224	112 (50.0)	7.6 (5.6,11.3)	0.9845 (0.7610,1.2738) [0.8957]	0.2704
	Yes	43	25 (58.1)	6.2 (3.0,18.2)	39	14 (35.9)	NE (4.8,NE)	1.4346 (0.7396,2.7829) [0.2818]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Social Functioning									
History of CNS Metastases	No	199	112 (56.3)	8.2 (5.6,12.2)	211	105 (49.8)	7.6 (5.6,11.7)	0.9832 (0.7526,1.2844) [0.8906]	0.3646
	Yes	62	35 (56.5)	7.2 (3.0,14.5)	52	21 (40.4)	10.3 (4.2,NE)	1.2600 (0.7268,2.1842) [0.4072]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Fatigue									
Age	<65	212	95 (44.8)	19.4 (10.2,NE)	206	73 (35.4)	NE (16.6,NE)	1.1137 (0.8193,1.5139) [0.4868]	0.1757
	>=65	49	19 (38.8)	15.7 (9.9,NE)	57	27 (47.4)	11.0 (4.4,NE)	0.6879 (0.3814,1.2410) [0.2095]	
Age	<75	253	112 (44.3)	19.4 (11.8,NE)	255	98 (38.4)	16.7 (11.0,NE)	0.9965 (0.7586,1.3089) [0.9799]	0.8511
	>=75	8	2 (25.0)	NE (3.2,NE)	8	2 (25.0)	NE (0.9,NE)	0.8972 (0.1250,6.4375) [0.9142]	
Region	Asia	149	61 (40.9)	NE (11.9,NE)	160	60 (37.5)	16.6 (11.0,NE)	0.8708 (0.6073,1.2485) [0.4517]	0.1193
	Europe	54	26 (48.1)	7.1 (2.2,NE)	50	18 (36.0)	16.7 (4.4,NE)	1.4176 (0.7763,2.5884) [0.2557]	
	North America	17	8 (47.1)	NE (1.4,NE)	17	3 (17.6)	NE (5.9,NE)	3.0077 (0.7969,11.3520) [0.0868]	
	Rest of World	41	19 (46.3)	NE (5.6,NE)	36	19 (52.8)	7.2 (2.8,NE)	0.6604 (0.3487,1.2509) [0.2050]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Fatigue									
Race	Asian	152	61 (40.1)	NE (11.9,NE)	162	60 (37.0)	20.5 (11.0,NE)	0.8750 (0.6104,1.2544) [0.4674]	0.1900
	Black Or African American	10	8 (80.0)	3.1 (1.4,12.5)	9	2 (22.2)	NE (2.8,NE)	4.2937 (0.9093,20.2746) [0.0411]	
	Other	28	12 (42.9)	19.4 (2.9,NE)	20	7 (35.0)	NE (1.5,NE)	1.0398 (0.4084,2.6473) [0.9293]	
	White	71	33 (46.5)	8.6 (3.8,NE)	72	31 (43.1)	8.3 (4.4,NE)	1.0000 (0.6118,1.6344) [0.9948]	
ECOG PS	0	154	71 (46.1)	19.4 (8.6,NE)	175	63 (36.0)	20.5 (11.8,NE)	1.1377 (0.8089,1.6002) [0.4571]	0.1254
	1	106	43 (40.6)	NE (11.1,NE)	87	37 (42.5)	16.7 (4.2,NE)	0.7755 (0.4981,1.2075) [0.2549]	
Hormone Receptor Status	Negative	126	57 (45.2)	14.8 (8.5,NE)	122	42 (34.4)	16.7 (11.0,NE)	1.1773 (0.7890,1.7565) [0.4254]	0.2549
	Positive	133	57 (42.9)	NE (9.9,NE)	139	57 (41.0)	20.5 (7.0,NE)	0.8890 (0.6144,1.2864) [0.5362]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Fatigue									
Estrogen Receptors	Negative	130	58 (44.6)	14.8 (8.5,NE)	128	45 (35.2)	16.7 (11.0,NE)	1.1377 (0.7697,1.6817) [0.5196]	0.3250
	Positive	129	56 (43.4)	NE (9.9,NE)	132	54 (40.9)	20.5 (7.0,NE)	0.8960 (0.6148,1.3058) [0.5709]	
Progesterone Receptors	Negative	177	78 (44.1)	15.7 (11.1,NE)	168	63 (37.5)	20.5 (10.9,NE)	1.0106 (0.7240,1.4108) [0.9505]	0.9146
	Positive	81	36 (44.4)	NE (4.4,NE)	92	36 (39.1)	11.8 (7.0,NE)	1.0252 (0.6443,1.6315) [0.9103]	
Prior Treatment with Pertuzumab	No	99	39 (39.4)	NE (11.9,NE)	105	43 (41.0)	11.8 (5.0,NE)	0.7690 (0.4967,1.1906) [0.2362]	0.1640
	Yes	162	75 (46.3)	15.7 (8.5,NE)	158	57 (36.1)	16.7 (11.8,NE)	1.1459 (0.8102,1.6208) [0.4402]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Fatigue									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	78 (41.5)	19.4 (12.1,NE)	191	74 (38.7)	16.7 (10.9,NE)	0.9077 (0.6591,1.2502) [0.5554]	0.2934
	>= 3	73	36 (49.3)	11.9 (5.6,NE)	72	26 (36.1)	NE (7.2,NE)	1.2494 (0.7526,2.0741) [0.3882]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	73 (46.8)	15.7 (8.3,NE)	152	56 (36.8)	16.7 (11.8,NE)	1.1632 (0.8192,1.6515) [0.3980]	0.9001
	>= 3	6	2 (33.3)	NE (8.6,NE)	6	1 (16.7)	NE (1.4,NE)	0.6703 (0.0562,8.0000) [0.7506]	
Renal Impairment at Baseline	Mild	92	44 (47.8)	11.9 (8.3,NE)	104	47 (45.2)	11.8 (5.9,NE)	1.0105 (0.6690,1.5263) [0.9675]	0.9651
	Moderate	30	15 (50.0)	9.9 (2.9,NE)	22	8 (36.4)	NE (2.0,NE)	1.1029 (0.4669,2.6052) [0.8317]	
	Normal	130	53 (40.8)	NE (12.3,NE)	130	43 (33.1)	NE (16.6,NE)	1.0065 (0.6700,1.5120) [0.9713]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Fatigue									
Hepatic Impairment	Mild	49	20 (40.8)	NE (7.0,NE)	49	14 (28.6)	NE (5.6,NE)	1.1352 (0.5723,2.2515) [0.7101]	0.7244
	Normal	208	94 (45.2)	19.4 (11.1,NE)	212	86 (40.6)	16.6 (10.9,NE)	0.9678 (0.7209,1.2991) [0.8268]	
Baseline Visceral Disease	No	66	30 (45.5)	15.7 (8.5,NE)	74	32 (43.2)	16.6 (3.3,NE)	0.8445 (0.5121,1.3929) [0.5118]	0.4089
	Yes	195	84 (43.1)	19.4 (11.8,NE)	189	68 (36.0)	20.5 (11.0,NE)	1.0646 (0.7716,1.4688) [0.7048]	
Baseline CNS Metastases	No	218	96 (44.0)	NE (10.7,NE)	224	85 (37.9)	20.5 (11.0,NE)	1.0074 (0.7515,1.3505) [0.9583]	0.8725
	Yes	43	18 (41.9)	19.4 (5.6,NE)	39	15 (38.5)	11.8 (4.8,NE)	0.8903 (0.4394,1.8037) [0.7417]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Fatigue									
History of CNS Metastases	No	199	89 (44.7)	NE (10.2,NE)	211	81 (38.4)	16.7 (10.9,NE)	1.0208 (0.7546,1.3810) [0.8925]	0.8874
	Yes	62	25 (40.3)	19.4 (7.4,NE)	52	19 (36.5)	11.8 (5.9,NE)	0.8861 (0.4820,1.6291) [0.6986]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Nausea and Vomiting									
Age	<65	212	158 (74.5)	2.8 (1.5,3.0)	206	94 (45.6)	8.8 (7.0,11.3)	1.9281 (1.4901,2.4950) [<.0001]	0.6087
	>=65	49	33 (67.3)	2.8 (1.4,8.3)	57	22 (38.6)	13.9 (8.3,NE)	2.1952 (1.2783,3.7696) [0.0036]	
Age	<75	253	185 (73.1)	2.8 (1.6,3.1)	255	115 (45.1)	9.3 (7.6,11.9)	1.9457 (1.5400,2.4583) [<.0001]	0.0508
	>=75	8	6 (75.0)	1.8 (0.8,NE)	8	1 (12.5)	NE (10.3,NE)	9.9633 (1.1781,84.2632) [0.0102]	
Region	Asia	149	107 (71.8)	2.9 (1.5,4.2)	160	68 (42.5)	9.7 (7.6,NE)	2.0796 (1.5330,2.8211) [<.0001]	0.9959
	Europe	54	38 (70.4)	1.6 (1.4,2.9)	50	21 (42.0)	9.8 (2.8,NE)	1.8991 (1.1107,3.2471) [0.0168]	
	North America	17	15 (88.2)	3.1 (0.9,12.4)	17	8 (47.1)	8.7 (1.7,NE)	1.7126 (0.7051,4.1596) [0.2282]	
	Rest of World	41	31 (75.6)	1.6 (1.4,4.2)	36	19 (52.8)	9.9 (4.1,13.9)	1.9279 (1.0848,3.4262) [0.0271]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Nausea and Vomiting									
Race	Asian	152	109 (71.7)	2.9 (1.5,4.2)	162	69 (42.6)	9.7 (7.6,NE)	2.0766 (1.5344,2.8103) [<.0001]	0.9776
	Black Or African American	10	8 (80.0)	3.5 (1.4,6.9)	9	3 (33.3)	NE (0.8,NE)	2.4004 (0.6346,9.0802) [0.1801]	
	Other	28	21 (75.0)	1.5 (1.4,17.3)	20	9 (45.0)	8.6 (1.5,NE)	1.8092 (0.8223,3.9804) [0.1446]	
	White	71	53 (74.6)	1.7 (1.4,3.0)	72	35 (48.6)	8.7 (4.2,13.9)	1.8765 (1.2207,2.8846) [0.0039]	
ECOG PS	0	154	113 (73.4)	2.8 (1.5,3.5)	175	80 (45.7)	8.7 (7.0,NE)	1.9275 (1.4451,2.5709) [<.0001]	0.5962
	1	106	78 (73.6)	2.9 (1.6,3.5)	87	36 (41.4)	10.8 (7.2,NE)	2.1745 (1.4620,3.2342) [<.0001]	
Hormone Receptor Status	Negative	126	87 (69.0)	2.9 (1.5,4.2)	122	52 (42.6)	10.8 (7.6,NE)	1.9290 (1.3658,2.7245) [0.0002]	0.7759
	Positive	133	103 (77.4)	2.0 (1.5,3.0)	139	64 (46.0)	8.8 (6.3,NE)	2.1101 (1.5423,2.8869) [<.0001]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Symptom Scales/Nausea and Vomiting									
Estrogen Receptors	Negative	130	91 (70.0)	2.9 (1.5,4.1)	128	56 (43.8)	9.8 (7.2,NE)	1.9524 (1.3972,2.7283) [<.0001]	0.8810
	Positive	129	99 (76.7)	2.1 (1.5,3.1)	132	60 (45.5)	8.9 (6.3,NE)	2.0437 (1.4806,2.8208) [<.0001]	
Progesterone Receptors	Negative	177	125 (70.6)	2.9 (1.5,4.2)	168	71 (42.3)	10.3 (8.3,NE)	1.9954 (1.4893,2.6734) [<.0001]	0.8408
	Positive	81	64 (79.0)	1.7 (1.5,3.0)	92	44 (47.8)	8.9 (4.8,NE)	2.1581 (1.4662,3.1767) [<.0001]	
Prior Treatment with Pertuzumab	No	99	67 (67.7)	2.9 (1.5,4.2)	105	52 (49.5)	7.1 (4.8,10.8)	1.5959 (1.1100,2.2944) [0.0120]	0.1013
	Yes	162	124 (76.5)	2.8 (1.5,3.0)	158	64 (40.5)	11.3 (8.4,NE)	2.3331 (1.7219,3.1613) [<.0001]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Nausea and Vomiting									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	135 (71.8)	1.9 (1.5,3.0)	191	81 (42.4)	9.8 (8.1,NE)	2.0510 (1.5549,2.7054) [<.0001]	0.7893
	>= 3	73	56 (76.7)	3.0 (1.7,4.3)	72	35 (48.6)	9.6 (6.3,13.9)	1.9765 (1.2918,3.0241) [0.0014]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	118 (75.6)	2.8 (1.5,3.0)	152	61 (40.1)	11.9 (8.4,NE)	2.3462 (1.7186,3.2031) [<.0001]	0.6876
	>= 3	6	6 (100.0)	3.0 (0.8,NE)	6	3 (50.0)	7.4 (0.8,NE)	2.6886 (0.5364,13.4773) [0.2114]	
Renal Impairment at Baseline	Mild	92	74 (80.4)	1.5 (1.4,2.8)	104	47 (45.2)	10.3 (6.6,NE)	2.5998 (1.7998,3.7555) [<.0001]	0.0465
	Moderate	30	21 (70.0)	3.0 (1.5,7.2)	22	5 (22.7)	NE (13.9,NE)	3.3756 (1.2698,8.9734) [0.0096]	
	Normal	130	92 (70.8)	3.0 (1.6,4.4)	130	62 (47.7)	8.5 (6.3,9.9)	1.5256 (1.1000,2.1157) [0.0121]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Nausea and Vomiting									
Hepatic Impairment	Mild	49	32 (65.3)	3.0 (1.4,6.9)	49	22 (44.9)	6.6 (4.1,NE)	1.4451 (0.8389,2.4894) [0.1892]	0.1614
	Normal	208	159 (76.4)	2.8 (1.5,3.0)	212	94 (44.3)	9.9 (8.6,NE)	2.1417 (1.6572,2.7678) [<.0001]	
Baseline Visceral Disease	No	66	51 (77.3)	2.8 (1.5,4.4)	74	34 (45.9)	9.7 (6.3,NE)	1.9333 (1.2506,2.9887) [0.0026]	0.8908
	Yes	195	140 (71.8)	2.8 (1.5,3.1)	189	82 (43.4)	9.6 (7.1,NE)	2.0419 (1.5525,2.6855) [<.0001]	
Baseline CNS Metastases	No	218	160 (73.4)	2.8 (1.5,3.1)	224	95 (42.4)	9.9 (8.4,NE)	2.0922 (1.6212,2.7000) [<.0001]	0.4139
	Yes	43	31 (72.1)	2.9 (1.5,4.3)	39	21 (53.8)	7.0 (4.3,10.3)	1.6052 (0.9152,2.8152) [0.1000]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale	Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Symptom Scales/Nausea and Vomiting										
	History of CNS Metastases	No	199	150 (75.4)	2.8 (1.5,3.0)	211	92 (43.6)	9.7 (7.6,NE)	2.1027 (1.6200,2.7292) [<.0001]	0.5133
		Yes	62	41 (66.1)	3.0 (1.6,6.2)	52	24 (46.2)	9.6 (6.6,11.3)	1.6734 (1.0036,2.7902) [0.0488]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Pain									
Age	<65	212	114 (53.8)	8.9 (5.7,15.7)	206	112 (54.4)	5.5 (4.2,8.3)	0.7354 (0.5650,0.9572) [0.0225]	0.0127
	>=65	49	28 (57.1)	5.6 (1.5,NE)	57	25 (43.9)	10.4 (8.1,NE)	1.5217 (0.8860,2.6137) [0.1296]	
Age	<75	253	139 (54.9)	8.5 (5.6,14.5)	255	132 (51.8)	6.9 (4.8,10.0)	0.8700 (0.6847,1.1055) [0.2570]	0.7569
	>=75	8	3 (37.5)	5.5 (0.8,NE)	8	5 (62.5)	7.5 (3.5,NE)	0.7560 (0.1758,3.2507) [0.7062]	
Region	Asia	149	87 (58.4)	7.0 (5.1,10.7)	160	78 (48.8)	8.3 (5.6,11.8)	1.0239 (0.7531,1.3922) [0.8781]	0.0260
	Europe	54	28 (51.9)	7.0 (2.9,NE)	50	28 (56.0)	5.5 (1.7,12.5)	0.8041 (0.4749,1.3615) [0.4128]	
	North America	17	12 (70.6)	3.1 (1.4,NE)	17	8 (47.1)	7.6 (1.5,NE)	1.3972 (0.5615,3.4771) [0.4681]	
	Rest of World	41	15 (36.6)	NE (7.0,NE)	36	23 (63.9)	4.2 (1.7,10.3)	0.3771 (0.1959,0.7261) [0.0023]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Pain									
Race	Asian	152	88 (57.9)	7.0 (5.1,10.7)	162	79 (48.8)	8.3 (5.6,11.8)	1.0226 (0.7535,1.3877) [0.8839]	0.0379
	Black Or African American	10	7 (70.0)	4.2 (1.4,NE)	9	3 (33.3)	NE (2.8,NE)	2.3354 (0.6012,9.0727) [0.2072]	
	Other	28	14 (50.0)	14.0 (2.9,NE)	20	13 (65.0)	1.5 (1.4,6.0)	0.4512 (0.2092,0.9731) [0.0350]	
	White	71	33 (46.5)	22.3 (3.0,NE)	72	42 (58.3)	5.6 (2.9,10.3)	0.6265 (0.3942,0.9957) [0.0441]	
ECOG PS	0	154	83 (53.9)	8.9 (5.6,16.4)	175	96 (54.9)	6.9 (4.8,8.9)	0.7943 (0.5910,1.0675) [0.1264]	0.4113
	1	106	59 (55.7)	7.3 (3.3,15.7)	87	41 (47.1)	7.6 (4.2,NE)	1.0031 (0.6721,1.4972) [0.9780]	
Hormone Receptor Status	Negative	126	76 (60.3)	5.8 (3.0,8.5)	122	60 (49.2)	8.3 (4.6,11.9)	1.1660 (0.8303,1.6374) [0.3789]	0.0201
	Positive	133	66 (49.6)	14.0 (7.0,NE)	139	76 (54.7)	6.1 (4.2,10.3)	0.6656 (0.4771,0.9284) [0.0163]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Pain									
Estrogen Receptors	Negative	130	78 (60.0)	5.6 (3.0,8.5)	128	63 (49.2)	8.3 (4.3,11.9)	1.1555 (0.8284,1.6118) [0.3968]	0.0164
	Positive	129	64 (49.6)	14.0 (7.0,NE)	132	73 (55.3)	6.1 (4.2,8.9)	0.6426 (0.4573,0.9030) [0.0105]	
Progesterone Receptors	Negative	177	106 (59.9)	5.8 (4.1,8.9)	168	90 (53.6)	7.6 (4.2,10.0)	1.0089 (0.7611,1.3374) [0.9507]	0.0778
	Positive	81	36 (44.4)	22.3 (8.5,NE)	92	46 (50.0)	6.1 (4.4,13.8)	0.6270 (0.4034,0.9746) [0.0370]	
Prior Treatment with Pertuzumab	No	99	44 (44.4)	16.4 (8.5,NE)	105	50 (47.6)	7.6 (5.6,13.9)	0.7283 (0.4844,1.0951) [0.1248]	0.3956
	Yes	162	98 (60.5)	5.8 (3.1,9.9)	158	87 (55.1)	5.6 (4.2,9.8)	0.9313 (0.6963,1.2458) [0.6346]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Pain									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	104 (55.3)	7.0 (5.6,14.0)	191	104 (54.5)	6.0 (4.2,8.6)	0.8150 (0.6201,1.0713) [0.1426]	0.4256
	>= 3	73	38 (52.1)	9.9 (3.3,NE)	72	33 (45.8)	11.8 (5.6,14.3)	0.9874 (0.6160,1.5827) [0.9595]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	94 (60.3)	5.6 (3.1,10.0)	152	85 (55.9)	5.5 (4.2,8.9)	0.9237 (0.6874,1.2413) [0.6007]	0.6196
	>= 3	6	4 (66.7)	7.8 (0.7,NE)	6	2 (33.3)	14.3 (1.4,NE)	1.4158 (0.2570,7.8000) [0.6882]	
Renal Impairment at Baseline	Mild	92	57 (62.0)	5.8 (4.2,10.2)	104	56 (53.8)	8.3 (5.6,10.7)	1.1142 (0.7702,1.6118) [0.5565]	0.0556
	Moderate	30	17 (56.7)	7.3 (1.7,NE)	22	8 (36.4)	13.9 (3.5,NE)	1.5251 (0.6573,3.5385) [0.3273]	
	Normal	130	68 (52.3)	10.0 (5.6,NE)	130	70 (53.8)	4.8 (4.2,10.0)	0.6881 (0.4894,0.9674) [0.0307]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Pain									
Hepatic Impairment	Mild	49	23 (46.9)	16.9 (3.3,NE)	49	22 (44.9)	5.6 (3.1,NE)	0.7992 (0.4447,1.4364) [0.4578]	0.7007
	Normal	208	119 (57.2)	8.5 (5.6,14.0)	212	115 (54.2)	7.6 (5.0,10.3)	0.8741 (0.6752,1.1314) [0.3057]	
Baseline Visceral Disease	No	66	36 (54.5)	9.9 (5.6,NE)	74	39 (52.7)	6.3 (3.7,13.9)	0.7768 (0.4924,1.2255) [0.2791]	0.5641
	Yes	195	106 (54.4)	7.3 (4.4,14.0)	189	98 (51.9)	7.6 (5.0,10.3)	0.8948 (0.6788,1.1796) [0.4309]	
Baseline CNS Metastases	No	218	117 (53.7)	8.5 (5.7,16.4)	224	119 (53.1)	6.0 (4.3,10.0)	0.8183 (0.6332,1.0574) [0.1259]	0.2639
	Yes	43	25 (58.1)	4.3 (2.9,11.7)	39	18 (46.2)	8.4 (5.0,10.7)	1.0960 (0.5901,2.0357) [0.7730]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Pain									
History of CNS Metastases	No	199	107 (53.8)	7.3 (5.6,16.4)	211	112 (53.1)	6.1 (4.3,10.0)	0.8223 (0.6302,1.0728) [0.1509]	0.3842
	Yes	62	35 (56.5)	10.0 (3.0,14.5)	52	25 (48.1)	8.3 (5.0,10.7)	0.9444 (0.5550,1.6070) [0.8250]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Dyspnoea									
Age	<65	212	77 (36.3)	NE (16.6,NE)	206	80 (38.8)	14.3 (8.4,NE)	0.7107 (0.5172,0.9764) [0.0349]	0.0207
	>=65	49	24 (49.0)	10.7 (4.2,NE)	57	18 (31.6)	20.5 (14.8,NE)	1.6454 (0.8904,3.0408) [0.1115]	
Age	<75	253	96 (37.9)	NE (16.6,NE)	255	95 (37.3)	15.2 (11.7,NE)	0.8130 (0.6105,1.0828) [0.1567]	0.0837
	>=75	8	5 (62.5)	2.7 (0.8,NE)	8	3 (37.5)	NE (2.8,NE)	2.8577 (0.6759,12.0827) [0.1360]	
Region	Asia	149	63 (42.3)	16.6 (12.5,NE)	160	59 (36.9)	14.8 (8.5,NE)	0.9243 (0.6444,1.3258) [0.6664]	0.1071
	Europe	54	17 (31.5)	NE (18.1,NE)	50	16 (32.0)	NE (5.1,NE)	0.8001 (0.4012,1.5955) [0.5266]	
	North America	17	12 (70.6)	4.3 (2.5,12.2)	17	7 (41.2)	NE (1.5,NE)	1.3782 (0.5416,3.5071) [0.4981]	
	Rest of World	41	9 (22.0)	NE (NE,NE)	36	16 (44.4)	11.7 (4.8,NE)	0.3496 (0.1533,0.7972) [0.0091]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Dyspnoea									
Race	Asian	152	63 (41.4)	16.6 (12.5,NE)	162	59 (36.4)	14.8 (8.5,NE)	0.9258 (0.6455,1.3279) [0.6728]	0.6315
	Black Or African American	10	3 (30.0)	NE (3.1,NE)	9	4 (44.4)	NE (0.8,NE)	0.3927 (0.0868,1.7770) [0.2186]	
	Other	28	7 (25.0)	NE (18.1,NE)	20	4 (20.0)	NE (4.2,NE)	0.9595 (0.2774,3.3194) [0.9496]	
	White	71	28 (39.4)	18.6 (8.7,NE)	72	31 (43.1)	11.7 (5.1,NE)	0.7554 (0.4515,1.2636) [0.2869]	
ECOG PS	0	154	58 (37.7)	NE (14.5,NE)	175	60 (34.3)	20.5 (13.8,NE)	0.8913 (0.6191,1.2832) [0.5395]	0.4940
	1	106	43 (40.6)	18.6 (12.5,NE)	87	38 (43.7)	8.4 (5.7,NE)	0.7217 (0.4632,1.1244) [0.1454]	
Hormone Receptor Status	Negative	126	50 (39.7)	18.1 (12.2,NE)	122	41 (33.6)	NE (7.0,NE)	0.9786 (0.6457,1.4832) [0.9192]	0.3965
	Positive	133	50 (37.6)	NE (15.8,NE)	139	56 (40.3)	14.8 (9.7,20.5)	0.7386 (0.5018,1.0870) [0.1234]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Dyspnoea									
Estrogen Receptors	Negative	130	51 (39.2)	18.1 (12.2,NE)	128	45 (35.2)	NE (7.0,NE)	0.9252 (0.6179,1.3851) [0.7044]	0.5741
	Positive	129	49 (38.0)	NE (15.8,NE)	132	52 (39.4)	14.3 (8.5,NE)	0.7546 (0.5078,1.1215) [0.1630]	
Progesterone Receptors	Negative	177	72 (40.7)	18.6 (13.8,NE)	168	63 (37.5)	20.5 (7.3,NE)	0.8734 (0.6212,1.2280) [0.4375]	0.6272
	Positive	81	27 (33.3)	NE (15.8,NE)	92	34 (37.0)	14.8 (9.7,NE)	0.7174 (0.4295,1.1984) [0.2036]	
Prior Treatment with Pertuzumab	No	99	37 (37.4)	NE (13.8,NE)	105	34 (32.4)	NE (11.7,NE)	0.9620 (0.6020,1.5372) [0.8663]	0.3720
	Yes	162	64 (39.5)	NE (14.5,NE)	158	64 (40.5)	14.8 (7.6,NE)	0.7723 (0.5430,1.0982) [0.1504]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Dyspnoea									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	67 (35.6)	NE (18.6,NE)	191	76 (39.8)	14.8 (7.3,NE)	0.7176 (0.5152,0.9996) [0.0489]	0.0323
	>= 3	73	34 (46.6)	15.8 (8.8,NE)	72	22 (30.6)	15.2 (11.7,NE)	1.2672 (0.7358,2.1822) [0.3944]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	61 (39.1)	NE (14.5,NE)	152	61 (40.1)	15.2 (7.6,NE)	0.7905 (0.5512,1.1336) [0.2015]	0.5098
	>= 3	6	3 (50.0)	9.9 (1.5,NE)	6	3 (50.0)	8.6 (0.7,NE)	0.5460 (0.1075,2.7736) [0.4593]	
Renal Impairment at Baseline	Mild	92	43 (46.7)	15.6 (10.7,18.6)	104	41 (39.4)	20.5 (7.3,NE)	1.0684 (0.6952,1.6419) [0.7612]	0.0267
	Moderate	30	13 (43.3)	14.5 (4.5,NE)	22	4 (18.2)	NE (4.2,NE)	1.9974 (0.6510,6.1279) [0.2173]	
	Normal	130	43 (33.1)	NE (NE,NE)	130	52 (40.0)	13.8 (7.0,NE)	0.5834 (0.3856,0.8828) [0.0100]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Dyspnoea									
Hepatic Impairment	Mild	49	15 (30.6)	NE (14.5,NE)	49	16 (32.7)	16.6 (8.1,NE)	0.7117 (0.3510,1.4433) [0.3456]	0.5906
	Normal	208	86 (41.3)	18.6 (14.5,NE)	212	82 (38.7)	15.2 (8.5,NE)	0.8738 (0.6432,1.1871) [0.3879]	
Baseline Visceral Disease	No	66	29 (43.9)	18.1 (10.7,NE)	74	32 (43.2)	13.8 (5.7,NE)	0.7053 (0.4243,1.1723) [0.1779]	0.5109
	Yes	195	72 (36.9)	NE (15.6,NE)	189	66 (34.9)	16.6 (14.3,NE)	0.9085 (0.6484,1.2729) [0.5785]	
Baseline CNS Metastases	No	218	90 (41.3)	18.6 (13.8,NE)	224	81 (36.2)	15.2 (13.8,NE)	0.9540 (0.7049,1.2912) [0.7595]	0.0264
	Yes	43	11 (25.6)	NE (15.8,NE)	39	17 (43.6)	6.9 (2.9,NE)	0.3883 (0.1763,0.8552) [0.0157]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Dyspnoea									
History of CNS Metastases	No	199	80 (40.2)	NE (14.5,NE)	211	77 (36.5)	15.2 (13.8,NE)	0.9276 (0.6768,1.2714) [0.6386]	0.2141
	Yes	62	21 (33.9)	NE (13.8,NE)	52	21 (40.4)	NE (4.2,NE)	0.5566 (0.2966,1.0444) [0.0659]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Insomnia									
Age	<65	212	97 (45.8)	16.1 (9.9,NE)	206	89 (43.2)	11.3 (5.4,NE)	0.8371 (0.6261,1.1191) [0.2329]	0.9347
	>=65	49	18 (36.7)	NE (5.7,NE)	57	23 (40.4)	NE (4.7,NE)	0.8724 (0.4701,1.6188) [0.6569]	
Age	<75	253	113 (44.7)	19.4 (10.7,NE)	255	108 (42.4)	12.7 (7.2,NE)	0.8733 (0.6698,1.1385) [0.3173]	0.4591
	>=75	8	2 (25.0)	NE (2.9,NE)	8	4 (50.0)	6.8 (1.5,NE)	0.5158 (0.0931,2.8569) [0.4405]	
Region	Asia	149	64 (43.0)	NE (10.6,NE)	160	69 (43.1)	15.2 (4.8,NE)	0.8087 (0.5742,1.1389) [0.2252]	0.8090
	Europe	54	23 (42.6)	16.1 (5.6,NE)	50	18 (36.0)	NE (7.0,NE)	1.0801 (0.5810,2.0077) [0.8032]	
	North America	17	10 (58.8)	9.2 (1.4,NE)	17	8 (47.1)	11.3 (2.9,NE)	0.9335 (0.3550,2.4543) [0.8980]	
	Rest of World	41	18 (43.9)	NE (5.6,NE)	36	17 (47.2)	9.6 (2.8,NE)	0.7555 (0.3889,1.4677) [0.4017]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Insomnia									
Race	Asian	152	65 (42.8)	NE (10.6,NE)	162	70 (43.2)	15.2 (4.8,NE)	0.8134 (0.5790,1.1427) [0.2343]	0.4272
	Black Or African American	10	7 (70.0)	5.4 (1.4,NE)	9	3 (33.3)	NE (2.8,NE)	2.2847 (0.5888,8.8652) [0.2228]	
	Other	28	9 (32.1)	NE (12.5,NE)	20	7 (35.0)	NE (1.5,NE)	0.6541 (0.2415,1.7720) [0.4047]	
	White	71	34 (47.9)	12.7 (5.6,NE)	72	32 (44.4)	8.3 (4.4,NE)	0.9352 (0.5742,1.5232) [0.7903]	
ECOG PS	0	154	69 (44.8)	19.4 (9.9,NE)	175	76 (43.4)	12.7 (7.0,NE)	0.8415 (0.6064,1.1679) [0.3037]	0.9718
	1	106	46 (43.4)	NE (7.4,NE)	87	36 (41.4)	10.3 (4.1,NE)	0.8811 (0.5685,1.3657) [0.5680]	
Hormone Receptor Status	Negative	126	58 (46.0)	14.5 (8.3,NE)	122	48 (39.3)	NE (4.7,NE)	0.9779 (0.6659,1.4362) [0.9138]	0.3676
	Positive	133	56 (42.1)	22.3 (11.7,NE)	139	63 (45.3)	9.8 (6.9,NE)	0.7681 (0.5349,1.1030) [0.1507]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Insomnia									
Estrogen Receptors	Negative	130	58 (44.6)	16.1 (9.2,NE)	128	50 (39.1)	NE (4.8,NE)	0.9556 (0.6533,1.3976) [0.8181]	0.4188
	Positive	129	56 (43.4)	22.3 (8.4,NE)	132	61 (46.2)	8.6 (5.3,NE)	0.7702 (0.5347,1.1095) [0.1587]	
Progesterone Receptors	Negative	177	78 (44.1)	19.4 (9.8,NE)	168	70 (41.7)	15.2 (5.3,NE)	0.8707 (0.6296,1.2041) [0.4069]	0.9669
	Positive	81	36 (44.4)	22.3 (8.3,NE)	92	41 (44.6)	10.3 (5.3,NE)	0.8424 (0.5370,1.3215) [0.4520]	
Prior Treatment with Pertuzumab	No	99	38 (38.4)	NE (11.7,NE)	105	46 (43.8)	12.7 (4.2,NE)	0.7173 (0.4660,1.1039) [0.1244]	0.3020
	Yes	162	77 (47.5)	16.1 (8.4,NE)	158	66 (41.8)	11.3 (7.2,NE)	0.9415 (0.6756,1.3120) [0.7284]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Insomnia									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	82 (43.6)	19.4 (10.6,NE)	191	84 (44.0)	9.8 (5.4,NE)	0.8042 (0.5920,1.0924) [0.1629]	0.4472
	>= 3	73	33 (45.2)	12.5 (7.3,NE)	72	28 (38.9)	NE (4.2,NE)	1.0105 (0.6092,1.6761) [0.9667]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	75 (48.1)	14.5 (8.3,NE)	152	64 (42.1)	11.3 (7.2,NE)	0.9587 (0.6846,1.3426) [0.8112]	0.5223
	>= 3	6	2 (33.3)	NE (0.8,NE)	6	2 (33.3)	NE (1.4,NE)	0.6325 (0.0885,4.5218) [0.6452]	
Renal Impairment at Baseline	Mild	92	47 (51.1)	11.7 (5.3,NE)	104	43 (41.3)	NE (5.0,NE)	1.1309 (0.7472,1.7114) [0.5522]	0.1905
	Moderate	30	11 (36.7)	NE (7.1,NE)	22	10 (45.5)	8.3 (3.7,NE)	0.6269 (0.2649,1.4835) [0.2760]	
	Normal	130	54 (41.5)	22.3 (12.7,NE)	130	58 (44.6)	9.8 (4.4,NE)	0.6849 (0.4696,0.9990) [0.0486]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Insomnia									
Hepatic Impairment	Mild	49	17 (34.7)	NE (8.3,NE)	49	17 (34.7)	12.7 (4.1,NE)	0.7289 (0.3700,1.4362) [0.3572]	0.6398
	Normal	208	98 (47.1)	16.1 (9.8,NE)	212	95 (44.8)	11.3 (6.9,NE)	0.8866 (0.6676,1.1774) [0.4103]	
Baseline Visceral Disease	No	66	36 (54.5)	10.6 (4.2,NE)	74	34 (45.9)	15.2 (3.3,NE)	1.0146 (0.6344,1.6226) [0.9474]	0.4450
	Yes	195	79 (40.5)	22.3 (14.5,NE)	189	78 (41.3)	11.3 (7.2,NE)	0.8022 (0.5852,1.0996) [0.1692]	
Baseline CNS Metastases	No	218	101 (46.3)	16.1 (9.2,NE)	224	95 (42.4)	12.7 (7.9,NE)	0.9219 (0.6960,1.2211) [0.5727]	0.1917
	Yes	43	14 (32.6)	19.4 (10.4,NE)	39	17 (43.6)	7.0 (3.5,NE)	0.5778 (0.2807,1.1895) [0.1321]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Insomnia									
History of CNS Metastases	No	199	90 (45.2)	16.1 (9.8,NE)	211	86 (40.8)	15.2 (7.9,NE)	0.9316 (0.6925,1.2533) [0.6423]	0.2299
	Yes	62	25 (40.3)	19.4 (9.2,NE)	52	26 (50.0)	5.0 (3.5,NE)	0.6207 (0.3542,1.0876) [0.0930]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Appetite Loss									
Age	<65	212	129 (60.8)	4.1 (2.9,5.6)	206	91 (44.2)	8.5 (5.8,NE)	1.4082 (1.0756,1.8436) [0.0126]	0.4858
	>=65	49	31 (63.3)	4.4 (1.8,14.3)	57	24 (42.1)	11.0 (5.7,NE)	1.7519 (1.0198,3.0096) [0.0411]	
Age	<75	253	154 (60.9)	4.3 (3.0,5.6)	255	111 (43.5)	10.3 (6.7,20.5)	1.4371 (1.1249,1.8359) [0.0037]	0.1491
	>=75	8	6 (75.0)	1.6 (0.8,NE)	8	4 (50.0)	4.2 (0.9,NE)	3.1013 (0.7552,12.7356) [0.1032]	
Region	Asia	149	91 (61.1)	4.3 (2.9,5.8)	160	74 (46.3)	8.5 (5.6,20.5)	1.3932 (1.0242,1.8952) [0.0353]	0.4708
	Europe	54	29 (53.7)	5.7 (2.8,NE)	50	20 (40.0)	10.3 (2.9,NE)	1.2381 (0.6986,2.1943) [0.4654]	
	North America	17	12 (70.6)	3.0 (1.5,14.4)	17	5 (29.4)	11.3 (5.5,NE)	2.7633 (0.9538,8.0053) [0.0508]	
	Rest of World	41	28 (68.3)	2.8 (1.6,5.6)	36	16 (44.4)	14.0 (2.9,NE)	1.6756 (0.9041,3.1055) [0.0999]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Appetite Loss									
Race	Asian	152	91 (59.9)	4.4 (3.0,8.5)	162	74 (45.7)	9.5 (5.6,20.5)	1.3879 (1.0204,1.8878) [0.0376]	0.1422
	Black Or African American	10	7 (70.0)	3.2 (1.5,NE)	9	6 (66.7)	2.8 (0.8,NE)	0.6539 (0.2185,1.9572) [0.4604]	
	Other	28	14 (50.0)	14.3 (1.5,NE)	20	8 (40.0)	NE (1.5,NE)	1.0170 (0.4242,2.4382) [0.9720]	
	White	71	48 (67.6)	2.8 (1.7,4.4)	72	27 (37.5)	NE (6.9,NE)	2.1226 (1.3222,3.4075) [0.0014]	
ECOG PS	0	154	92 (59.7)	4.7 (3.0,10.2)	175	79 (45.1)	10.2 (6.6,20.5)	1.3727 (1.0150,1.8564) [0.0401]	0.6360
	1	106	68 (64.2)	3.2 (2.1,4.5)	87	36 (41.4)	NE (4.3,NE)	1.5916 (1.0615,2.3866) [0.0226]	
Hormone Receptor Status	Negative	126	75 (59.5)	4.1 (2.9,8.5)	122	52 (42.6)	11.0 (4.3,NE)	1.4805 (1.0388,2.1099) [0.0295]	0.9874
	Positive	133	85 (63.9)	4.2 (2.8,7.1)	139	63 (45.3)	10.2 (5.8,NE)	1.4647 (1.0554,2.0328) [0.0223]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Appetite Loss									
Estrogen Receptors	Negative	130	78 (60.0)	4.1 (2.9,5.6)	128	55 (43.0)	11.0 (4.3,NE)	1.4781 (1.0462,2.0882) [0.0263]	0.9710
	Positive	129	82 (63.6)	4.3 (2.8,7.1)	132	60 (45.5)	10.2 (5.8,NE)	1.4378 (1.0280,2.0111) [0.0339]	
Progesterone Receptors	Negative	177	103 (58.2)	4.7 (3.0,10.2)	168	67 (39.9)	19.1 (8.4,NE)	1.5226 (1.1184,2.0730) [0.0074]	0.8515
	Positive	81	56 (69.1)	2.9 (2.0,4.4)	92	47 (51.1)	6.0 (4.8,14.0)	1.4851 (1.0063,2.1916) [0.0454]	
Prior Treatment with Pertuzumab	No	99	62 (62.6)	2.9 (2.1,4.2)	105	45 (42.9)	8.5 (5.7,NE)	1.7171 (1.1689,2.5226) [0.0056]	0.3079
	Yes	162	98 (60.5)	4.7 (3.0,10.2)	158	70 (44.3)	10.3 (6.0,20.5)	1.3167 (0.9669,1.7930) [0.0814]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Appetite Loss									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	112 (59.6)	4.4 (3.0,10.2)	191	86 (45.0)	9.5 (5.7,20.5)	1.3199 (0.9955,1.7499) [0.0542]	0.1967
	>= 3	73	48 (65.8)	3.0 (1.6,4.2)	72	29 (40.3)	14.0 (5.8,NE)	1.9162 (1.2050,3.0471) [0.0053]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	93 (59.6)	4.7 (3.0,10.3)	152	67 (44.1)	11.0 (6.0,20.5)	1.3127 (0.9569,1.8007) [0.0921]	0.9165
	>= 3	6	5 (83.3)	3.0 (0.8,NE)	6	3 (50.0)	4.5 (2.8,NE)	1.2030 (0.2666,5.4289) [0.8098]	
Renal Impairment at Baseline	Mild	92	58 (63.0)	4.1 (1.6,5.6)	104	42 (40.4)	20.5 (7.0,NE)	1.9840 (1.3326,2.9539) [0.0006]	0.1235
	Moderate	30	19 (63.3)	3.5 (2.1,15.0)	22	8 (36.4)	NE (2.0,NE)	1.4822 (0.6481,3.3898) [0.3444]	
	Normal	130	79 (60.8)	4.4 (2.9,12.0)	130	63 (48.5)	7.2 (5.1,14.0)	1.1177 (0.7988,1.5640) [0.5256]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Appetite Loss									
Hepatic Impairment	Mild	49	30 (61.2)	3.2 (1.5,5.6)	49	20 (40.8)	6.6 (2.9,NE)	1.4496 (0.8229,2.5538) [0.1985]	0.9006
	Normal	208	130 (62.5)	4.3 (2.9,7.1)	212	95 (44.8)	11.0 (7.0,20.5)	1.4562 (1.1163,1.8996) [0.0055]	
Baseline Visceral Disease	No	66	40 (60.6)	4.5 (2.9,15.0)	74	37 (50.0)	9.5 (3.3,19.1)	1.0752 (0.6850,1.6878) [0.7621]	0.1420
	Yes	195	120 (61.5)	3.2 (2.8,5.6)	189	78 (41.3)	11.3 (6.5,NE)	1.6520 (1.2413,2.1986) [0.0005]	
Baseline CNS Metastases	No	218	134 (61.5)	4.2 (2.9,5.6)	224	101 (45.1)	10.2 (6.0,20.5)	1.3903 (1.0728,1.8017) [0.0130]	0.3181
	Yes	43	26 (60.5)	3.0 (1.6,9.9)	39	14 (35.9)	NE (5.0,NE)	1.9908 (1.0380,3.8181) [0.0349]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Appetite Loss									
History of CNS Metastases	No	199	131 (65.8)	3.4 (2.8,4.7)	211	97 (46.0)	9.5 (5.8,19.1)	1.4945 (1.1485,1.9447) [0.0027]	0.8655
	Yes	62	29 (46.8)	9.9 (2.8,NE)	52	18 (34.6)	NE (5.0,NE)	1.4467 (0.8016,2.6110) [0.2185]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Constipation									
Age	<65	212	126 (59.4)	5.1 (4.2,8.3)	206	93 (45.1)	8.5 (5.7,12.9)	1.2799 (0.9777,1.6755) [0.0721]	0.6806
	>=65	49	28 (57.1)	7.3 (3.1,15.9)	57	29 (50.9)	8.4 (4.2,19.4)	1.1452 (0.6800,1.9288) [0.6166]	
Age	<75	253	150 (59.3)	5.6 (4.2,8.3)	255	116 (45.5)	8.6 (7.0,12.9)	1.2684 (0.9942,1.6182) [0.0560]	0.1884
	>=75	8	4 (50.0)	8.8 (1.4,NE)	8	6 (75.0)	2.8 (0.8,4.2)	0.4224 (0.1050,1.7002) [0.2114]	
Region	Asia	149	92 (61.7)	4.3 (3.1,7.3)	160	70 (43.8)	10.4 (7.0,NE)	1.5069 (1.1028,2.0593) [0.0098]	0.2040
	Europe	54	33 (61.1)	5.8 (3.0,8.3)	50	27 (54.0)	5.7 (4.2,11.3)	1.0241 (0.6150,1.7053) [0.9220]	
	North America	17	10 (58.8)	8.3 (1.7,NE)	17	10 (58.8)	5.7 (0.8,8.4)	0.6060 (0.2448,1.5005) [0.2776]	
	Rest of World	41	19 (46.3)	NE (2.9,NE)	36	15 (41.7)	8.6 (2.9,NE)	0.9815 (0.4970,1.9383) [0.9418]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Constipation									
Race	Asian	152	93 (61.2)	4.3 (3.1,7.3)	162	71 (43.8)	10.4 (7.0,NE)	1.4996 (1.0995,2.0452) [0.0102]	0.2519
	Black Or African American	10	6 (60.0)	3.0 (1.4,NE)	9	5 (55.6)	4.6 (0.8,NE)	1.0098 (0.3070,3.3212) [0.9956]	
	Other	28	17 (60.7)	5.8 (2.8,NE)	20	10 (50.0)	5.6 (2.9,NE)	1.1176 (0.5103,2.4475) [0.7958]	
	White	71	38 (53.5)	8.3 (4.4,NE)	72	36 (50.0)	5.7 (3.4,11.3)	0.8044 (0.5065,1.2777) [0.3543]	
ECOG PS	0	154	95 (61.7)	5.1 (3.2,8.3)	175	75 (42.9)	12.9 (7.0,NE)	1.4519 (1.0709,1.9683) [0.0162]	0.0695
	1	106	59 (55.7)	5.8 (3.2,14.3)	87	47 (54.0)	5.6 (3.5,9.8)	0.9071 (0.6164,1.3348) [0.6251]	
Hormone Receptor Status	Negative	126	69 (54.8)	6.9 (4.2,14.5)	122	59 (48.4)	7.3 (5.3,15.2)	1.0926 (0.7706,1.5492) [0.6336]	0.3358
	Positive	133	84 (63.2)	4.4 (3.1,7.0)	139	63 (45.3)	10.4 (5.9,NE)	1.3616 (0.9804,1.8910) [0.0647]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Constipation									
Estrogen Receptors	Negative	130	72 (55.4)	6.1 (3.2,11.0)	128	64 (50.0)	7.0 (4.8,11.3)	1.0714 (0.7641,1.5023) [0.7016]	0.2144
	Positive	129	81 (62.8)	4.4 (3.1,8.3)	132	57 (43.2)	11.3 (7.0,NE)	1.4205 (1.0102,1.9974) [0.0428]	
Progesterone Receptors	Negative	177	101 (57.1)	6.1 (4.2,8.9)	168	85 (50.6)	7.3 (5.6,10.4)	1.0742 (0.8042,1.4350) [0.6380]	0.1039
	Positive	81	52 (64.2)	4.0 (3.0,5.8)	92	37 (40.2)	12.6 (6.3,NE)	1.6075 (1.0509,2.4587) [0.0272]	
Prior Treatment with Pertuzumab	No	99	43 (43.4)	NE (4.9,NE)	105	41 (39.0)	19.4 (7.0,NE)	1.0897 (0.7094,1.6740) [0.7146]	0.3198
	Yes	162	111 (68.5)	4.2 (3.1,5.8)	158	81 (51.3)	7.6 (5.6,11.3)	1.3016 (0.9748,1.7380) [0.0719]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Constipation									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	113 (60.1)	5.6 (4.2,8.3)	191	94 (49.2)	7.6 (5.6,11.3)	1.1148 (0.8463,1.4683) [0.4399]	0.2129
	>= 3	73	41 (56.2)	5.6 (2.8,16.5)	72	28 (38.9)	19.4 (7.0,NE)	1.6045 (0.9911,2.5977) [0.0542]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	107 (68.6)	4.2 (3.1,5.8)	152	81 (53.3)	7.0 (5.6,9.8)	1.2576 (0.9395,1.6834) [0.1210]	0.0347
	>= 3	6	4 (66.7)	10.4 (2.2,NE)	6	0 (0.0)	NE (NE,NE)	NE	
Renal Impairment at Baseline	Mild	92	59 (64.1)	4.2 (2.9,5.8)	104	52 (50.0)	8.3 (5.6,15.2)	1.4554 (1.0011,2.1157) [0.0483]	0.5636
	Moderate	30	18 (60.0)	4.9 (1.5,16.5)	22	9 (40.9)	11.3 (2.8,NE)	1.5387 (0.6679,3.5446) [0.3121]	
	Normal	130	75 (57.7)	8.3 (4.2,12.9)	130	59 (45.4)	8.5 (5.7,NE)	1.1003 (0.7797,1.5526) [0.5886]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Constipation									
Hepatic Impairment	Mild	49	22 (44.9)	14.5 (3.1,NE)	49	22 (44.9)	6.3 (3.6,NE)	0.7748 (0.4275,1.4044) [0.3963]	0.0770
	Normal	208	132 (63.5)	4.5 (3.8,7.0)	212	100 (47.2)	8.6 (5.9,15.2)	1.3537 (1.0425,1.7579) [0.0227]	
Baseline Visceral Disease	No	66	45 (68.2)	5.6 (3.8,8.3)	74	38 (51.4)	9.8 (4.2,12.9)	1.2811 (0.8315,1.9740) [0.2581]	0.8177
	Yes	195	109 (55.9)	5.6 (3.2,11.0)	189	84 (44.4)	8.4 (5.7,NE)	1.2283 (0.9217,1.6368) [0.1640]	
Baseline CNS Metastases	No	218	133 (61.0)	4.9 (3.2,8.3)	224	105 (46.9)	8.5 (5.7,12.9)	1.2655 (0.9787,1.6363) [0.0728]	0.6071
	Yes	43	21 (48.8)	7.8 (4.2,NE)	39	17 (43.6)	7.0 (4.8,NE)	1.0780 (0.5638,2.0612) [0.8278]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Constipation									
History of CNS Metastases	No	199	123 (61.8)	4.4 (3.1,7.0)	211	99 (46.9)	8.4 (5.7,12.9)	1.2965 (0.9939,1.6913) [0.0557]	0.4829
	Yes	62	31 (50.0)	8.3 (4.2,NE)	52	23 (44.2)	9.8 (4.8,NE)	1.0343 (0.5995,1.7845) [0.9043]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Diarrhea									
Age	<65	212	86 (40.6)	NE (17.1,NE)	206	47 (22.8)	NE (17.8,NE)	1.7374 (1.2154,2.4834) [0.0022]	0.8580
	>=65	49	20 (40.8)	NE (4.2,NE)	57	15 (26.3)	NE (13.9,NE)	1.7851 (0.9125,3.4924) [0.0883]	
Age	<75	253	103 (40.7)	NE (17.1,NE)	255	60 (23.5)	NE (17.8,NE)	1.7401 (1.2644,2.3948) [0.0006]	0.6842
	>=75	8	3 (37.5)	NE (0.7,NE)	8	2 (25.0)	NE (0.9,NE)	2.3617 (0.3931,14.1891) [0.3329]	
Region	Asia	149	61 (40.9)	NE (9.5,NE)	160	38 (23.8)	NE (NE,NE)	1.6991 (1.1321,2.5500) [0.0098]	0.0607
	Europe	54	22 (40.7)	18.0 (2.1,NE)	50	11 (22.0)	NE (NE,NE)	2.1195 (1.0229,4.3915) [0.0395]	
	North America	17	11 (64.7)	3.0 (0.9,NE)	17	2 (11.8)	17.8 (NE,NE)	6.4923 (1.4362,29.3479) [0.0051]	
	Rest of World	41	12 (29.3)	NE (13.3,NE)	36	11 (30.6)	13.9 (10.3,NE)	0.8206 (0.3588,1.8766) [0.6366]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Diarrhea									
Race	Asian	152	63 (41.4)	NE (9.1,NE)	162	38 (23.5)	NE (NE,NE)	1.7693 (1.1820,2.6485) [0.0050]	0.8265
	Black Or African American	10	2 (20.0)	NE (1.5,NE)	9	2 (22.2)	NE (4.2,NE)	0.7451 (0.1023,5.4272) [0.7707]	
	Other	28	12 (42.9)	18.0 (1.5,NE)	20	6 (30.0)	NE (7.1,NE)	1.5298 (0.5710,4.0982) [0.3992]	
	White	71	29 (40.8)	NE (4.4,NE)	72	16 (22.2)	17.8 (13.9,NE)	1.9110 (1.0338,3.5328) [0.0354]	
ECOG PS	0	154	66 (42.9)	20.0 (9.1,NE)	175	41 (23.4)	NE (17.8,NE)	1.8692 (1.2641,2.7640) [0.0015]	0.5950
	1	106	40 (37.7)	NE (11.1,NE)	87	21 (24.1)	NE (13.9,NE)	1.5570 (0.9161,2.6461) [0.0995]	
Hormone Receptor Status	Negative	126	44 (34.9)	NE (NE,NE)	122	32 (26.2)	NE (13.9,NE)	1.3127 (0.8316,2.0721) [0.2422]	0.0529
	Positive	133	62 (46.6)	18.0 (6.3,NE)	139	29 (20.9)	NE (17.8,NE)	2.3787 (1.5285,3.7019) [<.0001]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Diarrhea									
Estrogen Receptors	Negative	130	47 (36.2)	NE (18.0,NE)	128	32 (25.0)	NE (13.9,NE)	1.4240 (0.9073,2.2350) [0.1232]	0.1575
	Positive	129	59 (45.7)	20.0 (6.3,NE)	132	29 (22.0)	NE (17.8,NE)	2.2083 (1.4139,3.4490) [0.0004]	
Progesterone Receptors	Negative	177	70 (39.5)	NE (17.1,NE)	168	45 (26.8)	NE (NE,NE)	1.4753 (1.0132,2.1482) [0.0417]	0.0777
	Positive	81	36 (44.4)	18.0 (5.7,NE)	92	16 (17.4)	NE (17.8,NE)	2.7109 (1.5017,4.8940) [0.0006]	
Prior Treatment with Pertuzumab	No	99	35 (35.4)	NE (13.3,NE)	105	30 (28.6)	NE (11.3,NE)	1.1651 (0.7143,1.9002) [0.5407]	0.0569
	Yes	162	71 (43.8)	20.0 (6.9,NE)	158	32 (20.3)	NE (17.8,NE)	2.2762 (1.4965,3.4621) [<.0001]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Diarrhea									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	82 (43.6)	20.0 (9.1,NE)	191	42 (22.0)	NE (NE,NE)	2.1001 (1.4465,3.0488) [<.0001]	0.0721
	>= 3	73	24 (32.9)	NE (NE,NE)	72	20 (27.8)	13.9 (11.1,NE)	1.0669 (0.5860,1.9426) [0.8291]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	69 (44.2)	20.0 (6.3,NE)	152	31 (20.4)	NE (17.8,NE)	2.3137 (1.5113,3.5422) [<.0001]	0.6872
	>= 3	6	2 (33.3)	NE (1.4,NE)	6	1 (16.7)	NE (6.0,NE)	1.6292 (0.1467,18.0995) [0.6882]	
Renal Impairment at Baseline	Mild	92	43 (46.7)	17.1 (5.6,NE)	104	25 (24.0)	NE (NE,NE)	2.3049 (1.4074,3.7748) [0.0006]	0.1675
	Moderate	30	15 (50.0)	18.0 (2.1,NE)	22	4 (18.2)	NE (7.1,NE)	2.7501 (0.9038,8.3683) [0.0646]	
	Normal	130	45 (34.6)	NE (NE,NE)	130	31 (23.8)	17.8 (17.8,NE)	1.3041 (0.8222,2.0686) [0.2588]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Diarrhea									
Hepatic Impairment	Mild	49	15 (30.6)	NE (13.3,NE)	49	13 (26.5)	NE (6.6,NE)	0.9585 (0.4546,2.0209) [0.9104]	0.0844
	Normal	208	91 (43.8)	20.0 (9.5,NE)	212	49 (23.1)	NE (17.8,NE)	1.9843 (1.4003,2.8117) [<.0001]	
Baseline Visceral Disease	No	66	28 (42.4)	NE (5.6,NE)	74	20 (27.0)	NE (11.2,NE)	1.4853 (0.8333,2.6475) [0.1813]	0.5750
	Yes	195	78 (40.0)	20.0 (13.3,NE)	189	42 (22.2)	NE (17.8,NE)	1.8749 (1.2874,2.7304) [0.0009]	
Baseline CNS Metastases	No	218	89 (40.8)	NE (17.1,NE)	224	53 (23.7)	NE (17.8,NE)	1.7329 (1.2318,2.4378) [0.0014]	0.9190
	Yes	43	17 (39.5)	NE (4.3,NE)	39	9 (23.1)	NE (8.3,NE)	1.8079 (0.8038,4.0659) [0.1462]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Diarrhea									
History of CNS Metastases	No	199	80 (40.2)	NE (17.1,NE)	211	52 (24.6)	NE (17.8,NE)	1.6237 (1.1435,2.3056) [0.0064]	0.3842
	Yes	62	26 (41.9)	NE (4.8,NE)	52	10 (19.2)	NE (NE,NE)	2.3312 (1.1229,4.8398) [0.0193]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale	Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Common Difficulties	Symptoms/Financial									
Age		<65	212	67 (31.6)	NE (NE,NE)	206	68 (33.0)	NE (11.1,NE)	0.7256 (0.5157,1.0210) [0.0645]	0.0706
		>=65	49	20 (40.8)	19.7 (10.7,NE)	57	16 (28.1)	NE (12.7,NE)	1.3696 (0.7084,2.6480) [0.3484]	
Age		<75	253	83 (32.8)	NE (19.7,NE)	255	82 (32.2)	NE (12.7,NE)	0.7879 (0.5789,1.0724) [0.1288]	0.1510
		>=75	8	4 (50.0)	7.4 (1.4,NE)	8	2 (25.0)	NE (1.6,NE)	2.4706 (0.4350,14.0329) [0.2932]	
Region		Asia	149	53 (35.6)	NE (18.2,NE)	160	49 (30.6)	NE (11.7,NE)	0.9167 (0.6189,1.3576) [0.6622]	0.7668
		Europe	54	11 (20.4)	24.0 (NE,NE)	50	13 (26.0)	NE (12.7,NE)	0.5476 (0.2387,1.2566) [0.1497]	
		North America	17	6 (35.3)	NE (1.6,NE)	17	5 (29.4)	NE (2.8,NE)	1.0639 (0.3237,3.4963) [0.9185]	
		Rest of World	41	17 (41.5)	NE (6.9,NE)	36	17 (47.2)	8.5 (2.8,NE)	0.6724 (0.3426,1.3195) [0.2463]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale	Subgroup		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
			n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Difficulties	Symptoms/Financial									
Race		Asian	152	53 (34.9)	NE (18.2,NE)	162	49 (30.2)	NE (11.7,NE)	0.9188 (0.6204,1.3607) [0.6705]	0.6298
		Black Or African American	10	6 (60.0)	6.2 (1.5,NE)	9	4 (44.4)	6.9 (1.4,NE)	1.0752 (0.3024,3.8236) [0.9028]	
		Other	28	8 (28.6)	24.0 (15.2,NE)	20	6 (30.0)	15.7 (7.1,NE)	0.6332 (0.2106,1.9035) [0.4120]	
		White	71	20 (28.2)	NE (NE,NE)	72	25 (34.7)	NE (8.6,NE)	0.6209 (0.3437,1.1217) [0.1107]	
ECOG PS		0	154	53 (34.4)	NE (19.7,NE)	175	52 (29.7)	NE (15.2,NE)	0.9180 (0.6244,1.3495) [0.6628]	0.2280
		1	106	34 (32.1)	24.0 (18.2,NE)	87	32 (36.8)	11.2 (8.6,NE)	0.6295 (0.3833,1.0337) [0.0640]	
Hormone Receptor Status		Negative	126	48 (38.1)	24.0 (14.1,NE)	122	40 (32.8)	15.7 (11.1,NE)	0.9096 (0.5942,1.3922) [0.6611]	0.3870
		Positive	133	39 (29.3)	NE (NE,NE)	139	43 (30.9)	NE (11.7,NE)	0.7409 (0.4789,1.1463) [0.1756]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Financial Difficulties									
Estrogen Receptors	Negative	130	50 (38.5)	18.2 (14.1,NE)	128	43 (33.6)	15.7 (11.1,NE)	0.9089 (0.6013,1.3737) [0.6499]	0.3759
	Positive	129	37 (28.7)	NE (NE,NE)	132	40 (30.3)	NE (11.7,NE)	0.7262 (0.4627,1.1399) [0.1614]	
Progesterone Receptors	Negative	177	64 (36.2)	24.0 (18.2,NE)	168	54 (32.1)	NE (12.7,NE)	0.8940 (0.6196,1.2897) [0.5459]	0.3801
	Positive	81	23 (28.4)	NE (NE,NE)	92	29 (31.5)	NE (10.3,NE)	0.6815 (0.3927,1.1827) [0.1709]	
Prior Treatment with Pertuzumab	No	99	36 (36.4)	18.2 (14.1,NE)	105	38 (36.2)	15.7 (8.4,NE)	0.8707 (0.5511,1.3755) [0.5486]	0.9125
	Yes	162	51 (31.5)	NE (24.0,NE)	158	46 (29.1)	NE (11.7,NE)	0.7940 (0.5298,1.1900) [0.2620]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Financial Difficulties									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	63 (33.5)	NE (24.0,NE)	191	67 (35.1)	15.7 (11.2,NE)	0.7366 (0.5204,1.0427) [0.0830]	0.2489
	>= 3	73	24 (32.9)	19.7 (14.1,NE)	72	17 (23.6)	NE (NE,NE)	1.1493 (0.6149,2.1482) [0.6606]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	49 (31.4)	NE (24.0,NE)	152	45 (29.6)	NE (11.7,NE)	0.7941 (0.5265,1.1979) [0.2697]	0.8807
	>= 3	6	2 (33.3)	NE (7.2,NE)	6	1 (16.7)	NE (1.4,NE)	0.9747 (0.0865,10.9763) [0.9835]	
Renal Impairment at Baseline	Mild	92	32 (34.8)	NE (13.4,NE)	104	38 (36.5)	NE (11.1,NE)	0.8185 (0.5105,1.3121) [0.4033]	0.4630
	Moderate	30	13 (43.3)	19.7 (11.5,NE)	22	5 (22.7)	NE (3.9,NE)	1.2813 (0.4494,3.6535) [0.6474]	
	Normal	130	40 (30.8)	NE (NE,NE)	130	40 (30.8)	15.7 (11.1,NE)	0.7490 (0.4799,1.1689) [0.2004]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Financial Difficulties									
Hepatic Impairment	Mild	49	16 (32.7)	NE (14.1,NE)	49	13 (26.5)	NE (7.0,NE)	0.8517 (0.4080,1.7781) [0.6716]	0.8502
	Normal	208	71 (34.1)	NE (19.7,NE)	212	71 (33.5)	NE (11.7,NE)	0.8101 (0.5809,1.1297) [0.2127]	
Baseline Visceral Disease	No	66	19 (28.8)	NE (24.0,NE)	74	23 (31.1)	NE (11.2,NE)	0.6870 (0.3692,1.2783) [0.2327]	0.6671
	Yes	195	68 (34.9)	NE (18.2,NE)	189	61 (32.3)	NE (11.0,NE)	0.8469 (0.5974,1.2007) [0.3497]	
Baseline CNS Metastases	No	218	77 (35.3)	NE (19.7,NE)	224	71 (31.7)	NE (12.7,NE)	0.8843 (0.6388,1.2242) [0.4572]	0.2026
	Yes	43	10 (23.3)	NE (18.2,NE)	39	13 (33.3)	NE (6.2,NE)	0.4888 (0.2095,1.1403) [0.0920]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 42 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale	Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Common Symptoms/Financial Difficulties										
	History of CNS Metastases	No	199	70 (35.2)	NE (19.7,NE)	211	69 (32.7)	NE (12.7,NE)	0.8471 (0.6058,1.1845) [0.3311]	0.7342
		Yes	62	17 (27.4)	NE (18.2,NE)	52	15 (28.8)	NE (7.0,NE)	0.6921 (0.3388,1.4138) [0.3090]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Functioning									
Age	<65	212	54 (25.5)	NE (NE,NE)	206	54 (26.2)	22.6 (22.6,NE)	0.8044 (0.5499,1.1768) [0.2583]	0.1554
	>=65	49	6 (12.2)	NE (NE,NE)	57	3 (5.3)	NE (NE,NE)	2.3163 (0.5793,9.2621) [0.2208]	
Age	<75	253	59 (23.3)	NE (NE,NE)	255	56 (22.0)	NE (22.6,NE)	0.9185 (0.6360,1.3264) [0.6459]	0.8804
	>=75	8	1 (12.5)	NE (2.1,NE)	8	1 (12.5)	NE (1.4,NE)	0.7454 (0.0464,11.9679) [0.8350]	
Region	Asia	149	22 (14.8)	NE (NE,NE)	160	30 (18.8)	NE (NE,NE)	0.6476 (0.3725,1.1260) [0.1204]	0.2412
	Europe	54	16 (29.6)	NE (19.4,NE)	50	10 (20.0)	22.6 (16.4,NE)	1.2677 (0.5706,2.8167) [0.5584]	
	North America	17	8 (47.1)	NE (1.4,NE)	17	4 (23.5)	NE (5.7,NE)	2.0918 (0.6287,6.9593) [0.2200]	
	Rest of World	41	14 (34.1)	NE (2.8,NE)	36	13 (36.1)	NE (1.5,NE)	0.8093 (0.3800,1.7237) [0.5874]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Functioning									
Race	Asian	152	22 (14.5)	NE (NE,NE)	162	30 (18.5)	NE (NE,NE)	0.6495 (0.3736,1.1292) [0.1229]	0.0305
	Black Or African American	10	1 (10.0)	NE (1.4,NE)	9	4 (44.4)	NE (0.8,NE)	0.1481 (0.0164,1.3381) [0.0486]	
	Other	28	8 (28.6)	NE (19.4,NE)	20	4 (20.0)	NE (3.5,NE)	1.1332 (0.3316,3.8725) [0.8450]	
	White	71	29 (40.8)	NE (2.1,NE)	72	19 (26.4)	22.6 (16.4,NE)	1.6025 (0.8894,2.8875) [0.1101]	
ECOG PS	0	154	40 (26.0)	NE (NE,NE)	175	41 (23.4)	NE (NE,NE)	0.9781 (0.6314,1.5152) [0.9170]	0.7015
	1	106	20 (18.9)	NE (NE,NE)	87	16 (18.4)	22.6 (NE,NE)	0.8495 (0.4382,1.6468) [0.6275]	
Hormone Receptor Status	Negative	126	31 (24.6)	NE (NE,NE)	122	19 (15.6)	NE (NE,NE)	1.4437 (0.8140,2.5605) [0.2096]	0.0386
	Positive	133	29 (21.8)	NE (NE,NE)	139	38 (27.3)	NE (22.6,NE)	0.6505 (0.3999,1.0581) [0.0811]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Functioning									
Estrogen Receptors	Negative	130	32 (24.6)	NE (NE,NE)	128	21 (16.4)	NE (NE,NE)	1.3730 (0.7902,2.3858) [0.2635]	0.0560
	Positive	129	28 (21.7)	NE (NE,NE)	132	35 (26.5)	NE (22.6,NE)	0.6662 (0.4040,1.0985) [0.1096]	
Progesterone Receptors	Negative	177	39 (22.0)	NE (NE,NE)	168	28 (16.7)	NE (NE,NE)	1.1474 (0.7047,1.8684) [0.5867]	0.2169
	Positive	81	21 (25.9)	NE (NE,NE)	92	29 (31.5)	22.6 (22.6,NE)	0.7214 (0.4106,1.2675) [0.2554]	
Prior Treatment with Pertuzumab	No	99	21 (21.2)	NE (NE,NE)	105	26 (24.8)	NE (NE,NE)	0.7615 (0.4279,1.3553) [0.3524]	0.3646
	Yes	162	39 (24.1)	NE (NE,NE)	158	31 (19.6)	22.6 (22.6,NE)	1.0360 (0.6439,1.6669) [0.8885]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Functioning									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	43 (22.9)	NE (NE,NE)	191	39 (20.4)	NE (NE,NE)	0.9566 (0.6190,1.4781) [0.8444]	0.8557
	>= 3	73	17 (23.3)	NE (NE,NE)	72	18 (25.0)	22.6 (22.6,NE)	0.8523 (0.4382,1.6578) [0.6321]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	39 (25.0)	NE (NE,NE)	152	30 (19.7)	22.6 (22.6,NE)	1.0849 (0.6714,1.7529) [0.7424]	0.1484
	>= 3	6	0 (0.0)	NE (NE,NE)	6	1 (16.7)	NE (3.3,NE)	0.0000 (0.0000,.) [0.2207]	
Renal Impairment at Baseline	Mild	92	16 (17.4)	NE (NE,NE)	104	17 (16.3)	NE (NE,NE)	0.9248 (0.4657,1.8364) [0.8240]	0.1614
	Moderate	30	7 (23.3)	NE (NE,NE)	22	1 (4.5)	NE (NE,NE)	4.3568 (0.5358,35.4258) [0.1290]	
	Normal	130	35 (26.9)	NE (NE,NE)	130	38 (29.2)	NE (NE,NE)	0.7515 (0.4725,1.1951) [0.2243]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Functioning									
Hepatic Impairment	Mild	49	4 (8.2)	NE (NE,NE)	49	10 (20.4)	NE (NE,NE)	0.3036 (0.0949,0.9712) [0.0335]	0.0282
	Normal	208	56 (26.9)	NE (NE,NE)	212	47 (22.2)	22.6 (22.6,NE)	1.0725 (0.7261,1.5841) [0.7266]	
Baseline Visceral Disease	No	66	10 (15.2)	NE (NE,NE)	74	14 (18.9)	22.6 (22.6,NE)	0.6656 (0.2935,1.5093) [0.3236]	0.4046
	Yes	195	50 (25.6)	NE (NE,NE)	189	43 (22.8)	NE (NE,NE)	0.9813 (0.6514,1.4782) [0.9286]	
Baseline CNS Metastases	No	218	50 (22.9)	NE (NE,NE)	224	48 (21.4)	NE (22.6,NE)	0.9320 (0.6263,1.3868) [0.7250]	0.8590
	Yes	43	10 (23.3)	NE (19.4,NE)	39	9 (23.1)	NE (NE,NE)	0.8303 (0.3325,2.0730) [0.6898]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Sexual Functioning									
History of CNS Metastases	No	199	45 (22.6)	NE (NE,NE)	211	48 (22.7)	NE (22.6,NE)	0.8509 (0.5656,1.2801) [0.4345]	0.4226
	Yes	62	15 (24.2)	NE (19.4,NE)	52	9 (17.3)	NE (NE,NE)	1.2514 (0.5439,2.8789) [0.5985]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Enjoyment									
Age	<65	212	23 (10.8)	7.2 (2.9,NE)	206	11 (5.3)	NE (NE,NE)	2.4373 (1.1869,5.0047) [0.0117]	0.9996
	>=65	49	0 (0.0)	NE (NE,NE)	57	0 (0.0)	NE (NE,NE)	NE	
Age	<75	253	23 (9.1)	13.4 (3.6,NE)	255	11 (4.3)	NE (NE,NE)	2.4122 (1.1750,4.9525) [0.0128]	NE
	>=75	8	0 (0.0)	NE (NE,NE)	8	0 (0.0)	NE (NE,NE)	NE	
Region	Asia	149	5 (3.4)	NE (2.6,NE)	160	2 (1.3)	NE (NE,NE)	4.1186 (0.7884,21.5168) [0.0698]	0.4610
	Europe	54	7 (13.0)	NE (2.8,NE)	50	1 (2.0)	NE (1.4,NE)	3.8581 (0.4733,31.4501) [0.1744]	
	North America	17	1 (5.9)	NE (0.9,NE)	17	3 (17.6)	8.7 (1.4,NE)	0.6702 (0.0694,6.4698) [0.7275]	
	Rest of World	41	10 (24.4)	2.9 (1.4,9.7)	36	5 (13.9)	6.9 (1.4,NE)	1.8695 (0.6341,5.5119) [0.2410]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Enjoyment									
Race	Asian	152	5 (3.3)	NE (2.6,NE)	162	2 (1.2)	NE (NE,NE)	3.8458 (0.7373,20.0602) [0.0862]	0.4502
	Black Or African American	10	1 (10.0)	NE (1.4,NE)	9	3 (33.3)	6.3 (1.4,NE)	1.0199 (0.1032,10.0786) [0.9794]	
	Other	28	4 (14.3)	NE (1.6,NE)	20	0 (0.0)	NE (NE,NE)	NE	
	White	71	13 (18.3)	4.2 (1.6,NE)	72	6 (8.3)	NE (3.0,NE)	2.1254 (0.8046,5.6141) [0.1162]	
ECOG PS	0	154	18 (11.7)	9.7 (3.6,NE)	175	10 (5.7)	NE (8.7,NE)	1.9512 (0.8993,4.2334) [0.0822]	0.2151
	1	106	5 (4.7)	NE (1.4,NE)	87	1 (1.1)	NE (NE,NE)	6.9668 (0.8123,59.7519) [0.0406]	
Hormone Receptor Status	Negative	126	12 (9.5)	9.7 (2.9,NE)	122	4 (3.3)	NE (5.7,NE)	1.9467 (0.6272,6.0424) [0.2415]	0.5461
	Positive	133	11 (8.3)	13.4 (1.6,NE)	139	7 (5.0)	NE (NE,NE)	2.9040 (1.1240,7.5030) [0.0202]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Enjoyment									
Estrogen Receptors	Negative	130	12 (9.2)	NE (4.2,NE)	128	4 (3.1)	NE (5.7,NE)	2.1413 (0.6899,6.6465) [0.1780]	0.6645
	Positive	129	11 (8.5)	9.5 (1.6,NE)	132	7 (5.3)	NE (NE,NE)	2.7991 (1.0827,7.2364) [0.0253]	
Progesterone Receptors	Negative	177	14 (7.9)	13.4 (4.2,NE)	168	4 (2.4)	NE (NE,NE)	3.2740 (1.0768,9.9544) [0.0272]	0.6095
	Positive	81	9 (11.1)	4.6 (1.6,NE)	92	7 (7.6)	NE (6.3,NE)	2.1997 (0.8178,5.9163) [0.1051]	
Prior Treatment with Pertuzumab	No	99	9 (9.1)	4.2 (1.4,NE)	105	6 (5.7)	NE (6.9,NE)	2.7679 (0.9812,7.8076) [0.0434]	0.8711
	Yes	162	14 (8.6)	NE (4.2,NE)	158	5 (3.2)	NE (NE,NE)	2.4640 (0.8865,6.8486) [0.0735]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Enjoyment									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	19 (10.1)	8.5 (2.8,NE)	191	11 (5.8)	NE (6.9,NE)	1.7899 (0.8514,3.7628) [0.1160]	0.0306
	>= 3	73	4 (5.5)	NE (1.4,NE)	72	0 (0.0)	NE (NE,NE)	NE	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	14 (9.0)	NE (4.2,NE)	152	5 (3.3)	NE (8.7,NE)	2.3302 (0.8380,6.4796) [0.0946]	NE
	>= 3	6	0 (0.0)	NE (NE,NE)	6	0 (0.0)	NE (NE,NE)	NE	
Renal Impairment at Baseline	Mild	92	4 (4.3)	NE (1.4,NE)	104	3 (2.9)	NE (1.5,NE)	1.4351 (0.3209,6.4176) [0.6330]	0.7058
	Moderate	30	1 (3.3)	NE (2.8,NE)	22	0 (0.0)	NE (NE,NE)	NE	
	Normal	130	16 (12.3)	7.2 (2.8,NE)	130	8 (6.2)	NE (8.7,NE)	2.4193 (1.0326,5.6679) [0.0341]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Enjoyment									
Hepatic Impairment	Mild	49	1 (2.0)	NE (1.4,NE)	49	2 (4.1)	NE (1.4,NE)	1.3241 (0.1197,14.6433) [0.8184]	0.6241
	Normal	208	22 (10.6)	9.7 (3.6,NE)	212	9 (4.2)	NE (NE,NE)	2.5976 (1.1950,5.6464) [0.0119]	
Baseline Visceral Disease	No	66	6 (9.1)	7.2 (1.4,NE)	74	1 (1.4)	NE (8.7,NE)	8.5852 (1.0323,71.3998) [0.0167]	0.1356
	Yes	195	17 (8.7)	13.4 (2.8,NE)	189	10 (5.3)	NE (NE,NE)	1.8391 (0.8406,4.0239) [0.1185]	
Baseline CNS Metastases	No	218	19 (8.7)	13.4 (4.2,NE)	224	9 (4.0)	NE (NE,NE)	2.5000 (1.1302,5.5302) [0.0189]	0.9211
	Yes	43	4 (9.3)	2.8 (1.6,NE)	39	2 (5.1)	NE (1.4,NE)	1.8648 (0.3396,10.2412) [0.4662]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Enjoyment									
History of CNS Metastases	No	199	18 (9.0)	13.4 (3.6,NE)	211	9 (4.3)	NE (NE,NE)	2.5692 (1.1530,5.7249) [0.0164]	0.7502
	Yes	62	5 (8.1)	NE (1.6,NE)	52	2 (3.8)	NE (1.4,NE)	1.7930 (0.3472,9.2600) [0.4794]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Future Perspective									
Age	<65	212	72 (34.0)	NE (19.4,NE)	206	52 (25.2)	NE (16.7,NE)	1.0602 (0.7381,1.5228) [0.7452]	0.3475
	>=65	49	16 (32.7)	NE (8.5,NE)	57	21 (36.8)	21.2 (4.9,NE)	0.7572 (0.3938,1.4558) [0.4004]	
Age	<75	253	86 (34.0)	NE (19.4,NE)	255	70 (27.5)	21.2 (16.7,NE)	0.9887 (0.7187,1.3600) [0.9481]	0.5567
	>=75	8	2 (25.0)	NE (1.4,NE)	8	3 (37.5)	NE (0.9,NE)	0.6328 (0.1053,3.8022) [0.6139]	
Region	Asia	149	55 (36.9)	NE (19.0,NE)	160	46 (28.8)	21.2 (15.7,NE)	1.0197 (0.6865,1.5147) [0.9200]	0.8271
	Europe	54	17 (31.5)	NE (15.2,NE)	50	11 (22.0)	NE (16.7,NE)	1.1302 (0.5255,2.4306) [0.7529]	
	North America	17	6 (35.3)	NE (1.5,NE)	17	6 (35.3)	10.4 (2.9,NE)	0.8913 (0.2862,2.7759) [0.8424]	
	Rest of World	41	10 (24.4)	NE (NE,NE)	36	10 (27.8)	NE (7.1,NE)	0.7788 (0.3238,1.8729) [0.5730]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Future Perspective									
Race	Asian	152	55 (36.2)	NE (19.0,NE)	162	47 (29.0)	21.2 (15.7,NE)	0.9963 (0.6721,1.4767) [0.9877]	0.9404
	Black Or African American	10	4 (40.0)	NE (1.4,NE)	9	4 (44.4)	10.4 (1.4,NE)	0.7106 (0.1765,2.8600) [0.6458]	
	Other	28	7 (25.0)	19.4 (15.1,NE)	20	3 (15.0)	NE (NE,NE)	1.0391 (0.2535,4.2599) [0.9573]	
	White	71	22 (31.0)	NE (NE,NE)	72	19 (26.4)	NE (16.7,NE)	1.0199 (0.5510,1.8878) [0.9516]	
ECOG PS	0	154	60 (39.0)	NE (19.0,NE)	175	43 (24.6)	21.2 (21.2,NE)	1.2966 (0.8734,1.9249) [0.1950]	0.0135
	1	106	28 (26.4)	NE (NE,NE)	87	30 (34.5)	15.7 (8.4,NE)	0.5837 (0.3464,0.9836) [0.0411]	
Hormone Receptor Status	Negative	126	47 (37.3)	19.4 (14.8,NE)	122	29 (23.8)	NE (16.7,NE)	1.3369 (0.8387,2.1312) [0.2192]	0.0537
	Positive	133	41 (30.8)	NE (NE,NE)	139	44 (31.7)	21.2 (15.7,NE)	0.7380 (0.4796,1.1357) [0.1657]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Future Perspective									
Estrogen Receptors	Negative	130	48 (36.9)	19.4 (15.2,NE)	128	31 (24.2)	NE (16.7,NE)	1.2788 (0.8109,2.0167) [0.2878]	0.0812
	Positive	129	40 (31.0)	NE (NE,NE)	132	41 (31.1)	21.2 (15.7,NE)	0.7677 (0.4941,1.1927) [0.2388]	
Progesterone Receptors	Negative	177	62 (35.0)	NE (19.0,NE)	168	43 (25.6)	21.2 (16.7,NE)	1.1238 (0.7589,1.6641) [0.5572]	0.1822
	Positive	81	26 (32.1)	NE (15.2,NE)	92	30 (32.6)	NE (7.1,NE)	0.7593 (0.4468,1.2902) [0.3076]	
Prior Treatment with Pertuzumab	No	99	39 (39.4)	19.0 (11.9,NE)	105	32 (30.5)	NE (17.2,NE)	1.1363 (0.7106,1.8170) [0.5909]	0.4034
	Yes	162	49 (30.2)	NE (NE,NE)	158	41 (25.9)	21.2 (15.7,NE)	0.8800 (0.5768,1.3427) [0.5519]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Future Perspective									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	59 (31.4)	NE (19.4,NE)	191	55 (28.8)	21.2 (16.7,NE)	0.8294 (0.5712,1.2042) [0.3235]	0.1262
	>= 3	73	29 (39.7)	NE (8.4,NE)	72	18 (25.0)	NE (15.7,NE)	1.4355 (0.7942,2.5948) [0.2238]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	47 (30.1)	NE (19.4,NE)	152	40 (26.3)	21.2 (16.7,NE)	0.8805 (0.5733,1.3524) [0.5596]	0.8068
	>= 3	6	2 (33.3)	NE (3.1,NE)	6	1 (16.7)	15.7 (NE,NE)	1.1535 (0.1010,13.1682) [0.9084]	
Renal Impairment at Baseline	Mild	92	33 (35.9)	NE (14.8,NE)	104	40 (38.5)	16.7 (10.4,NE)	0.7703 (0.4835,1.2271) [0.2736]	0.3892
	Moderate	30	11 (36.7)	NE (7.6,NE)	22	5 (22.7)	NE (4.2,NE)	1.3236 (0.4582,3.8235) [0.6032]	
	Normal	130	43 (33.1)	NE (19.4,NE)	130	27 (20.8)	NE (NE,NE)	1.2128 (0.7430,1.9797) [0.4379]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Future Perspective									
Hepatic Impairment	Mild	49	16 (32.7)	NE (8.2,NE)	49	16 (32.7)	15.7 (4.3,NE)	0.6392 (0.3179,1.2851) [0.2090]	0.2858
	Normal	208	72 (34.6)	NE (19.4,NE)	212	57 (26.9)	21.2 (17.2,NE)	1.0493 (0.7378,1.4922) [0.7891]	
Baseline Visceral Disease	No	66	20 (30.3)	NE (19.4,NE)	74	19 (25.7)	NE (14.4,NE)	0.9313 (0.4947,1.7530) [0.8189]	0.9339
	Yes	195	68 (34.9)	NE (19.0,NE)	189	54 (28.6)	21.2 (15.7,NE)	0.9723 (0.6768,1.3966) [0.8843]	
Baseline CNS Metastases	No	218	72 (33.0)	NE (19.4,NE)	224	65 (29.0)	21.2 (16.7,NE)	0.9166 (0.6535,1.2856) [0.6162]	0.3044
	Yes	43	16 (37.2)	19.4 (8.4,NE)	39	8 (20.5)	NE (NE,NE)	1.3543 (0.5674,3.2324) [0.4897]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Future Perspective									
History of CNS Metastases	No	199	66 (33.2)	NE (19.4,NE)	211	61 (28.9)	21.2 (16.7,NE)	0.9286 (0.6535,1.3195) [0.6805]	0.4730
	Yes	62	22 (35.5)	19.4 (10.0,NE)	52	12 (23.1)	NE (NE,NE)	1.1438 (0.5570,2.3487) [0.7124]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Systemic Therapy Side Effects									
Age	<65	212	84 (39.6)	NE (16.5,NE)	206	59 (28.6)	NE (13.8,NE)	1.2104 (0.8657,1.6922) [0.2656]	0.9546
	>=65	49	23 (46.9)	19.8 (4.3,NE)	57	22 (38.6)	15.2 (7.6,NE)	1.2091 (0.6736,2.1704) [0.5244]	
Age	<75	253	103 (40.7)	NE (16.5,NE)	255	79 (31.0)	NE (13.8,NE)	1.1544 (0.8598,1.5501) [0.3423]	0.2830
	>=75	8	4 (50.0)	3.7 (0.8,NE)	8	2 (25.0)	NE (1.5,NE)	2.4706 (0.4512,13.5273) [0.2810]	
Region	Asia	149	65 (43.6)	NE (9.7,NE)	160	45 (28.1)	17.1 (15.2,NE)	1.3721 (0.9355,2.0123) [0.1046]	0.4919
	Europe	54	21 (38.9)	19.8 (5.6,NE)	50	17 (34.0)	NE (7.0,NE)	0.9873 (0.5199,1.8749) [0.9752]	
	North America	17	7 (41.2)	NE (1.5,NE)	17	5 (29.4)	13.8 (3.0,NE)	1.4340 (0.4538,4.5312) [0.5421]	
	Rest of World	41	14 (34.1)	NE (16.6,NE)	36	14 (38.9)	NE (7.2,NE)	0.7867 (0.3746,1.6520) [0.5045]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Systemic Therapy Side Effects									
Race	Asian	152	65 (42.8)	NE (9.7,NE)	162	45 (27.8)	17.1 (15.2,NE)	1.3721 (0.9355,2.0124) [0.1046]	0.2012
	Black Or African American	10	5 (50.0)	NE (1.4,NE)	9	4 (44.4)	13.8 (1.5,NE)	1.1325 (0.3030,4.2322) [0.8650]	
	Other	28	8 (28.6)	19.8 (16.6,NE)	20	9 (45.0)	9.7 (1.4,NE)	0.4605 (0.1765,1.2017) [0.1057]	
	White	71	29 (40.8)	NE (4.5,NE)	72	23 (31.9)	NE (11.7,NE)	1.2174 (0.7038,2.1060) [0.4825]	
ECOG PS	0	154	65 (42.2)	NE (11.0,NE)	175	58 (33.1)	17.1 (11.7,NE)	1.1155 (0.7813,1.5926) [0.5510]	0.6750
	1	106	42 (39.6)	19.8 (12.5,NE)	87	23 (26.4)	NE (NE,NE)	1.3392 (0.8034,2.2323) [0.2574]	
Hormone Receptor Status	Negative	126	54 (42.9)	19.8 (9.1,NE)	122	35 (28.7)	NE (13.8,NE)	1.3798 (0.9004,2.1145) [0.1385]	0.3681
	Positive	133	53 (39.8)	NE (14.9,NE)	139	45 (32.4)	NE (11.7,NE)	1.0587 (0.7098,1.5790) [0.7800]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Systemic Therapy Side Effects									
Estrogen Receptors	Negative	130	56 (43.1)	19.8 (9.1,NE)	128	37 (28.9)	NE (13.8,NE)	1.3978 (0.9215,2.1201) [0.1152]	0.2928
	Positive	129	51 (39.5)	NE (14.9,NE)	132	43 (32.6)	17.1 (11.7,NE)	1.0195 (0.6773,1.5345) [0.9253]	
Progesterone Receptors	Negative	177	76 (42.9)	19.8 (10.6,NE)	168	47 (28.0)	NE (15.2,NE)	1.4321 (0.9937,2.0639) [0.0534]	0.1104
	Positive	81	31 (38.3)	NE (14.9,NE)	92	33 (35.9)	13.4 (8.5,NE)	0.8655 (0.5286,1.4171) [0.5667]	
Prior Treatment with Pertuzumab	No	99	38 (38.4)	NE (12.3,NE)	105	34 (32.4)	NE (9.7,NE)	1.1153 (0.7005,1.7758) [0.6627]	0.6979
	Yes	162	69 (42.6)	NE (11.0,NE)	158	47 (29.7)	17.1 (13.8,NE)	1.2292 (0.8464,1.7851) [0.2761]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Systemic Therapy Side Effects									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	75 (39.9)	NE (16.5,NE)	191	67 (35.1)	17.1 (11.7,NE)	0.9605 (0.6895,1.3379) [0.8081]	0.0171
	>= 3	73	32 (43.8)	NE (4.3,NE)	72	14 (19.4)	NE (NE,NE)	2.3051 (1.2276,4.3286) [0.0076]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	67 (42.9)	NE (10.6,NE)	152	47 (30.9)	17.1 (13.8,NE)	1.1994 (0.8238,1.7461) [0.3402]	0.1658
	>= 3	6	2 (33.3)	NE (1.5,NE)	6	0 (0.0)	NE (NE,NE)	NE	
Renal Impairment at Baseline	Mild	92	48 (52.2)	9.7 (4.4,NE)	104	33 (31.7)	17.1 (13.8,NE)	1.6930 (1.0859,2.6395) [0.0185]	0.1028
	Moderate	30	15 (50.0)	13.1 (2.9,NE)	22	7 (31.8)	NE (2.8,NE)	1.3401 (0.5433,3.3058) [0.5231]	
	Normal	130	43 (33.1)	NE (NE,NE)	130	39 (30.0)	NE (9.9,NE)	0.9173 (0.5920,1.4214) [0.6914]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Systemic Therapy Side Effects									
Hepatic Impairment	Mild	49	13 (26.5)	NE (NE,NE)	49	10 (20.4)	NE (9.7,NE)	0.9526 (0.4145,2.1888) [0.9049]	0.6237
	Normal	208	94 (45.2)	19.8 (9.7,NE)	212	71 (33.5)	17.1 (13.4,NE)	1.2337 (0.9051,1.6817) [0.1843]	
Baseline Visceral Disease	No	66	30 (45.5)	19.8 (5.6,NE)	74	26 (35.1)	NE (9.1,NE)	1.1693 (0.6907,1.9798) [0.5562]	0.9171
	Yes	195	77 (39.5)	NE (14.9,NE)	189	55 (29.1)	17.1 (13.4,NE)	1.1912 (0.8406,1.6882) [0.3296]	
Baseline CNS Metastases	No	218	96 (44.0)	19.8 (9.1,NE)	224	71 (31.7)	NE (13.8,NE)	1.2933 (0.9507,1.7594) [0.1016]	0.2166
	Yes	43	11 (25.6)	NE (16.5,NE)	39	10 (25.6)	NE (6.6,NE)	0.6158 (0.2501,1.5158) [0.2871]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Systemic Therapy Side Effects									
History of CNS Metastases	No	199	91 (45.7)	19.8 (6.2,NE)	211	69 (32.7)	NE (13.4,NE)	1.3064 (0.9544,1.7882) [0.0949]	0.3338
	Yes	62	16 (25.8)	NE (16.5,NE)	52	12 (23.1)	NE (NE,NE)	0.7999 (0.3709,1.7251) [0.5657]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Breast Symptoms									
Age	<65	212	45 (21.2)	NE (NE,NE)	206	40 (19.4)	NE (NE,NE)	0.8201 (0.5338,1.2601) [0.3663]	0.6667
	>=65	49	11 (22.4)	NE (16.5,NE)	57	12 (21.1)	NE (12.7,NE)	0.9741 (0.4290,2.2114) [0.9479]	
Age	<75	253	53 (20.9)	NE (NE,NE)	255	52 (20.4)	NE (NE,NE)	0.7883 (0.5361,1.1591) [0.2257]	0.0148
	>=75	8	3 (37.5)	9.9 (2.9,NE)	8	0 (0.0)	NE (NE,NE)	NE	
Region	Asia	149	34 (22.8)	NE (NE,NE)	160	31 (19.4)	NE (15.7,NE)	0.8648 (0.5284,1.4154) [0.5631]	0.6398
	Europe	54	10 (18.5)	NE (NE,NE)	50	8 (16.0)	NE (13.1,NE)	0.9537 (0.3752,2.4242) [0.9208]	
	North America	17	4 (23.5)	NE (10.2,NE)	17	2 (11.8)	NE (NE,NE)	1.4850 (0.2681,8.2246) [0.6486]	
	Rest of World	41	8 (19.5)	NE (NE,NE)	36	11 (30.6)	NE (7.2,NE)	0.5600 (0.2250,1.3941) [0.2041]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Breast Symptoms									
Race	Asian	152	34 (22.4)	NE (NE,NE)	162	31 (19.1)	NE (15.7,NE)	0.8677 (0.5302,1.4201) [0.5720]	0.9123
	Black Or African American	10	3 (30.0)	NE (2.8,NE)	9	2 (22.2)	NE (2.8,NE)	1.2512 (0.2090,7.4921) [0.8057]	
	Other	28	5 (17.9)	NE (NE,NE)	20	5 (25.0)	NE (9.8,NE)	0.5795 (0.1643,2.0436) [0.3908]	
	White	71	14 (19.7)	NE (NE,NE)	72	14 (19.4)	NE (NE,NE)	0.8189 (0.3897,1.7209) [0.5972]	
ECOG PS	0	154	30 (19.5)	NE (NE,NE)	175	33 (18.9)	NE (NE,NE)	0.7757 (0.4709,1.2777) [0.3180]	0.7543
	1	106	26 (24.5)	NE (NE,NE)	87	19 (21.8)	NE (15.7,NE)	0.8970 (0.4950,1.6254) [0.7223]	
Hormone Receptor Status	Negative	126	22 (17.5)	NE (NE,NE)	122	23 (18.9)	NE (NE,NE)	0.7538 (0.4190,1.3560) [0.3438]	0.4676
	Positive	133	34 (25.6)	NE (NE,NE)	139	28 (20.1)	NE (15.7,NE)	0.9562 (0.5772,1.5842) [0.8634]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Breast Symptoms									
Estrogen Receptors	Negative	130	24 (18.5)	NE (NE,NE)	128	24 (18.8)	NE (NE,NE)	0.7918 (0.4486,1.3978) [0.4201]	0.5818
	Positive	129	32 (24.8)	NE (NE,NE)	132	26 (19.7)	NE (15.7,NE)	0.9592 (0.5688,1.6177) [0.8763]	
Progesterone Receptors	Negative	177	34 (19.2)	NE (NE,NE)	168	32 (19.0)	NE (NE,NE)	0.8037 (0.4942,1.3070) [0.3769]	0.5368
	Positive	81	22 (27.2)	NE (NE,NE)	92	19 (20.7)	NE (13.1,NE)	0.9907 (0.5337,1.8389) [0.9784]	
Prior Treatment with Pertuzumab	No	99	17 (17.2)	NE (NE,NE)	105	25 (23.8)	NE (NE,NE)	0.5521 (0.2969,1.0268) [0.0573]	0.0714
	Yes	162	39 (24.1)	NE (NE,NE)	158	27 (17.1)	NE (NE,NE)	1.1049 (0.6738,1.8116) [0.6921]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Breast Symptoms									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	40 (21.3)	NE (NE,NE)	191	38 (19.9)	NE (NE,NE)	0.8282 (0.5298,1.2947) [0.4081]	0.8494
	>= 3	73	16 (21.9)	NE (NE,NE)	72	14 (19.4)	NE (15.7,NE)	0.8830 (0.4275,1.8240) [0.7366]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	38 (24.4)	NE (NE,NE)	152	26 (17.1)	NE (NE,NE)	1.1507 (0.6965,1.9012) [0.5828]	0.6550
	>= 3	6	1 (16.7)	NE (16.5,NE)	6	1 (16.7)	15.7 (NE,NE)	0.0000 (0.0000,.) [0.1573]	
Renal Impairment at Baseline	Mild	92	26 (28.3)	NE (NE,NE)	104	25 (24.0)	NE (NE,NE)	1.0662 (0.6151,1.8483) [0.8173]	0.4472
	Moderate	30	5 (16.7)	NE (16.5,NE)	22	2 (9.1)	NE (9.1,NE)	1.1100 (0.2141,5.7563) [0.9010]	
	Normal	130	24 (18.5)	NE (NE,NE)	130	25 (19.2)	NE (15.7,NE)	0.6880 (0.3900,1.2138) [0.1943]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Breast Symptoms									
Hepatic Impairment	Mild	49	12 (24.5)	NE (NE,NE)	49	13 (26.5)	15.7 (7.0,NE)	0.6167 (0.2788,1.3640) [0.2293]	0.3616
	Normal	208	44 (21.2)	NE (NE,NE)	212	39 (18.4)	NE (NE,NE)	0.9044 (0.5858,1.3961) [0.6516]	
Baseline Visceral Disease	No	66	11 (16.7)	NE (NE,NE)	74	15 (20.3)	NE (13.8,NE)	0.5764 (0.2625,1.2657) [0.1651]	0.4135
	Yes	195	45 (23.1)	NE (NE,NE)	189	37 (19.6)	NE (NE,NE)	0.9362 (0.6043,1.4504) [0.7679]	
Baseline CNS Metastases	No	218	46 (21.1)	NE (NE,NE)	224	44 (19.6)	NE (NE,NE)	0.8340 (0.5503,1.2641) [0.3924]	0.9622
	Yes	43	10 (23.3)	NE (NE,NE)	39	8 (20.5)	NE (8.3,NE)	0.9095 (0.3563,2.3218) [0.8456]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Breast Symptoms									
History of CNS Metastases	No	199	44 (22.1)	NE (NE,NE)	211	44 (20.9)	NE (NE,NE)	0.8146 (0.5349,1.2404) [0.3384]	0.7652
	Yes	62	12 (19.4)	NE (NE,NE)	52	8 (15.4)	NE (NE,NE)	1.0398 (0.4228,2.5571) [0.9301]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Arm Symptoms									
Age	<65	212	63 (29.7)	NE (NE,NE)	206	72 (35.0)	18.2 (9.3,NE)	0.5899 (0.4187,0.8310) [0.0022]	0.4687
	>=65	49	12 (24.5)	19.7 (15.4,NE)	57	15 (26.3)	NE (11.3,NE)	0.8124 (0.3796,1.7384) [0.5915]	
Age	<75	253	73 (28.9)	NE (19.7,NE)	255	86 (33.7)	18.2 (11.3,NE)	0.6128 (0.4472,0.8397) [0.0021]	0.2520
	>=75	8	2 (25.0)	NE (2.9,NE)	8	1 (12.5)	NE (4.7,NE)	2.4438 (0.2200,27.1496) [0.4524]	
Region	Asia	149	51 (34.2)	NE (18.7,NE)	160	56 (35.0)	23.7 (9.3,NE)	0.7025 (0.4789,1.0306) [0.0689]	0.1837
	Europe	54	9 (16.7)	NE (NE,NE)	50	13 (26.0)	NE (11.3,NE)	0.4886 (0.2078,1.1487) [0.0933]	
	North America	17	6 (35.3)	16.8 (3.1,NE)	17	3 (17.6)	NE (8.4,NE)	1.8038 (0.4479,7.2650) [0.3999]	
	Rest of World	41	9 (22.0)	NE (NE,NE)	36	15 (41.7)	18.2 (5.6,NE)	0.3488 (0.1502,0.8099) [0.0103]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Arm Symptoms									
Race	Asian	152	52 (34.2)	NE (18.7,NE)	162	58 (35.8)	16.6 (8.5,NE)	0.6920 (0.4742,1.0099) [0.0545]	0.2924
	Black Or African American	10	6 (60.0)	10.7 (1.4,NE)	9	3 (33.3)	NE (2.8,NE)	1.6284 (0.4063,6.5263) [0.4869]	
	Other	28	4 (14.3)	NE (NE,NE)	20	6 (30.0)	NE (5.4,NE)	0.3117 (0.0867,1.1209) [0.0599]	
	White	71	13 (18.3)	NE (NE,NE)	72	20 (27.8)	18.2 (18.2,NE)	0.4924 (0.2431,0.9974) [0.0445]	
ECOG PS	0	154	39 (25.3)	NE (19.7,NE)	175	58 (33.1)	23.7 (16.6,NE)	0.5235 (0.3469,0.7901) [0.0017]	0.2443
	1	106	36 (34.0)	NE (15.3,NE)	87	29 (33.3)	NE (8.4,NE)	0.7968 (0.4878,1.3015) [0.3603]	
Hormone Receptor Status	Negative	126	37 (29.4)	NE (NE,NE)	122	37 (30.3)	18.2 (16.6,NE)	0.7369 (0.4655,1.1664) [0.1876]	0.5169
	Positive	133	38 (28.6)	NE (18.7,NE)	139	50 (36.0)	23.7 (9.3,NE)	0.5686 (0.3713,0.8707) [0.0085]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Arm Symptoms									
Estrogen Receptors	Negative	130	38 (29.2)	NE (NE,NE)	128	39 (30.5)	18.2 (16.6,NE)	0.7188 (0.4581,1.1278) [0.1465]	0.5401
	Positive	129	37 (28.7)	NE (18.7,NE)	132	48 (36.4)	23.7 (8.4,NE)	0.5650 (0.3663,0.8716) [0.0089]	
Progesterone Receptors	Negative	177	55 (31.1)	NE (19.7,NE)	168	57 (33.9)	18.2 (10.2,NE)	0.6648 (0.4569,0.9673) [0.0311]	0.5978
	Positive	81	20 (24.7)	NE (16.8,NE)	92	30 (32.6)	23.7 (9.3,NE)	0.5581 (0.3152,0.9882) [0.0425]	
Prior Treatment with Pertuzumab	No	99	25 (25.3)	NE (18.7,NE)	105	29 (27.6)	23.7 (16.6,NE)	0.7018 (0.4096,1.2024) [0.1939]	0.5041
	Yes	162	50 (30.9)	NE (19.7,NE)	158	58 (36.7)	18.2 (8.4,NE)	0.5928 (0.4040,0.8697) [0.0068]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Arm Symptoms									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	52 (27.7)	NE (NE,NE)	191	70 (36.6)	18.2 (8.5,NE)	0.5171 (0.3598,0.7431) [0.0003]	0.0371
	>= 3	73	23 (31.5)	NE (19.7,NE)	72	17 (23.6)	NE (NE,NE)	1.1362 (0.6037,2.1384) [0.6965]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	49 (31.4)	NE (19.7,NE)	152	58 (38.2)	18.2 (7.9,NE)	0.5799 (0.3943,0.8528) [0.0050]	0.1960
	>= 3	6	1 (16.7)	NE (9.9,NE)	6	0 (0.0)	NE (NE,NE)	NE	
Renal Impairment at Baseline	Mild	92	26 (28.3)	NE (15.3,NE)	104	35 (33.7)	18.2 (9.3,NE)	0.6482 (0.3888,1.0806) [0.0936]	0.8644
	Moderate	30	9 (30.0)	19.7 (9.9,NE)	22	8 (36.4)	16.6 (3.9,NE)	0.6396 (0.2460,1.6625) [0.3527]	
	Normal	130	39 (30.0)	NE (NE,NE)	130	43 (33.1)	NE (8.4,NE)	0.6266 (0.4034,0.9735) [0.0360]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Arm Symptoms									
Hepatic Impairment	Mild	49	12 (24.5)	NE (NE,NE)	49	16 (32.7)	23.7 (8.4,NE)	0.4749 (0.2227,1.0127) [0.0492]	0.3854
	Normal	208	63 (30.3)	NE (19.7,NE)	212	71 (33.5)	18.2 (16.6,NE)	0.6697 (0.4752,0.9437) [0.0209]	
Baseline Visceral Disease	No	66	19 (28.8)	NE (NE,NE)	74	24 (32.4)	NE (11.3,NE)	0.6812 (0.3721,1.2472) [0.2107]	0.9021
	Yes	195	56 (28.7)	NE (18.7,NE)	189	63 (33.3)	18.2 (9.3,NE)	0.6141 (0.4266,0.8842) [0.0081]	
Baseline CNS Metastases	No	218	61 (28.0)	NE (19.7,NE)	224	72 (32.1)	23.7 (16.6,NE)	0.6350 (0.4502,0.8958) [0.0090]	0.8301
	Yes	43	14 (32.6)	NE (9.7,NE)	39	15 (38.5)	18.2 (6.2,NE)	0.5990 (0.2855,1.2565) [0.1682]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Arm Symptoms									
History of CNS Metastases	No	199	59 (29.6)	NE (19.7,NE)	211	64 (30.3)	23.7 (16.6,NE)	0.7050 (0.4934,1.0072) [0.0533]	0.1395
	Yes	62	16 (25.8)	NE (NE,NE)	52	23 (44.2)	8.4 (6.2,NE)	0.4290 (0.2243,0.8203) [0.0084]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Upset by Hair Loss									
Age	<65	212	21 (9.9)	21.2 (3.1,NE)	206	8 (3.9)	NE (8.2,NE)	1.6170 (0.7108,3.6785) [0.2512]	0.3929
	>=65	49	5 (10.2)	NE (1.4,NE)	57	1 (1.8)	21.7 (NE,NE)	4.1374 (0.4814,35.5618) [0.1614]	
Age	<75	253	25 (9.9)	21.2 (4.1,NE)	255	9 (3.5)	21.7 (NE,NE)	1.8245 (0.8482,3.9247) [0.1209]	NE
	>=75	8	1 (12.5)	1.4 (NE,NE)	8	0 (0.0)	NE (NE,NE)	NE	
Region	Asia	149	17 (11.4)	21.2 (1.5,NE)	160	3 (1.9)	21.7 (NE,NE)	4.7858 (1.3928,16.4439) [0.0062]	0.0550
	Europe	54	3 (5.6)	11.1 (2.8,NE)	50	3 (6.0)	4.8 (0.8,NE)	0.5634 (0.1126,2.8194) [0.4792]	
	North America	17	2 (11.8)	NE (0.9,NE)	17	1 (5.9)	4.1 (NE,NE)	0.2658 (0.0239,2.9543) [0.2468]	
	Rest of World	41	4 (9.8)	NE (1.4,NE)	36	2 (5.6)	NE (5.8,NE)	1.0939 (0.1997,5.9928) [0.9308]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Upset by Hair Loss									
Race	Asian	152	17 (11.2)	21.2 (2.0,NE)	162	4 (2.5)	21.7 (NE,NE)	3.5788 (1.1951,10.7171) [0.0154]	0.1197
	Black Or African American	10	0 (0.0)	NE (NE,NE)	9	0 (0.0)	NE (NE,NE)	NE	
	Other	28	3 (10.7)	11.1 (2.8,NE)	20	1 (5.0)	NE (1.4,NE)	0.4524 (0.0401,5.1100) [0.5109]	
	White	71	6 (8.5)	NE (1.4,NE)	72	4 (5.6)	8.2 (0.8,NE)	0.6947 (0.1952,2.4729) [0.5440]	
ECOG PS	0	154	14 (9.1)	21.2 (8.2,NE)	175	5 (2.9)	21.7 (NE,NE)	1.8663 (0.6681,5.2131) [0.2276]	0.9474
	1	106	12 (11.3)	NE (1.4,NE)	87	4 (4.6)	NE (1.5,NE)	1.9289 (0.6206,5.9951) [0.2653]	
Hormone Receptor Status	Negative	126	15 (11.9)	4.1 (1.5,NE)	122	6 (4.9)	NE (1.4,NE)	1.5556 (0.6016,4.0225) [0.3677]	0.5827
	Positive	133	11 (8.3)	NE (11.1,NE)	139	3 (2.2)	21.7 (NE,NE)	2.3817 (0.6557,8.6515) [0.1759]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Upset by Hair Loss									
Estrogen Receptors	Negative	130	16 (12.3)	8.2 (1.5,NE)	128	6 (4.7)	NE (4.1,NE)	1.7370 (0.6778,4.4513) [0.2504]	0.8371
	Positive	129	10 (7.8)	NE (21.2,NE)	132	3 (2.3)	21.7 (NE,NE)	2.1203 (0.5761,7.8042) [0.2499]	
Progesterone Receptors	Negative	177	16 (9.0)	NE (2.8,NE)	168	8 (4.8)	NE (5.8,NE)	1.1355 (0.4856,2.6553) [0.7841]	0.0210
	Positive	81	10 (12.3)	21.2 (1.4,NE)	92	1 (1.1)	21.7 (NE,NE)	9.2690 (1.1809,72.7555) [0.0102]	
Prior Treatment with Pertuzumab	No	99	13 (13.1)	NE (2.1,NE)	105	1 (1.0)	NE (NE,NE)	6.6591 (0.8704,50.9481) [0.0347]	0.1423
	Yes	162	13 (8.0)	21.2 (3.1,NE)	158	8 (5.1)	21.7 (7.9,NE)	1.3183 (0.5436,3.1971) [0.5445]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Upset by Hair Loss									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	16 (8.5)	21.2 (8.2,NE)	191	7 (3.7)	21.7 (NE,NE)	1.3952 (0.5715,3.4056) [0.4718]	0.2728
	>= 3	73	10 (13.7)	NE (1.4,NE)	72	2 (2.8)	NE (5.8,NE)	3.8866 (0.8490,17.7924) [0.0598]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	13 (8.3)	21.2 (2.8,NE)	152	8 (5.3)	21.7 (7.9,NE)	1.5065 (0.6229,3.6436) [0.3633]	NE
	>= 3	6	0 (0.0)	NE (NE,NE)	6	0 (0.0)	NE (NE,NE)	NE	
Renal Impairment at Baseline	Mild	92	9 (9.8)	NE (1.4,NE)	104	6 (5.8)	21.7 (8.2,NE)	1.6128 (0.5733,4.5368) [0.3670]	0.6192
	Moderate	30	4 (13.3)	11.1 (0.9,NE)	22	0 (0.0)	NE (NE,NE)	NE	
	Normal	130	12 (9.2)	21.2 (2.0,NE)	130	3 (2.3)	NE (7.9,NE)	2.5591 (0.7127,9.1893) [0.1369]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Upset by Hair Loss									
Hepatic Impairment	Mild	49	8 (16.3)	NE (2.0,NE)	49	1 (2.0)	NE (4.1,NE)	2.9478 (0.3674,23.6524) [0.2858]	0.7444
	Normal	208	18 (8.7)	21.2 (4.1,NE)	212	8 (3.8)	21.7 (NE,NE)	1.6996 (0.7338,3.9367) [0.2186]	
Baseline Visceral Disease	No	66	2 (3.0)	NE (0.9,NE)	74	4 (5.4)	8.2 (1.4,NE)	0.4999 (0.0901,2.7728) [0.4130]	0.0823
	Yes	195	24 (12.3)	21.2 (2.8,NE)	189	5 (2.6)	21.7 (NE,NE)	2.8171 (1.0710,7.4101) [0.0291]	
Baseline CNS Metastases	No	218	20 (9.2)	NE (4.1,NE)	224	8 (3.6)	21.7 (8.2,NE)	1.6168 (0.7101,3.6813) [0.2524]	0.3360
	Yes	43	6 (14.0)	12.2 (0.8,NE)	39	1 (2.6)	NE (0.8,NE)	3.7922 (0.4411,32.5992) [0.1940]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Upset by Hair Loss									
History of CNS Metastases	No	199	21 (10.6)	21.2 (2.8,NE)	211	8 (3.8)	21.7 (8.2,NE)	1.6890 (0.7445,3.8316) [0.2069]	0.5177
	Yes	62	5 (8.1)	NE (1.4,NE)	52	1 (1.9)	NE (0.8,NE)	3.3458 (0.3902,28.6892) [0.2486]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Body Image									
Age	<65	212	103 (48.6)	14.5 (7.2,21.0)	206	63 (30.6)	NE (11.7,NE)	1.4551 (1.0616,1.9944) [0.0196]	0.4194
	>=65	49	18 (36.7)	17.6 (10.7,NE)	57	18 (31.6)	NE (10.4,NE)	1.0277 (0.5335,1.9796) [0.9366]	
Age	<75	253	118 (46.6)	17.3 (9.7,21.0)	255	79 (31.0)	NE (13.6,NE)	1.3705 (1.0296,1.8243) [0.0310]	0.7276
	>=75	8	3 (37.5)	11.5 (0.8,NE)	8	2 (25.0)	12.4 (10.3,NE)	1.3050 (0.2129,7.9997) [0.7729]	
Region	Asia	149	69 (46.3)	17.3 (9.0,NE)	160	46 (28.8)	NE (13.6,NE)	1.4800 (1.0166,2.1547) [0.0405]	0.6179
	Europe	54	24 (44.4)	19.4 (5.6,NE)	50	13 (26.0)	NE (10.3,NE)	1.4577 (0.7376,2.8806) [0.2723]	
	North America	17	6 (35.3)	21.0 (3.1,NE)	17	3 (17.6)	NE (NE,NE)	1.2953 (0.3063,5.4771) [0.7244]	
	Rest of World	41	22 (53.7)	6.9 (2.8,NE)	36	19 (52.8)	7.1 (3.5,NE)	0.9305 (0.5034,1.7197) [0.8013]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Body Image									
Race	Asian	152	70 (46.1)	17.3 (9.0,NE)	162	47 (29.0)	NE (13.6,NE)	1.4709 (1.0138,2.1341) [0.0421]	0.4130
	Black Or African American	10	7 (70.0)	5.0 (1.4,NE)	9	2 (22.2)	NE (1.5,NE)	3.4635 (0.7169,16.7320) [0.0974]	
	Other	28	11 (39.3)	19.4 (4.2,NE)	20	5 (25.0)	NE (3.5,NE)	1.2731 (0.4368,3.7100) [0.6590]	
	White	71	33 (46.5)	11.6 (5.6,NE)	72	27 (37.5)	12.4 (7.0,NE)	1.0573 (0.6353,1.7596) [0.8353]	
ECOG PS	0	154	74 (48.1)	17.3 (8.6,20.2)	175	54 (30.9)	NE (11.7,NE)	1.4193 (0.9979,2.0186) [0.0510]	0.6682
	1	106	47 (44.3)	14.9 (6.2,NE)	87	27 (31.0)	NE (11.7,NE)	1.2910 (0.8025,2.0769) [0.2956]	
Hormone Receptor Status	Negative	126	64 (50.8)	9.7 (5.6,NE)	122	33 (27.0)	NE (13.6,NE)	1.9428 (1.2753,2.9597) [0.0017]	0.0355
	Positive	133	57 (42.9)	17.6 (12.8,NE)	139	47 (33.8)	14.1 (10.7,NE)	1.0403 (0.7053,1.5344) [0.8450]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Body Image									
Estrogen Receptors	Negative	130	66 (50.8)	9.7 (5.6,NE)	128	36 (28.1)	NE (13.6,NE)	1.8710 (1.2453,2.8109) [0.0023]	0.0451
	Positive	129	55 (42.6)	17.6 (13.6,NE)	132	44 (33.3)	NE (10.7,NE)	1.0283 (0.6898,1.5328) [0.8930]	
Progesterone Receptors	Negative	177	83 (46.9)	17.3 (7.6,NE)	168	49 (29.2)	NE (14.1,NE)	1.5371 (1.0786,2.1905) [0.0169]	0.4436
	Positive	81	38 (46.9)	14.9 (7.2,NE)	92	31 (33.7)	11.7 (10.3,NE)	1.1710 (0.7265,1.8877) [0.5205]	
Prior Treatment with Pertuzumab	No	99	38 (38.4)	17.3 (13.6,NE)	105	41 (39.0)	12.4 (7.1,NE)	0.8490 (0.5445,1.3238) [0.4574]	0.0065
	Yes	162	83 (51.2)	11.6 (6.9,20.2)	158	40 (25.3)	NE (13.6,NE)	1.8818 (1.2877,2.7500) [0.0009]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Body Image									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	85 (45.2)	17.3 (10.7,NE)	191	59 (30.9)	NE (12.4,NE)	1.2944 (0.9272,1.8069) [0.1314]	0.5155
	>= 3	73	36 (49.3)	11.6 (4.2,20.2)	72	22 (30.6)	NE (9.0,NE)	1.6146 (0.9482,2.7493) [0.0763]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	79 (50.6)	12.8 (6.2,20.2)	152	39 (25.7)	NE (13.6,NE)	1.8636 (1.2671,2.7410) [0.0013]	0.8541
	>= 3	6	4 (66.7)	8.6 (1.4,NE)	6	1 (16.7)	NE (0.7,NE)	1.8365 (0.2009,16.7848) [0.5848]	
Renal Impairment at Baseline	Mild	92	45 (48.9)	11.6 (4.3,NE)	104	41 (39.4)	13.6 (10.4,NE)	1.2113 (0.7930,1.8503) [0.3811]	0.1566
	Moderate	30	14 (46.7)	14.5 (6.9,NE)	22	2 (9.1)	NE (10.3,NE)	4.5241 (1.0262,19.9448) [0.0287]	
	Normal	130	60 (46.2)	19.4 (9.0,NE)	130	37 (28.5)	NE (11.7,NE)	1.3784 (0.9097,2.0886) [0.1317]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Body Image									
Hepatic Impairment	Mild	49	21 (42.9)	20.2 (2.9,NE)	49	14 (28.6)	14.1 (7.0,NE)	1.2971 (0.6584,2.5556) [0.4553]	0.9175
	Normal	208	100 (48.1)	17.3 (9.0,21.0)	212	67 (31.6)	NE (12.4,NE)	1.3850 (1.0148,1.8903) [0.0402]	
Baseline Visceral Disease	No	66	32 (48.5)	20.2 (4.2,NE)	74	27 (36.5)	NE (10.5,NE)	1.2006 (0.7187,2.0058) [0.4901]	0.4775
	Yes	195	89 (45.6)	14.9 (11.5,21.0)	189	54 (28.6)	NE (11.7,NE)	1.4457 (1.0287,2.0317) [0.0336]	
Baseline CNS Metastases	No	218	102 (46.8)	17.3 (9.7,21.0)	224	69 (30.8)	NE (12.4,NE)	1.3888 (1.0219,1.8875) [0.0363]	0.8127
	Yes	43	19 (44.2)	19.4 (4.4,NE)	39	12 (30.8)	NE (4.8,NE)	1.2906 (0.6234,2.6719) [0.4872]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 44 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Body Image									
History of CNS Metastases	No	199	96 (48.2)	14.9 (7.6,21.0)	211	66 (31.3)	NE (11.7,NE)	1.4244 (1.0401,1.9509) [0.0277]	0.7051
	Yes	62	25 (40.3)	19.4 (9.0,NE)	52	15 (28.8)	14.1 (14.1,NE)	1.1864 (0.6202,2.2698) [0.6035]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 15 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 34 - Analysis of time to first deterioration of EQ-5D-5L-VAS by pre-specified Subgroup
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
EQ-5D-5L Score VAS									
Age	<65	212	109 (51.4)	12.5 (5.7,20.2)	206	101 (49.0)	8.5 (5.8,10.3)	0.8472 (0.6432,1.1158) [0.2368]	0.8884
	>=65	49	25 (51.0)	9.9 (2.9,NE)	57	31 (54.4)	6.6 (2.8,NE)	0.8347 (0.4922,1.4156) [0.5036]	
Age	<75	253	129 (51.0)	12.5 (6.1,18.2)	255	128 (50.2)	8.4 (5.6,9.9)	0.8316 (0.6492,1.0653) [0.1432]	0.3224
	>=75	8	5 (62.5)	3.8 (0.8,NE)	8	4 (50.0)	4.0 (1.4,NE)	1.5863 (0.4234,5.9426) [0.4665]	
Region	Asia	149	80 (53.7)	10.4 (5.3,20.2)	160	87 (54.4)	7.0 (4.8,9.8)	0.7431 (0.5451,1.0130) [0.0603]	0.1814
	Europe	54	24 (44.4)	15.1 (2.9,NE)	50	26 (52.0)	5.6 (2.9,11.2)	0.7482 (0.4265,1.3126) [0.3076]	
	North America	17	11 (64.7)	2.9 (1.4,NE)	17	7 (41.2)	14.7 (2.4,NE)	1.7656 (0.6831,4.5635) [0.2363]	
	Rest of World	41	19 (46.3)	18.2 (4.2,NE)	36	12 (33.3)	NE (8.4,NE)	1.2961 (0.6268,2.6801) [0.4874]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 34 - Analysis of time to first deterioration of EQ-5D-5L-VAS by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
EQ-5D-5L Score VAS									
Race	Asian	152	80 (52.6)	10.7 (5.6,24.6)	162	87 (53.7)	7.6 (4.8,9.8)	0.7470 (0.5480,1.0183) [0.0649]	0.1411
	Black Or African American	10	6 (60.0)	7.4 (1.4,NE)	9	2 (22.2)	NE (0.8,NE)	2.8695 (0.5766,14.2792) [0.1780]	
	Other	28	11 (39.3)	NE (2.8,NE)	20	11 (55.0)	8.3 (2.9,NE)	0.5751 (0.2435,1.3585) [0.2008]	
	White	71	37 (52.1)	8.5 (2.8,NE)	72	32 (44.4)	8.8 (4.2,NE)	1.1297 (0.7027,1.8162) [0.6246]	
ECOG PS	0	154	87 (56.5)	9.4 (4.2,14.1)	175	89 (50.9)	8.4 (5.5,9.8)	0.9719 (0.7210,1.3102) [0.8397]	0.1565
	1	106	47 (44.3)	20.2 (7.4,NE)	87	43 (49.4)	9.8 (4.2,14.4)	0.6883 (0.4519,1.0485) [0.0854]	
Hormone Receptor Status	Negative	126	68 (54.0)	9.4 (4.3,12.7)	122	54 (44.3)	9.8 (6.6,NE)	1.0553 (0.7361,1.5128) [0.7681]	0.0798
	Positive	133	65 (48.9)	15.0 (5.3,NE)	139	77 (55.4)	6.7 (4.2,9.8)	0.6878 (0.4906,0.9644) [0.0290]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 34 - Analysis of time to first deterioration of EQ-5D-5L-VAS by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
EQ-5D-5L Score VAS									
Estrogen Receptors	Negative	130	71 (54.6)	9.3 (4.2,12.5)	128	56 (43.8)	11.2 (6.6,NE)	1.1104 (0.7803,1.5803) [0.5604]	0.0231
	Positive	129	62 (48.1)	15.1 (5.8,NE)	132	75 (56.8)	6.0 (4.2,9.7)	0.6230 (0.4399,0.8823) [0.0072]	
Progesterone Receptors	Negative	177	90 (50.8)	10.7 (5.6,NE)	168	83 (49.4)	8.4 (5.4,14.3)	0.8480 (0.6274,1.1460) [0.2888]	0.9041
	Positive	81	42 (51.9)	14.1 (4.4,20.2)	92	48 (52.2)	8.4 (4.2,10.3)	0.8143 (0.5341,1.2417) [0.3350]	
Prior Treatment with Pertuzumab	No	99	47 (47.5)	12.5 (5.8,NE)	105	50 (47.6)	8.5 (5.6,14.4)	0.8507 (0.5694,1.2712) [0.4282]	0.9805
	Yes	162	87 (53.7)	10.7 (4.4,20.2)	158	82 (51.9)	8.3 (4.5,12.4)	0.8490 (0.6252,1.1531) [0.2921]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 34 - Analysis of time to first deterioration of EQ-5D-5L-VAS by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
EQ-5D-5L Score VAS									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	96 (51.1)	12.5 (5.3,24.6)	191	101 (52.9)	8.3 (4.2,9.9)	0.7828 (0.5900,1.0385) [0.0888]	0.2241
	>= 3	73	38 (52.1)	8.5 (4.2,NE)	72	31 (43.1)	9.7 (6.0,NE)	1.0667 (0.6591,1.7265) [0.7944]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	84 (53.8)	10.4 (4.4,20.2)	152	80 (52.6)	8.3 (4.6,11.2)	0.8503 (0.6234,1.1598) [0.3044]	0.9002
	>= 3	6	3 (50.0)	15.0 (1.4,NE)	6	2 (33.3)	NE (3.3,NE)	0.7952 (0.1114,5.6750) [0.8188]	
Renal Impairment at Baseline	Mild	92	49 (53.3)	5.8 (4.2,NE)	104	57 (54.8)	8.4 (4.4,10.3)	0.9519 (0.6493,1.3956) [0.7959]	0.6981
	Moderate	30	17 (56.7)	9.4 (2.8,NE)	22	13 (59.1)	2.8 (1.4,NE)	0.6589 (0.3180,1.3650) [0.2673]	
	Normal	130	67 (51.5)	13.6 (7.4,24.6)	130	61 (46.9)	8.5 (5.4,14.3)	0.7712 (0.5386,1.1043) [0.1536]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 34 - Analysis of time to first deterioration of EQ-5D-5L-VAS by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
EQ-5D-5L Score VAS									
Hepatic Impairment	Mild	49	21 (42.9)	14.7 (5.6,NE)	49	23 (46.9)	8.3 (2.9,9.9)	0.6698 (0.3688,1.2165) [0.1887]	0.3689
	Normal	208	113 (54.3)	10.7 (4.6,18.2)	212	109 (51.4)	8.4 (5.4,12.4)	0.8941 (0.6849,1.1672) [0.4080]	
Baseline Visceral Disease	No	66	36 (54.5)	10.7 (4.2,NE)	74	39 (52.7)	7.0 (2.9,14.3)	0.7968 (0.5037,1.2603) [0.3340]	0.6843
	Yes	195	98 (50.3)	12.5 (5.3,24.6)	189	93 (49.2)	8.4 (5.3,11.2)	0.8711 (0.6535,1.1610) [0.3455]	
Baseline CNS Metastases	No	218	114 (52.3)	12.1 (5.8,18.2)	224	113 (50.4)	8.4 (5.3,9.9)	0.8590 (0.6601,1.1178) [0.2579]	0.7694
	Yes	43	20 (46.5)	10.4 (4.2,NE)	39	19 (48.7)	9.8 (4.2,14.4)	0.7998 (0.4237,1.5095) [0.4904]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 34 - Analysis of time to first deterioration of EQ-5D-5L-VAS by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
EQ-5D-5L Score VAS									
History of CNS Metastases	No	199	104 (52.3)	12.5 (5.7,18.2)	211	105 (49.8)	8.4 (5.1,11.2)	0.8527 (0.6479,1.1221) [0.2575]	0.9019
	Yes	62	30 (48.4)	10.4 (4.2,NE)	52	27 (51.9)	8.3 (4.2,14.4)	0.8410 (0.4972,1.4223) [0.5113]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Global Health Status									
Age	<65	212	114 (53.8)	9.7 (4.4,14.5)	206	98 (47.6)	8.4 (6.1,11.3)	1.0195 (0.7766,1.3383) [0.9029]	0.9626
	>=65	49	32 (65.3)	4.4 (2.1,8.5)	57	37 (64.9)	7.0 (2.8,9.0)	1.0489 (0.6489,1.6954) [0.8503]	
Age	<75	253	141 (55.7)	7.3 (4.4,11.3)	255	129 (50.6)	7.6 (6.3,10.6)	1.0019 (0.7879,1.2741) [0.9932]	0.5033
	>=75	8	5 (62.5)	3.9 (0.8,NE)	8	6 (75.0)	1.4 (0.9,4.8)	0.5937 (0.1751,2.0129) [0.4094]	
Region	Asia	149	86 (57.7)	7.3 (4.7,10.4)	160	95 (59.4)	6.9 (4.4,8.4)	0.7804 (0.5804,1.0494) [0.0952]	0.0651
	Europe	54	29 (53.7)	3.6 (1.5,NE)	50	19 (38.0)	NE (4.2,NE)	1.5781 (0.8836,2.8185) [0.1203]	
	North America	17	10 (58.8)	3.1 (0.9,NE)	17	5 (29.4)	NE (1.9,NE)	2.2629 (0.7724,6.6290) [0.1215]	
	Rest of World	41	21 (51.2)	11.7 (3.0,NE)	36	16 (44.4)	7.2 (4.8,NE)	1.1207 (0.5839,2.1509) [0.7297]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Global Health Status									
Race	Asian	152	87 (57.2)	7.3 (4.7,10.4)	162	96 (59.3)	6.5 (4.5,8.4)	0.7842 (0.5842,1.0527) [0.0998]	0.0920
	Black Or African American	10	5 (50.0)	13.8 (1.6,NE)	9	2 (22.2)	NE (4.2,NE)	2.4660 (0.4746,12.8129) [0.2673]	
	Other	28	15 (53.6)	9.9 (1.5,NE)	20	6 (30.0)	NE (2.9,NE)	1.7427 (0.6729,4.5133) [0.2535]	
	White	71	39 (54.9)	3.7 (2.1,14.8)	72	31 (43.1)	11.1 (4.8,NE)	1.3902 (0.8671,2.2291) [0.1683]	
ECOG PS	0	154	98 (63.6)	4.7 (2.9,9.4)	175	89 (50.9)	7.6 (5.6,11.6)	1.1997 (0.8986,1.6017) [0.2227]	0.0341
	1	106	48 (45.3)	NE (5.5,NE)	87	46 (52.9)	7.0 (4.8,10.3)	0.7288 (0.4854,1.0943) [0.1212]	
Hormone Receptor Status	Negative	126	75 (59.5)	7.3 (4.4,9.9)	122	59 (48.4)	8.3 (6.3,12.3)	1.0972 (0.7789,1.5457) [0.6061]	0.3543
	Positive	133	71 (53.4)	5.7 (3.1,NE)	139	75 (54.0)	7.0 (4.8,10.6)	0.9332 (0.6732,1.2937) [0.6702]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Global Health Status									
Estrogen Receptors	Negative	130	77 (59.2)	7.3 (4.4,9.9)	128	63 (49.2)	7.6 (6.1,11.3)	1.0816 (0.7740,1.5114) [0.6613]	0.3635
	Positive	129	69 (53.5)	5.7 (3.1,NE)	132	71 (53.8)	7.1 (4.5,10.6)	0.9236 (0.6615,1.2895) [0.6342]	
Progesterone Receptors	Negative	177	106 (59.9)	6.1 (3.4,9.7)	168	86 (51.2)	7.6 (6.1,11.3)	1.0885 (0.8175,1.4494) [0.5725]	0.2534
	Positive	81	39 (48.1)	14.7 (3.6,NE)	92	47 (51.1)	7.2 (4.2,11.1)	0.8433 (0.5502,1.2923) [0.4311]	
Prior Treatment with Pertuzumab	No	99	50 (50.5)	9.8 (5.6,NE)	105	56 (53.3)	6.9 (4.2,7.3)	0.7628 (0.5181,1.1231) [0.1597]	0.1144
	Yes	162	96 (59.3)	5.7 (3.0,9.7)	158	79 (50.0)	10.0 (6.1,12.3)	1.1513 (0.8537,1.5527) [0.3631]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Global Health Status									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	107 (56.9)	6.0 (3.0,11.7)	191	101 (52.9)	7.0 (5.1,10.3)	0.9578 (0.7281,1.2599) [0.7433]	0.5744
	>= 3	73	39 (53.4)	7.3 (4.4,NE)	72	34 (47.2)	9.0 (6.1,17.1)	1.1002 (0.6927,1.7473) [0.6888]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	92 (59.0)	5.7 (3.0,9.8)	152	76 (50.0)	10.0 (6.1,12.3)	1.1529 (0.8495,1.5647) [0.3673]	0.9708
	>= 3	6	4 (66.7)	5.7 (0.8,NE)	6	3 (50.0)	10.8 (0.8,NE)	1.5861 (0.2885,8.7190) [0.5925]	
Renal Impairment at Baseline	Mild	92	52 (56.5)	6.8 (2.9,11.7)	104	62 (59.6)	7.0 (4.8,11.1)	0.9676 (0.6686,1.4004) [0.8392]	0.3368
	Moderate	30	17 (56.7)	8.5 (2.1,NE)	22	13 (59.1)	2.0 (1.4,7.0)	0.5855 (0.2821,1.2150) [0.1466]	
	Normal	130	75 (57.7)	6.2 (3.1,14.7)	130	59 (45.4)	8.5 (6.1,17.1)	1.1050 (0.7816,1.5622) [0.5819]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Global Health Status									
Hepatic Impairment	Mild	49	23 (46.9)	9.8 (5.3,NE)	49	19 (38.8)	9.0 (5.3,NE)	1.0069 (0.5469,1.8538) [0.9810]	0.9640
	Normal	208	123 (59.1)	5.7 (3.6,9.9)	212	116 (54.7)	7.1 (5.6,10.3)	0.9984 (0.7733,1.2890) [0.9746]	
Baseline Visceral Disease	No	66	41 (62.1)	4.2 (1.6,9.7)	74	41 (55.4)	5.6 (2.9,12.3)	1.0422 (0.6754,1.6081) [0.8586]	0.9836
	Yes	195	105 (53.8)	8.7 (5.3,14.5)	189	94 (49.7)	8.4 (6.5,10.6)	0.9773 (0.7381,1.2940) [0.8613]	
Baseline CNS Metastases	No	218	125 (57.3)	6.0 (4.2,9.9)	224	115 (51.3)	7.3 (5.6,10.6)	1.0357 (0.8031,1.3358) [0.7985]	0.4775
	Yes	43	21 (48.8)	10.4 (3.0,NE)	39	20 (51.3)	7.0 (4.5,11.6)	0.7332 (0.3906,1.3763) [0.3271]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Global Health Status									
History of CNS Metastases	No	199	115 (57.8)	5.7 (3.7,9.8)	211	111 (52.6)	7.0 (5.3,10.3)	1.0023 (0.7713,1.3024) [0.9945]	0.9306
	Yes	62	31 (50.0)	10.4 (3.4,NE)	52	24 (46.2)	8.4 (6.1,11.6)	0.9269 (0.5373,1.5991) [0.7675]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup			T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Functioning	Scales/Physical									
Age		<65	212	88 (41.5)	NE (14.5,NE)	206	79 (38.3)	17.2 (7.9,NE)	0.8753 (0.6440,1.1897) [0.3936]	0.9881
		>=65	49	21 (42.9)	15.0 (5.6,NE)	57	25 (43.9)	10.4 (6.9,NE)	0.8534 (0.4758,1.5306) [0.5900]	
Age		<75	253	106 (41.9)	NE (14.5,NE)	255	101 (39.6)	17.2 (8.3,NE)	0.8694 (0.6606,1.1443) [0.3159]	0.8656
		>=75	8	3 (37.5)	14.3 (1.4,NE)	8	3 (37.5)	6.9 (0.9,NE)	0.7488 (0.1241,4.5198) [0.7517]	
Region		Asia	149	64 (43.0)	NE (13.2,NE)	160	60 (37.5)	12.0 (8.3,NE)	0.9054 (0.6330,1.2951) [0.5841]	0.0120
		Europe	54	17 (31.5)	NE (4.5,NE)	50	19 (38.0)	22.6 (3.1,NE)	0.7346 (0.3816,1.4139) [0.3537]	
		North America	17	10 (58.8)	3.1 (1.4,NE)	17	3 (17.6)	NE (6.9,NE)	3.7681 (1.0343,13.7283) [0.0308]	
		Rest of World	41	18 (43.9)	NE (5.8,NE)	36	22 (61.1)	4.8 (1.9,7.2)	0.4670 (0.2495,0.8740) [0.0148]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Physical Functioning									
Race	Asian	152	65 (42.8)	NE (13.2,NE)	162	61 (37.7)	12.0 (8.3,NE)	0.9053 (0.6348,1.2912) [0.5809]	0.3789
	Black Or African American	10	6 (60.0)	9.0 (2.7,NE)	9	3 (33.3)	NE (1.4,NE)	1.3052 (0.3255,5.2347) [0.7062]	
	Other	28	6 (21.4)	NE (NE,NE)	20	8 (40.0)	NE (2.9,NE)	0.3960 (0.1363,1.1508) [0.0789]	
	White	71	32 (45.1)	NE (4.2,NE)	72	32 (44.4)	7.2 (4.2,NE)	0.9246 (0.5662,1.5100) [0.7553]	
ECOG PS	0	154	66 (42.9)	NE (13.2,NE)	175	62 (35.4)	NE (9.1,NE)	1.0140 (0.7145,1.4390) [0.9372]	0.0908
	1	106	43 (40.6)	NE (10.8,NE)	87	42 (48.3)	7.6 (4.8,12.0)	0.6421 (0.4180,0.9861) [0.0400]	
Hormone Receptor Status	Negative	126	62 (49.2)	12.5 (5.6,NE)	122	48 (39.3)	17.2 (7.7,NE)	1.0958 (0.7499,1.6010) [0.6378]	0.0994
	Positive	133	47 (35.3)	NE (NE,NE)	139	55 (39.6)	10.4 (7.5,NE)	0.7019 (0.4739,1.0398) [0.0763]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	No. of Events (%)	Median (95% CI) [a] (months)	T-DM1 (N=263) n	No. of Events (%)	Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Physical Functioning									
Estrogen Receptors	Negative	130	63 (48.5)	12.5 (5.8,NE)	128	51 (39.8)	17.2 (7.1,NE)	1.0521 (0.7255,1.5258) [0.7912]	0.1476
	Positive	129	46 (35.7)	NE (NE,NE)	132	52 (39.4)	10.4 (7.5,NE)	0.7086 (0.4745,1.0580) [0.0909]	
Progesterone Receptors	Negative	177	76 (42.9)	NE (11.7,NE)	168	70 (41.7)	12.0 (7.5,NE)	0.8348 (0.6014,1.1589) [0.2786]	0.4920
	Positive	81	33 (40.7)	NE (7.9,NE)	92	32 (34.8)	22.6 (7.6,NE)	1.0292 (0.6313,1.6780) [0.9092]	
Prior Treatment with Pertuzumab	No	99	37 (37.4)	NE (11.3,NE)	105	45 (42.9)	9.9 (6.9,NE)	0.7344 (0.4743,1.1372) [0.1634]	0.3748
	Yes	162	72 (44.4)	NE (10.8,NE)	158	59 (37.3)	22.6 (8.3,NE)	0.9592 (0.6771,1.3590) [0.8176]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Physical Functioning									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	72 (38.3)	NE (14.5,NE)	191	70 (36.6)	17.2 (8.4,NE)	0.8246 (0.5915,1.1494) [0.2545]	0.4982
	>= 3	73	37 (50.7)	7.3 (4.2,NE)	72	34 (47.2)	9.1 (6.9,22.6)	1.0141 (0.6347,1.6204) [0.9591]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	69 (44.2)	NE (10.8,NE)	152	55 (36.2)	22.6 (8.3,NE)	1.0174 (0.7111,1.4556) [0.9221]	0.1111
	>= 3	6	3 (50.0)	15.0 (1.5,NE)	6	4 (66.7)	4.5 (0.7,NE)	0.2527 (0.0457,1.3980) [0.1077]	
Renal Impairment at Baseline	Mild	92	46 (50.0)	13.2 (5.8,NE)	104	49 (47.1)	8.3 (5.8,NE)	0.9278 (0.6191,1.3905) [0.7184]	0.5784
	Moderate	30	12 (40.0)	16.5 (5.6,NE)	22	10 (45.5)	7.1 (1.7,NE)	0.6228 (0.2682,1.4462) [0.2663]	
	Normal	130	50 (38.5)	NE (NE,NE)	130	43 (33.1)	NE (8.4,NE)	0.9700 (0.6430,1.4633) [0.8869]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	 No. of Events (%)	 Median (95% CI) [a] (months)	T-DM1 (N=263) n	 No. of Events (%)	 Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Physical Functioning									
Hepatic Impairment	Mild	49	20 (40.8)	16.5 (7.0,NE)	49	17 (34.7)	9.9 (4.1,NE)	0.8022 (0.4168,1.5441) [0.5075]	0.8981
	Normal	208	89 (42.8)	NE (12.5,NE)	212	87 (41.0)	17.2 (8.3,NE)	0.8814 (0.6544,1.1872) [0.4057]	
Baseline Visceral Disease	No	66	29 (43.9)	NE (5.9,NE)	74	35 (47.3)	9.9 (3.3,NE)	0.7058 (0.4302,1.1580) [0.1650]	0.3115
	Yes	195	80 (41.0)	NE (14.3,NE)	189	69 (36.5)	12.0 (8.3,NE)	0.9422 (0.6803,1.3049) [0.7144]	
Baseline CNS Metastases	No	218	95 (43.6)	NE (12.5,NE)	224	87 (38.8)	17.2 (8.4,NE)	0.9202 (0.6866,1.2332) [0.5766]	0.2954
	Yes	43	14 (32.6)	NE (5.6,NE)	39	17 (43.6)	8.3 (4.8,NE)	0.6241 (0.3034,1.2836) [0.1939]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	 No. of Events (%)	 Median (95% CI) [a] (months)	T-DM1 (N=263) n	 No. of Events (%)	 Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Physical Functioning									
History of CNS Metastases	No	199	87 (43.7)	NE (12.5,NE)	211	83 (39.3)	17.2 (7.9,NE)	0.9178 (0.6782,1.2422) [0.5762]	0.4694
	Yes	62	22 (35.5)	NE (11.7,NE)	52	21 (40.4)	8.3 (5.7,NE)	0.6930 (0.3748,1.2814) [0.2385]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Role Functioning									
Age	<65	212	102 (48.1)	13.6 (6.1,NE)	206	106 (51.5)	6.3 (4.3,8.9)	0.7166 (0.5441,0.9439) [0.0168]	0.3664
	>=65	49	28 (57.1)	9.4 (4.1,16.4)	57	32 (56.1)	6.9 (3.3,15.2)	0.9228 (0.5550,1.5344) [0.7612]	
Age	<75	253	125 (49.4)	11.7 (6.2,NE)	255	133 (52.2)	6.3 (4.7,9.9)	0.7393 (0.5776,0.9463) [0.0157]	0.6535
	>=75	8	5 (62.5)	4.5 (1.8,NE)	8	5 (62.5)	6.9 (0.9,NE)	0.9216 (0.2402,3.5360) [0.9050]	
Region	Asia	149	85 (57.0)	7.3 (4.4,13.6)	160	86 (53.8)	6.3 (4.7,9.9)	0.8521 (0.6286,1.1552) [0.2970]	<.0001
	Europe	54	23 (42.6)	16.4 (4.2,NE)	50	27 (54.0)	4.3 (2.8,16.7)	0.6520 (0.3732,1.1391) [0.1284]	
	North America	17	10 (58.8)	4.3 (1.4,NE)	17	2 (11.8)	NE (NE,NE)	5.6404 (1.2318,25.8272) [0.0122]	
	Rest of World	41	12 (29.3)	NE (11.7,NE)	36	23 (63.9)	4.1 (1.4,8.4)	0.2459 (0.1209,0.5004) [<.0001]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Role Functioning									
Race	Asian	152	85 (55.9)	8.3 (4.5,13.7)	162	87 (53.7)	6.3 (4.7,9.9)	0.8386 (0.6191,1.1359) [0.2496]	0.3593
	Black Or African American	10	5 (50.0)	6.9 (1.4,NE)	9	3 (33.3)	NE (1.4,NE)	1.2755 (0.3037,5.3570) [0.7390]	
	Other	28	10 (35.7)	NE (4.9,NE)	20	10 (50.0)	7.1 (1.4,NE)	0.5006 (0.2068,1.2120) [0.1193]	
	White	71	30 (42.3)	NE (5.9,NE)	72	38 (52.8)	4.2 (2.9,13.9)	0.6099 (0.3764,0.9885) [0.0423]	
ECOG PS	0	154	75 (48.7)	12.1 (6.2,NE)	175	89 (50.9)	7.1 (4.8,11.8)	0.7635 (0.5597,1.0414) [0.0862]	0.7158
	1	106	55 (51.9)	11.5 (4.3,16.4)	87	49 (56.3)	4.8 (2.9,8.9)	0.6785 (0.4592,1.0026) [0.0503]	
Hormone Receptor Status	Negative	126	69 (54.8)	7.3 (5.6,13.4)	122	69 (56.6)	4.7 (3.5,8.1)	0.7719 (0.5514,1.0804) [0.1288]	0.7180
	Positive	133	61 (45.9)	16.4 (7.1,NE)	139	69 (49.6)	8.3 (5.6,11.3)	0.7169 (0.5057,1.0163) [0.0597]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Role Functioning									
Estrogen Receptors	Negative	130	70 (53.8)	9.4 (5.6,13.7)	128	69 (53.9)	5.3 (4.2,10.0)	0.8026 (0.5742,1.1218) [0.1953]	0.4662
	Positive	129	60 (46.5)	16.4 (5.6,NE)	132	69 (52.3)	7.1 (4.8,10.2)	0.6780 (0.4771,0.9634) [0.0287]	
Progesterone Receptors	Negative	177	93 (52.5)	10.7 (5.9,16.4)	168	93 (55.4)	5.8 (4.2,8.4)	0.7302 (0.5458,0.9769) [0.0330]	0.8737
	Positive	81	37 (45.7)	NE (4.3,NE)	92	44 (47.8)	8.4 (4.2,11.8)	0.7994 (0.5151,1.2406) [0.3152]	
Prior Treatment with Pertuzumab	No	99	38 (38.4)	23.7 (13.4,NE)	105	58 (55.2)	5.6 (4.1,8.4)	0.4541 (0.2985,0.6908) [0.0002]	0.0085
	Yes	162	92 (56.8)	5.6 (4.2,11.5)	158	80 (50.6)	8.1 (4.3,12.5)	0.9616 (0.7112,1.3002) [0.7968]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Role Functioning									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	93 (49.5)	12.1 (6.9,NE)	191	103 (53.9)	5.4 (4.2,8.9)	0.6920 (0.5207,0.9195) [0.0104]	0.3657
	>= 3	73	37 (50.7)	7.3 (4.3,NE)	72	35 (48.6)	7.0 (5.5,13.9)	0.8929 (0.5610,1.4211) [0.6348]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	89 (57.1)	5.6 (4.2,11.5)	152	77 (50.7)	8.3 (4.3,12.5)	0.9794 (0.7204,1.3315) [0.8926]	0.5023
	>= 3	6	3 (50.0)	8.3 (1.4,NE)	6	3 (50.0)	5.1 (0.8,NE)	0.5413 (0.1078,2.7178) [0.4491]	
Renal Impairment at Baseline	Mild	92	57 (62.0)	5.6 (4.1,11.5)	104	59 (56.7)	5.8 (4.2,11.8)	1.0172 (0.7065,1.4646) [0.9265]	0.1445
	Moderate	30	16 (53.3)	9.4 (3.0,NE)	22	13 (59.1)	4.2 (1.4,13.9)	0.6123 (0.2942,1.2744) [0.1867]	
	Normal	130	56 (43.1)	23.7 (10.4,NE)	130	63 (48.5)	7.0 (4.4,10.3)	0.6504 (0.4501,0.9398) [0.0201]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Role Functioning									
Hepatic Impairment	Mild	49	21 (42.9)	13.7 (5.6,NE)	49	20 (40.8)	6.9 (3.1,NE)	0.7102 (0.3833,1.3159) [0.2760]	0.8167
	Normal	208	109 (52.4)	11.5 (5.6,16.4)	212	118 (55.7)	6.3 (4.3,8.9)	0.7496 (0.5758,0.9759) [0.0310]	
Baseline Visceral Disease	No	66	35 (53.0)	10.4 (4.3,NE)	74	44 (59.5)	6.9 (3.0,10.2)	0.6667 (0.4265,1.0422) [0.0727]	0.6010
	Yes	195	95 (48.7)	11.7 (6.2,NE)	189	94 (49.7)	6.0 (4.7,10.3)	0.7846 (0.5878,1.0472) [0.0979]	
Baseline CNS Metastases	No	218	104 (47.7)	14.5 (7.3,NE)	224	121 (54.0)	6.0 (4.2,8.5)	0.6773 (0.5197,0.8827) [0.0036]	0.0659
	Yes	43	26 (60.5)	5.6 (3.1,11.6)	39	17 (43.6)	7.0 (4.4,NE)	1.2030 (0.6436,2.2489) [0.5649]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Role Functioning									
History of CNS Metastases	No	199	96 (48.2)	13.7 (6.9,NE)	211	114 (54.0)	5.8 (4.2,8.5)	0.6911 (0.5254,0.9091) [0.0078]	0.1949
	Yes	62	34 (54.8)	6.2 (4.4,14.5)	52	24 (46.2)	7.0 (4.7,NE)	0.9484 (0.5550,1.6206) [0.8408]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Emotional Functioning									
Age	<65	212	95 (44.8)	17.1 (14.1,21.7)	206	83 (40.3)	12.7 (8.5,15.2)	0.7623 (0.5637,1.0310) [0.0768]	0.4734
	>=65	49	22 (44.9)	11.7 (7.6,NE)	57	24 (42.1)	8.6 (7.0,NE)	0.8698 (0.4857,1.5576) [0.6347]	
Age	<75	253	114 (45.1)	16.7 (12.9,21.7)	255	104 (40.8)	11.1 (8.4,15.2)	0.7944 (0.6063,1.0408) [0.0938]	0.7077
	>=75	8	3 (37.5)	7.6 (2.9,NE)	8	3 (37.5)	NE (1.5,NE)	1.2079 (0.2397,6.0864) [0.8186]	
Region	Asia	149	68 (45.6)	17.1 (12.5,21.7)	160	60 (37.5)	13.8 (8.9,NE)	0.8599 (0.6036,1.2250) [0.4034]	0.3948
	Europe	54	22 (40.7)	15.8 (9.4,NE)	50	20 (40.0)	15.2 (5.6,NE)	0.7659 (0.4140,1.4169) [0.3907]	
	North America	17	11 (64.7)	9.0 (1.4,NE)	17	8 (47.1)	7.0 (2.8,NE)	1.2473 (0.4972,3.1289) [0.6420]	
	Rest of World	41	16 (39.0)	NE (8.7,NE)	36	19 (52.8)	7.9 (2.9,NE)	0.4968 (0.2536,0.9733) [0.0379]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Emotional Functioning									
Race	Asian	152	70 (46.1)	16.7 (12.5,21.7)	162	62 (38.3)	12.7 (8.5,NE)	0.8529 (0.6018,1.2087) [0.3706]	0.4443
	Black Or African American	10	7 (70.0)	4.4 (1.4,NE)	9	4 (44.4)	10.1 (1.5,NE)	1.5093 (0.4407,5.1695) [0.4946]	
	Other	28	12 (42.9)	19.4 (7.7,NE)	20	8 (40.0)	NE (2.9,NE)	0.7038 (0.2808,1.7635) [0.4485]	
	White	71	28 (39.4)	NE (9.4,NE)	72	33 (45.8)	7.9 (4.2,NE)	0.6262 (0.3761,1.0427) [0.0694]	
ECOG PS	0	154	64 (41.6)	17.3 (15.8,NE)	175	74 (42.3)	10.5 (8.1,NE)	0.6986 (0.4971,0.9818) [0.0370]	0.2615
	1	106	53 (50.0)	12.8 (7.6,NE)	87	33 (37.9)	11.1 (8.4,NE)	0.9550 (0.6135,1.4865) [0.8429]	
Hormone Receptor Status	Negative	126	62 (49.2)	14.1 (10.4,18.5)	122	48 (39.3)	12.7 (8.3,NE)	0.9522 (0.6488,1.3974) [0.7972]	0.1636
	Positive	133	55 (41.4)	18.8 (12.9,NE)	139	58 (41.7)	9.8 (7.6,NE)	0.6896 (0.4743,1.0027) [0.0502]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Emotional Functioning									
Estrogen Receptors	Negative	130	65 (50.0)	14.1 (8.7,18.5)	128	50 (39.1)	11.1 (8.4,NE)	0.9796 (0.6732,1.4256) [0.9092]	0.0777
	Positive	129	52 (40.3)	18.8 (15.0,NE)	132	56 (42.4)	9.8 (6.9,NE)	0.6497 (0.4427,0.9536) [0.0263]	
Progesterone Receptors	Negative	177	81 (45.8)	16.7 (11.8,21.7)	168	71 (42.3)	10.5 (8.4,15.2)	0.8005 (0.5790,1.1068) [0.1763]	0.9205
	Positive	81	36 (44.4)	16.5 (10.8,NE)	92	35 (38.0)	15.2 (7.6,NE)	0.8170 (0.5096,1.3099) [0.3991]	
Prior Treatment with Pertuzumab	No	99	40 (40.4)	17.3 (12.5,NE)	105	45 (42.9)	9.0 (5.6,NE)	0.7221 (0.4688,1.1123) [0.1368]	0.3172
	Yes	162	77 (47.5)	14.5 (11.8,21.7)	158	62 (39.2)	14.3 (8.3,NE)	0.8600 (0.6118,1.2087) [0.3857]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Emotional Functioning									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	77 (41.0)	18.8 (14.5,NE)	191	79 (41.4)	11.1 (8.3,NE)	0.6742 (0.4900,0.9277) [0.0149]	0.0627
	>= 3	73	40 (54.8)	10.4 (3.2,18.5)	72	28 (38.9)	12.7 (7.9,NE)	1.1981 (0.7346,1.9541) [0.4767]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	74 (47.4)	14.5 (11.8,21.7)	152	62 (40.8)	11.1 (8.1,NE)	0.8211 (0.5820,1.1584) [0.2619]	0.0466
	>= 3	6	3 (50.0)	8.5 (1.5,NE)	6	0 (0.0)	NE (NE,NE)	NE	
Renal Impairment at Baseline	Mild	92	41 (44.6)	15.0 (10.7,NE)	104	48 (46.2)	9.8 (7.0,NE)	0.7847 (0.5156,1.1944) [0.2573]	0.1650
	Moderate	30	18 (60.0)	9.4 (5.7,15.8)	22	6 (27.3)	13.8 (5.3,NE)	1.5746 (0.6231,3.9787) [0.3346]	
	Normal	130	57 (43.8)	18.8 (14.1,NE)	130	51 (39.2)	11.1 (7.9,NE)	0.7167 (0.4841,1.0611) [0.0942]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Emotional Functioning									
Hepatic Impairment	Mild	49	20 (40.8)	16.7 (7.3,NE)	49	18 (36.7)	8.7 (5.6,NE)	0.7202 (0.3765,1.3778) [0.3202]	0.6337
	Normal	208	97 (46.6)	16.5 (12.2,21.7)	212	89 (42.0)	12.7 (8.4,NE)	0.8197 (0.6121,1.0978) [0.1809]	
Baseline Visceral Disease	No	66	31 (47.0)	14.1 (9.2,NE)	74	35 (47.3)	10.5 (7.2,15.2)	0.7315 (0.4486,1.1927) [0.2074]	0.6856
	Yes	195	86 (44.1)	17.1 (12.8,19.4)	189	72 (38.1)	12.7 (8.4,NE)	0.8460 (0.6155,1.1627) [0.3029]	
Baseline CNS Metastases	No	218	101 (46.3)	16.7 (12.2,21.7)	224	89 (39.7)	13.8 (8.6,NE)	0.8695 (0.6515,1.1605) [0.3399]	0.1042
	Yes	43	16 (37.2)	19.4 (10.4,NE)	39	18 (46.2)	8.3 (2.9,NE)	0.4896 (0.2417,0.9917) [0.0444]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	 No. of Events (%)	 Median (95% CI) [a] (months)	T-DM1 (N=263) n	 No. of Events (%)	 Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Emotional Functioning									
History of CNS Metastases	No	199	90 (45.2)	17.1 (12.5,NE)	211	85 (40.3)	13.8 (8.5,NE)	0.8268 (0.6124,1.1162) [0.2128]	0.7011
	Yes	62	27 (43.5)	14.5 (10.4,NE)	52	22 (42.3)	10.1 (4.8,NE)	0.6571 (0.3641,1.1858) [0.1611]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup			T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Functioning	Scales/Cognitive									
Age		<65	212	110 (51.9)	10.6 (8.6,15.3)	206	105 (51.0)	8.3 (4.8,10.5)	0.7373 (0.5619,0.9673) [0.0274]	0.4668
		>=65	49	28 (57.1)	9.9 (5.6,15.3)	57	30 (52.6)	8.3 (3.3,20.5)	0.8982 (0.5347,1.5086) [0.6822]	
Age		<75	253	134 (53.0)	10.3 (8.6,14.5)	255	130 (51.0)	8.3 (4.8,10.5)	0.7684 (0.6018,0.9811) [0.0343]	0.8846
		>=75	8	4 (50.0)	6.6 (1.4,NE)	8	5 (62.5)	2.8 (0.9,NE)	0.5397 (0.1273,2.2878) [0.3956]	
Region		Asia	149	84 (56.4)	10.3 (6.9,14.1)	160	80 (50.0)	8.4 (4.8,14.1)	0.8707 (0.6378,1.1888) [0.3828]	0.3325
		Europe	54	26 (48.1)	9.9 (7.4,NE)	50	29 (58.0)	4.2 (1.4,9.8)	0.5558 (0.3252,0.9498) [0.0294]	
		North America	17	7 (41.2)	19.6 (1.5,NE)	17	6 (35.3)	NE (4.4,NE)	1.0746 (0.3461,3.3364) [0.9090]	
		Rest of World	41	21 (51.2)	12.0 (6.0,NE)	36	20 (55.6)	7.2 (2.1,10.5)	0.5677 (0.3059,1.0534) [0.0702]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Cognitive Functioning									
Race	Asian	152	84 (55.3)	10.3 (6.9,14.1)	162	80 (49.4)	8.4 (4.8,14.1)	0.8739 (0.6401,1.1930) [0.3952]	0.0123
	Black Or African American	10	9 (90.0)	4.9 (1.4,6.9)	9	4 (44.4)	9.6 (1.5,NE)	5.4230 (1.1259,26.1209) [0.0192]	
	Other	28	13 (46.4)	19.4 (5.8,NE)	20	12 (60.0)	1.5 (0.9,NE)	0.3301 (0.1423,0.7658) [0.0073]	
	White	71	32 (45.1)	15.3 (7.7,NE)	72	39 (54.2)	5.6 (2.8,10.5)	0.5885 (0.3663,0.9454) [0.0264]	
ECOG PS	0	154	81 (52.6)	10.6 (8.6,16.4)	175	86 (49.1)	8.7 (4.8,12.9)	0.8094 (0.5958,1.0997) [0.1735]	0.3755
	1	106	57 (53.8)	10.3 (5.6,14.8)	87	49 (56.3)	5.3 (2.8,10.3)	0.6625 (0.4486,0.9783) [0.0376]	
Hormone Receptor Status	Negative	126	76 (60.3)	6.9 (4.7,10.3)	122	59 (48.4)	8.3 (4.2,20.7)	1.0384 (0.7368,1.4635) [0.8212]	0.0240
	Positive	133	62 (46.6)	14.1 (10.1,NE)	139	75 (54.0)	7.2 (4.5,10.3)	0.5824 (0.4138,0.8198) [0.0017]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	No. of Events (%)	Median (95% CI) [a] (months)	T-DM1 (N=263) n	No. of Events (%)	Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Cognitive Functioning									
Estrogen Receptors	Negative	130	78 (60.0)	7.4 (5.6,10.3)	128	64 (50.0)	8.3 (4.2,14.1)	1.0015 (0.7174,1.3980) [0.9885]	0.0433
	Positive	129	60 (46.5)	14.1 (10.1,NE)	132	69 (52.3)	8.4 (4.8,11.1)	0.5981 (0.4208,0.8502) [0.0037]	
Progesterone Receptors	Negative	177	102 (57.6)	8.6 (5.8,12.4)	168	84 (50.0)	8.4 (4.3,12.9)	0.9245 (0.6906,1.2376) [0.6046]	0.0628
	Positive	81	36 (44.4)	16.4 (9.9,NE)	92	49 (53.3)	5.7 (4.4,11.1)	0.5356 (0.3458,0.8297) [0.0045]	
Prior Treatment with Pertuzumab	No	99	50 (50.5)	12.0 (6.9,16.4)	105	54 (51.4)	8.4 (4.2,14.1)	0.7113 (0.4818,1.0501) [0.0843]	0.7017
	Yes	162	88 (54.3)	9.9 (7.7,14.1)	158	81 (51.3)	8.3 (4.4,11.1)	0.8032 (0.5914,1.0908) [0.1601]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Cognitive Functioning									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	97 (51.6)	12.4 (8.6,15.3)	191	102 (53.4)	8.3 (4.2,9.8)	0.6790 (0.5119,0.9006) [0.0069]	0.1808
	>= 3	73	41 (56.2)	7.7 (4.7,12.5)	72	33 (45.8)	9.0 (4.5,NE)	1.0274 (0.6479,1.6293) [0.9041]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	86 (55.1)	9.7 (7.4,14.1)	152	78 (51.3)	8.3 (4.4,11.1)	0.8365 (0.6130,1.1415) [0.2600]	0.1825
	>= 3	6	2 (33.3)	NE (5.8,NE)	6	3 (50.0)	3.8 (0.8,NE)	0.2680 (0.0437,1.6426) [0.1284]	
Renal Impairment at Baseline	Mild	92	50 (54.3)	10.7 (5.6,16.4)	104	62 (59.6)	5.6 (3.0,9.7)	0.6919 (0.4738,1.0104) [0.0561]	0.7375
	Moderate	30	18 (60.0)	9.9 (6.9,12.4)	22	10 (45.5)	5.3 (1.5,NE)	0.9465 (0.4290,2.0883) [0.8935]	
	Normal	130	68 (52.3)	12.0 (7.0,19.6)	130	62 (47.7)	8.7 (4.5,14.1)	0.7931 (0.5579,1.1275) [0.1943]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Cognitive Functioning									
Hepatic Impairment	Mild	49	22 (44.9)	10.3 (6.0,NE)	49	19 (38.8)	9.8 (4.2,NE)	0.7839 (0.4214,1.4583) [0.4473]	0.9811
	Normal	208	116 (55.8)	10.3 (8.2,14.1)	212	116 (54.7)	7.2 (4.5,10.3)	0.7668 (0.5908,0.9952) [0.0451]	
Baseline Visceral Disease	No	66	29 (43.9)	NE (9.0,NE)	74	41 (55.4)	5.0 (3.0,12.9)	0.4943 (0.3050,0.8013) [0.0036]	0.0397
	Yes	195	109 (55.9)	8.8 (6.0,13.6)	189	94 (49.7)	8.4 (4.8,11.1)	0.8824 (0.6673,1.1669) [0.3795]	
Baseline CNS Metastases	No	218	113 (51.8)	11.1 (8.6,15.3)	224	116 (51.8)	8.3 (4.5,9.8)	0.7239 (0.5570,0.9409) [0.0152]	0.2521
	Yes	43	25 (58.1)	7.7 (2.9,14.8)	39	19 (48.7)	8.3 (3.5,NE)	1.0298 (0.5602,1.8930) [0.9199]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	 No. of Events (%)	 Median (95% CI) [a] (months)	T-DM1 (N=263) n	 No. of Events (%)	 Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Cognitive Functioning									
History of CNS Metastases	No	199	106 (53.3)	10.3 (8.6,15.3)	211	109 (51.7)	7.2 (4.3,10.5)	0.7429 (0.5670,0.9732) [0.0304]	0.6226
	Yes	62	32 (51.6)	9.7 (3.0,19.4)	52	26 (50.0)	9.6 (4.2,14.1)	0.8412 (0.4939,1.4325) [0.5254]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Social Functioning									
Age	<65	212	117 (55.2)	8.3 (5.6,13.6)	206	99 (48.1)	7.1 (5.6,11.7)	0.9556 (0.7295,1.2517) [0.7375]	0.1610
	>=65	49	30 (61.2)	5.8 (2.8,10.7)	57	27 (47.4)	11.3 (5.8,NE)	1.4208 (0.8435,2.3934) [0.1868]	
Age	<75	253	143 (56.5)	7.3 (5.7,11.9)	255	122 (47.8)	8.4 (5.7,11.7)	1.0300 (0.8080,1.3131) [0.8169]	0.6580
	>=75	8	4 (50.0)	7.4 (1.4,NE)	8	4 (50.0)	6.9 (1.5,NE)	1.3938 (0.3375,5.7558) [0.6450]	
Region	Asia	149	87 (58.4)	7.3 (4.9,11.8)	160	79 (49.4)	7.1 (5.6,12.0)	1.0109 (0.7438,1.3739) [0.9440]	0.6232
	Europe	54	29 (53.7)	5.6 (2.8,17.5)	50	25 (50.0)	8.6 (4.2,16.7)	1.0845 (0.6332,1.8572) [0.7842]	
	North America	17	12 (70.6)	3.0 (1.4,16.8)	17	6 (35.3)	NE (1.9,NE)	1.8330 (0.6835,4.9162) [0.2137]	
	Rest of World	41	19 (46.3)	13.6 (6.4,NE)	36	16 (44.4)	11.7 (3.0,NE)	0.8880 (0.4561,1.7288) [0.7192]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Social Functioning									
Race	Asian	152	87 (57.2)	8.3 (5.5,11.8)	162	80 (49.4)	7.1 (5.6,12.0)	0.9915 (0.7303,1.3462) [0.9576]	0.8452
	Black Or African American	10	8 (80.0)	6.2 (1.4,8.3)	9	4 (44.4)	NE (0.8,NE)	1.5039 (0.4504,5.0217) [0.4848]	
	Other	28	16 (57.1)	4.5 (1.5,NE)	20	10 (50.0)	9.8 (1.5,NE)	1.1329 (0.5063,2.5349) [0.7788]	
	White	71	36 (50.7)	13.1 (5.6,17.5)	72	32 (44.4)	8.4 (5.3,NE)	1.0005 (0.6195,1.6156) [0.9893]	
ECOG PS	0	154	84 (54.5)	9.9 (6.4,14.5)	175	84 (48.0)	8.4 (5.6,16.6)	0.9312 (0.6868,1.2626) [0.6438]	0.3228
	1	106	63 (59.4)	5.6 (3.0,10.4)	87	42 (48.3)	8.4 (5.6,16.7)	1.1877 (0.8016,1.7598) [0.3986]	
Hormone Receptor Status	Negative	126	73 (57.9)	7.0 (5.5,13.4)	122	57 (46.7)	7.9 (5.3,NE)	1.1219 (0.7926,1.5880) [0.5153]	0.6068
	Positive	133	74 (55.6)	8.6 (4.5,13.6)	139	68 (48.9)	8.4 (5.6,11.3)	0.9830 (0.7052,1.3701) [0.9056]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Social Functioning									
Estrogen Receptors	Negative	130	75 (57.7)	6.9 (5.5,13.4)	128	61 (47.7)	7.9 (5.3,16.7)	1.0987 (0.7829,1.5419) [0.5841]	0.7521
	Positive	129	72 (55.8)	8.6 (4.5,13.6)	132	63 (47.7)	8.4 (5.7,11.7)	1.0111 (0.7189,1.4221) [0.9644]	
Progesterone Receptors	Negative	177	101 (57.1)	7.0 (5.6,11.8)	168	80 (47.6)	8.4 (5.6,16.7)	1.0928 (0.8142,1.4668) [0.5584]	0.8470
	Positive	81	46 (56.8)	8.3 (3.3,13.6)	92	44 (47.8)	8.4 (5.6,11.7)	1.0039 (0.6612,1.5242) [0.9887]	
Prior Treatment with Pertuzumab	No	99	54 (54.5)	6.9 (3.2,18.2)	105	54 (51.4)	7.1 (4.8,11.7)	1.0101 (0.6920,1.4743) [0.9774]	0.7741
	Yes	162	93 (57.4)	8.5 (5.8,13.4)	158	72 (45.6)	10.2 (5.8,NE)	1.0565 (0.7749,1.4404) [0.7259]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Social Functioning									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	99 (52.7)	11.5 (6.9,16.8)	191	98 (51.3)	6.2 (5.6,10.3)	0.8194 (0.6180,1.0864) [0.1633]	0.0021
	>= 3	73	48 (65.8)	4.3 (2.9,6.9)	72	28 (38.9)	12.0 (7.1,NE)	1.9046 (1.1942,3.0376) [0.0060]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	90 (57.7)	8.5 (5.7,13.4)	152	71 (46.7)	9.8 (5.8,20.5)	1.0482 (0.7660,1.4345) [0.7666]	0.6076
	>= 3	6	3 (50.0)	9.9 (1.5,NE)	6	1 (16.7)	NE (0.8,NE)	1.8191 (0.1887,17.5373) [0.5994]	
Renal Impairment at Baseline	Mild	92	62 (67.4)	5.6 (3.1,8.5)	104	55 (52.9)	7.6 (4.8,16.7)	1.2698 (0.8824,1.8273) [0.1954]	0.1886
	Moderate	30	19 (63.3)	6.9 (2.9,14.5)	22	9 (40.9)	11.3 (5.3,NE)	1.5022 (0.6750,3.3430) [0.3130]	
	Normal	130	64 (49.2)	13.4 (5.9,NE)	130	60 (46.2)	8.4 (5.6,NE)	0.8853 (0.6198,1.2645) [0.4934]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Social Functioning									
Hepatic Impairment	Mild	49	30 (61.2)	4.5 (2.9,8.5)	49	18 (36.7)	9.0 (4.8,NE)	1.4638 (0.8155,2.6274) [0.1972]	0.1812
	Normal	208	117 (56.3)	8.6 (5.8,13.4)	212	108 (50.9)	7.6 (5.6,12.0)	0.9608 (0.7382,1.2506) [0.7590]	
Baseline Visceral Disease	No	66	38 (57.6)	6.9 (4.2,13.4)	74	36 (48.6)	8.6 (5.6,NE)	1.0908 (0.6904,1.7235) [0.7168]	0.8191
	Yes	195	109 (55.9)	8.2 (5.6,13.1)	189	90 (47.6)	8.4 (5.6,12.0)	1.0111 (0.7633,1.3395) [0.9446]	
Baseline CNS Metastases	No	218	122 (56.0)	8.3 (5.7,12.2)	224	112 (50.0)	7.6 (5.6,11.3)	0.9845 (0.7610,1.2738) [0.8957]	0.2704
	Yes	43	25 (58.1)	6.2 (3.0,18.2)	39	14 (35.9)	NE (4.8,NE)	1.4346 (0.7396,2.7829) [0.2818]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Social Functioning									
History of CNS Metastases	No	199	112 (56.3)	8.2 (5.6,12.2)	211	105 (49.8)	7.6 (5.6,11.7)	0.9832 (0.7526,1.2844) [0.8906]	0.3646
	Yes	62	35 (56.5)	7.2 (3.0,14.5)	52	21 (40.4)	10.3 (4.2,NE)	1.2600 (0.7268,2.1842) [0.4072]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Fatigue									
Age	<65	212	122 (57.5)	4.3 (2.9,10.1)	206	117 (56.8)	4.4 (2.8,6.2)	0.8765 (0.6793,1.1309) [0.3127]	0.6282
	>=65	49	28 (57.1)	7.8 (2.1,15.7)	57	36 (63.2)	2.9 (1.5,4.2)	0.7606 (0.4621,1.2518) [0.2809]	
Age	<75	253	146 (57.7)	5.6 (3.0,10.1)	255	149 (58.4)	3.5 (2.8,5.5)	0.8412 (0.6689,1.0578) [0.1406]	0.6569
	>=75	8	4 (50.0)	2.7 (1.4,NE)	8	4 (50.0)	4.2 (0.9,NE)	1.2178 (0.3012,4.9237) [0.7819]	
Region	Asia	149	88 (59.1)	5.6 (3.0,11.8)	160	94 (58.8)	4.2 (2.8,5.7)	0.8652 (0.6458,1.1592) [0.3329]	0.4017
	Europe	54	30 (55.6)	2.9 (1.5,19.4)	50	27 (54.0)	4.2 (1.7,16.7)	0.9753 (0.5795,1.6412) [0.9347]	
	North America	17	10 (58.8)	2.8 (0.9,NE)	17	8 (47.1)	5.5 (1.5,NE)	1.2109 (0.4754,3.0842) [0.6749]	
	Rest of World	41	22 (53.7)	5.6 (2.8,NE)	36	24 (66.7)	1.5 (1.4,5.8)	0.5385 (0.3010,0.9634) [0.0351]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Fatigue									
Race	Asian	152	89 (58.6)	5.6 (3.0,11.8)	162	96 (59.3)	4.2 (2.8,5.6)	0.8480 (0.6343,1.1336) [0.2667]	0.2080
	Black Or African American	10	8 (80.0)	2.2 (1.4,3.3)	9	4 (44.4)	9.6 (2.0,NE)	2.4894 (0.7430,8.3413) [0.1201]	
	Other	28	15 (53.6)	15.7 (1.5,NE)	20	12 (60.0)	1.5 (0.8,NE)	0.5471 (0.2551,1.1730) [0.1178]	
	White	71	38 (53.5)	3.0 (1.7,NE)	72	41 (56.9)	4.1 (1.5,6.9)	0.8303 (0.5334,1.2925) [0.4164]	
ECOG PS	0	154	92 (59.7)	4.3 (2.8,10.7)	175	101 (57.7)	4.3 (2.9,6.2)	0.9218 (0.6941,1.2242) [0.5743]	0.2955
	1	106	58 (54.7)	6.1 (2.9,15.7)	87	52 (59.8)	2.8 (1.5,5.3)	0.7368 (0.5059,1.0731) [0.1104]	
Hormone Receptor Status	Negative	126	72 (57.1)	5.6 (2.9,14.5)	122	69 (56.6)	3.5 (2.0,6.5)	0.9188 (0.6599,1.2794) [0.6109]	0.5811
	Positive	133	77 (57.9)	6.9 (2.9,12.1)	139	83 (59.7)	4.1 (2.8,5.7)	0.7947 (0.5817,1.0858) [0.1493]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Fatigue									
Estrogen Receptors	Negative	130	74 (56.9)	5.6 (2.9,14.5)	128	72 (56.3)	3.5 (2.8,6.5)	0.9314 (0.6729,1.2893) [0.6606]	0.4438
	Positive	129	75 (58.1)	6.9 (2.8,12.1)	132	80 (60.6)	3.6 (2.8,5.7)	0.7661 (0.5576,1.0525) [0.0996]	
Progesterone Receptors	Negative	177	99 (55.9)	6.0 (3.0,11.8)	168	98 (58.3)	3.1 (2.0,5.5)	0.8201 (0.6197,1.0854) [0.1645]	0.5434
	Positive	81	49 (60.5)	3.0 (2.8,12.1)	92	53 (57.6)	4.8 (2.8,6.9)	0.9399 (0.6358,1.3892) [0.7643]	
Prior Treatment with Pertuzumab	No	99	53 (53.5)	6.1 (2.9,NE)	105	57 (54.3)	4.8 (3.5,7.0)	0.8700 (0.5977,1.2663) [0.4677]	0.7172
	Yes	162	97 (59.9)	4.3 (2.8,10.7)	158	96 (60.8)	2.9 (1.6,4.8)	0.8186 (0.6164,1.0871) [0.1658]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Fatigue									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	106 (56.4)	6.0 (2.9,12.1)	191	113 (59.2)	3.0 (2.8,5.5)	0.7966 (0.6103,1.0399) [0.0954]	0.3619
	>= 3	73	44 (60.3)	5.6 (2.9,8.3)	72	40 (55.6)	4.6 (2.8,11.8)	0.9958 (0.6485,1.5292) [0.9824]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	94 (60.3)	4.2 (2.8,10.7)	152	93 (61.2)	2.9 (1.6,4.8)	0.8345 (0.6255,1.1133) [0.2183]	0.4898
	>= 3	6	3 (50.0)	8.3 (1.4,NE)	6	3 (50.0)	2.2 (0.7,NE)	0.5121 (0.1017,2.5776) [0.4082]	
Renal Impairment at Baseline	Mild	92	58 (63.0)	4.3 (1.6,10.1)	104	66 (63.5)	3.5 (2.8,6.5)	0.9463 (0.6644,1.3479) [0.7555]	0.2271
	Moderate	30	19 (63.3)	2.9 (1.5,15.7)	22	9 (40.9)	4.2 (1.5,NE)	1.4539 (0.6571,3.2172) [0.3460]	
	Normal	130	71 (54.6)	6.9 (3.0,19.4)	130	75 (57.7)	4.2 (2.8,5.7)	0.7450 (0.5365,1.0344) [0.0772]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Fatigue									
Hepatic Impairment	Mild	49	28 (57.1)	4.3 (2.2,NE)	49	26 (53.1)	4.6 (1.5,8.1)	0.8640 (0.5064,1.4742) [0.5988]	0.9216
	Normal	208	122 (58.7)	5.7 (2.9,11.8)	212	127 (59.9)	3.5 (2.8,5.5)	0.8412 (0.6553,1.0799) [0.1758]	
Baseline Visceral Disease	No	66	40 (60.6)	6.9 (2.9,12.1)	74	44 (59.5)	2.9 (1.6,8.1)	0.8168 (0.5306,1.2573) [0.3586]	0.8649
	Yes	195	110 (56.4)	4.3 (2.9,11.8)	189	109 (57.7)	4.2 (2.9,5.6)	0.8621 (0.6610,1.1245) [0.2721]	
Baseline CNS Metastases	No	218	126 (57.8)	4.3 (2.9,10.7)	224	131 (58.5)	3.3 (2.8,5.5)	0.8405 (0.6577,1.0742) [0.1687]	0.7399
	Yes	43	24 (55.8)	7.6 (3.0,19.4)	39	22 (56.4)	4.8 (2.8,NE)	0.8605 (0.4785,1.5475) [0.6087]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Fatigue									
History of CNS Metastases	No	199	119 (59.8)	3.4 (2.8,7.0)	211	124 (58.8)	3.1 (2.8,5.3)	0.8781 (0.6824,1.1300) [0.3176]	0.7482
	Yes	62	31 (50.0)	10.1 (4.2,NE)	52	29 (55.8)	4.8 (2.8,11.8)	0.7436 (0.4453,1.2417) [0.2526]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale	Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Symptom Scales/Nausea and Vomiting										
Age		<65	212	158 (74.5)	2.8 (1.5,3.0)	206	94 (45.6)	8.8 (7.0,11.3)	1.9281 (1.4901,2.4950) [<.0001]	0.6087
		>=65	49	33 (67.3)	2.8 (1.4,8.3)	57	22 (38.6)	13.9 (8.3,NE)	2.1952 (1.2783,3.7696) [0.0036]	
Age		<75	253	185 (73.1)	2.8 (1.6,3.1)	255	115 (45.1)	9.3 (7.6,11.9)	1.9457 (1.5400,2.4583) [<.0001]	0.0508
		>=75	8	6 (75.0)	1.8 (0.8,NE)	8	1 (12.5)	NE (10.3,NE)	9.9633 (1.1781,84.2632) [0.0102]	
Region		Asia	149	107 (71.8)	2.9 (1.5,4.2)	160	68 (42.5)	9.7 (7.6,NE)	2.0796 (1.5330,2.8211) [<.0001]	0.9959
		Europe	54	38 (70.4)	1.6 (1.4,2.9)	50	21 (42.0)	9.8 (2.8,NE)	1.8991 (1.1107,3.2471) [0.0168]	
		North America	17	15 (88.2)	3.1 (0.9,12.4)	17	8 (47.1)	8.7 (1.7,NE)	1.7126 (0.7051,4.1596) [0.2282]	
		Rest of World	41	31 (75.6)	1.6 (1.4,4.2)	36	19 (52.8)	9.9 (4.1,13.9)	1.9279 (1.0848,3.4262) [0.0271]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Nausea and Vomiting									
Race	Asian	152	109 (71.7)	2.9 (1.5,4.2)	162	69 (42.6)	9.7 (7.6,NE)	2.0766 (1.5344,2.8103) [<.0001]	0.9776
	Black Or African American	10	8 (80.0)	3.5 (1.4,6.9)	9	3 (33.3)	NE (0.8,NE)	2.4004 (0.6346,9.0802) [0.1801]	
	Other	28	21 (75.0)	1.5 (1.4,17.3)	20	9 (45.0)	8.6 (1.5,NE)	1.8092 (0.8223,3.9804) [0.1446]	
	White	71	53 (74.6)	1.7 (1.4,3.0)	72	35 (48.6)	8.7 (4.2,13.9)	1.8765 (1.2207,2.8846) [0.0039]	
ECOG PS	0	154	113 (73.4)	2.8 (1.5,3.5)	175	80 (45.7)	8.7 (7.0,NE)	1.9275 (1.4451,2.5709) [<.0001]	0.5962
	1	106	78 (73.6)	2.9 (1.6,3.5)	87	36 (41.4)	10.8 (7.2,NE)	2.1745 (1.4620,3.2342) [<.0001]	
Hormone Receptor Status	Negative	126	87 (69.0)	2.9 (1.5,4.2)	122	52 (42.6)	10.8 (7.6,NE)	1.9290 (1.3658,2.7245) [0.0002]	0.7759
	Positive	133	103 (77.4)	2.0 (1.5,3.0)	139	64 (46.0)	8.8 (6.3,NE)	2.1101 (1.5423,2.8869) [<.0001]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Symptom Scales/Nausea and Vomiting									
Estrogen Receptors	Negative	130	91 (70.0)	2.9 (1.5,4.1)	128	56 (43.8)	9.8 (7.2,NE)	1.9524 (1.3972,2.7283) [<.0001]	0.8810
	Positive	129	99 (76.7)	2.1 (1.5,3.1)	132	60 (45.5)	8.9 (6.3,NE)	2.0437 (1.4806,2.8208) [<.0001]	
Progesterone Receptors	Negative	177	125 (70.6)	2.9 (1.5,4.2)	168	71 (42.3)	10.3 (8.3,NE)	1.9954 (1.4893,2.6734) [<.0001]	0.8408
	Positive	81	64 (79.0)	1.7 (1.5,3.0)	92	44 (47.8)	8.9 (4.8,NE)	2.1581 (1.4662,3.1767) [<.0001]	
Prior Treatment with Pertuzumab	No	99	67 (67.7)	2.9 (1.5,4.2)	105	52 (49.5)	7.1 (4.8,10.8)	1.5959 (1.1100,2.2944) [0.0120]	0.1013
	Yes	162	124 (76.5)	2.8 (1.5,3.0)	158	64 (40.5)	11.3 (8.4,NE)	2.3331 (1.7219,3.1613) [<.0001]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Nausea and Vomiting									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	135 (71.8)	1.9 (1.5,3.0)	191	81 (42.4)	9.8 (8.1,NE)	2.0510 (1.5549,2.7054) [<.0001]	0.7893
	>= 3	73	56 (76.7)	3.0 (1.7,4.3)	72	35 (48.6)	9.6 (6.3,13.9)	1.9765 (1.2918,3.0241) [0.0014]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	118 (75.6)	2.8 (1.5,3.0)	152	61 (40.1)	11.9 (8.4,NE)	2.3462 (1.7186,3.2031) [<.0001]	0.6876
	>= 3	6	6 (100.0)	3.0 (0.8,NE)	6	3 (50.0)	7.4 (0.8,NE)	2.6886 (0.5364,13.4773) [0.2114]	
Renal Impairment at Baseline	Mild	92	74 (80.4)	1.5 (1.4,2.8)	104	47 (45.2)	10.3 (6.6,NE)	2.5998 (1.7998,3.7555) [<.0001]	0.0465
	Moderate	30	21 (70.0)	3.0 (1.5,7.2)	22	5 (22.7)	NE (13.9,NE)	3.3756 (1.2698,8.9734) [0.0096]	
	Normal	130	92 (70.8)	3.0 (1.6,4.4)	130	62 (47.7)	8.5 (6.3,9.9)	1.5256 (1.1000,2.1157) [0.0121]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Symptom Scales/Nausea and Vomiting									
Hepatic Impairment	Mild	49	32 (65.3)	3.0 (1.4,6.9)	49	22 (44.9)	6.6 (4.1,NE)	1.4451 (0.8389,2.4894) [0.1892]	0.1614
	Normal	208	159 (76.4)	2.8 (1.5,3.0)	212	94 (44.3)	9.9 (8.6,NE)	2.1417 (1.6572,2.7678) [<.0001]	
Baseline Visceral Disease	No	66	51 (77.3)	2.8 (1.5,4.4)	74	34 (45.9)	9.7 (6.3,NE)	1.9333 (1.2506,2.9887) [0.0026]	0.8908
	Yes	195	140 (71.8)	2.8 (1.5,3.1)	189	82 (43.4)	9.6 (7.1,NE)	2.0419 (1.5525,2.6855) [<.0001]	
Baseline CNS Metastases	No	218	160 (73.4)	2.8 (1.5,3.1)	224	95 (42.4)	9.9 (8.4,NE)	2.0922 (1.6212,2.7000) [<.0001]	0.4139
	Yes	43	31 (72.1)	2.9 (1.5,4.3)	39	21 (53.8)	7.0 (4.3,10.3)	1.6052 (0.9152,2.8152) [0.1000]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Symptom Scales/Nausea and Vomiting									
History of CNS Metastases	No	199	150 (75.4)	2.8 (1.5,3.0)	211	92 (43.6)	9.7 (7.6,NE)	2.1027 (1.6200,2.7292) [<.0001]	0.5133
	Yes	62	41 (66.1)	3.0 (1.6,6.2)	52	24 (46.2)	9.6 (6.6,11.3)	1.6734 (1.0036,2.7902) [0.0488]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Pain									
Age	<65	212	114 (53.8)	8.9 (5.7,15.7)	206	112 (54.4)	5.5 (4.2,8.3)	0.7354 (0.5650,0.9572) [0.0225]	0.0127
	>=65	49	28 (57.1)	5.6 (1.5,NE)	57	25 (43.9)	10.4 (8.1,NE)	1.5217 (0.8860,2.6137) [0.1296]	
Age	<75	253	139 (54.9)	8.5 (5.6,14.5)	255	132 (51.8)	6.9 (4.8,10.0)	0.8700 (0.6847,1.1055) [0.2570]	0.7569
	>=75	8	3 (37.5)	5.5 (0.8,NE)	8	5 (62.5)	7.5 (3.5,NE)	0.7560 (0.1758,3.2507) [0.7062]	
Region	Asia	149	87 (58.4)	7.0 (5.1,10.7)	160	78 (48.8)	8.3 (5.6,11.8)	1.0239 (0.7531,1.3922) [0.8781]	0.0260
	Europe	54	28 (51.9)	7.0 (2.9,NE)	50	28 (56.0)	5.5 (1.7,12.5)	0.8041 (0.4749,1.3615) [0.4128]	
	North America	17	12 (70.6)	3.1 (1.4,NE)	17	8 (47.1)	7.6 (1.5,NE)	1.3972 (0.5615,3.4771) [0.4681]	
	Rest of World	41	15 (36.6)	NE (7.0,NE)	36	23 (63.9)	4.2 (1.7,10.3)	0.3771 (0.1959,0.7261) [0.0023]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Pain									
Race	Asian	152	88 (57.9)	7.0 (5.1,10.7)	162	79 (48.8)	8.3 (5.6,11.8)	1.0226 (0.7535,1.3877) [0.8839]	0.0379
	Black Or African American	10	7 (70.0)	4.2 (1.4,NE)	9	3 (33.3)	NE (2.8,NE)	2.3354 (0.6012,9.0727) [0.2072]	
	Other	28	14 (50.0)	14.0 (2.9,NE)	20	13 (65.0)	1.5 (1.4,6.0)	0.4512 (0.2092,0.9731) [0.0350]	
	White	71	33 (46.5)	22.3 (3.0,NE)	72	42 (58.3)	5.6 (2.9,10.3)	0.6265 (0.3942,0.9957) [0.0441]	
ECOG PS	0	154	83 (53.9)	8.9 (5.6,16.4)	175	96 (54.9)	6.9 (4.8,8.9)	0.7943 (0.5910,1.0675) [0.1264]	0.4113
	1	106	59 (55.7)	7.3 (3.3,15.7)	87	41 (47.1)	7.6 (4.2,NE)	1.0031 (0.6721,1.4972) [0.9780]	
Hormone Receptor Status	Negative	126	76 (60.3)	5.8 (3.0,8.5)	122	60 (49.2)	8.3 (4.6,11.9)	1.1660 (0.8303,1.6374) [0.3789]	0.0201
	Positive	133	66 (49.6)	14.0 (7.0,NE)	139	76 (54.7)	6.1 (4.2,10.3)	0.6656 (0.4771,0.9284) [0.0163]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Pain									
Estrogen Receptors	Negative	130	78 (60.0)	5.6 (3.0,8.5)	128	63 (49.2)	8.3 (4.3,11.9)	1.1555 (0.8284,1.6118) [0.3968]	0.0164
	Positive	129	64 (49.6)	14.0 (7.0,NE)	132	73 (55.3)	6.1 (4.2,8.9)	0.6426 (0.4573,0.9030) [0.0105]	
Progesterone Receptors	Negative	177	106 (59.9)	5.8 (4.1,8.9)	168	90 (53.6)	7.6 (4.2,10.0)	1.0089 (0.7611,1.3374) [0.9507]	0.0778
	Positive	81	36 (44.4)	22.3 (8.5,NE)	92	46 (50.0)	6.1 (4.4,13.8)	0.6270 (0.4034,0.9746) [0.0370]	
Prior Treatment with Pertuzumab	No	99	44 (44.4)	16.4 (8.5,NE)	105	50 (47.6)	7.6 (5.6,13.9)	0.7283 (0.4844,1.0951) [0.1248]	0.3956
	Yes	162	98 (60.5)	5.8 (3.1,9.9)	158	87 (55.1)	5.6 (4.2,9.8)	0.9313 (0.6963,1.2458) [0.6346]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Pain									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	104 (55.3)	7.0 (5.6,14.0)	191	104 (54.5)	6.0 (4.2,8.6)	0.8150 (0.6201,1.0713) [0.1426]	0.4256
	>= 3	73	38 (52.1)	9.9 (3.3,NE)	72	33 (45.8)	11.8 (5.6,14.3)	0.9874 (0.6160,1.5827) [0.9595]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	94 (60.3)	5.6 (3.1,10.0)	152	85 (55.9)	5.5 (4.2,8.9)	0.9237 (0.6874,1.2413) [0.6007]	0.6196
	>= 3	6	4 (66.7)	7.8 (0.7,NE)	6	2 (33.3)	14.3 (1.4,NE)	1.4158 (0.2570,7.8000) [0.6882]	
Renal Impairment at Baseline	Mild	92	57 (62.0)	5.8 (4.2,10.2)	104	56 (53.8)	8.3 (5.6,10.7)	1.1142 (0.7702,1.6118) [0.5565]	0.0556
	Moderate	30	17 (56.7)	7.3 (1.7,NE)	22	8 (36.4)	13.9 (3.5,NE)	1.5251 (0.6573,3.5385) [0.3273]	
	Normal	130	68 (52.3)	10.0 (5.6,NE)	130	70 (53.8)	4.8 (4.2,10.0)	0.6881 (0.4894,0.9674) [0.0307]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Pain									
Hepatic Impairment	Mild	49	23 (46.9)	16.9 (3.3,NE)	49	22 (44.9)	5.6 (3.1,NE)	0.7992 (0.4447,1.4364) [0.4578]	0.7007
	Normal	208	119 (57.2)	8.5 (5.6,14.0)	212	115 (54.2)	7.6 (5.0,10.3)	0.8741 (0.6752,1.1314) [0.3057]	
Baseline Visceral Disease	No	66	36 (54.5)	9.9 (5.6,NE)	74	39 (52.7)	6.3 (3.7,13.9)	0.7768 (0.4924,1.2255) [0.2791]	0.5641
	Yes	195	106 (54.4)	7.3 (4.4,14.0)	189	98 (51.9)	7.6 (5.0,10.3)	0.8948 (0.6788,1.1796) [0.4309]	
Baseline CNS Metastases	No	218	117 (53.7)	8.5 (5.7,16.4)	224	119 (53.1)	6.0 (4.3,10.0)	0.8183 (0.6332,1.0574) [0.1259]	0.2639
	Yes	43	25 (58.1)	4.3 (2.9,11.7)	39	18 (46.2)	8.4 (5.0,10.7)	1.0960 (0.5901,2.0357) [0.7730]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Pain									
History of CNS Metastases	No	199	107 (53.8)	7.3 (5.6,16.4)	211	112 (53.1)	6.1 (4.3,10.0)	0.8223 (0.6302,1.0728) [0.1509]	0.3842
	Yes	62	35 (56.5)	10.0 (3.0,14.5)	52	25 (48.1)	8.3 (5.0,10.7)	0.9444 (0.5550,1.6070) [0.8250]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Dyspnoea									
Age	<65	212	77 (36.3)	NE (16.6,NE)	206	80 (38.8)	14.3 (8.4,NE)	0.7107 (0.5172,0.9764) [0.0349]	0.0207
	>=65	49	24 (49.0)	10.7 (4.2,NE)	57	18 (31.6)	20.5 (14.8,NE)	1.6454 (0.8904,3.0408) [0.1115]	
Age	<75	253	96 (37.9)	NE (16.6,NE)	255	95 (37.3)	15.2 (11.7,NE)	0.8130 (0.6105,1.0828) [0.1567]	0.0837
	>=75	8	5 (62.5)	2.7 (0.8,NE)	8	3 (37.5)	NE (2.8,NE)	2.8577 (0.6759,12.0827) [0.1360]	
Region	Asia	149	63 (42.3)	16.6 (12.5,NE)	160	59 (36.9)	14.8 (8.5,NE)	0.9243 (0.6444,1.3258) [0.6664]	0.1071
	Europe	54	17 (31.5)	NE (18.1,NE)	50	16 (32.0)	NE (5.1,NE)	0.8001 (0.4012,1.5955) [0.5266]	
	North America	17	12 (70.6)	4.3 (2.5,12.2)	17	7 (41.2)	NE (1.5,NE)	1.3782 (0.5416,3.5071) [0.4981]	
	Rest of World	41	9 (22.0)	NE (NE,NE)	36	16 (44.4)	11.7 (4.8,NE)	0.3496 (0.1533,0.7972) [0.0091]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Dyspnoea									
Race	Asian	152	63 (41.4)	16.6 (12.5,NE)	162	59 (36.4)	14.8 (8.5,NE)	0.9258 (0.6455,1.3279) [0.6728]	0.6315
	Black Or African American	10	3 (30.0)	NE (3.1,NE)	9	4 (44.4)	NE (0.8,NE)	0.3927 (0.0868,1.7770) [0.2186]	
	Other	28	7 (25.0)	NE (18.1,NE)	20	4 (20.0)	NE (4.2,NE)	0.9595 (0.2774,3.3194) [0.9496]	
	White	71	28 (39.4)	18.6 (8.7,NE)	72	31 (43.1)	11.7 (5.1,NE)	0.7554 (0.4515,1.2636) [0.2869]	
ECOG PS	0	154	58 (37.7)	NE (14.5,NE)	175	60 (34.3)	20.5 (13.8,NE)	0.8913 (0.6191,1.2832) [0.5395]	0.4940
	1	106	43 (40.6)	18.6 (12.5,NE)	87	38 (43.7)	8.4 (5.7,NE)	0.7217 (0.4632,1.1244) [0.1454]	
Hormone Receptor Status	Negative	126	50 (39.7)	18.1 (12.2,NE)	122	41 (33.6)	NE (7.0,NE)	0.9786 (0.6457,1.4832) [0.9192]	0.3965
	Positive	133	50 (37.6)	NE (15.8,NE)	139	56 (40.3)	14.8 (9.7,20.5)	0.7386 (0.5018,1.0870) [0.1234]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Dyspnoea									
Estrogen Receptors	Negative	130	51 (39.2)	18.1 (12.2,NE)	128	45 (35.2)	NE (7.0,NE)	0.9252 (0.6179,1.3851) [0.7044]	0.5741
	Positive	129	49 (38.0)	NE (15.8,NE)	132	52 (39.4)	14.3 (8.5,NE)	0.7546 (0.5078,1.1215) [0.1630]	
Progesterone Receptors	Negative	177	72 (40.7)	18.6 (13.8,NE)	168	63 (37.5)	20.5 (7.3,NE)	0.8734 (0.6212,1.2280) [0.4375]	0.6272
	Positive	81	27 (33.3)	NE (15.8,NE)	92	34 (37.0)	14.8 (9.7,NE)	0.7174 (0.4295,1.1984) [0.2036]	
Prior Treatment with Pertuzumab	No	99	37 (37.4)	NE (13.8,NE)	105	34 (32.4)	NE (11.7,NE)	0.9620 (0.6020,1.5372) [0.8663]	0.3720
	Yes	162	64 (39.5)	NE (14.5,NE)	158	64 (40.5)	14.8 (7.6,NE)	0.7723 (0.5430,1.0982) [0.1504]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Dyspnoea									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	67 (35.6)	NE (18.6,NE)	191	76 (39.8)	14.8 (7.3,NE)	0.7176 (0.5152,0.9996) [0.0489]	0.0323
	>= 3	73	34 (46.6)	15.8 (8.8,NE)	72	22 (30.6)	15.2 (11.7,NE)	1.2672 (0.7358,2.1822) [0.3944]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	61 (39.1)	NE (14.5,NE)	152	61 (40.1)	15.2 (7.6,NE)	0.7905 (0.5512,1.1336) [0.2015]	0.5098
	>= 3	6	3 (50.0)	9.9 (1.5,NE)	6	3 (50.0)	8.6 (0.7,NE)	0.5460 (0.1075,2.7736) [0.4593]	
Renal Impairment at Baseline	Mild	92	43 (46.7)	15.6 (10.7,18.6)	104	41 (39.4)	20.5 (7.3,NE)	1.0684 (0.6952,1.6419) [0.7612]	0.0267
	Moderate	30	13 (43.3)	14.5 (4.5,NE)	22	4 (18.2)	NE (4.2,NE)	1.9974 (0.6510,6.1279) [0.2173]	
	Normal	130	43 (33.1)	NE (NE,NE)	130	52 (40.0)	13.8 (7.0,NE)	0.5834 (0.3856,0.8828) [0.0100]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Dyspnoea									
Hepatic Impairment	Mild	49	15 (30.6)	NE (14.5,NE)	49	16 (32.7)	16.6 (8.1,NE)	0.7117 (0.3510,1.4433) [0.3456]	0.5906
	Normal	208	86 (41.3)	18.6 (14.5,NE)	212	82 (38.7)	15.2 (8.5,NE)	0.8738 (0.6432,1.1871) [0.3879]	
Baseline Visceral Disease	No	66	29 (43.9)	18.1 (10.7,NE)	74	32 (43.2)	13.8 (5.7,NE)	0.7053 (0.4243,1.1723) [0.1779]	0.5109
	Yes	195	72 (36.9)	NE (15.6,NE)	189	66 (34.9)	16.6 (14.3,NE)	0.9085 (0.6484,1.2729) [0.5785]	
Baseline CNS Metastases	No	218	90 (41.3)	18.6 (13.8,NE)	224	81 (36.2)	15.2 (13.8,NE)	0.9540 (0.7049,1.2912) [0.7595]	0.0264
	Yes	43	11 (25.6)	NE (15.8,NE)	39	17 (43.6)	6.9 (2.9,NE)	0.3883 (0.1763,0.8552) [0.0157]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Dyspnoea									
History of CNS Metastases	No	199	80 (40.2)	NE (14.5,NE)	211	77 (36.5)	15.2 (13.8,NE)	0.9276 (0.6768,1.2714) [0.6386]	0.2141
	Yes	62	21 (33.9)	NE (13.8,NE)	52	21 (40.4)	NE (4.2,NE)	0.5566 (0.2966,1.0444) [0.0659]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Insomnia									
Age	<65	212	97 (45.8)	16.1 (9.9,NE)	206	89 (43.2)	11.3 (5.4,NE)	0.8371 (0.6261,1.1191) [0.2329]	0.9347
	>=65	49	18 (36.7)	NE (5.7,NE)	57	23 (40.4)	NE (4.7,NE)	0.8724 (0.4701,1.6188) [0.6569]	
Age	<75	253	113 (44.7)	19.4 (10.7,NE)	255	108 (42.4)	12.7 (7.2,NE)	0.8733 (0.6698,1.1385) [0.3173]	0.4591
	>=75	8	2 (25.0)	NE (2.9,NE)	8	4 (50.0)	6.8 (1.5,NE)	0.5158 (0.0931,2.8569) [0.4405]	
Region	Asia	149	64 (43.0)	NE (10.6,NE)	160	69 (43.1)	15.2 (4.8,NE)	0.8087 (0.5742,1.1389) [0.2252]	0.8090
	Europe	54	23 (42.6)	16.1 (5.6,NE)	50	18 (36.0)	NE (7.0,NE)	1.0801 (0.5810,2.0077) [0.8032]	
	North America	17	10 (58.8)	9.2 (1.4,NE)	17	8 (47.1)	11.3 (2.9,NE)	0.9335 (0.3550,2.4543) [0.8980]	
	Rest of World	41	18 (43.9)	NE (5.6,NE)	36	17 (47.2)	9.6 (2.8,NE)	0.7555 (0.3889,1.4677) [0.4017]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Insomnia									
Race	Asian	152	65 (42.8)	NE (10.6,NE)	162	70 (43.2)	15.2 (4.8,NE)	0.8134 (0.5790,1.1427) [0.2343]	0.4272
	Black Or African American	10	7 (70.0)	5.4 (1.4,NE)	9	3 (33.3)	NE (2.8,NE)	2.2847 (0.5888,8.8652) [0.2228]	
	Other	28	9 (32.1)	NE (12.5,NE)	20	7 (35.0)	NE (1.5,NE)	0.6541 (0.2415,1.7720) [0.4047]	
	White	71	34 (47.9)	12.7 (5.6,NE)	72	32 (44.4)	8.3 (4.4,NE)	0.9352 (0.5742,1.5232) [0.7903]	
ECOG PS	0	154	69 (44.8)	19.4 (9.9,NE)	175	76 (43.4)	12.7 (7.0,NE)	0.8415 (0.6064,1.1679) [0.3037]	0.9718
	1	106	46 (43.4)	NE (7.4,NE)	87	36 (41.4)	10.3 (4.1,NE)	0.8811 (0.5685,1.3657) [0.5680]	
Hormone Receptor Status	Negative	126	58 (46.0)	14.5 (8.3,NE)	122	48 (39.3)	NE (4.7,NE)	0.9779 (0.6659,1.4362) [0.9138]	0.3676
	Positive	133	56 (42.1)	22.3 (11.7,NE)	139	63 (45.3)	9.8 (6.9,NE)	0.7681 (0.5349,1.1030) [0.1507]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Insomnia									
Estrogen Receptors	Negative	130	58 (44.6)	16.1 (9.2,NE)	128	50 (39.1)	NE (4.8,NE)	0.9556 (0.6533,1.3976) [0.8181]	0.4188
	Positive	129	56 (43.4)	22.3 (8.4,NE)	132	61 (46.2)	8.6 (5.3,NE)	0.7702 (0.5347,1.1095) [0.1587]	
Progesterone Receptors	Negative	177	78 (44.1)	19.4 (9.8,NE)	168	70 (41.7)	15.2 (5.3,NE)	0.8707 (0.6296,1.2041) [0.4069]	0.9669
	Positive	81	36 (44.4)	22.3 (8.3,NE)	92	41 (44.6)	10.3 (5.3,NE)	0.8424 (0.5370,1.3215) [0.4520]	
Prior Treatment with Pertuzumab	No	99	38 (38.4)	NE (11.7,NE)	105	46 (43.8)	12.7 (4.2,NE)	0.7173 (0.4660,1.1039) [0.1244]	0.3020
	Yes	162	77 (47.5)	16.1 (8.4,NE)	158	66 (41.8)	11.3 (7.2,NE)	0.9415 (0.6756,1.3120) [0.7284]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Insomnia									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	82 (43.6)	19.4 (10.6,NE)	191	84 (44.0)	9.8 (5.4,NE)	0.8042 (0.5920,1.0924) [0.1629]	0.4472
	>= 3	73	33 (45.2)	12.5 (7.3,NE)	72	28 (38.9)	NE (4.2,NE)	1.0105 (0.6092,1.6761) [0.9667]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	75 (48.1)	14.5 (8.3,NE)	152	64 (42.1)	11.3 (7.2,NE)	0.9587 (0.6846,1.3426) [0.8112]	0.5223
	>= 3	6	2 (33.3)	NE (0.8,NE)	6	2 (33.3)	NE (1.4,NE)	0.6325 (0.0885,4.5218) [0.6452]	
Renal Impairment at Baseline	Mild	92	47 (51.1)	11.7 (5.3,NE)	104	43 (41.3)	NE (5.0,NE)	1.1309 (0.7472,1.7114) [0.5522]	0.1905
	Moderate	30	11 (36.7)	NE (7.1,NE)	22	10 (45.5)	8.3 (3.7,NE)	0.6269 (0.2649,1.4835) [0.2760]	
	Normal	130	54 (41.5)	22.3 (12.7,NE)	130	58 (44.6)	9.8 (4.4,NE)	0.6849 (0.4696,0.9990) [0.0486]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Insomnia									
Hepatic Impairment	Mild	49	17 (34.7)	NE (8.3,NE)	49	17 (34.7)	12.7 (4.1,NE)	0.7289 (0.3700,1.4362) [0.3572]	0.6398
	Normal	208	98 (47.1)	16.1 (9.8,NE)	212	95 (44.8)	11.3 (6.9,NE)	0.8866 (0.6676,1.1774) [0.4103]	
Baseline Visceral Disease	No	66	36 (54.5)	10.6 (4.2,NE)	74	34 (45.9)	15.2 (3.3,NE)	1.0146 (0.6344,1.6226) [0.9474]	0.4450
	Yes	195	79 (40.5)	22.3 (14.5,NE)	189	78 (41.3)	11.3 (7.2,NE)	0.8022 (0.5852,1.0996) [0.1692]	
Baseline CNS Metastases	No	218	101 (46.3)	16.1 (9.2,NE)	224	95 (42.4)	12.7 (7.9,NE)	0.9219 (0.6960,1.2211) [0.5727]	0.1917
	Yes	43	14 (32.6)	19.4 (10.4,NE)	39	17 (43.6)	7.0 (3.5,NE)	0.5778 (0.2807,1.1895) [0.1321]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Insomnia									
History of CNS Metastases	No	199	90 (45.2)	16.1 (9.8,NE)	211	86 (40.8)	15.2 (7.9,NE)	0.9316 (0.6925,1.2533) [0.6423]	0.2299
	Yes	62	25 (40.3)	19.4 (9.2,NE)	52	26 (50.0)	5.0 (3.5,NE)	0.6207 (0.3542,1.0876) [0.0930]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Appetite Loss									
Age	<65	212	129 (60.8)	4.1 (2.9,5.6)	206	91 (44.2)	8.5 (5.8,NE)	1.4082 (1.0756,1.8436) [0.0126]	0.4858
	>=65	49	31 (63.3)	4.4 (1.8,14.3)	57	24 (42.1)	11.0 (5.7,NE)	1.7519 (1.0198,3.0096) [0.0411]	
Age	<75	253	154 (60.9)	4.3 (3.0,5.6)	255	111 (43.5)	10.3 (6.7,20.5)	1.4371 (1.1249,1.8359) [0.0037]	0.1491
	>=75	8	6 (75.0)	1.6 (0.8,NE)	8	4 (50.0)	4.2 (0.9,NE)	3.1013 (0.7552,12.7356) [0.1032]	
Region	Asia	149	91 (61.1)	4.3 (2.9,5.8)	160	74 (46.3)	8.5 (5.6,20.5)	1.3932 (1.0242,1.8952) [0.0353]	0.4708
	Europe	54	29 (53.7)	5.7 (2.8,NE)	50	20 (40.0)	10.3 (2.9,NE)	1.2381 (0.6986,2.1943) [0.4654]	
	North America	17	12 (70.6)	3.0 (1.5,14.4)	17	5 (29.4)	11.3 (5.5,NE)	2.7633 (0.9538,8.0053) [0.0508]	
	Rest of World	41	28 (68.3)	2.8 (1.6,5.6)	36	16 (44.4)	14.0 (2.9,NE)	1.6756 (0.9041,3.1055) [0.0999]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Appetite Loss									
Race	Asian	152	91 (59.9)	4.4 (3.0,8.5)	162	74 (45.7)	9.5 (5.6,20.5)	1.3879 (1.0204,1.8878) [0.0376]	0.1422
	Black Or African American	10	7 (70.0)	3.2 (1.5,NE)	9	6 (66.7)	2.8 (0.8,NE)	0.6539 (0.2185,1.9572) [0.4604]	
	Other	28	14 (50.0)	14.3 (1.5,NE)	20	8 (40.0)	NE (1.5,NE)	1.0170 (0.4242,2.4382) [0.9720]	
	White	71	48 (67.6)	2.8 (1.7,4.4)	72	27 (37.5)	NE (6.9,NE)	2.1226 (1.3222,3.4075) [0.0014]	
ECOG PS	0	154	92 (59.7)	4.7 (3.0,10.2)	175	79 (45.1)	10.2 (6.6,20.5)	1.3727 (1.0150,1.8564) [0.0401]	0.6360
	1	106	68 (64.2)	3.2 (2.1,4.5)	87	36 (41.4)	NE (4.3,NE)	1.5916 (1.0615,2.3866) [0.0226]	
Hormone Receptor Status	Negative	126	75 (59.5)	4.1 (2.9,8.5)	122	52 (42.6)	11.0 (4.3,NE)	1.4805 (1.0388,2.1099) [0.0295]	0.9874
	Positive	133	85 (63.9)	4.2 (2.8,7.1)	139	63 (45.3)	10.2 (5.8,NE)	1.4647 (1.0554,2.0328) [0.0223]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Common Symptoms/Appetite Loss									
Estrogen Receptors	Negative	130	78 (60.0)	4.1 (2.9,5.6)	128	55 (43.0)	11.0 (4.3,NE)	1.4781 (1.0462,2.0882) [0.0263]	0.9710
	Positive	129	82 (63.6)	4.3 (2.8,7.1)	132	60 (45.5)	10.2 (5.8,NE)	1.4378 (1.0280,2.0111) [0.0339]	
Progesterone Receptors	Negative	177	103 (58.2)	4.7 (3.0,10.2)	168	67 (39.9)	19.1 (8.4,NE)	1.5226 (1.1184,2.0730) [0.0074]	0.8515
	Positive	81	56 (69.1)	2.9 (2.0,4.4)	92	47 (51.1)	6.0 (4.8,14.0)	1.4851 (1.0063,2.1916) [0.0454]	
Prior Treatment with Pertuzumab	No	99	62 (62.6)	2.9 (2.1,4.2)	105	45 (42.9)	8.5 (5.7,NE)	1.7171 (1.1689,2.5226) [0.0056]	0.3079
	Yes	162	98 (60.5)	4.7 (3.0,10.2)	158	70 (44.3)	10.3 (6.0,20.5)	1.3167 (0.9669,1.7930) [0.0814]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Appetite Loss									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	112 (59.6)	4.4 (3.0,10.2)	191	86 (45.0)	9.5 (5.7,20.5)	1.3199 (0.9955,1.7499) [0.0542]	0.1967
	>= 3	73	48 (65.8)	3.0 (1.6,4.2)	72	29 (40.3)	14.0 (5.8,NE)	1.9162 (1.2050,3.0471) [0.0053]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	93 (59.6)	4.7 (3.0,10.3)	152	67 (44.1)	11.0 (6.0,20.5)	1.3127 (0.9569,1.8007) [0.0921]	0.9165
	>= 3	6	5 (83.3)	3.0 (0.8,NE)	6	3 (50.0)	4.5 (2.8,NE)	1.2030 (0.2666,5.4289) [0.8098]	
Renal Impairment at Baseline	Mild	92	58 (63.0)	4.1 (1.6,5.6)	104	42 (40.4)	20.5 (7.0,NE)	1.9840 (1.3326,2.9539) [0.0006]	0.1235
	Moderate	30	19 (63.3)	3.5 (2.1,15.0)	22	8 (36.4)	NE (2.0,NE)	1.4822 (0.6481,3.3898) [0.3444]	
	Normal	130	79 (60.8)	4.4 (2.9,12.0)	130	63 (48.5)	7.2 (5.1,14.0)	1.1177 (0.7988,1.5640) [0.5256]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Appetite Loss									
Hepatic Impairment	Mild	49	30 (61.2)	3.2 (1.5,5.6)	49	20 (40.8)	6.6 (2.9,NE)	1.4496 (0.8229,2.5538) [0.1985]	0.9006
	Normal	208	130 (62.5)	4.3 (2.9,7.1)	212	95 (44.8)	11.0 (7.0,20.5)	1.4562 (1.1163,1.8996) [0.0055]	
Baseline Visceral Disease	No	66	40 (60.6)	4.5 (2.9,15.0)	74	37 (50.0)	9.5 (3.3,19.1)	1.0752 (0.6850,1.6878) [0.7621]	0.1420
	Yes	195	120 (61.5)	3.2 (2.8,5.6)	189	78 (41.3)	11.3 (6.5,NE)	1.6520 (1.2413,2.1986) [0.0005]	
Baseline CNS Metastases	No	218	134 (61.5)	4.2 (2.9,5.6)	224	101 (45.1)	10.2 (6.0,20.5)	1.3903 (1.0728,1.8017) [0.0130]	0.3181
	Yes	43	26 (60.5)	3.0 (1.6,9.9)	39	14 (35.9)	NE (5.0,NE)	1.9908 (1.0380,3.8181) [0.0349]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Common Symptoms/Appetite Loss									
History of CNS Metastases	No	199	131 (65.8)	3.4 (2.8,4.7)	211	97 (46.0)	9.5 (5.8,19.1)	1.4945 (1.1485,1.9447) [0.0027]	0.8655
	Yes	62	29 (46.8)	9.9 (2.8,NE)	52	18 (34.6)	NE (5.0,NE)	1.4467 (0.8016,2.6110) [0.2185]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Constipation									
Age	<65	212	126 (59.4)	5.1 (4.2,8.3)	206	93 (45.1)	8.5 (5.7,12.9)	1.2799 (0.9777,1.6755) [0.0721]	0.6806
	>=65	49	28 (57.1)	7.3 (3.1,15.9)	57	29 (50.9)	8.4 (4.2,19.4)	1.1452 (0.6800,1.9288) [0.6166]	
Age	<75	253	150 (59.3)	5.6 (4.2,8.3)	255	116 (45.5)	8.6 (7.0,12.9)	1.2684 (0.9942,1.6182) [0.0560]	0.1884
	>=75	8	4 (50.0)	8.8 (1.4,NE)	8	6 (75.0)	2.8 (0.8,4.2)	0.4224 (0.1050,1.7002) [0.2114]	
Region	Asia	149	92 (61.7)	4.3 (3.1,7.3)	160	70 (43.8)	10.4 (7.0,NE)	1.5069 (1.1028,2.0593) [0.0098]	0.2040
	Europe	54	33 (61.1)	5.8 (3.0,8.3)	50	27 (54.0)	5.7 (4.2,11.3)	1.0241 (0.6150,1.7053) [0.9220]	
	North America	17	10 (58.8)	8.3 (1.7,NE)	17	10 (58.8)	5.7 (0.8,8.4)	0.6060 (0.2448,1.5005) [0.2776]	
	Rest of World	41	19 (46.3)	NE (2.9,NE)	36	15 (41.7)	8.6 (2.9,NE)	0.9815 (0.4970,1.9383) [0.9418]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Constipation									
Race	Asian	152	93 (61.2)	4.3 (3.1,7.3)	162	71 (43.8)	10.4 (7.0,NE)	1.4996 (1.0995,2.0452) [0.0102]	0.2519
	Black Or African American	10	6 (60.0)	3.0 (1.4,NE)	9	5 (55.6)	4.6 (0.8,NE)	1.0098 (0.3070,3.3212) [0.9956]	
	Other	28	17 (60.7)	5.8 (2.8,NE)	20	10 (50.0)	5.6 (2.9,NE)	1.1176 (0.5103,2.4475) [0.7958]	
	White	71	38 (53.5)	8.3 (4.4,NE)	72	36 (50.0)	5.7 (3.4,11.3)	0.8044 (0.5065,1.2777) [0.3543]	
ECOG PS	0	154	95 (61.7)	5.1 (3.2,8.3)	175	75 (42.9)	12.9 (7.0,NE)	1.4519 (1.0709,1.9683) [0.0162]	0.0695
	1	106	59 (55.7)	5.8 (3.2,14.3)	87	47 (54.0)	5.6 (3.5,9.8)	0.9071 (0.6164,1.3348) [0.6251]	
Hormone Receptor Status	Negative	126	69 (54.8)	6.9 (4.2,14.5)	122	59 (48.4)	7.3 (5.3,15.2)	1.0926 (0.7706,1.5492) [0.6336]	0.3358
	Positive	133	84 (63.2)	4.4 (3.1,7.0)	139	63 (45.3)	10.4 (5.9,NE)	1.3616 (0.9804,1.8910) [0.0647]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Constipation									
Estrogen Receptors	Negative	130	72 (55.4)	6.1 (3.2,11.0)	128	64 (50.0)	7.0 (4.8,11.3)	1.0714 (0.7641,1.5023) [0.7016]	0.2144
	Positive	129	81 (62.8)	4.4 (3.1,8.3)	132	57 (43.2)	11.3 (7.0,NE)	1.4205 (1.0102,1.9974) [0.0428]	
Progesterone Receptors	Negative	177	101 (57.1)	6.1 (4.2,8.9)	168	85 (50.6)	7.3 (5.6,10.4)	1.0742 (0.8042,1.4350) [0.6380]	0.1039
	Positive	81	52 (64.2)	4.0 (3.0,5.8)	92	37 (40.2)	12.6 (6.3,NE)	1.6075 (1.0509,2.4587) [0.0272]	
Prior Treatment with Pertuzumab	No	99	43 (43.4)	NE (4.9,NE)	105	41 (39.0)	19.4 (7.0,NE)	1.0897 (0.7094,1.6740) [0.7146]	0.3198
	Yes	162	111 (68.5)	4.2 (3.1,5.8)	158	81 (51.3)	7.6 (5.6,11.3)	1.3016 (0.9748,1.7380) [0.0719]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Constipation									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	113 (60.1)	5.6 (4.2,8.3)	191	94 (49.2)	7.6 (5.6,11.3)	1.1148 (0.8463,1.4683) [0.4399]	0.2129
	>= 3	73	41 (56.2)	5.6 (2.8,16.5)	72	28 (38.9)	19.4 (7.0,NE)	1.6045 (0.9911,2.5977) [0.0542]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	107 (68.6)	4.2 (3.1,5.8)	152	81 (53.3)	7.0 (5.6,9.8)	1.2576 (0.9395,1.6834) [0.1210]	0.0347
	>= 3	6	4 (66.7)	10.4 (2.2,NE)	6	0 (0.0)	NE (NE,NE)	NE	
Renal Impairment at Baseline	Mild	92	59 (64.1)	4.2 (2.9,5.8)	104	52 (50.0)	8.3 (5.6,15.2)	1.4554 (1.0011,2.1157) [0.0483]	0.5636
	Moderate	30	18 (60.0)	4.9 (1.5,16.5)	22	9 (40.9)	11.3 (2.8,NE)	1.5387 (0.6679,3.5446) [0.3121]	
	Normal	130	75 (57.7)	8.3 (4.2,12.9)	130	59 (45.4)	8.5 (5.7,NE)	1.1003 (0.7797,1.5526) [0.5886]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Constipation									
Hepatic Impairment	Mild	49	22 (44.9)	14.5 (3.1,NE)	49	22 (44.9)	6.3 (3.6,NE)	0.7748 (0.4275,1.4044) [0.3963]	0.0770
	Normal	208	132 (63.5)	4.5 (3.8,7.0)	212	100 (47.2)	8.6 (5.9,15.2)	1.3537 (1.0425,1.7579) [0.0227]	
Baseline Visceral Disease	No	66	45 (68.2)	5.6 (3.8,8.3)	74	38 (51.4)	9.8 (4.2,12.9)	1.2811 (0.8315,1.9740) [0.2581]	0.8177
	Yes	195	109 (55.9)	5.6 (3.2,11.0)	189	84 (44.4)	8.4 (5.7,NE)	1.2283 (0.9217,1.6368) [0.1640]	
Baseline CNS Metastases	No	218	133 (61.0)	4.9 (3.2,8.3)	224	105 (46.9)	8.5 (5.7,12.9)	1.2655 (0.9787,1.6363) [0.0728]	0.6071
	Yes	43	21 (48.8)	7.8 (4.2,NE)	39	17 (43.6)	7.0 (4.8,NE)	1.0780 (0.5638,2.0612) [0.8278]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Constipation									
History of CNS Metastases	No	199	123 (61.8)	4.4 (3.1,7.0)	211	99 (46.9)	8.4 (5.7,12.9)	1.2965 (0.9939,1.6913) [0.0557]	0.4829
	Yes	62	31 (50.0)	8.3 (4.2,NE)	52	23 (44.2)	9.8 (4.8,NE)	1.0343 (0.5995,1.7845) [0.9043]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Diarrhea									
Age	<65	212	86 (40.6)	NE (17.1,NE)	206	47 (22.8)	NE (17.8,NE)	1.7374 (1.2154,2.4834) [0.0022]	0.8580
	>=65	49	20 (40.8)	NE (4.2,NE)	57	15 (26.3)	NE (13.9,NE)	1.7851 (0.9125,3.4924) [0.0883]	
Age	<75	253	103 (40.7)	NE (17.1,NE)	255	60 (23.5)	NE (17.8,NE)	1.7401 (1.2644,2.3948) [0.0006]	0.6842
	>=75	8	3 (37.5)	NE (0.7,NE)	8	2 (25.0)	NE (0.9,NE)	2.3617 (0.3931,14.1891) [0.3329]	
Region	Asia	149	61 (40.9)	NE (9.5,NE)	160	38 (23.8)	NE (NE,NE)	1.6991 (1.1321,2.5500) [0.0098]	0.0607
	Europe	54	22 (40.7)	18.0 (2.1,NE)	50	11 (22.0)	NE (NE,NE)	2.1195 (1.0229,4.3915) [0.0395]	
	North America	17	11 (64.7)	3.0 (0.9,NE)	17	2 (11.8)	17.8 (NE,NE)	6.4923 (1.4362,29.3479) [0.0051]	
	Rest of World	41	12 (29.3)	NE (13.3,NE)	36	11 (30.6)	13.9 (10.3,NE)	0.8206 (0.3588,1.8766) [0.6366]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Diarrhea									
Race	Asian	152	63 (41.4)	NE (9.1,NE)	162	38 (23.5)	NE (NE,NE)	1.7693 (1.1820,2.6485) [0.0050]	0.8265
	Black Or African American	10	2 (20.0)	NE (1.5,NE)	9	2 (22.2)	NE (4.2,NE)	0.7451 (0.1023,5.4272) [0.7707]	
	Other	28	12 (42.9)	18.0 (1.5,NE)	20	6 (30.0)	NE (7.1,NE)	1.5298 (0.5710,4.0982) [0.3992]	
	White	71	29 (40.8)	NE (4.4,NE)	72	16 (22.2)	17.8 (13.9,NE)	1.9110 (1.0338,3.5328) [0.0354]	
ECOG PS	0	154	66 (42.9)	20.0 (9.1,NE)	175	41 (23.4)	NE (17.8,NE)	1.8692 (1.2641,2.7640) [0.0015]	0.5950
	1	106	40 (37.7)	NE (11.1,NE)	87	21 (24.1)	NE (13.9,NE)	1.5570 (0.9161,2.6461) [0.0995]	
Hormone Receptor Status	Negative	126	44 (34.9)	NE (NE,NE)	122	32 (26.2)	NE (13.9,NE)	1.3127 (0.8316,2.0721) [0.2422]	0.0529
	Positive	133	62 (46.6)	18.0 (6.3,NE)	139	29 (20.9)	NE (17.8,NE)	2.3787 (1.5285,3.7019) [<.0001]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Diarrhea									
Estrogen Receptors	Negative	130	47 (36.2)	NE (18.0,NE)	128	32 (25.0)	NE (13.9,NE)	1.4240 (0.9073,2.2350) [0.1232]	0.1575
	Positive	129	59 (45.7)	20.0 (6.3,NE)	132	29 (22.0)	NE (17.8,NE)	2.2083 (1.4139,3.4490) [0.0004]	
Progesterone Receptors	Negative	177	70 (39.5)	NE (17.1,NE)	168	45 (26.8)	NE (NE,NE)	1.4753 (1.0132,2.1482) [0.0417]	0.0777
	Positive	81	36 (44.4)	18.0 (5.7,NE)	92	16 (17.4)	NE (17.8,NE)	2.7109 (1.5017,4.8940) [0.0006]	
Prior Treatment with Pertuzumab	No	99	35 (35.4)	NE (13.3,NE)	105	30 (28.6)	NE (11.3,NE)	1.1651 (0.7143,1.9002) [0.5407]	0.0569
	Yes	162	71 (43.8)	20.0 (6.9,NE)	158	32 (20.3)	NE (17.8,NE)	2.2762 (1.4965,3.4621) [<.0001]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Diarrhea									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	82 (43.6)	20.0 (9.1,NE)	191	42 (22.0)	NE (NE,NE)	2.1001 (1.4465,3.0488) [<.0001]	0.0721
	>= 3	73	24 (32.9)	NE (NE,NE)	72	20 (27.8)	13.9 (11.1,NE)	1.0669 (0.5860,1.9426) [0.8291]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	69 (44.2)	20.0 (6.3,NE)	152	31 (20.4)	NE (17.8,NE)	2.3137 (1.5113,3.5422) [<.0001]	0.6872
	>= 3	6	2 (33.3)	NE (1.4,NE)	6	1 (16.7)	NE (6.0,NE)	1.6292 (0.1467,18.0995) [0.6882]	
Renal Impairment at Baseline	Mild	92	43 (46.7)	17.1 (5.6,NE)	104	25 (24.0)	NE (NE,NE)	2.3049 (1.4074,3.7748) [0.0006]	0.1675
	Moderate	30	15 (50.0)	18.0 (2.1,NE)	22	4 (18.2)	NE (7.1,NE)	2.7501 (0.9038,8.3683) [0.0646]	
	Normal	130	45 (34.6)	NE (NE,NE)	130	31 (23.8)	17.8 (17.8,NE)	1.3041 (0.8222,2.0686) [0.2588]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Diarrhea									
Hepatic Impairment	Mild	49	15 (30.6)	NE (13.3,NE)	49	13 (26.5)	NE (6.6,NE)	0.9585 (0.4546,2.0209) [0.9104]	0.0844
	Normal	208	91 (43.8)	20.0 (9.5,NE)	212	49 (23.1)	NE (17.8,NE)	1.9843 (1.4003,2.8117) [<.0001]	
Baseline Visceral Disease	No	66	28 (42.4)	NE (5.6,NE)	74	20 (27.0)	NE (11.2,NE)	1.4853 (0.8333,2.6475) [0.1813]	0.5750
	Yes	195	78 (40.0)	20.0 (13.3,NE)	189	42 (22.2)	NE (17.8,NE)	1.8749 (1.2874,2.7304) [0.0009]	
Baseline CNS Metastases	No	218	89 (40.8)	NE (17.1,NE)	224	53 (23.7)	NE (17.8,NE)	1.7329 (1.2318,2.4378) [0.0014]	0.9190
	Yes	43	17 (39.5)	NE (4.3,NE)	39	9 (23.1)	NE (8.3,NE)	1.8079 (0.8038,4.0659) [0.1462]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Diarrhea									
History of CNS Metastases	No	199	80 (40.2)	NE (17.1,NE)	211	52 (24.6)	NE (17.8,NE)	1.6237 (1.1435,2.3056) [0.0064]	0.3842
	Yes	62	26 (41.9)	NE (4.8,NE)	52	10 (19.2)	NE (NE,NE)	2.3312 (1.1229,4.8398) [0.0193]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale	Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Common Difficulties	Symptoms/Financial									
Age		<65	212	67 (31.6)	NE (NE,NE)	206	68 (33.0)	NE (11.1,NE)	0.7256 (0.5157,1.0210) [0.0645]	0.0706
		>=65	49	20 (40.8)	19.7 (10.7,NE)	57	16 (28.1)	NE (12.7,NE)	1.3696 (0.7084,2.6480) [0.3484]	
Age		<75	253	83 (32.8)	NE (19.7,NE)	255	82 (32.2)	NE (12.7,NE)	0.7879 (0.5789,1.0724) [0.1288]	0.1510
		>=75	8	4 (50.0)	7.4 (1.4,NE)	8	2 (25.0)	NE (1.6,NE)	2.4706 (0.4350,14.0329) [0.2932]	
Region		Asia	149	53 (35.6)	NE (18.2,NE)	160	49 (30.6)	NE (11.7,NE)	0.9167 (0.6189,1.3576) [0.6622]	0.7668
		Europe	54	11 (20.4)	24.0 (NE,NE)	50	13 (26.0)	NE (12.7,NE)	0.5476 (0.2387,1.2566) [0.1497]	
		North America	17	6 (35.3)	NE (1.6,NE)	17	5 (29.4)	NE (2.8,NE)	1.0639 (0.3237,3.4963) [0.9185]	
		Rest of World	41	17 (41.5)	NE (6.9,NE)	36	17 (47.2)	8.5 (2.8,NE)	0.6724 (0.3426,1.3195) [0.2463]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale	Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Common Difficulties	Symptoms/Financial									
Race		Asian	152	53 (34.9)	NE (18.2,NE)	162	49 (30.2)	NE (11.7,NE)	0.9188 (0.6204,1.3607) [0.6705]	0.6298
		Black Or African American	10	6 (60.0)	6.2 (1.5,NE)	9	4 (44.4)	6.9 (1.4,NE)	1.0752 (0.3024,3.8236) [0.9028]	
		Other	28	8 (28.6)	24.0 (15.2,NE)	20	6 (30.0)	15.7 (7.1,NE)	0.6332 (0.2106,1.9035) [0.4120]	
		White	71	20 (28.2)	NE (NE,NE)	72	25 (34.7)	NE (8.6,NE)	0.6209 (0.3437,1.1217) [0.1107]	
ECOG PS		0	154	53 (34.4)	NE (19.7,NE)	175	52 (29.7)	NE (15.2,NE)	0.9180 (0.6244,1.3495) [0.6628]	0.2280
		1	106	34 (32.1)	24.0 (18.2,NE)	87	32 (36.8)	11.2 (8.6,NE)	0.6295 (0.3833,1.0337) [0.0640]	
Hormone Receptor Status		Negative	126	48 (38.1)	24.0 (14.1,NE)	122	40 (32.8)	15.7 (11.1,NE)	0.9096 (0.5942,1.3922) [0.6611]	0.3870
		Positive	133	39 (29.3)	NE (NE,NE)	139	43 (30.9)	NE (11.7,NE)	0.7409 (0.4789,1.1463) [0.1756]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	No. of Events (%)	Median (95% CI) [a] (months)	T-DM1 (N=263) n	No. of Events (%)	Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Common Symptoms/Financial Difficulties									
Estrogen Receptors	Negative	130	50 (38.5)	18.2 (14.1,NE)	128	43 (33.6)	15.7 (11.1,NE)	0.9089 (0.6013,1.3737) [0.6499]	0.3759
	Positive	129	37 (28.7)	NE (NE,NE)	132	40 (30.3)	NE (11.7,NE)	0.7262 (0.4627,1.1399) [0.1614]	
Progesterone Receptors	Negative	177	64 (36.2)	24.0 (18.2,NE)	168	54 (32.1)	NE (12.7,NE)	0.8940 (0.6196,1.2897) [0.5459]	0.3801
	Positive	81	23 (28.4)	NE (NE,NE)	92	29 (31.5)	NE (10.3,NE)	0.6815 (0.3927,1.1827) [0.1709]	
Prior Treatment with Pertuzumab	No	99	36 (36.4)	18.2 (14.1,NE)	105	38 (36.2)	15.7 (8.4,NE)	0.8707 (0.5511,1.3755) [0.5486]	0.9125
	Yes	162	51 (31.5)	NE (24.0,NE)	158	46 (29.1)	NE (11.7,NE)	0.7940 (0.5298,1.1900) [0.2620]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Financial Difficulties									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	63 (33.5)	NE (24.0,NE)	191	67 (35.1)	15.7 (11.2,NE)	0.7366 (0.5204,1.0427) [0.0830]	0.2489
	>= 3	73	24 (32.9)	19.7 (14.1,NE)	72	17 (23.6)	NE (NE,NE)	1.1493 (0.6149,2.1482) [0.6606]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	49 (31.4)	NE (24.0,NE)	152	45 (29.6)	NE (11.7,NE)	0.7941 (0.5265,1.1979) [0.2697]	0.8807
	>= 3	6	2 (33.3)	NE (7.2,NE)	6	1 (16.7)	NE (1.4,NE)	0.9747 (0.0865,10.9763) [0.9835]	
Renal Impairment at Baseline	Mild	92	32 (34.8)	NE (13.4,NE)	104	38 (36.5)	NE (11.1,NE)	0.8185 (0.5105,1.3121) [0.4033]	0.4630
	Moderate	30	13 (43.3)	19.7 (11.5,NE)	22	5 (22.7)	NE (3.9,NE)	1.2813 (0.4494,3.6535) [0.6474]	
	Normal	130	40 (30.8)	NE (NE,NE)	130	40 (30.8)	15.7 (11.1,NE)	0.7490 (0.4799,1.1689) [0.2004]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Common Symptoms/Financial Difficulties									
Hepatic Impairment	Mild	49	16 (32.7)	NE (14.1,NE)	49	13 (26.5)	NE (7.0,NE)	0.8517 (0.4080,1.7781) [0.6716]	0.8502
	Normal	208	71 (34.1)	NE (19.7,NE)	212	71 (33.5)	NE (11.7,NE)	0.8101 (0.5809,1.1297) [0.2127]	
Baseline Visceral Disease	No	66	19 (28.8)	NE (24.0,NE)	74	23 (31.1)	NE (11.2,NE)	0.6870 (0.3692,1.2783) [0.2327]	0.6671
	Yes	195	68 (34.9)	NE (18.2,NE)	189	61 (32.3)	NE (11.0,NE)	0.8469 (0.5974,1.2007) [0.3497]	
Baseline CNS Metastases	No	218	77 (35.3)	NE (19.7,NE)	224	71 (31.7)	NE (12.7,NE)	0.8843 (0.6388,1.2242) [0.4572]	0.2026
	Yes	43	10 (23.3)	NE (18.2,NE)	39	13 (33.3)	NE (6.2,NE)	0.4888 (0.2095,1.1403) [0.0920]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 30 - Analysis of time to first deterioration of EORTC QLQ-C30 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Common Symptoms/Financial Difficulties									
History of CNS Metastases	No	199	70 (35.2)	NE (19.7,NE)	211	69 (32.7)	NE (12.7,NE)	0.8471 (0.6058,1.1845) [0.3311]	0.7342
	Yes	62	17 (27.4)	NE (18.2,NE)	52	15 (28.8)	NE (7.0,NE)	0.6921 (0.3388,1.4138) [0.3090]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Functioning									
Age	<65	212	54 (25.5)	NE (NE,NE)	206	54 (26.2)	22.6 (22.6,NE)	0.8044 (0.5499,1.1768) [0.2583]	0.1554
	>=65	49	6 (12.2)	NE (NE,NE)	57	3 (5.3)	NE (NE,NE)	2.3163 (0.5793,9.2621) [0.2208]	
Age	<75	253	59 (23.3)	NE (NE,NE)	255	56 (22.0)	NE (22.6,NE)	0.9185 (0.6360,1.3264) [0.6459]	0.8804
	>=75	8	1 (12.5)	NE (2.1,NE)	8	1 (12.5)	NE (1.4,NE)	0.7454 (0.0464,11.9679) [0.8350]	
Region	Asia	149	22 (14.8)	NE (NE,NE)	160	30 (18.8)	NE (NE,NE)	0.6476 (0.3725,1.1260) [0.1204]	0.2412
	Europe	54	16 (29.6)	NE (19.4,NE)	50	10 (20.0)	22.6 (16.4,NE)	1.2677 (0.5706,2.8167) [0.5584]	
	North America	17	8 (47.1)	NE (1.4,NE)	17	4 (23.5)	NE (5.7,NE)	2.0918 (0.6287,6.9593) [0.2200]	
	Rest of World	41	14 (34.1)	NE (2.8,NE)	36	13 (36.1)	NE (1.5,NE)	0.8093 (0.3800,1.7237) [0.5874]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Functioning									
Race	Asian	152	22 (14.5)	NE (NE,NE)	162	30 (18.5)	NE (NE,NE)	0.6495 (0.3736,1.1292) [0.1229]	0.0305
	Black Or African American	10	1 (10.0)	NE (1.4,NE)	9	4 (44.4)	NE (0.8,NE)	0.1481 (0.0164,1.3381) [0.0486]	
	Other	28	8 (28.6)	NE (19.4,NE)	20	4 (20.0)	NE (3.5,NE)	1.1332 (0.3316,3.8725) [0.8450]	
	White	71	29 (40.8)	NE (2.1,NE)	72	19 (26.4)	22.6 (16.4,NE)	1.6025 (0.8894,2.8875) [0.1101]	
ECOG PS	0	154	40 (26.0)	NE (NE,NE)	175	41 (23.4)	NE (NE,NE)	0.9781 (0.6314,1.5152) [0.9170]	0.7015
	1	106	20 (18.9)	NE (NE,NE)	87	16 (18.4)	22.6 (NE,NE)	0.8495 (0.4382,1.6468) [0.6275]	
Hormone Receptor Status	Negative	126	31 (24.6)	NE (NE,NE)	122	19 (15.6)	NE (NE,NE)	1.4437 (0.8140,2.5605) [0.2096]	0.0386
	Positive	133	29 (21.8)	NE (NE,NE)	139	38 (27.3)	NE (22.6,NE)	0.6505 (0.3999,1.0581) [0.0811]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Functioning									
Estrogen Receptors	Negative	130	32 (24.6)	NE (NE,NE)	128	21 (16.4)	NE (NE,NE)	1.3730 (0.7902,2.3858) [0.2635]	0.0560
	Positive	129	28 (21.7)	NE (NE,NE)	132	35 (26.5)	NE (22.6,NE)	0.6662 (0.4040,1.0985) [0.1096]	
Progesterone Receptors	Negative	177	39 (22.0)	NE (NE,NE)	168	28 (16.7)	NE (NE,NE)	1.1474 (0.7047,1.8684) [0.5867]	0.2169
	Positive	81	21 (25.9)	NE (NE,NE)	92	29 (31.5)	22.6 (22.6,NE)	0.7214 (0.4106,1.2675) [0.2554]	
Prior Treatment with Pertuzumab	No	99	21 (21.2)	NE (NE,NE)	105	26 (24.8)	NE (NE,NE)	0.7615 (0.4279,1.3553) [0.3524]	0.3646
	Yes	162	39 (24.1)	NE (NE,NE)	158	31 (19.6)	22.6 (22.6,NE)	1.0360 (0.6439,1.6669) [0.8885]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Functioning									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	43 (22.9)	NE (NE,NE)	191	39 (20.4)	NE (NE,NE)	0.9566 (0.6190,1.4781) [0.8444]	0.8557
	>= 3	73	17 (23.3)	NE (NE,NE)	72	18 (25.0)	22.6 (22.6,NE)	0.8523 (0.4382,1.6578) [0.6321]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	39 (25.0)	NE (NE,NE)	152	30 (19.7)	22.6 (22.6,NE)	1.0849 (0.6714,1.7529) [0.7424]	0.1484
	>= 3	6	0 (0.0)	NE (NE,NE)	6	1 (16.7)	NE (3.3,NE)	0.0000 (0.0000,.) [0.2207]	
Renal Impairment at Baseline	Mild	92	16 (17.4)	NE (NE,NE)	104	17 (16.3)	NE (NE,NE)	0.9248 (0.4657,1.8364) [0.8240]	0.1614
	Moderate	30	7 (23.3)	NE (NE,NE)	22	1 (4.5)	NE (NE,NE)	4.3568 (0.5358,35.4258) [0.1290]	
	Normal	130	35 (26.9)	NE (NE,NE)	130	38 (29.2)	NE (NE,NE)	0.7515 (0.4725,1.1951) [0.2243]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Functioning									
Hepatic Impairment	Mild	49	4 (8.2)	NE (NE,NE)	49	10 (20.4)	NE (NE,NE)	0.3036 (0.0949,0.9712) [0.0335]	0.0282
	Normal	208	56 (26.9)	NE (NE,NE)	212	47 (22.2)	22.6 (22.6,NE)	1.0725 (0.7261,1.5841) [0.7266]	
Baseline Visceral Disease	No	66	10 (15.2)	NE (NE,NE)	74	14 (18.9)	22.6 (22.6,NE)	0.6656 (0.2935,1.5093) [0.3236]	0.4046
	Yes	195	50 (25.6)	NE (NE,NE)	189	43 (22.8)	NE (NE,NE)	0.9813 (0.6514,1.4782) [0.9286]	
Baseline CNS Metastases	No	218	50 (22.9)	NE (NE,NE)	224	48 (21.4)	NE (22.6,NE)	0.9320 (0.6263,1.3868) [0.7250]	0.8590
	Yes	43	10 (23.3)	NE (19.4,NE)	39	9 (23.1)	NE (NE,NE)	0.8303 (0.3325,2.0730) [0.6898]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Functioning									
History of CNS Metastases	No	199	45 (22.6)	NE (NE,NE)	211	48 (22.7)	NE (22.6,NE)	0.8509 (0.5656,1.2801) [0.4345]	0.4226
	Yes	62	15 (24.2)	NE (19.4,NE)	52	9 (17.3)	NE (NE,NE)	1.2514 (0.5439,2.8789) [0.5985]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Enjoyment									
Age	<65	212	23 (10.8)	7.2 (2.9,NE)	206	11 (5.3)	NE (NE,NE)	2.4373 (1.1869,5.0047) [0.0117]	0.9996
	>=65	49	0 (0.0)	NE (NE,NE)	57	0 (0.0)	NE (NE,NE)	NE	
Age	<75	253	23 (9.1)	13.4 (3.6,NE)	255	11 (4.3)	NE (NE,NE)	2.4122 (1.1750,4.9525) [0.0128]	NE
	>=75	8	0 (0.0)	NE (NE,NE)	8	0 (0.0)	NE (NE,NE)	NE	
Region	Asia	149	5 (3.4)	NE (2.6,NE)	160	2 (1.3)	NE (NE,NE)	4.1186 (0.7884,21.5168) [0.0698]	0.4610
	Europe	54	7 (13.0)	NE (2.8,NE)	50	1 (2.0)	NE (1.4,NE)	3.8581 (0.4733,31.4501) [0.1744]	
	North America	17	1 (5.9)	NE (0.9,NE)	17	3 (17.6)	8.7 (1.4,NE)	0.6702 (0.0694,6.4698) [0.7275]	
	Rest of World	41	10 (24.4)	2.9 (1.4,9.7)	36	5 (13.9)	6.9 (1.4,NE)	1.8695 (0.6341,5.5119) [0.2410]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Enjoyment									
Race	Asian	152	5 (3.3)	NE (2.6,NE)	162	2 (1.2)	NE (NE,NE)	3.8458 (0.7373,20.0602) [0.0862]	0.4502
	Black Or African American	10	1 (10.0)	NE (1.4,NE)	9	3 (33.3)	6.3 (1.4,NE)	1.0199 (0.1032,10.0786) [0.9794]	
	Other	28	4 (14.3)	NE (1.6,NE)	20	0 (0.0)	NE (NE,NE)	NE	
	White	71	13 (18.3)	4.2 (1.6,NE)	72	6 (8.3)	NE (3.0,NE)	2.1254 (0.8046,5.6141) [0.1162]	
ECOG PS	0	154	18 (11.7)	9.7 (3.6,NE)	175	10 (5.7)	NE (8.7,NE)	1.9512 (0.8993,4.2334) [0.0822]	0.2151
	1	106	5 (4.7)	NE (1.4,NE)	87	1 (1.1)	NE (NE,NE)	6.9668 (0.8123,59.7519) [0.0406]	
Hormone Receptor Status	Negative	126	12 (9.5)	9.7 (2.9,NE)	122	4 (3.3)	NE (5.7,NE)	1.9467 (0.6272,6.0424) [0.2415]	0.5461
	Positive	133	11 (8.3)	13.4 (1.6,NE)	139	7 (5.0)	NE (NE,NE)	2.9040 (1.1240,7.5030) [0.0202]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Enjoyment									
Estrogen Receptors	Negative	130	12 (9.2)	NE (4.2,NE)	128	4 (3.1)	NE (5.7,NE)	2.1413 (0.6899,6.6465) [0.1780]	0.6645
	Positive	129	11 (8.5)	9.5 (1.6,NE)	132	7 (5.3)	NE (NE,NE)	2.7991 (1.0827,7.2364) [0.0253]	
Progesterone Receptors	Negative	177	14 (7.9)	13.4 (4.2,NE)	168	4 (2.4)	NE (NE,NE)	3.2740 (1.0768,9.9544) [0.0272]	0.6095
	Positive	81	9 (11.1)	4.6 (1.6,NE)	92	7 (7.6)	NE (6.3,NE)	2.1997 (0.8178,5.9163) [0.1051]	
Prior Treatment with Pertuzumab	No	99	9 (9.1)	4.2 (1.4,NE)	105	6 (5.7)	NE (6.9,NE)	2.7679 (0.9812,7.8076) [0.0434]	0.8711
	Yes	162	14 (8.6)	NE (4.2,NE)	158	5 (3.2)	NE (NE,NE)	2.4640 (0.8865,6.8486) [0.0735]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Enjoyment									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	19 (10.1)	8.5 (2.8,NE)	191	11 (5.8)	NE (6.9,NE)	1.7899 (0.8514,3.7628) [0.1160]	0.0306
	>= 3	73	4 (5.5)	NE (1.4,NE)	72	0 (0.0)	NE (NE,NE)	NE	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	14 (9.0)	NE (4.2,NE)	152	5 (3.3)	NE (8.7,NE)	2.3302 (0.8380,6.4796) [0.0946]	NE
	>= 3	6	0 (0.0)	NE (NE,NE)	6	0 (0.0)	NE (NE,NE)	NE	
Renal Impairment at Baseline	Mild	92	4 (4.3)	NE (1.4,NE)	104	3 (2.9)	NE (1.5,NE)	1.4351 (0.3209,6.4176) [0.6330]	0.7058
	Moderate	30	1 (3.3)	NE (2.8,NE)	22	0 (0.0)	NE (NE,NE)	NE	
	Normal	130	16 (12.3)	7.2 (2.8,NE)	130	8 (6.2)	NE (8.7,NE)	2.4193 (1.0326,5.6679) [0.0341]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Sexual Enjoyment									
Hepatic Impairment	Mild	49	1 (2.0)	NE (1.4,NE)	49	2 (4.1)	NE (1.4,NE)	1.3241 (0.1197,14.6433) [0.8184]	0.6241
	Normal	208	22 (10.6)	9.7 (3.6,NE)	212	9 (4.2)	NE (NE,NE)	2.5976 (1.1950,5.6464) [0.0119]	
Baseline Visceral Disease	No	66	6 (9.1)	7.2 (1.4,NE)	74	1 (1.4)	NE (8.7,NE)	8.5852 (1.0323,71.3998) [0.0167]	0.1356
	Yes	195	17 (8.7)	13.4 (2.8,NE)	189	10 (5.3)	NE (NE,NE)	1.8391 (0.8406,4.0239) [0.1185]	
Baseline CNS Metastases	No	218	19 (8.7)	13.4 (4.2,NE)	224	9 (4.0)	NE (NE,NE)	2.5000 (1.1302,5.5302) [0.0189]	0.9211
	Yes	43	4 (9.3)	2.8 (1.6,NE)	39	2 (5.1)	NE (1.4,NE)	1.8648 (0.3396,10.2412) [0.4662]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Sexual Enjoyment									
History of CNS Metastases	No	199	18 (9.0)	13.4 (3.6,NE)	211	9 (4.3)	NE (NE,NE)	2.5692 (1.1530,5.7249) [0.0164]	0.7502
	Yes	62	5 (8.1)	NE (1.6,NE)	52	2 (3.8)	NE (1.4,NE)	1.7930 (0.3472,9.2600) [0.4794]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Future Perspective									
Age	<65	212	72 (34.0)	NE (19.4,NE)	206	52 (25.2)	NE (16.7,NE)	1.0602 (0.7381,1.5228) [0.7452]	0.3475
	>=65	49	16 (32.7)	NE (8.5,NE)	57	21 (36.8)	21.2 (4.9,NE)	0.7572 (0.3938,1.4558) [0.4004]	
Age	<75	253	86 (34.0)	NE (19.4,NE)	255	70 (27.5)	21.2 (16.7,NE)	0.9887 (0.7187,1.3600) [0.9481]	0.5567
	>=75	8	2 (25.0)	NE (1.4,NE)	8	3 (37.5)	NE (0.9,NE)	0.6328 (0.1053,3.8022) [0.6139]	
Region	Asia	149	55 (36.9)	NE (19.0,NE)	160	46 (28.8)	21.2 (15.7,NE)	1.0197 (0.6865,1.5147) [0.9200]	0.8271
	Europe	54	17 (31.5)	NE (15.2,NE)	50	11 (22.0)	NE (16.7,NE)	1.1302 (0.5255,2.4306) [0.7529]	
	North America	17	6 (35.3)	NE (1.5,NE)	17	6 (35.3)	10.4 (2.9,NE)	0.8913 (0.2862,2.7759) [0.8424]	
	Rest of World	41	10 (24.4)	NE (NE,NE)	36	10 (27.8)	NE (7.1,NE)	0.7788 (0.3238,1.8729) [0.5730]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Future Perspective									
Race	Asian	152	55 (36.2)	NE (19.0,NE)	162	47 (29.0)	21.2 (15.7,NE)	0.9963 (0.6721,1.4767) [0.9877]	0.9404
	Black Or African American	10	4 (40.0)	NE (1.4,NE)	9	4 (44.4)	10.4 (1.4,NE)	0.7106 (0.1765,2.8600) [0.6458]	
	Other	28	7 (25.0)	19.4 (15.1,NE)	20	3 (15.0)	NE (NE,NE)	1.0391 (0.2535,4.2599) [0.9573]	
	White	71	22 (31.0)	NE (NE,NE)	72	19 (26.4)	NE (16.7,NE)	1.0199 (0.5510,1.8878) [0.9516]	
ECOG PS	0	154	60 (39.0)	NE (19.0,NE)	175	43 (24.6)	21.2 (21.2,NE)	1.2966 (0.8734,1.9249) [0.1950]	0.0135
	1	106	28 (26.4)	NE (NE,NE)	87	30 (34.5)	15.7 (8.4,NE)	0.5837 (0.3464,0.9836) [0.0411]	
Hormone Receptor Status	Negative	126	47 (37.3)	19.4 (14.8,NE)	122	29 (23.8)	NE (16.7,NE)	1.3369 (0.8387,2.1312) [0.2192]	0.0537
	Positive	133	41 (30.8)	NE (NE,NE)	139	44 (31.7)	21.2 (15.7,NE)	0.7380 (0.4796,1.1357) [0.1657]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Future Perspective									
Estrogen Receptors	Negative	130	48 (36.9)	19.4 (15.2,NE)	128	31 (24.2)	NE (16.7,NE)	1.2788 (0.8109,2.0167) [0.2878]	0.0812
	Positive	129	40 (31.0)	NE (NE,NE)	132	41 (31.1)	21.2 (15.7,NE)	0.7677 (0.4941,1.1927) [0.2388]	
Progesterone Receptors	Negative	177	62 (35.0)	NE (19.0,NE)	168	43 (25.6)	21.2 (16.7,NE)	1.1238 (0.7589,1.6641) [0.5572]	0.1822
	Positive	81	26 (32.1)	NE (15.2,NE)	92	30 (32.6)	NE (7.1,NE)	0.7593 (0.4468,1.2902) [0.3076]	
Prior Treatment with Pertuzumab	No	99	39 (39.4)	19.0 (11.9,NE)	105	32 (30.5)	NE (17.2,NE)	1.1363 (0.7106,1.8170) [0.5909]	0.4034
	Yes	162	49 (30.2)	NE (NE,NE)	158	41 (25.9)	21.2 (15.7,NE)	0.8800 (0.5768,1.3427) [0.5519]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Future Perspective									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	59 (31.4)	NE (19.4,NE)	191	55 (28.8)	21.2 (16.7,NE)	0.8294 (0.5712,1.2042) [0.3235]	0.1262
	>= 3	73	29 (39.7)	NE (8.4,NE)	72	18 (25.0)	NE (15.7,NE)	1.4355 (0.7942,2.5948) [0.2238]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	47 (30.1)	NE (19.4,NE)	152	40 (26.3)	21.2 (16.7,NE)	0.8805 (0.5733,1.3524) [0.5596]	0.8068
	>= 3	6	2 (33.3)	NE (3.1,NE)	6	1 (16.7)	15.7 (NE,NE)	1.1535 (0.1010,13.1682) [0.9084]	
Renal Impairment at Baseline	Mild	92	33 (35.9)	NE (14.8,NE)	104	40 (38.5)	16.7 (10.4,NE)	0.7703 (0.4835,1.2271) [0.2736]	0.3892
	Moderate	30	11 (36.7)	NE (7.6,NE)	22	5 (22.7)	NE (4.2,NE)	1.3236 (0.4582,3.8235) [0.6032]	
	Normal	130	43 (33.1)	NE (19.4,NE)	130	27 (20.8)	NE (NE,NE)	1.2128 (0.7430,1.9797) [0.4379]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Future Perspective									
Hepatic Impairment	Mild	49	16 (32.7)	NE (8.2,NE)	49	16 (32.7)	15.7 (4.3,NE)	0.6392 (0.3179,1.2851) [0.2090]	0.2858
	Normal	208	72 (34.6)	NE (19.4,NE)	212	57 (26.9)	21.2 (17.2,NE)	1.0493 (0.7378,1.4922) [0.7891]	
Baseline Visceral Disease	No	66	20 (30.3)	NE (19.4,NE)	74	19 (25.7)	NE (14.4,NE)	0.9313 (0.4947,1.7530) [0.8189]	0.9339
	Yes	195	68 (34.9)	NE (19.0,NE)	189	54 (28.6)	21.2 (15.7,NE)	0.9723 (0.6768,1.3966) [0.8843]	
Baseline CNS Metastases	No	218	72 (33.0)	NE (19.4,NE)	224	65 (29.0)	21.2 (16.7,NE)	0.9166 (0.6535,1.2856) [0.6162]	0.3044
	Yes	43	16 (37.2)	19.4 (8.4,NE)	39	8 (20.5)	NE (NE,NE)	1.3543 (0.5674,3.2324) [0.4897]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Functional Scales/Future Perspective									
History of CNS Metastases	No	199	66 (33.2)	NE (19.4,NE)	211	61 (28.9)	21.2 (16.7,NE)	0.9286 (0.6535,1.3195) [0.6805]	0.4730
	Yes	62	22 (35.5)	19.4 (10.0,NE)	52	12 (23.1)	NE (NE,NE)	1.1438 (0.5570,2.3487) [0.7124]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Systemic Therapy Side Effects									
Age	<65	212	117 (55.2)	6.1 (4.4,12.0)	206	85 (41.3)	11.7 (8.3,NE)	1.2425 (0.9387,1.6447) [0.1313]	0.9272
	>=65	49	28 (57.1)	4.3 (2.8,NE)	57	28 (49.1)	9.0 (4.4,NE)	1.2787 (0.7568,2.1606) [0.3609]	
Age	<75	253	141 (55.7)	5.7 (4.3,11.1)	255	111 (43.5)	11.7 (8.3,16.7)	1.2083 (0.9416,1.5506) [0.1400]	0.1884
	>=75	8	4 (50.0)	1.6 (0.8,NE)	8	2 (25.0)	NE (1.5,NE)	3.2603 (0.5889,18.0500) [0.1601]	
Region	Asia	149	85 (57.0)	6.1 (4.1,12.0)	160	63 (39.4)	14.1 (8.4,NE)	1.4240 (1.0262,1.9760) [0.0347]	0.5807
	Europe	54	27 (50.0)	8.5 (4.2,NE)	50	23 (46.0)	8.3 (2.7,NE)	0.9554 (0.5474,1.6676) [0.8798]	
	North America	17	9 (52.9)	4.4 (1.5,NE)	17	9 (52.9)	7.2 (2.8,NE)	1.0856 (0.4297,2.7427) [0.8680]	
	Rest of World	41	24 (58.5)	4.9 (2.8,NE)	36	18 (50.0)	9.7 (2.7,NE)	1.0998 (0.5964,2.0279) [0.7831]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Systemic Therapy Side Effects									
Race	Asian	152	86 (56.6)	6.1 (4.1,12.0)	162	64 (39.5)	14.1 (8.4,NE)	1.4234 (1.0280,1.9707) [0.0338]	0.1182
	Black Or African American	10	6 (60.0)	4.3 (1.4,NE)	9	4 (44.4)	13.8 (1.5,NE)	1.5113 (0.4249,5.3759) [0.5456]	
	Other	28	12 (42.9)	16.6 (5.6,NE)	20	12 (60.0)	7.0 (1.4,15.7)	0.5193 (0.2318,1.1636) [0.1057]	
	White	71	41 (57.7)	4.4 (2.8,9.7)	72	33 (45.8)	11.7 (3.0,NE)	1.2454 (0.7874,1.9699) [0.3442]	
ECOG PS	0	154	84 (54.5)	6.9 (4.3,16.6)	175	79 (45.1)	10.4 (7.2,15.7)	1.1573 (0.8504,1.5749) [0.3621]	0.5160
	1	106	61 (57.5)	4.5 (3.0,11.1)	87	34 (39.1)	16.7 (6.9,NE)	1.3784 (0.9052,2.0989) [0.1289]	
Hormone Receptor Status	Negative	126	73 (57.9)	4.9 (3.2,11.0)	122	53 (43.4)	13.8 (6.6,17.0)	1.3314 (0.9339,1.8980) [0.1156]	0.6071
	Positive	133	72 (54.1)	7.2 (4.2,NE)	139	59 (42.4)	11.7 (6.9,NE)	1.1955 (0.8467,1.6881) [0.3117]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Symptom Scales/Systemic Therapy Side Effects									
Estrogen Receptors	Negative	130	75 (57.7)	4.9 (3.2,11.0)	128	56 (43.8)	13.8 (6.6,17.0)	1.3379 (0.9457,1.8927) [0.1030]	0.5493
	Positive	129	70 (54.3)	7.2 (4.2,NE)	132	56 (42.4)	11.7 (6.9,NE)	1.1740 (0.8253,1.6701) [0.3723]	
Progesterone Receptors	Negative	177	100 (56.5)	5.9 (4.2,11.1)	168	71 (42.3)	13.8 (8.3,17.0)	1.3113 (0.9666,1.7791) [0.0829]	0.5960
	Positive	81	45 (55.6)	4.9 (3.0,NE)	92	41 (44.6)	11.7 (4.8,NE)	1.1662 (0.7633,1.7819) [0.4785]	
Prior Treatment with Pertuzumab	No	99	53 (53.5)	6.1 (3.5,16.6)	105	48 (45.7)	9.0 (4.8,NE)	1.1074 (0.7484,1.6387) [0.6312]	0.4915
	Yes	162	92 (56.8)	5.6 (4.2,11.0)	158	65 (41.1)	13.8 (8.3,NE)	1.3307 (0.9677,1.8300) [0.0784]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Systemic Therapy Side Effects									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	98 (52.1)	7.2 (4.4,NE)	191	91 (47.6)	8.5 (5.7,14.1)	0.9888 (0.7426,1.3168) [0.9247]	0.0028
	>= 3	73	47 (64.4)	4.3 (2.8,8.3)	72	22 (30.6)	NE (11.7,NE)	2.3403 (1.4088,3.8876) [0.0007]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	89 (57.1)	4.9 (4.2,11.0)	152	65 (42.8)	13.8 (8.3,17.0)	1.2963 (0.9404,1.7869) [0.1130]	0.0936
	>= 3	6	3 (50.0)	NE (1.5,NE)	6	0 (0.0)	NE (NE,NE)	NE	
Renal Impairment at Baseline	Mild	92	62 (67.4)	3.5 (2.8,4.4)	104	51 (49.0)	11.7 (5.7,17.0)	1.6360 (1.1273,2.3744) [0.0093]	0.1587
	Moderate	30	18 (60.0)	5.7 (2.8,NE)	22	7 (31.8)	NE (2.8,NE)	1.6060 (0.6696,3.8520) [0.2825]	
	Normal	130	63 (48.5)	12.3 (5.9,NE)	130	52 (40.0)	11.7 (6.9,NE)	1.0209 (0.7047,1.4789) [0.9219]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Systemic Therapy Side Effects									
Hepatic Impairment	Mild	49	21 (42.9)	12.3 (6.1,NE)	49	16 (32.7)	9.7 (6.6,NE)	0.9852 (0.5121,1.8954) [0.9581]	0.5674
	Normal	208	124 (59.6)	4.5 (3.9,7.2)	212	97 (45.8)	11.7 (7.2,16.7)	1.2948 (0.9918,1.6902) [0.0582]	
Baseline Visceral Disease	No	66	40 (60.6)	5.9 (4.2,11.1)	74	33 (44.6)	15.7 (4.4,NE)	1.2902 (0.8133,2.0467) [0.2780]	0.8470
	Yes	195	105 (53.8)	5.7 (4.1,15.6)	189	80 (42.3)	11.7 (8.3,16.7)	1.2134 (0.9060,1.6252) [0.2004]	
Baseline CNS Metastases	No	218	125 (57.3)	5.5 (4.2,9.7)	224	98 (43.8)	11.7 (8.3,17.0)	1.2825 (0.9841,1.6714) [0.0664]	0.5869
	Yes	43	20 (46.5)	15.6 (4.3,NE)	39	15 (38.5)	9.8 (5.0,NE)	0.9925 (0.5004,1.9688) [0.9788]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	 No. of Events (%)	 Median (95% CI) [a] (months)	T-DM1 (N=263) n	 No. of Events (%)	 Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Symptom Scales/Systemic Therapy Side Effects									
History of CNS Metastases	No	199	118 (59.3)	4.5 (3.9,7.2)	211	94 (44.5)	11.7 (7.0,16.7)	1.3040 (0.9940,1.7105) [0.0552]	0.5764
	Yes	62	27 (43.5)	15.6 (6.2,NE)	52	19 (36.5)	NE (6.6,NE)	1.0533 (0.5808,1.9103) [0.8753]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Symptom Scales/Breast Symptoms									
Age	<65	212	45 (21.2)	NE (NE,NE)	206	40 (19.4)	NE (NE,NE)	0.8201 (0.5338,1.2601) [0.3663]	0.6667
	>=65	49	11 (22.4)	NE (16.5,NE)	57	12 (21.1)	NE (12.7,NE)	0.9741 (0.4290,2.2114) [0.9479]	
Age	<75	253	53 (20.9)	NE (NE,NE)	255	52 (20.4)	NE (NE,NE)	0.7883 (0.5361,1.1591) [0.2257]	0.0148
	>=75	8	3 (37.5)	9.9 (2.9,NE)	8	0 (0.0)	NE (NE,NE)	NE	
Region	Asia	149	34 (22.8)	NE (NE,NE)	160	31 (19.4)	NE (15.7,NE)	0.8648 (0.5284,1.4154) [0.5631]	0.6398
	Europe	54	10 (18.5)	NE (NE,NE)	50	8 (16.0)	NE (13.1,NE)	0.9537 (0.3752,2.4242) [0.9208]	
	North America	17	4 (23.5)	NE (10.2,NE)	17	2 (11.8)	NE (NE,NE)	1.4850 (0.2681,8.2246) [0.6486]	
	Rest of World	41	8 (19.5)	NE (NE,NE)	36	11 (30.6)	NE (7.2,NE)	0.5600 (0.2250,1.3941) [0.2041]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Breast Symptoms									
Race	Asian	152	34 (22.4)	NE (NE,NE)	162	31 (19.1)	NE (15.7,NE)	0.8677 (0.5302,1.4201) [0.5720]	0.9123
	Black Or African American	10	3 (30.0)	NE (2.8,NE)	9	2 (22.2)	NE (2.8,NE)	1.2512 (0.2090,7.4921) [0.8057]	
	Other	28	5 (17.9)	NE (NE,NE)	20	5 (25.0)	NE (9.8,NE)	0.5795 (0.1643,2.0436) [0.3908]	
	White	71	14 (19.7)	NE (NE,NE)	72	14 (19.4)	NE (NE,NE)	0.8189 (0.3897,1.7209) [0.5972]	
ECOG PS	0	154	30 (19.5)	NE (NE,NE)	175	33 (18.9)	NE (NE,NE)	0.7757 (0.4709,1.2777) [0.3180]	0.7543
	1	106	26 (24.5)	NE (NE,NE)	87	19 (21.8)	NE (15.7,NE)	0.8970 (0.4950,1.6254) [0.7223]	
Hormone Receptor Status	Negative	126	22 (17.5)	NE (NE,NE)	122	23 (18.9)	NE (NE,NE)	0.7538 (0.4190,1.3560) [0.3438]	0.4676
	Positive	133	34 (25.6)	NE (NE,NE)	139	28 (20.1)	NE (15.7,NE)	0.9562 (0.5772,1.5842) [0.8634]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Symptom Scales/Breast Symptoms									
Estrogen Receptors	Negative	130	24 (18.5)	NE (NE,NE)	128	24 (18.8)	NE (NE,NE)	0.7918 (0.4486,1.3978) [0.4201]	0.5818
	Positive	129	32 (24.8)	NE (NE,NE)	132	26 (19.7)	NE (15.7,NE)	0.9592 (0.5688,1.6177) [0.8763]	
Progesterone Receptors	Negative	177	34 (19.2)	NE (NE,NE)	168	32 (19.0)	NE (NE,NE)	0.8037 (0.4942,1.3070) [0.3769]	0.5368
	Positive	81	22 (27.2)	NE (NE,NE)	92	19 (20.7)	NE (13.1,NE)	0.9907 (0.5337,1.8389) [0.9784]	
Prior Treatment with Pertuzumab	No	99	17 (17.2)	NE (NE,NE)	105	25 (23.8)	NE (NE,NE)	0.5521 (0.2969,1.0268) [0.0573]	0.0714
	Yes	162	39 (24.1)	NE (NE,NE)	158	27 (17.1)	NE (NE,NE)	1.1049 (0.6738,1.8116) [0.6921]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Breast Symptoms									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	40 (21.3)	NE (NE,NE)	191	38 (19.9)	NE (NE,NE)	0.8282 (0.5298,1.2947) [0.4081]	0.8494
	>= 3	73	16 (21.9)	NE (NE,NE)	72	14 (19.4)	NE (15.7,NE)	0.8830 (0.4275,1.8240) [0.7366]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	38 (24.4)	NE (NE,NE)	152	26 (17.1)	NE (NE,NE)	1.1507 (0.6965,1.9012) [0.5828]	0.6550
	>= 3	6	1 (16.7)	NE (16.5,NE)	6	1 (16.7)	15.7 (NE,NE)	0.0000 (0.0000,.) [0.1573]	
Renal Impairment at Baseline	Mild	92	26 (28.3)	NE (NE,NE)	104	25 (24.0)	NE (NE,NE)	1.0662 (0.6151,1.8483) [0.8173]	0.4472
	Moderate	30	5 (16.7)	NE (16.5,NE)	22	2 (9.1)	NE (9.1,NE)	1.1100 (0.2141,5.7563) [0.9010]	
	Normal	130	24 (18.5)	NE (NE,NE)	130	25 (19.2)	NE (15.7,NE)	0.6880 (0.3900,1.2138) [0.1943]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Breast Symptoms									
Hepatic Impairment	Mild	49	12 (24.5)	NE (NE,NE)	49	13 (26.5)	15.7 (7.0,NE)	0.6167 (0.2788,1.3640) [0.2293]	0.3616
	Normal	208	44 (21.2)	NE (NE,NE)	212	39 (18.4)	NE (NE,NE)	0.9044 (0.5858,1.3961) [0.6516]	
Baseline Visceral Disease	No	66	11 (16.7)	NE (NE,NE)	74	15 (20.3)	NE (13.8,NE)	0.5764 (0.2625,1.2657) [0.1651]	0.4135
	Yes	195	45 (23.1)	NE (NE,NE)	189	37 (19.6)	NE (NE,NE)	0.9362 (0.6043,1.4504) [0.7679]	
Baseline CNS Metastases	No	218	46 (21.1)	NE (NE,NE)	224	44 (19.6)	NE (NE,NE)	0.8340 (0.5503,1.2641) [0.3924]	0.9622
	Yes	43	10 (23.3)	NE (NE,NE)	39	8 (20.5)	NE (8.3,NE)	0.9095 (0.3563,2.3218) [0.8456]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Breast Symptoms									
History of CNS Metastases	No	199	44 (22.1)	NE (NE,NE)	211	44 (20.9)	NE (NE,NE)	0.8146 (0.5349,1.2404) [0.3384]	0.7652
	Yes	62	12 (19.4)	NE (NE,NE)	52	8 (15.4)	NE (NE,NE)	1.0398 (0.4228,2.5571) [0.9301]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Arm Symptoms									
Age	<65	212	113 (53.3)	9.5 (6.1,16.7)	206	111 (53.9)	4.4 (3.3,6.9)	0.7262 (0.5569,0.9469) [0.0177]	0.7176
	>=65	49	21 (42.9)	15.9 (7.4,NE)	57	26 (45.6)	11.8 (5.3,NE)	0.7745 (0.4353,1.3780) [0.3821]	
Age	<75	253	131 (51.8)	10.3 (7.4,16.7)	255	136 (53.3)	5.6 (4.2,8.4)	0.7249 (0.5691,0.9234) [0.0088]	0.1634
	>=75	8	3 (37.5)	15.9 (2.9,NE)	8	1 (12.5)	NE (0.8,NE)	1.9874 (0.1793,22.0262) [0.5683]	
Region	Asia	149	86 (57.7)	7.9 (5.7,11.4)	160	88 (55.0)	4.7 (3.3,7.0)	0.8201 (0.6081,1.1060) [0.1916]	0.1093
	Europe	54	17 (31.5)	NE (14.8,NE)	50	24 (48.0)	9.0 (2.8,NE)	0.4571 (0.2441,0.8561) [0.0123]	
	North America	17	10 (58.8)	7.4 (3.1,NE)	17	5 (29.4)	NE (3.0,NE)	1.7940 (0.6111,5.2668) [0.2793]	
	Rest of World	41	21 (51.2)	19.4 (4.6,NE)	36	20 (55.6)	5.6 (2.7,NE)	0.6142 (0.3272,1.1530) [0.1249]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Arm Symptoms									
Race	Asian	152	87 (57.2)	7.9 (5.7,11.4)	162	90 (55.6)	4.7 (3.3,8.4)	0.8099 (0.6021,1.0894) [0.1615]	0.1166
	Black Or African American	10	8 (80.0)	4.3 (1.4,10.3)	9	3 (33.3)	NE (1.4,NE)	2.5003 (0.6591,9.4853) [0.1656]	
	Other	28	9 (32.1)	NE (7.7,NE)	20	10 (50.0)	11.8 (1.4,NE)	0.4516 (0.1818,1.1220) [0.0795]	
	White	71	30 (42.3)	19.4 (8.5,NE)	72	34 (47.2)	5.6 (3.0,NE)	0.5859 (0.3533,0.9718) [0.0370]	
ECOG PS	0	154	80 (51.9)	11.4 (7.9,19.4)	175	93 (53.1)	5.6 (4.2,9.3)	0.7104 (0.5251,0.9610) [0.0257]	0.8299
	1	106	54 (50.9)	8.3 (5.7,NE)	87	44 (50.6)	5.6 (3.0,NE)	0.7931 (0.5319,1.1826) [0.2506]	
Hormone Receptor Status	Negative	126	66 (52.4)	8.5 (5.7,19.4)	122	64 (52.5)	6.2 (3.7,12.4)	0.7739 (0.5469,1.0953) [0.1441]	0.6916
	Positive	133	67 (50.4)	11.1 (7.7,NE)	139	72 (51.8)	5.6 (3.4,11.8)	0.7135 (0.5101,0.9980) [0.0482]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Arm Symptoms									
Estrogen Receptors	Negative	130	68 (52.3)	8.5 (5.8,19.4)	128	67 (52.3)	6.2 (3.7,12.4)	0.7711 (0.5485,1.0842) [0.1320]	0.6982
	Positive	129	65 (50.4)	11.1 (7.7,NE)	132	68 (51.5)	5.6 (3.3,NE)	0.7176 (0.5093,1.0113) [0.0576]	
Progesterone Receptors	Negative	177	96 (54.2)	9.5 (6.6,14.8)	168	89 (53.0)	5.6 (4.2,9.3)	0.7891 (0.5900,1.0555) [0.1079]	0.3773
	Positive	81	37 (45.7)	15.9 (7.2,NE)	92	47 (51.1)	5.6 (3.0,NE)	0.6451 (0.4176,0.9963) [0.0468]	
Prior Treatment with Pertuzumab	No	99	45 (45.5)	16.7 (7.7,NE)	105	52 (49.5)	5.7 (4.2,12.4)	0.6981 (0.4674,1.0428) [0.0752]	0.8229
	Yes	162	89 (54.9)	8.5 (5.8,14.8)	158	85 (53.8)	5.6 (3.3,8.4)	0.7692 (0.5699,1.0383) [0.0865]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Arm Symptoms									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	97 (51.6)	10.0 (7.4,18.7)	191	102 (53.4)	5.6 (4.2,9.0)	0.6892 (0.5206,0.9123) [0.0089]	0.4084
	>= 3	73	37 (50.7)	11.1 (4.2,NE)	72	35 (48.6)	4.6 (3.0,NE)	0.9237 (0.5798,1.4716) [0.7148]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	88 (56.4)	8.3 (5.7,13.7)	152	85 (55.9)	4.7 (3.0,7.0)	0.7581 (0.5611,1.0244) [0.0714]	0.2344
	>= 3	6	1 (16.7)	NE (8.5,NE)	6	0 (0.0)	NE (NE,NE)	NE	
Renal Impairment at Baseline	Mild	92	49 (53.3)	8.3 (7.2,14.8)	104	56 (53.8)	6.7 (4.2,11.8)	0.8287 (0.5636,1.2185) [0.3383]	0.6276
	Moderate	30	13 (43.3)	15.9 (5.7,NE)	22	11 (50.0)	5.3 (2.0,NE)	0.5382 (0.2403,1.2057) [0.1268]	
	Normal	130	70 (53.8)	10.3 (5.8,19.4)	130	68 (52.3)	4.6 (3.0,NE)	0.7230 (0.5145,1.0160) [0.0607]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Arm Symptoms									
Hepatic Impairment	Mild	49	27 (55.1)	8.5 (4.6,19.4)	49	22 (44.9)	5.6 (1.7,NE)	0.8231 (0.4672,1.4500) [0.5028]	0.6882
	Normal	208	107 (51.4)	11.1 (7.7,19.6)	212	115 (54.2)	5.6 (4.2,10.6)	0.7237 (0.5548,0.9440) [0.0164]	
Baseline Visceral Disease	No	66	32 (48.5)	12.5 (7.2,NE)	74	46 (62.2)	4.2 (2.8,6.7)	0.5645 (0.3577,0.8908) [0.0127]	0.1042
	Yes	195	102 (52.3)	9.5 (7.0,15.9)	189	91 (48.1)	6.9 (4.4,13.8)	0.8301 (0.6241,1.1040) [0.2011]	
Baseline CNS Metastases	No	218	109 (50.0)	12.5 (7.9,19.4)	224	117 (52.2)	5.6 (4.2,9.3)	0.7030 (0.5404,0.9146) [0.0083]	0.3573
	Yes	43	25 (58.1)	5.7 (2.9,10.3)	39	20 (51.3)	4.4 (2.8,NE)	1.0116 (0.5599,1.8277) [0.9685]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Arm Symptoms									
History of CNS Metastases	No	199	103 (51.8)	11.1 (7.7,18.7)	211	109 (51.7)	5.6 (4.2,10.6)	0.7451 (0.5681,0.9772) [0.0325]	0.9288
	Yes	62	31 (50.0)	8.5 (4.4,NE)	52	28 (53.8)	4.2 (2.9,NE)	0.7192 (0.4257,1.2152) [0.2171]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Upset by Hair Loss									
Age	<65	212	21 (9.9)	21.2 (3.1,NE)	206	8 (3.9)	NE (8.2,NE)	1.6170 (0.7108,3.6785) [0.2512]	0.3929
	>=65	49	5 (10.2)	NE (1.4,NE)	57	1 (1.8)	21.7 (NE,NE)	4.1374 (0.4814,35.5618) [0.1614]	
Age	<75	253	25 (9.9)	21.2 (4.1,NE)	255	9 (3.5)	21.7 (NE,NE)	1.8245 (0.8482,3.9247) [0.1209]	NE
	>=75	8	1 (12.5)	1.4 (NE,NE)	8	0 (0.0)	NE (NE,NE)	NE	
Region	Asia	149	17 (11.4)	21.2 (1.5,NE)	160	3 (1.9)	21.7 (NE,NE)	4.7858 (1.3928,16.4439) [0.0062]	0.0550
	Europe	54	3 (5.6)	11.1 (2.8,NE)	50	3 (6.0)	4.8 (0.8,NE)	0.5634 (0.1126,2.8194) [0.4792]	
	North America	17	2 (11.8)	NE (0.9,NE)	17	1 (5.9)	4.1 (NE,NE)	0.2658 (0.0239,2.9543) [0.2468]	
	Rest of World	41	4 (9.8)	NE (1.4,NE)	36	2 (5.6)	NE (5.8,NE)	1.0939 (0.1997,5.9928) [0.9308]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Upset by Hair Loss									
Race	Asian	152	17 (11.2)	21.2 (2.0,NE)	162	4 (2.5)	21.7 (NE,NE)	3.5788 (1.1951,10.7171) [0.0154]	0.1197
	Black Or African American	10	0 (0.0)	NE (NE,NE)	9	0 (0.0)	NE (NE,NE)	NE	
	Other	28	3 (10.7)	11.1 (2.8,NE)	20	1 (5.0)	NE (1.4,NE)	0.4524 (0.0401,5.1100) [0.5109]	
	White	71	6 (8.5)	NE (1.4,NE)	72	4 (5.6)	8.2 (0.8,NE)	0.6947 (0.1952,2.4729) [0.5440]	
ECOG PS	0	154	14 (9.1)	21.2 (8.2,NE)	175	5 (2.9)	21.7 (NE,NE)	1.8663 (0.6681,5.2131) [0.2276]	0.9474
	1	106	12 (11.3)	NE (1.4,NE)	87	4 (4.6)	NE (1.5,NE)	1.9289 (0.6206,5.9951) [0.2653]	
Hormone Receptor Status	Negative	126	15 (11.9)	4.1 (1.5,NE)	122	6 (4.9)	NE (1.4,NE)	1.5556 (0.6016,4.0225) [0.3677]	0.5827
	Positive	133	11 (8.3)	NE (11.1,NE)	139	3 (2.2)	21.7 (NE,NE)	2.3817 (0.6557,8.6515) [0.1759]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Upset by Hair Loss									
Estrogen Receptors	Negative	130	16 (12.3)	8.2 (1.5,NE)	128	6 (4.7)	NE (4.1,NE)	1.7370 (0.6778,4.4513) [0.2504]	0.8371
	Positive	129	10 (7.8)	NE (21.2,NE)	132	3 (2.3)	21.7 (NE,NE)	2.1203 (0.5761,7.8042) [0.2499]	
Progesterone Receptors	Negative	177	16 (9.0)	NE (2.8,NE)	168	8 (4.8)	NE (5.8,NE)	1.1355 (0.4856,2.6553) [0.7841]	0.0210
	Positive	81	10 (12.3)	21.2 (1.4,NE)	92	1 (1.1)	21.7 (NE,NE)	9.2690 (1.1809,72.7555) [0.0102]	
Prior Treatment with Pertuzumab	No	99	13 (13.1)	NE (2.1,NE)	105	1 (1.0)	NE (NE,NE)	6.6591 (0.8704,50.9481) [0.0347]	0.1423
	Yes	162	13 (8.0)	21.2 (3.1,NE)	158	8 (5.1)	21.7 (7.9,NE)	1.3183 (0.5436,3.1971) [0.5445]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Upset by Hair Loss									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	16 (8.5)	21.2 (8.2,NE)	191	7 (3.7)	21.7 (NE,NE)	1.3952 (0.5715,3.4056) [0.4718]	0.2728
	>= 3	73	10 (13.7)	NE (1.4,NE)	72	2 (2.8)	NE (5.8,NE)	3.8866 (0.8490,17.7924) [0.0598]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	13 (8.3)	21.2 (2.8,NE)	152	8 (5.3)	21.7 (7.9,NE)	1.5065 (0.6229,3.6436) [0.3633]	NE
	>= 3	6	0 (0.0)	NE (NE,NE)	6	0 (0.0)	NE (NE,NE)	NE	
Renal Impairment at Baseline	Mild	92	9 (9.8)	NE (1.4,NE)	104	6 (5.8)	21.7 (8.2,NE)	1.6128 (0.5733,4.5368) [0.3670]	0.6192
	Moderate	30	4 (13.3)	11.1 (0.9,NE)	22	0 (0.0)	NE (NE,NE)	NE	
	Normal	130	12 (9.2)	21.2 (2.0,NE)	130	3 (2.3)	NE (7.9,NE)	2.5591 (0.7127,9.1893) [0.1369]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Symptom Scales/Upset by Hair Loss									
Hepatic Impairment	Mild	49	8 (16.3)	NE (2.0,NE)	49	1 (2.0)	NE (4.1,NE)	2.9478 (0.3674,23.6524) [0.2858]	0.7444
	Normal	208	18 (8.7)	21.2 (4.1,NE)	212	8 (3.8)	21.7 (NE,NE)	1.6996 (0.7338,3.9367) [0.2186]	
Baseline Visceral Disease	No	66	2 (3.0)	NE (0.9,NE)	74	4 (5.4)	8.2 (1.4,NE)	0.4999 (0.0901,2.7728) [0.4130]	0.0823
	Yes	195	24 (12.3)	21.2 (2.8,NE)	189	5 (2.6)	21.7 (NE,NE)	2.8171 (1.0710,7.4101) [0.0291]	
Baseline CNS Metastases	No	218	20 (9.2)	NE (4.1,NE)	224	8 (3.6)	21.7 (8.2,NE)	1.6168 (0.7101,3.6813) [0.2524]	0.3360
	Yes	43	6 (14.0)	12.2 (0.8,NE)	39	1 (2.6)	NE (0.8,NE)	3.7922 (0.4411,32.5992) [0.1940]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

Scale/Sub-scale Subgroup		T-DXd (N=261) n	T-DXd (N=261) No. of Events (%)	T-DXd (N=261) Median (95% CI) [a] (months)	T-DM1 (N=263) n	T-DM1 (N=263) No. of Events (%)	T-DM1 (N=263) Median (95% CI) [a] (months)	T-DXd vs T-DM1 Hazard Ratio (95% CI) p-value [b]	Interaction P-value [c]
Symptom Scales/Upset by Hair Loss									
History of CNS Metastases	No	199	21 (10.6)	21.2 (2.8,NE)	211	8 (3.8)	21.7 (8.2,NE)	1.6890 (0.7445,3.8316) [0.2069]	0.5177
	Yes	62	5 (8.1)	NE (1.4,NE)	52	1 (1.9)	NE (0.8,NE)	3.3458 (0.3902,28.6892) [0.2486]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Body Image									
Age	<65	212	103 (48.6)	14.5 (7.2,21.0)	206	63 (30.6)	NE (11.7,NE)	1.4551 (1.0616,1.9944) [0.0196]	0.4194
	>=65	49	18 (36.7)	17.6 (10.7,NE)	57	18 (31.6)	NE (10.4,NE)	1.0277 (0.5335,1.9796) [0.9366]	
Age	<75	253	118 (46.6)	17.3 (9.7,21.0)	255	79 (31.0)	NE (13.6,NE)	1.3705 (1.0296,1.8243) [0.0310]	0.7276
	>=75	8	3 (37.5)	11.5 (0.8,NE)	8	2 (25.0)	12.4 (10.3,NE)	1.3050 (0.2129,7.9997) [0.7729]	
Region	Asia	149	69 (46.3)	17.3 (9.0,NE)	160	46 (28.8)	NE (13.6,NE)	1.4800 (1.0166,2.1547) [0.0405]	0.6179
	Europe	54	24 (44.4)	19.4 (5.6,NE)	50	13 (26.0)	NE (10.3,NE)	1.4577 (0.7376,2.8806) [0.2723]	
	North America	17	6 (35.3)	21.0 (3.1,NE)	17	3 (17.6)	NE (NE,NE)	1.2953 (0.3063,5.4771) [0.7244]	
	Rest of World	41	22 (53.7)	6.9 (2.8,NE)	36	19 (52.8)	7.1 (3.5,NE)	0.9305 (0.5034,1.7197) [0.8013]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Body Image									
Race	Asian	152	70 (46.1)	17.3 (9.0,NE)	162	47 (29.0)	NE (13.6,NE)	1.4709 (1.0138,2.1341) [0.0421]	0.4130
	Black Or African American	10	7 (70.0)	5.0 (1.4,NE)	9	2 (22.2)	NE (1.5,NE)	3.4635 (0.7169,16.7320) [0.0974]	
	Other	28	11 (39.3)	19.4 (4.2,NE)	20	5 (25.0)	NE (3.5,NE)	1.2731 (0.4368,3.7100) [0.6590]	
	White	71	33 (46.5)	11.6 (5.6,NE)	72	27 (37.5)	12.4 (7.0,NE)	1.0573 (0.6353,1.7596) [0.8353]	
ECOG PS	0	154	74 (48.1)	17.3 (8.6,20.2)	175	54 (30.9)	NE (11.7,NE)	1.4193 (0.9979,2.0186) [0.0510]	0.6682
	1	106	47 (44.3)	14.9 (6.2,NE)	87	27 (31.0)	NE (11.7,NE)	1.2910 (0.8025,2.0769) [0.2956]	
Hormone Receptor Status	Negative	126	64 (50.8)	9.7 (5.6,NE)	122	33 (27.0)	NE (13.6,NE)	1.9428 (1.2753,2.9597) [0.0017]	0.0355
	Positive	133	57 (42.9)	17.6 (12.8,NE)	139	47 (33.8)	14.1 (10.7,NE)	1.0403 (0.7053,1.5344) [0.8450]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Body Image									
Estrogen Receptors	Negative	130	66 (50.8)	9.7 (5.6,NE)	128	36 (28.1)	NE (13.6,NE)	1.8710 (1.2453,2.8109) [0.0023]	0.0451
	Positive	129	55 (42.6)	17.6 (13.6,NE)	132	44 (33.3)	NE (10.7,NE)	1.0283 (0.6898,1.5328) [0.8930]	
Progesterone Receptors	Negative	177	83 (46.9)	17.3 (7.6,NE)	168	49 (29.2)	NE (14.1,NE)	1.5371 (1.0786,2.1905) [0.0169]	0.4436
	Positive	81	38 (46.9)	14.9 (7.2,NE)	92	31 (33.7)	11.7 (10.3,NE)	1.1710 (0.7265,1.8877) [0.5205]	
Prior Treatment with Pertuzumab	No	99	38 (38.4)	17.3 (13.6,NE)	105	41 (39.0)	12.4 (7.1,NE)	0.8490 (0.5445,1.3238) [0.4574]	0.0065
	Yes	162	83 (51.2)	11.6 (6.9,20.2)	158	40 (25.3)	NE (13.6,NE)	1.8818 (1.2877,2.7500) [0.0009]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Body Image									
Lines of Prior Systemic Therapy Not Including Hormone Therapy	< 3	188	85 (45.2)	17.3 (10.7,NE)	191	59 (30.9)	NE (12.4,NE)	1.2944 (0.9272,1.8069) [0.1314]	0.5155
	>= 3	73	36 (49.3)	11.6 (4.2,20.2)	72	22 (30.6)	NE (9.0,NE)	1.6146 (0.9482,2.7493) [0.0763]	
Lines of Systemic Therapy Prior to Pertuzumab Treatment	< 3	156	79 (50.6)	12.8 (6.2,20.2)	152	39 (25.7)	NE (13.6,NE)	1.8636 (1.2671,2.7410) [0.0013]	0.8541
	>= 3	6	4 (66.7)	8.6 (1.4,NE)	6	1 (16.7)	NE (0.7,NE)	1.8365 (0.2009,16.7848) [0.5848]	
Renal Impairment at Baseline	Mild	92	45 (48.9)	11.6 (4.3,NE)	104	41 (39.4)	13.6 (10.4,NE)	1.2113 (0.7930,1.8503) [0.3811]	0.1566
	Moderate	30	14 (46.7)	14.5 (6.9,NE)	22	2 (9.1)	NE (10.3,NE)	4.5241 (1.0262,19.9448) [0.0287]	
	Normal	130	60 (46.2)	19.4 (9.0,NE)	130	37 (28.5)	NE (11.7,NE)	1.3784 (0.9097,2.0886) [0.1317]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Body Image									
Hepatic Impairment	Mild	49	21 (42.9)	20.2 (2.9,NE)	49	14 (28.6)	14.1 (7.0,NE)	1.2971 (0.6584,2.5556) [0.4553]	0.9175
	Normal	208	100 (48.1)	17.3 (9.0,21.0)	212	67 (31.6)	NE (12.4,NE)	1.3850 (1.0148,1.8903) [0.0402]	
Baseline Visceral Disease	No	66	32 (48.5)	20.2 (4.2,NE)	74	27 (36.5)	NE (10.5,NE)	1.2006 (0.7187,2.0058) [0.4901]	0.4775
	Yes	195	89 (45.6)	14.9 (11.5,21.0)	189	54 (28.6)	NE (11.7,NE)	1.4457 (1.0287,2.0317) [0.0336]	
Baseline CNS Metastases	No	218	102 (46.8)	17.3 (9.7,21.0)	224	69 (30.8)	NE (12.4,NE)	1.3888 (1.0219,1.8875) [0.0363]	0.8127
	Yes	43	19 (44.2)	19.4 (4.4,NE)	39	12 (30.8)	NE (4.8,NE)	1.2906 (0.6234,2.6719) [0.4872]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 32 - Analysis of time to first deterioration of EORTC QLQ-BR23 by pre-specified Subgroup [continued]
Full Analysis Set

		T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Scale/Sub-scale Subgroup		n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value [b]	P-value [c]
Functional Scales/Body Image									
History of CNS Metastases	No	199	96 (48.2)	14.9 (7.6,21.0)	211	66 (31.3)	NE (11.7,NE)	1.4244 (1.0401,1.9509) [0.0277]	0.7051
	Yes	62	25 (40.3)	19.4 (9.0,NE)	52	15 (28.8)	14.1 (14.1,NE)	1.1864 (0.6202,2.2698) [0.6035]	

Notes: Time to first deterioration is defined as the time from randomization until the date of the first clinically meaningful symptom deterioration. Deterioration is defined as an increase of 10 or more points each scale/subscale. Death is censored in this analysis.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.

Table 56 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 15 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	47 (22.2)	NE (24.6 , NE)	206	50 (24.3)	NE (14.4 , NE)	0.6403 (0.4267 , 0.9610) 0.0300	0.9001
>=65	49	12 (24.5)	NE (17.6 , NE)	57	17 (29.8)	20.5 (9.1 , NE)	0.7013 (0.3338 , 1.4736) 0.3476	
Age								
<75	253	56 (22.1)	NE (24.6 , NE)	255	65 (25.5)	NE (16.9 , NE)	0.6165 (0.4288 , 0.8864) 0.0084	0.1510
>=75	8	3 (37.5)	NE (0.8 , NE)	8	2 (25.0)	NE (7.2 , NE)	2.8712 (0.4693 , 17.567) 0.2336	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 56 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 15 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	35 (23.5)	NE (19.5 , NE)	160	47 (29.4)	20.5 (14.1 , NE)	0.5188 (0.3313 , 0.8124) 0.0035	0.3506
North America	17	4 (23.5)	NE (10.2 , NE)	17	1 (5.9)	NE (NE , NE)	3.1320 (0.3423 , 28.655) 0.2878	
Europe	54	12 (22.2)	NE (NE , NE)	50	11 (22.0)	NE (NE , NE)	0.8555 (0.3740 , 1.9567) 0.7094	
Rest of World	41	8 (19.5)	NE (NE , NE)	36	8 (22.2)	NE (11.7 , NE)	0.8025 (0.3004 , 2.1434) 0.6570	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 56 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 15 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	19 (26.8)	NE (NE , NE)	72	17 (23.6)	NE (12.0 , NE)	0.9674 (0.5013 , 1.8668) 0.9201	0.3150
Black or African American	10	1 (10.0)	NE (2.7 , NE)	9	0	NE (NE , NE)	NE (NE, NE) 0.3458	
Asian	152	35 (23.0)	NE (24.6 , NE)	162	47 (29.0)	20.5 (14.1 , NE)	0.5205 (0.3324 , 0.8150) 0.0037	
Other	28	4 (14.3)	NE (NE , NE)	20	3 (15.0)	NE (NE , NE)	0.7924 (0.1708 , 3.6758) 0.7658	
ECOG PS								
0	154	35 (22.7)	NE (NE , NE)	175	44 (25.1)	NE (16.9 , NE)	0.6572 (0.4191 , 1.0306) 0.0651	0.9285
1	106	24 (22.6)	NE (17.9 , NE)	87	23 (26.4)	NE (14.1 , NE)	0.6267 (0.3510 , 1.1191) 0.1114	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 56 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 15 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	34 (25.6)	NE (NE , NE)	139	38 (27.3)	20.5 (14.1 , NE)	0.6606 (0.4122 , 1.0587) 0.0823	0.9260
Negative	126	25 (19.8)	NE (24.6 , NE)	122	28 (23.0)	NE (NE , NE)	0.6370 (0.3676 , 1.1039) 0.1050	
Estrogen Receptors								
Positive	129	33 (25.6)	NE (19.5 , NE)	132	37 (28.0)	20.5 (14.1 , NE)	0.6287 (0.3892 , 1.0154) 0.0555	0.9433
Negative	130	26 (20.0)	NE (24.6 , NE)	128	29 (22.7)	NE (NE , NE)	0.6586 (0.3840 , 1.1295) 0.1261	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 56 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 15 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	21 (25.9)	NE (17.9 , NE)	92	21 (22.8)	NE (12.0 , NE)	0.8032 (0.4347 , 1.4841) 0.4822	0.2964
Negative	177	38 (21.5)	NE (24.6 , NE)	168	45 (26.8)	NE (20.5 , NE)	0.5875 (0.3783 , 0.9124) 0.0167	
Prior Treatment with Pertuzumab								
Yes	162	44 (27.2)	NE (24.6 , NE)	158	38 (24.1)	20.5 (20.5 , NE)	0.8305 (0.5340 , 1.2917) 0.4070	0.0615
No	99	15 (15.2)	NE (NE , NE)	105	29 (27.6)	NE (12.0 , NE)	0.3909 (0.2080 , 0.7349) 0.0026	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 56 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 15 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	45 (23.9)	NE (24.6 , NE)	191	53 (27.7)	NE (16.9 , NE)	0.6381 (0.4261 , 0.9556) 0.0278	0.7897
>= 3 lines	73	14 (19.2)	NE (NE , NE)	72	14 (19.4)	NE (14.4 , NE)	0.6488 (0.3030 , 1.3896) 0.2623	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	42 (26.9)	NE (24.6 , NE)	152	38 (25.0)	20.5 (16.9 , NE)	0.8053 (0.5152 , 1.2586) 0.3387	0.1368
>= 3 lines	6	2 (33.3)	NE (7.2 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.3202	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 56 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 15 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	28 (21.5)	NE (24.6 , NE)	130	33 (25.4)	NE (12.4 , NE)	0.5292 (0.3133 , 0.8939) 0.0157	0.5649
Mild Impairment	92	23 (25.0)	NE (17.9 , NE)	104	27 (26.0)	20.5 (16.9 , NE)	0.8011 (0.4579 , 1.4013) 0.4338	
Moderate Impairment	30	8 (26.7)	NE (15.0 , NE)	22	7 (31.8)	NE (7.2 , NE)	0.6106 (0.2197 , 1.6971) 0.3424	
Hepatic Impairment								
Within Normal Range	208	53 (25.5)	NE (24.6 , NE)	212	53 (25.0)	NE (20.5 , NE)	0.7611 (0.5169 , 1.1207) 0.1644	0.0256
Mild Impairment	49	6 (12.2)	NE (NE , NE)	49	14 (28.6)	NE (6.7 , NE)	0.2593 (0.0985 , 0.6829) 0.0034	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 56 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 15 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	43 (22.1)	NE (24.6 , NE)	189	51 (27.0)	20.5 (14.1 , NE)	0.5471 (0.3605 , 0.8304) 0.0040	0.3999
No	66	16 (24.2)	NE (NE , NE)	74	16 (21.6)	NE (NE , NE)	0.9259 (0.4616 , 1.8573) 0.8290	
Baseline CNS Metastases								
Yes	43	7 (16.3)	NE (NE , NE)	39	13 (33.3)	14.4 (7.0 , NE)	0.2707 (0.1031 , 0.7107) 0.0049	0.0658
No	218	52 (23.9)	NE (24.6 , NE)	224	54 (24.1)	NE (20.5 , NE)	0.7426 (0.5049 , 1.0924) 0.1293	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 56 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 15 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	12 (19.4)	NE (NE , NE)	52	18 (34.6)	14.1 (10.3 , NE)	0.3523 (0.1638 , 0.7577) 0.0055	0.1186
No	199	47 (23.6)	NE (24.6 , NE)	211	49 (23.2)	NE (20.5 , NE)	0.7523 (0.5015 , 1.1286) 0.1679	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	82 (38.7)	19.4 (14.7 , NE)	206	76 (36.9)	16.6 (10.3 , NE)	0.8240 (0.6011 , 1.1296) 0.2256	0.3906
>=65	49	26 (53.1)	7.6 (4.9 , NE)	57	28 (49.1)	9.0 (6.2 , NE)	1.0986 (0.6426 , 1.8780) 0.7318	
Age								
<75	253	105 (41.5)	17.5 (13.6 , NE)	255	101 (39.6)	15.2 (10.0 , 20.5)	0.8620 (0.6547 , 1.1349) 0.2851	0.9453
>=75	8	3 (37.5)	6.5 (4.9 , NE)	8	3 (37.5)	NE (0.9 , NE)	1.0286 (0.2059 , 5.1376) 0.9726	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	64 (43.0)	NE (11.1 , NE)	160	72 (45.0)	10.3 (7.6 , 17.1)	0.7150 (0.5084 , 1.0057) 0.0517	0.3168
North America	17	6 (35.3)	NE (1.6 , NE)	17	4 (23.5)	NE (5.7 , NE)	1.5227 (0.4295 , 5.3991) 0.5107	
Europe	54	24 (44.4)	16.8 (4.9 , 19.4)	50	16 (32.0)	19.1 (7.3 , NE)	1.4284 (0.7549 , 2.7027) 0.2694	
Rest of World	41	14 (34.1)	NE (11.7 , NE)	36	12 (33.3)	NE (7.1 , NE)	0.9582 (0.4423 , 2.0759) 0.9122	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	27 (38.0)	17.5 (10.6 , NE)	72	25 (34.7)	19.1 (7.3 , NE)	1.0754 (0.6226 , 1.8576) 0.7950	0.1268
Black or African American	10	4 (40.0)	NE (1.6 , NE)	9	1 (11.1)	NE (4.2 , NE)	3.7188 (0.4144 , 33.373) 0.2082	
Asian	152	64 (42.1)	NE (11.1 , NE)	162	73 (45.1)	10.3 (7.6 , 17.1)	0.7046 (0.5015 , 0.9901) 0.0417	
Other	28	13 (46.4)	15.2 (4.3 , 19.4)	20	5 (25.0)	NE (7.0 , NE)	1.8422 (0.6533 , 5.1947) 0.2453	
ECOG PS								
0	154	71 (46.1)	15.7 (10.6 , NE)	175	70 (40.0)	15.2 (9.0 , NE)	0.9870 (0.7080 , 1.3760) 0.9332	0.2010
1	106	37 (34.9)	NE (13.6 , NE)	87	34 (39.1)	14.4 (7.3 , NE)	0.7063 (0.4419 , 1.1287) 0.1425	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	54 (40.6)	NE (13.6 , NE)	139	55 (39.6)	16.6 (9.1 , NE)	0.8770 (0.6011 , 1.2797) 0.4953	0.8378
Negative	126	54 (42.9)	15.2 (10.6 , NE)	122	48 (39.3)	14.4 (8.3 , NE)	0.8793 (0.5947 , 1.3002) 0.5113	
Estrogen Receptors								
Positive	129	53 (41.1)	NE (13.6 , NE)	132	51 (38.6)	17.1 (9.1 , NE)	0.9011 (0.6117 , 1.3275) 0.5981	0.9726
Negative	130	55 (42.3)	15.2 (10.6 , NE)	128	52 (40.6)	14.4 (7.6 , NE)	0.8460 (0.5779 , 1.2385) 0.3814	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	31 (38.3)	NE (11.7 , NE)	92	35 (38.0)	16.6 (7.2 , NE)	0.8487 (0.5219 , 1.3803) 0.5071	0.7302
Negative	177	77 (43.5)	16.8 (11.0 , NE)	168	67 (39.9)	15.2 (9.0 , 20.5)	0.9100 (0.6546 , 1.2652) 0.5711	
Prior Treatment with Pertuzumab								
Yes	162	68 (42.0)	19.4 (14.5 , NE)	158	58 (36.7)	19.1 (10.3 , NE)	0.9747 (0.6850 , 1.3868) 0.8837	0.3714
No	99	40 (40.4)	14.7 (11.1 , NE)	105	46 (43.8)	9.1 (6.9 , NE)	0.7262 (0.4739 , 1.1130) 0.1368	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	75 (39.9)	19.4 (14.7 , NE)	191	75 (39.3)	19.1 (10.0 , NE)	0.8093 (0.5860 , 1.1177) 0.1971	0.3386
>= 3 lines	73	33 (45.2)	11.1 (6.9 , NE)	72	29 (40.3)	14.4 (7.3 , NE)	1.0501 (0.6363 , 1.7333) 0.8516	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	64 (41.0)	19.4 (15.2 , NE)	152	56 (36.8)	19.1 (10.2 , NE)	0.9525 (0.6637 , 1.3672) 0.7907	0.4935
>= 3 lines	6	4 (66.7)	5.7 (1.5 , NE)	6	2 (33.3)	17.1 (0.8 , 17.1)	2.7813 (0.3078 , 25.130) 0.3421	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	53 (40.8)	NE (13.6 , NE)	130	46 (35.4)	16.6 (8.7 , NE)	0.8339 (0.5570 , 1.2484) 0.3727	0.9511
Mild Impairment	92	40 (43.5)	16.8 (8.7 , NE)	104	48 (46.2)	11.6 (7.0 , 20.5)	0.9163 (0.6016 , 1.3956) 0.6742	
Moderate Impairment	30	14 (46.7)	14.5 (6.5 , NE)	22	9 (40.9)	15.2 (1.9 , NE)	0.8863 (0.3806 , 2.0639) 0.7769	
Hepatic Impairment								
Within Normal Range	208	92 (44.2)	16.8 (12.5 , NE)	212	88 (41.5)	14.4 (9.1 , NE)	0.8915 (0.6640 , 1.1968) 0.4420	0.6689
Mild Impairment	49	16 (32.7)	NE (8.6 , NE)	49	16 (32.7)	16.6 (5.7 , NE)	0.7816 (0.3892 , 1.5696) 0.4891	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	77 (39.5)	19.4 (13.6 , NE)	189	74 (39.2)	14.4 (9.0 , 19.1)	0.8140 (0.5899 , 1.1233) 0.2075	0.6791
No	66	31 (47.0)	16.8 (6.8 , NE)	74	30 (40.5)	NE (5.0 , NE)	0.9914 (0.5995 , 1.6396) 0.9700	
Baseline CNS Metastases								
Yes	43	16 (37.2)	19.4 (9.7 , NE)	39	16 (41.0)	10.3 (7.0 , NE)	0.5758 (0.2806 , 1.1817) 0.1294	0.4720
No	218	92 (42.2)	17.5 (12.5 , NE)	224	88 (39.3)	16.6 (10.0 , NE)	0.9145 (0.6818 , 1.2265) 0.5478	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	26 (41.9)	15.2 (9.7 , NE)	52	18 (34.6)	11.6 (8.4 , NE)	0.8676 (0.4662 , 1.6146) 0.6472	0.5229
No	199	82 (41.2)	NE (12.5 , NE)	211	86 (40.8)	16.6 (8.7 , 20.5)	0.8495 (0.6269 , 1.1511) 0.2905	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	40 (18.9)	NE (NE , NE)	206	34 (16.5)	NE (NE , NE)	0.8202 (0.5153 , 1.3056) 0.4032	0.4121
>=65	49	14 (28.6)	NE (16.1 , NE)	57	13 (22.8)	NE (13.4 , NE)	1.1569 (0.5424 , 2.4675) 0.7128	
Age								
<75	253	52 (20.6)	NE (NE , NE)	255	46 (18.0)	NE (20.5 , NE)	0.8507 (0.5693 , 1.2710) 0.4287	0.5327
>=75	8	2 (25.0)	16.1 (1.4 , NE)	8	1 (12.5)	NE (5.3 , NE)	1.4142 (0.0848 , 23.573) 0.8084	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	35 (23.5)	NE (NE , NE)	160	28 (17.5)	NE (20.5 , NE)	0.9959 (0.6012 , 1.6496) 0.9847	0.5804
North America	17	3 (17.6)	NE (NE , NE)	17	2 (11.8)	NE (NE , NE)	1.3290 (0.2219 , 7.9594) 0.7547	
Europe	54	8 (14.8)	NE (NE , NE)	50	7 (14.0)	NE (NE , NE)	0.8727 (0.3145 , 2.4215) 0.7960	
Rest of World	41	8 (19.5)	NE (18.0 , NE)	36	10 (27.8)	NE (8.5 , NE)	0.4593 (0.1793 , 1.1763) 0.0974	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	14 (19.7)	NE (18.0 , NE)	72	13 (18.1)	NE (16.6 , NE)	0.8529 (0.3986 , 1.8253) 0.6792	0.2063
Black or African American	10	4 (40.0)	16.7 (3.1 , NE)	9	2 (22.2)	NE (1.4 , NE)	1.1747 (0.2126 , 6.4890) 0.8534	
Asian	152	35 (23.0)	NE (NE , NE)	162	28 (17.3)	NE (20.5 , NE)	0.9961 (0.6012 , 1.6502) 0.9854	
Other	28	1 (3.6)	NE (NE , NE)	20	4 (20.0)	NE (7.1 , NE)	0.1546 (0.0173 , 1.3838) 0.0539	
ECOG PS								
0	154	31 (20.1)	NE (NE , NE)	175	27 (15.4)	NE (20.5 , NE)	0.9133 (0.5412 , 1.5413) 0.7346	0.4860
1	106	23 (21.7)	NE (NE , NE)	87	20 (23.0)	NE (13.8 , NE)	0.7531 (0.4112 , 1.3793) 0.3509	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	18 (13.5)	NE (NE , NE)	139	24 (17.3)	NE (20.5 , NE)	0.5631 (0.3030 , 1.0465) 0.0658	0.0494
Negative	126	36 (28.6)	NE (16.7 , NE)	122	22 (18.0)	NE (NE , NE)	1.2545 (0.7347 , 2.1420) 0.4097	
Estrogen Receptors								
Positive	129	18 (14.0)	NE (NE , NE)	132	23 (17.4)	NE (20.5 , NE)	0.5804 (0.3104 , 1.0855) 0.0849	0.0653
Negative	130	36 (27.7)	NE (18.0 , NE)	128	23 (18.0)	NE (NE , NE)	1.2092 (0.7132 , 2.0499) 0.4851	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	10 (12.3)	NE (NE , NE)	92	15 (16.3)	NE (16.6 , NE)	0.5449 (0.2426 , 1.2240) 0.1353	0.1875
Negative	177	44 (24.9)	NE (NE , NE)	168	31 (18.5)	NE (20.5 , NE)	1.0337 (0.6493 , 1.6456) 0.8915	
Prior Treatment with Pertuzumab								
Yes	162	36 (22.2)	NE (NE , NE)	158	22 (13.9)	NE (20.5 , NE)	1.1779 (0.6875 , 2.0182) 0.5514	0.0790
No	99	18 (18.2)	NE (18.0 , NE)	105	25 (23.8)	NE (16.6 , NE)	0.5849 (0.3171 , 1.0789) 0.0824	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	34 (18.1)	NE (NE , NE)	191	34 (17.8)	NE (20.5 , NE)	0.7425 (0.4587 , 1.2019) 0.2243	0.2599
>= 3 lines	73	20 (27.4)	NE (17.6 , NE)	72	13 (18.1)	NE (16.6 , NE)	1.2126 (0.5987 , 2.4557) 0.5951	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	36 (23.1)	NE (NE , NE)	152	21 (13.8)	NE (20.5 , NE)	1.2521 (0.7251 , 2.1622) 0.4193	0.0959
>= 3 lines	6	0	NE (NE , NE)	6	1 (16.7)	NE (0.7 , NE)	0.0000 (NE, NE) 0.2207	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	24 (18.5)	NE (NE , NE)	130	22 (16.9)	NE (16.6 , NE)	0.7018 (0.3861 , 1.2756) 0.2434	0.5470
Mild Impairment	92	24 (26.1)	NE (16.1 , NE)	104	21 (20.2)	NE (20.5 , NE)	1.1020 (0.6108 , 1.9883) 0.7489	
Moderate Impairment	30	6 (20.0)	NE (17.6 , NE)	22	4 (18.2)	NE (5.3 , NE)	0.7998 (0.2248 , 2.8458) 0.7296	
Hepatic Impairment								
Within Normal Range	208	45 (21.6)	NE (NE , NE)	212	35 (16.5)	NE (20.5 , NE)	1.0016 (0.6404 , 1.5666) 0.9963	0.1224
Mild Impairment	49	9 (18.4)	NE (18.0 , NE)	49	12 (24.5)	16.6 (9.0 , NE)	0.4857 (0.2024 , 1.1657) 0.0988	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	41 (21.0)	NE (NE , NE)	189	32 (16.9)	NE (20.5 , NE)	0.9268 (0.5790 , 1.4835) 0.7502	0.5707
No	66	13 (19.7)	NE (NE , NE)	74	15 (20.3)	NE (NE , NE)	0.7204 (0.3412 , 1.5211) 0.3880	
Baseline CNS Metastases								
Yes	43	9 (20.9)	NE (NE , NE)	39	7 (17.9)	NE (8.4 , NE)	0.8709 (0.3168 , 2.3941) 0.7886	0.9487
No	218	45 (20.6)	NE (NE , NE)	224	40 (17.9)	NE (20.5 , NE)	0.8660 (0.5630 , 1.3322) 0.5106	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	13 (21.0)	NE (NE , NE)	52	9 (17.3)	NE (NE , NE)	0.8485 (0.3526 , 2.0418) 0.7117	0.9952
No	199	41 (20.6)	NE (NE , NE)	211	38 (18.0)	NE (20.5 , NE)	0.8633 (0.5526 , 1.3485) 0.5146	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	73 (34.4)	NE (19.0 , NE)	206	77 (37.4)	13.8 (10.0 , NE)	0.6586 (0.4748 , 0.9137) 0.0118	0.6062
>=65	49	21 (42.9)	16.4 (7.3 , NE)	57	27 (47.4)	13.8 (4.8 , NE)	0.7918 (0.4466 , 1.4041) 0.4258	
Age								
<75	253	90 (35.6)	NE (19.0 , NE)	255	100 (39.2)	16.7 (10.0 , 20.5)	0.6779 (0.5077 , 0.9052) 0.0080	0.7759
>=75	8	4 (50.0)	6.9 (1.8 , NE)	8	4 (50.0)	8.1 (0.9 , 13.8)	0.6904 (0.1517 , 3.1421) 0.6300	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	65 (43.6)	16.4 (12.7 , NE)	160	65 (40.6)	11.8 (8.4 , NE)	0.8009 (0.5638 , 1.1375) 0.2123	0.0010
North America	17	8 (47.1)	NE (1.4 , NE)	17	2 (11.8)	NE (8.1 , NE)	4.2334 (0.8966 , 19.989) 0.0479	
Europe	54	15 (27.8)	NE (16.1 , NE)	50	21 (42.0)	16.7 (9.0 , 19.1)	0.5088 (0.2604 , 0.9942) 0.0447	
Rest of World	41	6 (14.6)	NE (NE , NE)	36	16 (44.4)	8.7 (4.4 , NE)	0.1941 (0.0750 , 0.5025) 0.0002	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	23 (32.4)	NE (14.2 , NE)	72	27 (37.5)	16.7 (8.7 , NE)	0.6866 (0.3922 , 1.2017) 0.1872	0.1860
Black or African American	10	2 (20.0)	NE (1.4 , NE)	9	3 (33.3)	NE (1.4 , NE)	0.3811 (0.0627 , 2.3161) 0.2770	
Asian	152	65 (42.8)	19.0 (12.7 , NE)	162	66 (40.7)	11.8 (8.4 , NE)	0.7884 (0.5558 , 1.1183) 0.1802	
Other	28	4 (14.3)	NE (16.4 , NE)	20	8 (40.0)	11.3 (2.9 , NE)	0.2219 (0.0642 , 0.7668) 0.0098	
ECOG PS								
0	154	55 (35.7)	NE (19.0 , NE)	175	64 (36.6)	16.9 (11.3 , NE)	0.7456 (0.5171 , 1.0752) 0.1147	0.2637
1	106	39 (36.8)	NE (13.7 , NE)	87	40 (46.0)	9.9 (4.4 , 16.7)	0.5525 (0.3528 , 0.8653) 0.0086	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	46 (34.6)	NE (19.0 , NE)	139	56 (40.3)	11.3 (8.7 , NE)	0.6217 (0.4182 , 0.9241) 0.0178	0.4890
Negative	126	48 (38.1)	NE (13.4 , NE)	122	48 (39.3)	16.7 (8.9 , NE)	0.7537 (0.5027 , 1.1302) 0.1691	
Estrogen Receptors								
Positive	129	45 (34.9)	NE (19.0 , NE)	132	56 (42.4)	11.3 (8.4 , NE)	0.5821 (0.3900 , 0.8687) 0.0074	0.3037
Negative	130	49 (37.7)	NE (13.7 , NE)	128	48 (37.5)	16.7 (9.0 , NE)	0.7843 (0.5242 , 1.1734) 0.2351	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	28 (34.6)	NE (14.1 , NE)	92	36 (39.1)	11.3 (8.4 , NE)	0.6578 (0.3987 , 1.0854) 0.0998	0.8697
Negative	177	66 (37.3)	NE (16.1 , NE)	168	67 (39.9)	16.7 (9.0 , 20.5)	0.7001 (0.4957 , 0.9889) 0.0418	
Prior Treatment with Pertuzumab								
Yes	162	68 (42.0)	NE (11.7 , NE)	158	59 (37.3)	16.7 (10.1 , NE)	0.8949 (0.6284 , 1.2745) 0.5361	0.0246
No	99	26 (26.3)	NE (19.0 , NE)	105	45 (42.9)	11.3 (7.1 , NE)	0.4084 (0.2500 , 0.6671) 0.0002	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	68 (36.2)	NE (16.4 , NE)	191	82 (42.9)	11.3 (8.4 , 19.1)	0.6033 (0.4351 , 0.8367) 0.0022	0.1661
>= 3 lines	73	26 (35.6)	NE (12.3 , NE)	72	22 (30.6)	NE (10.1 , NE)	0.9604 (0.5400 , 1.7079) 0.8902	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	65 (41.7)	NE (12.7 , NE)	152	56 (36.8)	19.1 (10.2 , NE)	0.9107 (0.6338 , 1.3086) 0.6129	0.5889
>= 3 lines	6	3 (50.0)	9.9 (1.4 , NE)	6	3 (50.0)	7.2 (0.8 , NE)	0.6811 (0.1362 , 3.4044) 0.6379	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	40 (30.8)	NE (NE , NE)	130	44 (33.8)	NE (9.9 , NE)	0.6394 (0.4103 , 0.9963) 0.0457	0.5019
Mild Impairment	92	42 (45.7)	16.1 (10.9 , NE)	104	48 (46.2)	13.8 (7.1 , 20.5)	0.8496 (0.5607 , 1.2873) 0.4438	
Moderate Impairment	30	12 (40.0)	14.5 (9.7 , NE)	22	10 (45.5)	11.3 (4.2 , NE)	0.6226 (0.2687 , 1.4428) 0.2630	
Hepatic Impairment								
Within Normal Range	208	81 (38.9)	NE (16.1 , NE)	212	88 (41.5)	13.8 (10.0 , 20.5)	0.7093 (0.5220 , 0.9637) 0.0275	0.4068
Mild Impairment	49	13 (26.5)	NE (NE , NE)	49	16 (32.7)	10.1 (5.8 , NE)	0.5349 (0.2538 , 1.1270) 0.0942	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	71 (36.4)	NE (14.5 , NE)	189	68 (36.0)	16.7 (10.3 , 20.5)	0.7924 (0.5654 , 1.1105) 0.1754	0.1188
No	66	23 (34.8)	NE (16.4 , NE)	74	36 (48.6)	9.9 (4.7 , NE)	0.4694 (0.2759 , 0.7985) 0.0044	
Baseline CNS Metastases								
Yes	43	18 (41.9)	13.1 (8.6 , NE)	39	11 (28.2)	NE (5.8 , NE)	1.1007 (0.5102 , 2.3747) 0.8050	0.1064
No	218	76 (34.9)	NE (19.0 , NE)	224	93 (41.5)	13.8 (8.9 , 19.1)	0.6200 (0.4557 , 0.8434) 0.0021	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	25 (40.3)	14.5 (11.5 , NE)	52	18 (34.6)	11.8 (8.1 , NE)	0.7750 (0.4125 , 1.4561) 0.4263	0.3019
No	199	69 (34.7)	NE (19.0 , NE)	211	86 (40.8)	13.8 (9.9 , 20.5)	0.6380 (0.4627 , 0.8797) 0.0057	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	65 (30.7)	25.6 (19.4 , NE)	206	53 (25.7)	NE (15.2 , NE)	0.7642 (0.5259 , 1.1107) 0.1587	0.3787
>=65	49	15 (30.6)	NE (12.4 , NE)	57	14 (24.6)	NE (12.0 , NE)	1.0326 (0.4968 , 2.1466) 0.9332	
Age								
<75	253	78 (30.8)	25.6 (19.9 , NE)	255	67 (26.3)	NE (14.1 , NE)	0.7867 (0.5634 , 1.0987) 0.1591	0.0826
>=75	8	2 (25.0)	16.4 (3.2 , NE)	8	0	NE (NE , NE)	NE (NE, NE) 0.3173	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	49 (32.9)	25.6 (16.7 , NE)	160	40 (25.0)	NE (13.8 , NE)	0.8266 (0.5376 , 1.2710) 0.3856	0.0110
North America	17	9 (52.9)	12.2 (1.4 , NE)	17	1 (5.9)	NE (NE , NE)	7.8289 (0.9857 , 62.179) 0.0215	
Europe	54	14 (25.9)	NE (19.4 , NE)	50	13 (26.0)	15.2 (12.7 , NE)	0.6442 (0.2953 , 1.4055) 0.2671	
Rest of World	41	8 (19.5)	NE (NE , NE)	36	13 (36.1)	NE (8.4 , NE)	0.4058 (0.1674 , 0.9837) 0.0393	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	18 (25.4)	NE (19.9 , NE)	72	20 (27.8)	NE (12.7 , NE)	0.7306 (0.3831 , 1.3933) 0.3361	0.7312
Black or African American	10	4 (40.0)	NE (1.4 , NE)	9	2 (22.2)	NE (8.4 , NE)	1.6738 (0.3058 , 9.1636) 0.5482	
Asian	152	50 (32.9)	25.6 (16.7 , NE)	162	40 (24.7)	NE (13.8 , NE)	0.8445 (0.5505 , 1.2957) 0.4392	
Other	28	8 (28.6)	NE (15.0 , NE)	20	5 (25.0)	14.1 (12.0 , NE)	0.5590 (0.1763 , 1.7723) 0.3175	
ECOG PS								
0	154	43 (27.9)	25.6 (19.9 , NE)	175	42 (24.0)	NE (15.2 , NE)	0.7559 (0.4882 , 1.1705) 0.2084	0.8810
1	106	37 (34.9)	NE (15.0 , NE)	87	25 (28.7)	15.2 (12.0 , NE)	0.8303 (0.4952 , 1.3924) 0.4815	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	41 (30.8)	26.4 (18.8 , NE)	139	33 (23.7)	NE (15.2 , NE)	0.8699 (0.5451 , 1.3885) 0.5615	0.8826
Negative	126	39 (31.0)	25.6 (16.7 , NE)	122	33 (27.0)	NE (12.7 , NE)	0.7873 (0.4894 , 1.2667) 0.3221	
Estrogen Receptors								
Positive	129	38 (29.5)	26.4 (18.8 , NE)	132	31 (23.5)	NE (15.2 , NE)	0.8372 (0.5157 , 1.3593) 0.4740	0.9349
Negative	130	42 (32.3)	25.6 (16.4 , NE)	128	35 (27.3)	15.2 (12.7 , NE)	0.8026 (0.5065 , 1.2717) 0.3476	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	26 (32.1)	19.9 (16.2 , NE)	92	19 (20.7)	NE (15.2 , NE)	1.0372 (0.5694 , 1.8894) 0.9014	0.2868
Negative	177	54 (30.5)	25.6 (19.4 , NE)	168	47 (28.0)	NE (12.7 , NE)	0.7467 (0.5000 , 1.1152) 0.1518	
Prior Treatment with Pertuzumab								
Yes	162	51 (31.5)	NE (18.8 , NE)	158	35 (22.2)	NE (15.2 , NE)	0.9227 (0.5940 , 1.4332) 0.7239	0.2912
No	99	29 (29.3)	25.6 (16.7 , 26.4)	105	32 (30.5)	14.1 (12.0 , NE)	0.6645 (0.3954 , 1.1165) 0.1200	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	51 (27.1)	26.4 (19.9 , NE)	191	50 (26.2)	NE (14.1 , NE)	0.6735 (0.4521 , 1.0033) 0.0508	0.0895
>= 3 lines	73	29 (39.7)	25.6 (12.2 , 25.6)	72	17 (23.6)	15.2 (12.0 , NE)	1.2565 (0.6803 , 2.3206) 0.4657	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	49 (31.4)	NE (18.8 , NE)	152	35 (23.0)	NE (15.2 , NE)	0.8911 (0.5713 , 1.3901) 0.6148	0.1406
>= 3 lines	6	2 (33.3)	15.0 (7.8 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.2945	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	35 (26.9)	26.4 (NE , NE)	130	31 (23.8)	NE (12.0 , NE)	0.6774 (0.4091 , 1.1216) 0.1278	0.0223
Mild Impairment	92	32 (34.8)	25.6 (14.3 , NE)	104	34 (32.7)	NE (12.7 , NE)	0.8209 (0.5027 , 1.3407) 0.4319	
Moderate Impairment	30	12 (40.0)	15.2 (11.7 , NE)	22	1 (4.5)	NE (13.8 , NE)	5.5331 (0.7166 , 42.724) 0.0650	
Hepatic Impairment								
Within Normal Range	208	66 (31.7)	26.4 (19.4 , NE)	212	59 (27.8)	NE (14.1 , NE)	0.7894 (0.5512 , 1.1305) 0.1970	0.5034
Mild Impairment	49	14 (28.6)	25.6 (14.5 , 25.6)	49	8 (16.3)	NE (11.1 , NE)	0.9886 (0.4050 , 2.4131) 0.9836	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	61 (31.3)	25.6 (18.8 , 26.4)	189	46 (24.3)	NE (12.7 , NE)	0.8657 (0.5846 , 1.2818) 0.4722	0.4720
No	66	19 (28.8)	NE (NE , NE)	74	21 (28.4)	NE (13.8 , NE)	0.6890 (0.3675 , 1.2919) 0.2454	
Baseline CNS Metastases								
Yes	43	12 (27.9)	19.4 (14.3 , NE)	39	12 (30.8)	12.7 (6.9 , NE)	0.4233 (0.1776 , 1.0093) 0.0478	0.1977
No	218	68 (31.2)	25.6 (19.9 , NE)	224	55 (24.6)	NE (15.2 , NE)	0.8926 (0.6211 , 1.2827) 0.5398	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	21 (33.9)	16.5 (14.3 , NE)	52	15 (28.8)	12.7 (10.1 , NE)	0.5531 (0.2706 , 1.1308) 0.1027	0.7373
No	199	59 (29.6)	25.6 (25.6 , NE)	211	52 (24.6)	NE (15.2 , NE)	0.8465 (0.5786 , 1.2386) 0.3921	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	76 (35.8)	19.6 (16.4 , NE)	206	80 (38.8)	14.1 (10.1 , 20.7)	0.5956 (0.4319 , 0.8213) 0.0014	0.3498
>=65	49	21 (42.9)	15.3 (8.3 , NE)	57	24 (42.1)	11.8 (5.1 , NE)	0.8837 (0.4911 , 1.5903) 0.6774	
Age								
<75	253	94 (37.2)	19.6 (15.4 , NE)	255	100 (39.2)	14.1 (10.1 , 20.7)	0.6466 (0.4856 , 0.8610) 0.0027	0.7296
>=75	8	3 (37.5)	20.7 (1.4 , 20.7)	8	4 (50.0)	2.8 (0.9 , NE)	0.3710 (0.0663 , 2.0756) 0.2414	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	62 (41.6)	NE (13.6 , NE)	160	64 (40.0)	12.9 (9.7 , 21.2)	0.7128 (0.4990 , 1.0182) 0.0616	0.2063
North America	17	6 (35.3)	19.6 (1.7 , NE)	17	3 (17.6)	NE (NE , NE)	1.8149 (0.4335 , 7.5989) 0.4077	
Europe	54	17 (31.5)	19.4 (18.8 , NE)	50	22 (44.0)	13.4 (4.2 , NE)	0.4547 (0.2379 , 0.8690) 0.0149	
Rest of World	41	12 (29.3)	NE (15.4 , NE)	36	15 (41.7)	18.0 (4.2 , NE)	0.4527 (0.2104 , 0.9741) 0.0383	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	21 (29.6)	19.9 (19.6 , NE)	72	28 (38.9)	15.2 (6.8 , NE)	0.5579 (0.3149 , 0.9884) 0.0428	0.0367
Black or African American	10	6 (60.0)	13.8 (1.4 , NE)	9	2 (22.2)	18.0 (1.5 , NE)	5.4556 (0.6516 , 45.681) 0.0795	
Asian	152	62 (40.8)	NE (13.6 , NE)	162	64 (39.5)	12.9 (10.1 , 21.2)	0.7168 (0.5019 , 1.0239) 0.0661	
Other	28	8 (28.6)	19.4 (15.2 , NE)	20	10 (50.0)	7.7 (1.4 , NE)	0.2175 (0.0729 , 0.6485) 0.0029	
ECOG PS								
0	154	57 (37.0)	19.6 (15.4 , NE)	175	64 (36.6)	18.0 (11.8 , NE)	0.6796 (0.4728 , 0.9770) 0.0361	0.3416
1	106	40 (37.7)	20.7 (14.1 , NE)	87	40 (46.0)	10.3 (4.8 , 14.1)	0.5591 (0.3578 , 0.8738) 0.0098	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	47 (35.3)	19.6 (15.4 , NE)	139	60 (43.2)	11.8 (9.8 , 15.2)	0.4954 (0.3353 , 0.7318) 0.0003	0.1032
Negative	126	50 (39.7)	19.4 (13.8 , NE)	122	43 (35.2)	20.7 (9.7 , NE)	0.8943 (0.5924 , 1.3501) 0.5977	
Estrogen Receptors								
Positive	129	46 (35.7)	19.6 (15.4 , NE)	132	54 (40.9)	12.9 (10.1 , 18.0)	0.5338 (0.3573 , 0.7974) 0.0019	0.2725
Negative	130	51 (39.2)	19.4 (13.8 , NE)	128	48 (37.5)	20.7 (9.0 , NE)	0.8172 (0.5485 , 1.2175) 0.3211	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	25 (30.9)	19.6 (15.2 , 20.7)	92	37 (40.2)	11.8 (8.7 , NE)	0.4521 (0.2688 , 0.7603) 0.0022	0.1993
Negative	177	72 (40.7)	19.4 (13.6 , NE)	168	65 (38.7)	14.1 (9.7 , NE)	0.7791 (0.5548 , 1.0940) 0.1502	
Prior Treatment with Pertuzumab								
Yes	162	64 (39.5)	19.6 (14.8 , NE)	158	60 (38.0)	13.4 (10.1 , NE)	0.7074 (0.4932 , 1.0146) 0.0595	0.3716
No	99	33 (33.3)	NE (14.8 , NE)	105	44 (41.9)	14.1 (8.4 , 20.7)	0.5531 (0.3500 , 0.8742) 0.0101	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	68 (36.2)	19.6 (15.3 , NE)	191	77 (40.3)	14.1 (9.8 , 20.7)	0.5818 (0.4168 , 0.8120) 0.0013	0.3592
>= 3 lines	73	29 (39.7)	18.8 (9.6 , NE)	72	27 (37.5)	14.1 (7.6 , NE)	0.8248 (0.4859 , 1.4002) 0.4769	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	62 (39.7)	19.6 (14.8 , NE)	152	58 (38.2)	13.4 (9.8 , NE)	0.7218 (0.5002 , 1.0415) 0.0811	0.5996
>= 3 lines	6	2 (33.3)	NE (8.3 , NE)	6	2 (33.3)	10.1 (0.8 , NE)	0.5462 (0.0761 , 3.9214) 0.5417	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	43 (33.1)	NE (18.8 , NE)	130	48 (36.9)	12.9 (9.8 , 18.0)	0.5317 (0.3450 , 0.8195) 0.0037	0.4815
Mild Impairment	92	39 (42.4)	15.3 (10.7 , NE)	104	48 (46.2)	11.8 (8.3 , 21.2)	0.6967 (0.4548 , 1.0673) 0.0967	
Moderate Impairment	30	14 (46.7)	14.5 (10.3 , 20.7)	22	8 (36.4)	20.7 (2.0 , NE)	1.0158 (0.4211 , 2.4500) 0.9713	
Hepatic Impairment								
Within Normal Range	208	81 (38.9)	19.6 (15.2 , NE)	212	88 (41.5)	14.1 (10.1 , 20.7)	0.6383 (0.4694 , 0.8681) 0.0039	0.9876
Mild Impairment	49	16 (32.7)	18.8 (10.3 , NE)	49	16 (32.7)	14.1 (6.8 , NE)	0.6539 (0.3236 , 1.3211) 0.2350	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	78 (40.0)	16.4 (14.5 , 20.7)	189	72 (38.1)	14.1 (10.1 , 21.2)	0.7211 (0.5199 , 1.0002) 0.0497	0.0718
No	66	19 (28.8)	NE (18.8 , NE)	74	32 (43.2)	12.9 (7.1 , NE)	0.4377 (0.2466 , 0.7769) 0.0038	
Baseline CNS Metastases								
Yes	43	19 (44.2)	14.8 (5.9 , NE)	39	13 (33.3)	14.1 (8.3 , NE)	0.9388 (0.4502 , 1.9578) 0.8659	0.1597
No	218	78 (35.8)	20.7 (18.8 , NE)	224	91 (40.6)	13.4 (9.8 , 20.7)	0.5976 (0.4397 , 0.8122) 0.0009	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	24 (38.7)	19.4 (10.7 , NE)	52	17 (32.7)	14.1 (10.3 , NE)	0.8660 (0.4535 , 1.6538) 0.6623	0.2283
No	199	73 (36.7)	19.9 (16.4 , NE)	211	87 (41.2)	13.4 (9.7 , 21.2)	0.5927 (0.4323 , 0.8125) 0.0010	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	81 (38.2)	19.4 (15.7 , NE)	206	76 (36.9)	14.4 (10.5 , NE)	0.7617 (0.5540 , 1.0473) 0.0919	0.0345
>=65	49	25 (51.0)	11.0 (3.5 , NE)	57	20 (35.1)	NE (10.3 , NE)	1.6169 (0.8967 , 2.9155) 0.1081	
Age								
<75	253	103 (40.7)	18.2 (15.1 , NE)	255	93 (36.5)	15.2 (11.7 , NE)	0.8891 (0.6696 , 1.1804) 0.4115	0.6964
>=75	8	3 (37.5)	NE (1.4 , NE)	8	3 (37.5)	NE (3.1 , NE)	1.6706 (0.3286 , 8.4943) 0.5321	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	64 (43.0)	18.2 (13.6 , NE)	160	60 (37.5)	12.5 (10.3 , NE)	0.9034 (0.6320 , 1.2913) 0.5735	0.6550
North America	17	9 (52.9)	13.1 (1.4 , NE)	17	5 (29.4)	NE (2.8 , NE)	1.5809 (0.5221 , 4.7870) 0.4089	
Europe	54	21 (38.9)	17.5 (11.3 , NE)	50	18 (36.0)	16.7 (9.8 , NE)	0.9797 (0.5198 , 1.8465) 0.9470	
Rest of World	41	12 (29.3)	NE (15.2 , NE)	36	13 (36.1)	15.2 (7.9 , NE)	0.6122 (0.2777 , 1.3496) 0.2159	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	25 (35.2)	NE (13.6 , NE)	72	26 (36.1)	16.7 (8.5 , NE)	0.8183 (0.4701 , 1.4243) 0.4723	0.8782
Black or African American	10	5 (50.0)	10.5 (1.4 , NE)	9	4 (44.4)	NE (0.8 , NE)	0.8801 (0.2331 , 3.3229) 0.8736	
Asian	152	64 (42.1)	18.2 (13.6 , NE)	162	60 (37.0)	12.5 (10.3 , NE)	0.9067 (0.6344 , 1.2959) 0.5871	
Other	28	12 (42.9)	16.4 (11.3 , NE)	20	6 (30.0)	NE (7.1 , NE)	1.1568 (0.4304 , 3.1096) 0.7689	
ECOG PS								
0	154	60 (39.0)	19.4 (15.1 , NE)	175	64 (36.6)	16.6 (10.3 , NE)	0.7918 (0.5542 , 1.1313) 0.1982	0.4376
1	106	46 (43.4)	16.4 (6.9 , NE)	87	32 (36.8)	14.4 (10.3 , NE)	1.0327 (0.6540 , 1.6307) 0.9012	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	56 (42.1)	16.4 (13.6 , NE)	139	51 (36.7)	11.8 (10.3 , NE)	0.8510 (0.5787 , 1.2515) 0.4099	0.8740
Negative	126	50 (39.7)	19.4 (14.5 , NE)	122	44 (36.1)	16.6 (12.0 , NE)	0.9600 (0.6380 , 1.4443) 0.8375	
Estrogen Receptors								
Positive	129	54 (41.9)	16.8 (13.6 , NE)	132	48 (36.4)	11.8 (10.3 , NE)	0.8509 (0.5728 , 1.2640) 0.4211	0.8739
Negative	130	52 (40.0)	19.4 (14.5 , NE)	128	47 (36.7)	15.2 (12.0 , NE)	0.9365 (0.6289 , 1.3944) 0.7383	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	34 (42.0)	15.7 (12.8 , NE)	92	34 (37.0)	11.7 (10.2 , NE)	0.8370 (0.5160 , 1.3578) 0.4721	0.9319
Negative	177	72 (40.7)	19.4 (14.5 , NE)	168	60 (35.7)	16.7 (12.0 , NE)	0.9628 (0.6815 , 1.3603) 0.8228	
Prior Treatment with Pertuzumab								
Yes	162	66 (40.7)	19.4 (14.5 , NE)	158	54 (34.2)	16.7 (11.3 , NE)	0.8946 (0.6208 , 1.2891) 0.5495	0.8885
No	99	40 (40.4)	18.2 (13.6 , NE)	105	42 (40.0)	12.0 (8.4 , NE)	0.9091 (0.5882 , 1.4053) 0.6540	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	70 (37.2)	19.4 (16.4 , NE)	191	76 (39.8)	12.5 (10.2 , NE)	0.6918 (0.4979 , 0.9614) 0.0273	0.0040
>= 3 lines	73	36 (49.3)	12.8 (5.6 , NE)	72	20 (27.8)	NE (11.8 , NE)	1.7872 (1.0310 , 3.0981) 0.0371	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	64 (41.0)	17.5 (14.5 , NE)	152	53 (34.9)	16.7 (11.3 , NE)	0.8829 (0.6096 , 1.2787) 0.5096	0.7886
>= 3 lines	6	2 (33.3)	NE (1.5 , NE)	6	1 (16.7)	NE (0.8 , NE)	1.1724 (0.1059 , 12.978) 0.8967	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	48 (36.9)	NE (16.8 , NE)	130	44 (33.8)	15.2 (10.2 , NE)	0.8113 (0.5339 , 1.2329) 0.3227	0.6298
Mild Impairment	92	43 (46.7)	15.2 (11.1 , NE)	104	43 (41.3)	14.4 (10.3 , NE)	1.0022 (0.6552 , 1.5330) 0.9926	
Moderate Impairment	30	14 (46.7)	15.1 (4.9 , NE)	22	8 (36.4)	11.3 (5.3 , NE)	1.1533 (0.4820 , 2.7594) 0.7485	
Hepatic Impairment								
Within Normal Range	208	85 (40.9)	18.2 (15.2 , NE)	212	82 (38.7)	14.4 (11.3 , NE)	0.8385 (0.6165 , 1.1406) 0.2581	0.3781
Mild Impairment	49	21 (42.9)	14.5 (5.6 , NE)	49	14 (28.6)	15.2 (8.4 , NE)	1.2041 (0.6113 , 2.3717) 0.5898	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	81 (41.5)	16.8 (14.5 , NE)	189	69 (36.5)	15.2 (10.2 , NE)	0.8910 (0.6431 , 1.2345) 0.4822	0.8239
No	66	25 (37.9)	NE (12.5 , NE)	74	27 (36.5)	16.6 (10.5 , NE)	0.8607 (0.4976 , 1.4890) 0.5903	
Baseline CNS Metastases								
Yes	43	20 (46.5)	15.7 (5.6 , 19.4)	39	11 (28.2)	11.8 (10.3 , NE)	1.3528 (0.6351 , 2.8815) 0.4326	0.2203
No	218	86 (39.4)	NE (15.1 , NE)	224	85 (37.9)	15.2 (11.3 , NE)	0.8353 (0.6173 , 1.1303) 0.2403	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	28 (45.2)	15.7 (5.6 , NE)	52	16 (30.8)	11.8 (8.4 , NE)	1.2373 (0.6582 , 2.3261) 0.5072	0.2191
No	199	78 (39.2)	NE (15.2 , NE)	211	80 (37.9)	15.2 (11.3 , NE)	0.8170 (0.5965 , 1.1191) 0.2045	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	67 (31.6)	NE (19.4 , NE)	206	52 (25.2)	NE (16.7 , NE)	0.9871 (0.6845 , 1.4235) 0.9470	0.4872
>=65	49	13 (26.5)	24.0 (16.1 , NE)	57	18 (31.6)	20.5 (11.7 , NE)	0.7132 (0.3479 , 1.4623) 0.3501	
Age								
<75	253	78 (30.8)	NE (24.0 , NE)	255	70 (27.5)	NE (16.7 , NE)	0.8896 (0.6421 , 1.2325) 0.4802	0.0859
>=75	8	2 (25.0)	16.1 (3.2 , NE)	8	0	NE (NE , NE)	NE (NE, NE) 0.3173	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	42 (28.2)	NE (NE , NE)	160	41 (25.6)	NE (16.6 , NE)	0.8111 (0.5241 , 1.2553) 0.3454	0.1905
North America	17	7 (41.2)	NE (1.4 , NE)	17	2 (11.8)	NE (7.0 , NE)	3.7158 (0.7703 , 17.924) 0.0795	
Europe	54	18 (33.3)	19.4 (16.1 , 24.0)	50	13 (26.0)	NE (11.7 , NE)	1.0487 (0.5071 , 2.1687) 0.8971	
Rest of World	41	13 (31.7)	NE (12.5 , NE)	36	14 (38.9)	NE (7.1 , NE)	0.6738 (0.3160 , 1.4366) 0.3000	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	28 (39.4)	NE (7.6 , NE)	72	22 (30.6)	16.7 (11.7 , NE)	1.1889 (0.6793 , 2.0808) 0.5417	0.2827
Black or African American	10	4 (40.0)	NE (1.4 , NE)	9	1 (11.1)	NE (8.4 , NE)	3.4693 (0.3863 , 31.159) 0.2369	
Asian	152	42 (27.6)	NE (NE , NE)	162	41 (25.3)	NE (16.6 , NE)	0.8126 (0.5250 , 1.2576) 0.3497	
Other	28	6 (21.4)	24.0 (16.6 , 24.0)	20	6 (30.0)	NE (4.2 , NE)	0.4458 (0.1339 , 1.4842) 0.1761	
ECOG PS								
0	154	50 (32.5)	NE (19.4 , NE)	175	44 (25.1)	NE (20.5 , NE)	1.0477 (0.6967 , 1.5755) 0.8224	0.1884
1	106	30 (28.3)	NE (24.0 , NE)	87	26 (29.9)	NE (16.7 , NE)	0.7159 (0.4185 , 1.2245) 0.2171	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	40 (30.1)	NE (NE , NE)	139	41 (29.5)	NE (11.8 , NE)	0.7883 (0.5078 , 1.2239) 0.2883	0.2440
Negative	126	40 (31.7)	24.0 (16.1 , NE)	122	28 (23.0)	NE (16.6 , NE)	1.1345 (0.6957 , 1.8502) 0.6181	
Estrogen Receptors								
Positive	129	39 (30.2)	NE (NE , NE)	132	39 (29.5)	NE (11.8 , NE)	0.7883 (0.5034 , 1.2346) 0.2977	0.2764
Negative	130	41 (31.5)	24.0 (16.1 , NE)	128	30 (23.4)	NE (16.6 , NE)	1.0982 (0.6817 , 1.7693) 0.7054	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	29 (35.8)	NE (15.9 , NE)	92	26 (28.3)	NE (11.7 , NE)	1.0589 (0.6217 , 1.8035) 0.8307	0.5787
Negative	177	51 (28.8)	NE (19.4 , NE)	168	43 (25.6)	NE (16.7 , NE)	0.8685 (0.5752 , 1.3114) 0.4997	
Prior Treatment with Pertuzumab								
Yes	162	53 (32.7)	24.0 (19.4 , NE)	158	38 (24.1)	20.5 (16.6 , NE)	1.0561 (0.6922 , 1.6114) 0.7981	0.1928
No	99	27 (27.3)	NE (NE , NE)	105	32 (30.5)	NE (11.8 , NE)	0.7227 (0.4312 , 1.2111) 0.2125	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	57 (30.3)	NE (19.4 , NE)	191	52 (27.2)	NE (16.7 , NE)	0.8551 (0.5849 , 1.2501) 0.4197	0.5968
>= 3 lines	73	23 (31.5)	NE (16.0 , NE)	72	18 (25.0)	NE (11.8 , NE)	1.1334 (0.6084 , 2.1115) 0.7012	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	52 (33.3)	24.0 (16.6 , NE)	152	38 (25.0)	20.5 (16.6 , NE)	1.0471 (0.6850 , 1.6006) 0.8301	0.3434
>= 3 lines	6	1 (16.7)	NE (8.6 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.5271	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	33 (25.4)	NE (NE , NE)	130	31 (23.8)	NE (16.6 , NE)	0.7844 (0.4758 , 1.2932) 0.3408	0.2891
Mild Impairment	92	35 (38.0)	16.1 (14.5 , NE)	104	34 (32.7)	20.5 (11.7 , NE)	1.0311 (0.6418 , 1.6564) 0.9036	
Moderate Impairment	30	10 (33.3)	24.0 (10.2 , 24.0)	22	3 (13.6)	NE (NE , NE)	1.8637 (0.5043 , 6.8867) 0.3443	
Hepatic Impairment								
Within Normal Range	208	66 (31.7)	NE (19.4 , NE)	212	60 (28.3)	NE (16.6 , NE)	0.8857 (0.6215 , 1.2622) 0.4992	0.8149
Mild Impairment	49	14 (28.6)	NE (14.5 , NE)	49	10 (20.4)	NE (NE , NE)	1.0444 (0.4623 , 2.3593) 0.9081	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	59 (30.3)	NE (19.4 , NE)	189	45 (23.8)	NE (20.5 , NE)	1.0462 (0.7071 , 1.5478) 0.8240	0.2460
No	66	21 (31.8)	NE (16.1 , NE)	74	25 (33.8)	NE (11.7 , NE)	0.6789 (0.3758 , 1.2264) 0.1977	
Baseline CNS Metastases								
Yes	43	13 (30.2)	19.4 (14.8 , NE)	39	13 (33.3)	11.8 (7.0 , NE)	0.6267 (0.2798 , 1.4039) 0.2493	0.3470
No	218	67 (30.7)	NE (24.0 , NE)	224	57 (25.4)	NE (20.5 , NE)	0.9771 (0.6844 , 1.3951) 0.8982	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	14 (22.6)	NE (19.4 , NE)	52	15 (28.8)	NE (8.3 , NE)	0.5586 (0.2601 , 1.1994) 0.1306	0.1723
No	199	66 (33.2)	NE (24.0 , NE)	211	55 (26.1)	NE (20.5 , NE)	1.0277 (0.7166 , 1.4740) 0.8822	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	120 (56.6)	7.0 (4.2 , 12.5)	206	60 (29.1)	NE (NE , NE)	2.0968 (1.5357 , 2.8629) <.0001	0.4685
>=65	49	25 (51.0)	11.1 (2.9 , NE)	57	12 (21.1)	NE (NE , NE)	2.6790 (1.3441 , 5.3396) 0.0036	
Age								
<75	253	141 (55.7)	7.9 (4.4 , 12.5)	255	72 (28.2)	NE (NE , NE)	2.1397 (1.6097 , 2.8443) <.0001	0.0417
>=75	8	4 (50.0)	5.2 (0.8 , NE)	8	0	NE (NE , NE)	NE (NE, NE) 0.0228	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	85 (57.0)	7.9 (4.3 , 12.5)	160	46 (28.8)	NE (11.3 , NE)	2.1477 (1.4988 , 3.0774) <.0001	0.9151
North America	17	9 (52.9)	3.8 (0.9 , NE)	17	3 (17.6)	NE (5.7 , NE)	3.4528 (0.9328 , 12.780) 0.0476	
Europe	54	26 (48.1)	15.2 (2.8 , NE)	50	11 (22.0)	NE (NE , NE)	2.3087 (1.1363 , 4.6907) 0.0171	
Rest of World	41	25 (61.0)	4.4 (1.4 , 18.7)	36	12 (33.3)	NE (7.2 , NE)	1.9649 (0.9845 , 3.9213) 0.0552	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	42 (59.2)	4.2 (1.5 , 14.3)	72	15 (20.8)	NE (NE , NE)	3.5023 (1.9385 , 6.3276) <.0001	0.1629
Black or African American	10	4 (40.0)	NE (1.4 , NE)	9	3 (33.3)	NE (0.8 , NE)	0.9235 (0.2035 , 4.1905) 0.9197	
Asian	152	85 (55.9)	8.2 (4.3 , 12.5)	162	47 (29.0)	NE (11.3 , NE)	2.0925 (1.4640 , 2.9908) <.0001	
Other	28	14 (50.0)	17.8 (1.7 , NE)	20	7 (35.0)	NE (8.3 , NE)	1.2692 (0.5073 , 3.1757) 0.6126	
ECOG PS								
0	154	86 (55.8)	8.2 (4.4 , 15.2)	175	51 (29.1)	NE (NE , NE)	2.0792 (1.4687 , 2.9435) <.0001	0.5285
1	106	59 (55.7)	5.6 (3.2 , 16.8)	87	21 (24.1)	NE (11.7 , NE)	2.4941 (1.5142 , 4.1083) 0.0002	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	83 (62.4)	5.1 (3.0 , 8.8)	139	40 (28.8)	NE (NE , NE)	2.4791 (1.6984 , 3.6187) <.0001	0.4672
Negative	126	62 (49.2)	11.1 (4.7 , NE)	122	32 (26.2)	NE (12.0 , NE)	1.9719 (1.2853 , 3.0254) 0.0016	
Estrogen Receptors								
Positive	129	80 (62.0)	5.1 (3.0 , 8.8)	132	36 (27.3)	NE (NE , NE)	2.5790 (1.7385 , 3.8259) <.0001	0.2931
Negative	130	65 (50.0)	11.1 (4.4 , NE)	128	36 (28.1)	NE (11.7 , NE)	1.8705 (1.2428 , 2.8151) 0.0024	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	55 (67.9)	4.1 (1.5 , 7.2)	92	29 (31.5)	NE (9.7 , NE)	2.6727 (1.7021 , 4.1967) <.0001	0.4783
Negative	177	89 (50.3)	12.5 (6.0 , 19.4)	168	42 (25.0)	NE (NE , NE)	2.0948 (1.4495 , 3.0275) <.0001	
Prior Treatment with Pertuzumab								
Yes	162	92 (56.8)	7.0 (4.1 , 14.3)	158	40 (25.3)	NE (NE , NE)	2.5536 (1.7600 , 3.7050) <.0001	0.3162
No	99	53 (53.5)	9.8 (4.4 , 17.8)	105	32 (30.5)	NE (11.2 , NE)	1.8364 (1.1834 , 2.8498) 0.0065	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	103 (54.8)	7.9 (4.3 , 17.8)	191	52 (27.2)	NE (NE , NE)	2.2268 (1.5933 , 3.1121) <.0001	0.9905
>= 3 lines	73	42 (57.5)	8.2 (3.8 , 12.5)	72	20 (27.8)	NE (10.8 , NE)	2.1601 (1.2669 , 3.6833) 0.0037	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	87 (55.8)	7.1 (4.1 , 15.2)	152	39 (25.7)	NE (NE , NE)	2.4888 (1.7041 , 3.6349) <.0001	0.5468
>= 3 lines	6	5 (83.3)	3.0 (0.8 , NE)	6	1 (16.7)	NE (0.8 , NE)	3.9892 (0.4636 , 34.327) 0.1735	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	72 (55.4)	8.5 (4.2 , 19.4)	130	39 (30.0)	NE (11.3 , NE)	1.8485 (1.2468 , 2.7404) 0.0020	0.3404
Mild Impairment	92	56 (60.9)	6.0 (2.0 , 11.1)	104	30 (28.8)	NE (11.7 , NE)	2.5250 (1.6191 , 3.9378) <.0001	
Moderate Impairment	30	13 (43.3)	15.2 (3.1 , NE)	22	2 (9.1)	NE (NE , NE)	4.3864 (0.9885 , 19.464) 0.0332	
Hepatic Impairment								
Within Normal Range	208	121 (58.2)	7.2 (4.3 , 12.5)	212	57 (26.9)	NE (NE , NE)	2.4262 (1.7692 , 3.3272) <.0001	0.1754
Mild Impairment	49	24 (49.0)	11.1 (2.9 , NE)	49	15 (30.6)	NE (6.6 , NE)	1.4752 (0.7730 , 2.8155) 0.2384	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	108 (55.4)	7.9 (4.4 , 12.5)	189	49 (25.9)	NE (NE , NE)	2.3256 (1.6579 , 3.2624) <.0001	0.5609
No	66	37 (56.1)	7.0 (2.8 , NE)	74	23 (31.1)	NE (9.7 , NE)	1.9687 (1.1682 , 3.3180) 0.0097	
Baseline CNS Metastases								
Yes	43	25 (58.1)	4.6 (3.1 , 16.8)	39	10 (25.6)	NE (9.0 , NE)	2.4935 (1.1904 , 5.2233) 0.0126	0.7101
No	218	120 (55.0)	8.3 (4.3 , 15.2)	224	62 (27.7)	NE (NE , NE)	2.1675 (1.5941 , 2.9471) <.0001	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	28 (45.2)	16.8 (4.4 , NE)	52	12 (23.1)	NE (9.6 , NE)	1.9427 (0.9811 , 3.8469) 0.0531	0.7120
No	199	117 (58.8)	7.0 (3.2 , 9.8)	211	60 (28.4)	NE (NE , NE)	2.3086 (1.6900 , 3.1535) <.0001	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	79 (37.3)	24.6 (16.6 , NE)	206	78 (37.9)	12.9 (9.9 , 21.0)	0.6994 (0.5087 , 0.9616) 0.0270	0.0031
>=65	49	24 (49.0)	10.7 (3.5 , NE)	57	15 (26.3)	NE (10.3 , NE)	2.0107 (1.0538 , 3.8363) 0.0310	
Age								
<75	253	100 (39.5)	18.5 (16.4 , NE)	255	91 (35.7)	21.0 (11.1 , NE)	0.8617 (0.6470 , 1.1476) 0.3082	0.3854
>=75	8	3 (37.5)	8.3 (0.8 , NE)	8	2 (25.0)	NE (8.1 , NE)	2.0448 (0.3403 , 12.285) 0.4246	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	64 (43.0)	17.3 (11.9 , NE)	160	60 (37.5)	11.9 (9.1 , NE)	0.8693 (0.6084 , 1.2420) 0.4403	0.2163
North America	17	9 (52.9)	10.2 (3.0 , NE)	17	3 (17.6)	NE (NE , NE)	2.7143 (0.7298 , 10.095) 0.1209	
Europe	54	17 (31.5)	NE (16.4 , NE)	50	15 (30.0)	NE (8.9 , NE)	0.8453 (0.4179 , 1.7098) 0.6408	
Rest of World	41	13 (31.7)	NE (11.7 , NE)	36	15 (41.7)	21.0 (5.6 , 21.0)	0.6107 (0.2902 , 1.2848) 0.1875	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	24 (33.8)	NE (11.7 , NE)	72	23 (31.9)	21.0 (10.3 , 21.0)	0.9003 (0.5071 , 1.5983) 0.7162	0.1084
Black or African American	10	7 (70.0)	6.5 (3.0 , NE)	9	2 (22.2)	NE (2.8 , NE)	3.5901 (0.7367 , 17.496) 0.0919	
Asian	152	65 (42.8)	17.3 (11.9 , NE)	162	60 (37.0)	12.9 (9.8 , NE)	0.8938 (0.6265 , 1.2750) 0.5353	
Other	28	7 (25.0)	NE (16.4 , NE)	20	8 (40.0)	9.9 (1.4 , NE)	0.4069 (0.1453 , 1.1394) 0.0782	
ECOG PS								
0	154	56 (36.4)	NE (16.6 , NE)	175	68 (38.9)	13.8 (9.1 , NE)	0.7155 (0.5009 , 1.0219) 0.0644	0.0455
1	106	47 (44.3)	16.4 (10.2 , NE)	87	25 (28.7)	NE (10.3 , NE)	1.2350 (0.7542 , 2.0224) 0.4011	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	50 (37.6)	NE (16.4 , NE)	139	49 (35.3)	NE (9.9 , NE)	0.8238 (0.5541 , 1.2249) 0.3389	0.5122
Negative	126	53 (42.1)	18.2 (12.4 , NE)	122	43 (35.2)	21.0 (10.1 , NE)	0.9525 (0.6334 , 1.4323) 0.8117	
Estrogen Receptors								
Positive	129	48 (37.2)	NE (16.4 , NE)	132	47 (35.6)	NE (8.9 , NE)	0.7883 (0.5254 , 1.1826) 0.2506	0.3850
Negative	130	55 (42.3)	18.2 (12.0 , NE)	128	45 (35.2)	21.0 (10.1 , NE)	0.9751 (0.6542 , 1.4535) 0.8968	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	27 (33.3)	NE (11.9 , NE)	92	30 (32.6)	NE (8.5 , NE)	0.7478 (0.4426 , 1.2634) 0.2742	0.4971
Negative	177	76 (42.9)	17.3 (13.0 , NE)	168	62 (36.9)	21.0 (10.1 , NE)	0.9401 (0.6699 , 1.3193) 0.7213	
Prior Treatment with Pertuzumab								
Yes	162	71 (43.8)	18.5 (10.8 , NE)	158	58 (36.7)	12.9 (10.1 , NE)	0.9556 (0.6731 , 1.3566) 0.7972	0.3856
No	99	32 (32.3)	NE (16.4 , NE)	105	35 (33.3)	NE (8.5 , NE)	0.7540 (0.4655 , 1.2212) 0.2489	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	76 (40.4)	18.5 (14.5 , NE)	191	74 (38.7)	12.9 (9.9 , NE)	0.8072 (0.5844 , 1.1149) 0.1920	0.2929
>= 3 lines	73	27 (37.0)	NE (12.0 , NE)	72	19 (26.4)	NE (11.8 , NE)	1.1627 (0.6433 , 2.1016) 0.6175	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	69 (44.2)	16.6 (10.8 , NE)	152	58 (38.2)	11.9 (10.0 , NE)	0.9385 (0.6594 , 1.3358) 0.7222	0.1531
>= 3 lines	6	2 (33.3)	NE (8.6 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.3431	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	48 (36.9)	24.6 (16.6 , NE)	130	48 (36.9)	12.9 (9.8 , NE)	0.6706 (0.4448 , 1.0109) 0.0545	0.0847
Mild Impairment	92	41 (44.6)	16.4 (10.2 , NE)	104	39 (37.5)	21.0 (8.9 , NE)	1.1213 (0.7228 , 1.7394) 0.6097	
Moderate Impairment	30	14 (46.7)	14.5 (5.6 , NE)	22	5 (22.7)	NE (8.1 , NE)	1.7145 (0.6169 , 4.7648) 0.2955	
Hepatic Impairment								
Within Normal Range	208	87 (41.8)	18.5 (14.5 , NE)	212	79 (37.3)	21.0 (10.7 , NE)	0.9073 (0.6669 , 1.2344) 0.5345	0.6208
Mild Impairment	49	16 (32.7)	NE (10.2 , NE)	49	14 (28.6)	NE (6.6 , NE)	0.7479 (0.3639 , 1.5371) 0.4292	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	81 (41.5)	17.3 (12.0 , NE)	189	69 (36.5)	13.8 (9.9 , NE)	0.9216 (0.6669 , 1.2736) 0.6204	0.4569
No	66	22 (33.3)	NE (18.5 , NE)	74	24 (32.4)	NE (11.1 , NE)	0.7401 (0.4115 , 1.3311) 0.3150	
Baseline CNS Metastases								
Yes	43	20 (46.5)	13.1 (4.2 , NE)	39	14 (35.9)	10.7 (6.6 , 21.0)	1.0097 (0.5005 , 2.0372) 0.9828	0.5646
No	218	83 (38.1)	24.6 (16.4 , NE)	224	79 (35.3)	NE (11.1 , NE)	0.8527 (0.6252 , 1.1629) 0.3149	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	26 (41.9)	16.6 (10.7 , NE)	52	20 (38.5)	10.1 (6.9 , 21.0)	0.7737 (0.4216 , 1.4199) 0.3992	0.9537
No	199	77 (38.7)	24.6 (16.4 , NE)	211	73 (34.6)	NE (11.8 , NE)	0.8900 (0.6448 , 1.2282) 0.4816	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	50 (23.6)	NE (NE , NE)	206	51 (24.8)	NE (16.1 , NE)	0.6903 (0.4639 , 1.0272) 0.0662	0.0354
>=65	49	19 (38.8)	17.7 (11.3 , NE)	57	13 (22.8)	20.5 (13.8 , NE)	1.6022 (0.7881 , 3.2572) 0.1922	
Age								
<75	253	64 (25.3)	NE (NE , NE)	255	62 (24.3)	NE (16.6 , NE)	0.7748 (0.5435 , 1.1046) 0.1570	0.0727
>=75	8	5 (62.5)	9.8 (0.8 , 17.7)	8	2 (25.0)	12.8 (11.7 , 13.8)	1.5416 (0.2508 , 9.4764) 0.6380	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	43 (28.9)	NE (NE , NE)	160	38 (23.8)	20.5 (18.0 , NE)	0.9166 (0.5880 , 1.4288) 0.6997	0.0724
North America	17	9 (52.9)	12.2 (3.0 , NE)	17	4 (23.5)	NE (1.9 , NE)	1.7200 (0.5272 , 5.6109) 0.3628	
Europe	54	13 (24.1)	NE (17.7 , NE)	50	11 (22.0)	NE (13.8 , NE)	0.6823 (0.2952 , 1.5772) 0.3684	
Rest of World	41	4 (9.8)	NE (NE , NE)	36	11 (30.6)	16.6 (11.7 , NE)	0.2447 (0.0773 , 0.7746) 0.0096	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	19 (26.8)	NE (17.7 , NE)	72	20 (27.8)	16.6 (13.8 , NE)	0.6701 (0.3526 , 1.2736) 0.2195	0.8334
Black or African American	10	2 (20.0)	NE (3.1 , NE)	9	2 (22.2)	NE (0.8 , NE)	0.6219 (0.0866 , 4.4667) 0.6337	
Asian	152	43 (28.3)	NE (NE , NE)	162	38 (23.5)	20.5 (18.0 , NE)	0.9167 (0.5880 , 1.4291) 0.7000	
Other	28	5 (17.9)	NE (18.5 , NE)	20	4 (20.0)	NE (7.0 , NE)	0.6792 (0.1778 , 2.5942) 0.5697	
ECOG PS								
0	154	36 (23.4)	NE (NE , NE)	175	37 (21.1)	NE (16.6 , NE)	0.8287 (0.5197 , 1.3214) 0.4288	0.7753
1	106	33 (31.1)	18.5 (16.4 , NE)	87	27 (31.0)	NE (10.3 , NE)	0.6837 (0.4045 , 1.1557) 0.1518	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	36 (27.1)	NE (18.6 , NE)	139	36 (25.9)	20.5 (15.2 , NE)	0.7897 (0.4942 , 1.2619) 0.3225	0.9341
Negative	126	32 (25.4)	NE (18.5 , NE)	122	27 (22.1)	NE (18.0 , NE)	0.8334 (0.4942 , 1.4055) 0.4905	
Estrogen Receptors								
Positive	129	35 (27.1)	NE (18.6 , NE)	132	32 (24.2)	20.5 (14.8 , NE)	0.8315 (0.5109 , 1.3534) 0.4572	0.7441
Negative	130	33 (25.4)	NE (18.5 , NE)	128	31 (24.2)	NE (16.6 , NE)	0.7654 (0.4641 , 1.2623) 0.2895	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	23 (28.4)	NE (17.7 , NE)	92	20 (21.7)	16.6 (14.8 , NE)	1.0402 (0.5670 , 1.9084) 0.8970	0.2758
Negative	177	45 (25.4)	NE (NE , NE)	168	43 (25.6)	20.5 (18.0 , NE)	0.7139 (0.4664 , 1.0927) 0.1187	
Prior Treatment with Pertuzumab								
Yes	162	46 (28.4)	NE (NE , NE)	158	40 (25.3)	18.0 (14.8 , NE)	0.7823 (0.5048 , 1.2122) 0.2702	0.8492
No	99	23 (23.2)	NE (NE , NE)	105	24 (22.9)	NE (16.1 , NE)	0.8054 (0.4525 , 1.4336) 0.4587	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	46 (24.5)	NE (NE , NE)	191	51 (26.7)	20.5 (16.1 , NE)	0.6589 (0.4393 , 0.9883) 0.0421	0.0561
>= 3 lines	73	23 (31.5)	NE (15.8 , NE)	72	13 (18.1)	NE (15.2 , NE)	1.3978 (0.6996 , 2.7927) 0.3416	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	44 (28.2)	NE (18.6 , NE)	152	38 (25.0)	18.0 (14.8 , NE)	0.7853 (0.5009 , 1.2310) 0.2903	0.5600
>= 3 lines	6	2 (33.3)	NE (1.5 , NE)	6	2 (33.3)	NE (0.7 , NE)	0.5319 (0.0742 , 3.8112) 0.5232	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	27 (20.8)	NE (NE , NE)	130	33 (25.4)	16.6 (14.0 , NE)	0.5336 (0.3154 , 0.9026) 0.0174	0.0209
Mild Impairment	92	31 (33.7)	18.6 (16.1 , NE)	104	28 (26.9)	20.5 (14.8 , NE)	1.0834 (0.6477 , 1.8120) 0.7598	
Moderate Impairment	30	10 (33.3)	18.5 (14.5 , NE)	22	2 (9.1)	NE (NE , NE)	3.0522 (0.6674 , 13.959) 0.1301	
Hepatic Impairment								
Within Normal Range	208	62 (29.8)	NE (18.6 , NE)	212	52 (24.5)	20.5 (15.2 , NE)	0.9047 (0.6211 , 1.3178) 0.5994	0.0902
Mild Impairment	49	7 (14.3)	NE (NE , NE)	49	12 (24.5)	NE (16.6 , NE)	0.4192 (0.1642 , 1.0699) 0.0610	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	51 (26.2)	NE (NE , NE)	189	41 (21.7)	NE (16.1 , NE)	0.9263 (0.6101 , 1.4063) 0.7191	0.2544
No	66	18 (27.3)	NE (18.5 , NE)	74	23 (31.1)	18.0 (13.8 , NE)	0.5959 (0.3176 , 1.1179) 0.1034	
Baseline CNS Metastases								
Yes	43	7 (16.3)	NE (NE , NE)	39	12 (30.8)	NE (6.3 , NE)	0.3015 (0.1110 , 0.8188) 0.0136	0.0509
No	218	62 (28.4)	NE (NE , NE)	224	52 (23.2)	20.5 (16.6 , NE)	0.9304 (0.6402 , 1.3522) 0.7035	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	15 (24.2)	NE (15.6 , NE)	52	14 (26.9)	NE (11.7 , NE)	0.5673 (0.2623 , 1.2269) 0.1449	0.4959
No	199	54 (27.1)	NE (NE , NE)	211	50 (23.7)	20.5 (16.6 , NE)	0.8648 (0.5855 , 1.2773) 0.4634	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	61 (28.8)	NE (NE , NE)	206	62 (30.1)	NE (12.7 , NE)	0.7110 (0.4971 , 1.0169) 0.0608	0.5823
>=65	49	9 (18.4)	NE (19.7 , NE)	57	15 (26.3)	NE (11.7 , NE)	0.5687 (0.2479 , 1.3045) 0.1775	
Age								
<75	253	69 (27.3)	NE (NE , NE)	255	77 (30.2)	NE (NE , NE)	0.6753 (0.4863 , 0.9377) 0.0184	0.1765
>=75	8	1 (12.5)	NE (2.9 , NE)	8	0	NE (NE , NE)	NE (NE, NE) 0.3173	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	37 (24.8)	NE (NE , NE)	160	49 (30.6)	NE (12.6 , NE)	0.5849 (0.3795 , 0.9016) 0.0141	0.4586
North America	17	7 (41.2)	NE (2.5 , NE)	17	4 (23.5)	NE (4.4 , NE)	1.4108 (0.4114 , 4.8377) 0.5805	
Europe	54	16 (29.6)	NE (14.3 , NE)	50	13 (26.0)	NE (11.4 , NE)	0.8951 (0.4265 , 1.8786) 0.7678	
Rest of World	41	10 (24.4)	NE (NE , NE)	36	11 (30.6)	NE (9.6 , NE)	0.6587 (0.2791 , 1.5547) 0.3367	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	22 (31.0)	NE (14.3 , NE)	72	22 (30.6)	NE (11.4 , NE)	0.8255 (0.4560 , 1.4947) 0.5239	0.5715
Black or African American	10	4 (40.0)	NE (1.4 , NE)	9	2 (22.2)	NE (8.4 , NE)	1.7885 (0.3271 , 9.7778) 0.4963	
Asian	152	38 (25.0)	NE (NE , NE)	162	49 (30.2)	NE (NE , NE)	0.6081 (0.3959 , 0.9341) 0.0218	
Other	28	6 (21.4)	NE (19.4 , NE)	20	4 (20.0)	NE (8.4 , NE)	0.7518 (0.2072 , 2.7276) 0.6643	
ECOG PS								
0	154	42 (27.3)	NE (19.7 , NE)	175	54 (30.9)	NE (12.7 , NE)	0.6428 (0.4273 , 0.9670) 0.0326	0.6779
1	106	28 (26.4)	NE (NE , NE)	87	23 (26.4)	NE (NE , NE)	0.7922 (0.4550 , 1.3791) 0.4092	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	35 (26.3)	NE (NE , NE)	139	44 (31.7)	NE (12.5 , NE)	0.6066 (0.3875 , 0.9494) 0.0273	0.3798
Negative	126	35 (27.8)	NE (19.4 , NE)	122	32 (26.2)	NE (NE , NE)	0.8411 (0.5180 , 1.3657) 0.4847	
Estrogen Receptors								
Positive	129	35 (27.1)	NE (NE , NE)	132	42 (31.8)	NE (12.5 , NE)	0.6160 (0.3916 , 0.9692) 0.0346	0.4920
Negative	130	35 (26.9)	NE (19.4 , NE)	128	34 (26.6)	NE (NE , NE)	0.8033 (0.4984 , 1.2949) 0.3680	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	24 (29.6)	NE (NE , NE)	92	25 (27.2)	NE (12.7 , NE)	0.8904 (0.5067 , 1.5647) 0.6876	0.3230
Negative	177	46 (26.0)	NE (19.7 , NE)	168	51 (30.4)	NE (NE , NE)	0.6216 (0.4152 , 0.9307) 0.0200	
Prior Treatment with Pertuzumab								
Yes	162	49 (30.2)	NE (19.7 , NE)	158	46 (29.1)	NE (NE , NE)	0.7466 (0.4952 , 1.1258) 0.1622	0.3757
No	99	21 (21.2)	NE (NE , NE)	105	31 (29.5)	NE (12.7 , NE)	0.5664 (0.3244 , 0.9890) 0.0423	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	50 (26.6)	NE (NE , NE)	191	58 (30.4)	NE (NE , NE)	0.6547 (0.4468 , 0.9594) 0.0286	0.5958
>= 3 lines	73	20 (27.4)	NE (19.7 , NE)	72	19 (26.4)	NE (12.7 , NE)	0.8053 (0.4261 , 1.5218) 0.5034	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	49 (31.4)	NE (19.4 , NE)	152	44 (28.9)	NE (NE , NE)	0.7946 (0.5244 , 1.2038) 0.2772	0.0320
>= 3 lines	6	0	NE (NE , NE)	6	2 (33.3)	NE (1.4 , NE)	0.0000 (NE, NE) 0.0624	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	29 (22.3)	NE (NE , NE)	130	40 (30.8)	NE (12.6 , NE)	0.4984 (0.3058 , 0.8125) 0.0044	0.1438
Mild Impairment	92	31 (33.7)	NE (14.5 , NE)	104	33 (31.7)	NE (12.5 , NE)	0.8639 (0.5280 , 1.4137) 0.5644	
Moderate Impairment	30	7 (23.3)	NE (19.7 , NE)	22	3 (13.6)	NE (NE , NE)	1.3772 (0.3550 , 5.3429) 0.6452	
Hepatic Impairment								
Within Normal Range	208	60 (28.8)	NE (NE , NE)	212	67 (31.6)	NE (NE , NE)	0.6940 (0.4880 , 0.9869) 0.0410	0.9406
Mild Impairment	49	10 (20.4)	NE (NE , NE)	49	10 (20.4)	NE (12.5 , NE)	0.7002 (0.2890 , 1.6966) 0.4274	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	51 (26.2)	NE (NE , NE)	189	53 (28.0)	NE (12.7 , NE)	0.7223 (0.4898 , 1.0654) 0.0991	0.6575
No	66	19 (28.8)	NE (19.4 , NE)	74	24 (32.4)	NE (11.7 , NE)	0.6211 (0.3377 , 1.1424) 0.1233	
Baseline CNS Metastases								
Yes	43	11 (25.6)	NE (19.4 , NE)	39	14 (35.9)	NE (3.7 , NE)	0.5212 (0.2330 , 1.1658) 0.1069	0.3189
No	218	59 (27.1)	NE (NE , NE)	224	63 (28.1)	NE (NE , NE)	0.7346 (0.5134 , 1.0510) 0.0904	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	17 (27.4)	NE (19.4 , NE)	52	21 (40.4)	11.3 (4.8 , NE)	0.4871 (0.2538 , 0.9347) 0.0271	0.2410
No	199	53 (26.6)	NE (NE , NE)	211	56 (26.5)	NE (NE , NE)	0.7625 (0.5219 , 1.1139) 0.1597	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	101 (47.6)	15.2 (6.9 , NE)	206	60 (29.1)	19.1 (13.8 , NE)	1.5919 (1.1538 , 2.1963) 0.0044	0.3720
>=65	49	18 (36.7)	20.1 (5.6 , NE)	57	18 (31.6)	20.5 (10.1 , NE)	1.1662 (0.6052 , 2.2470) 0.6503	
Age								
<75	253	115 (45.5)	16.4 (9.9 , NE)	255	75 (29.4)	19.1 (13.8 , NE)	1.4893 (1.1112 , 1.9961) 0.0076	0.6954
>=75	8	4 (50.0)	1.6 (0.8 , NE)	8	3 (37.5)	NE (0.9 , NE)	1.8651 (0.4114 , 8.4562) 0.4294	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	73 (49.0)	15.6 (5.6 , NE)	160	51 (31.9)	19.1 (12.4 , NE)	1.5045 (1.0498 , 2.1562) 0.0258	0.3793
North America	17	10 (58.8)	3.0 (1.5 , NE)	17	3 (17.6)	NE (11.3 , NE)	4.1137 (1.1275 , 15.009) 0.0206	
Europe	54	17 (31.5)	NE (15.1 , NE)	50	12 (24.0)	NE (12.6 , NE)	1.1388 (0.5390 , 2.4061) 0.7373	
Rest of World	41	19 (46.3)	NE (2.9 , NE)	36	12 (33.3)	16.7 (9.0 , NE)	1.4402 (0.6978 , 2.9725) 0.3268	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	29 (40.8)	NE (4.4 , NE)	72	20 (27.8)	16.1 (12.6 , NE)	1.5250 (0.8603 , 2.7031) 0.1493	0.9865
Black or African American	10	6 (60.0)	5.0 (1.5 , NE)	9	3 (33.3)	16.7 (0.8 , NE)	2.1593 (0.5244 , 8.8907) 0.2758	
Asian	152	73 (48.0)	15.6 (5.6 , NE)	162	51 (31.5)	20.5 (12.4 , NE)	1.5001 (1.0466 , 2.1500) 0.0270	
Other	28	11 (39.3)	NE (5.6 , NE)	20	4 (20.0)	NE (5.6 , NE)	1.5811 (0.4956 , 5.0444) 0.4358	
ECOG PS								
0	154	71 (46.1)	16.4 (9.8 , NE)	175	50 (28.6)	19.1 (13.8 , NE)	1.5650 (1.0867 , 2.2536) 0.0158	0.4089
1	106	48 (45.3)	NE (4.4 , NE)	87	28 (32.2)	NE (11.7 , NE)	1.3577 (0.8506 , 2.1670) 0.1974	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	66 (49.6)	15.2 (4.3 , NE)	139	42 (30.2)	20.5 (13.8 , NE)	1.6454 (1.1142 , 2.4300) 0.0118	0.5283
Negative	126	53 (42.1)	16.4 (7.4 , NE)	122	36 (29.5)	19.1 (11.7 , NE)	1.3633 (0.8908 , 2.0865) 0.1537	
Estrogen Receptors								
Positive	129	63 (48.8)	19.0 (4.3 , NE)	132	39 (29.5)	16.7 (13.8 , NE)	1.6445 (1.0991 , 2.4604) 0.0150	0.5108
Negative	130	56 (43.1)	15.6 (7.4 , NE)	128	39 (30.5)	19.1 (11.7 , NE)	1.3465 (0.8927 , 2.0311) 0.1565	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	47 (58.0)	4.4 (2.8 , 15.2)	92	33 (35.9)	16.1 (11.3 , NE)	1.7696 (1.1315 , 2.7675) 0.0117	0.5086
Negative	177	72 (40.7)	20.1 (15.5 , NE)	168	45 (26.8)	20.5 (19.1 , NE)	1.4269 (0.9804 , 2.0768) 0.0631	
Prior Treatment with Pertuzumab								
Yes	162	72 (44.4)	20.1 (9.9 , NE)	158	46 (29.1)	19.1 (12.6 , NE)	1.4273 (0.9813 , 2.0762) 0.0627	0.6498
No	99	47 (47.5)	15.5 (5.5 , NE)	105	32 (30.5)	NE (13.8 , NE)	1.6443 (1.0485 , 2.5786) 0.0295	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	81 (43.1)	19.0 (12.2 , NE)	191	57 (29.8)	19.1 (12.7 , NE)	1.3690 (0.9732 , 1.9256) 0.0718	0.3709
>= 3 lines	73	38 (52.1)	6.9 (3.2 , NE)	72	21 (29.2)	16.7 (13.8 , NE)	1.8898 (1.1051 , 3.2319) 0.0183	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	68 (43.6)	20.1 (12.2 , NE)	152	46 (30.3)	19.1 (12.4 , NE)	1.3309 (0.9105 , 1.9453) 0.1408	0.0278
>= 3 lines	6	4 (66.7)	3.0 (0.8 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.0532	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	60 (46.2)	19.0 (6.8 , NE)	130	38 (29.2)	16.7 (13.8 , NE)	1.4509 (0.9617 , 2.1889) 0.0761	0.8742
Mild Impairment	92	43 (46.7)	15.5 (4.5 , NE)	104	33 (31.7)	20.5 (11.7 , NE)	1.6040 (1.0172 , 2.5294) 0.0420	
Moderate Impairment	30	12 (40.0)	20.1 (5.6 , NE)	22	5 (22.7)	NE (4.2 , NE)	1.4128 (0.4955 , 4.0280) 0.5092	
Hepatic Impairment								
Within Normal Range	208	97 (46.6)	16.4 (9.8 , NE)	212	64 (30.2)	19.1 (13.8 , NE)	1.5083 (1.0968 , 2.0742) 0.0114	0.7418
Mild Impairment	49	22 (44.9)	15.5 (3.2 , NE)	49	14 (28.6)	NE (6.6 , NE)	1.3695 (0.7001 , 2.6790) 0.3588	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	92 (47.2)	15.2 (6.8 , 20.1)	189	52 (27.5)	20.5 (13.8 , NE)	1.7261 (1.2257 , 2.4308) 0.0016	0.0884
No	66	27 (40.9)	NE (5.6 , NE)	74	26 (35.1)	19.1 (12.6 , NE)	1.0444 (0.6075 , 1.7957) 0.8802	
Baseline CNS Metastases								
Yes	43	19 (44.2)	15.6 (3.0 , NE)	39	10 (25.6)	NE (7.0 , NE)	1.7909 (0.8265 , 3.8807) 0.1367	0.6721
No	218	100 (45.9)	16.4 (9.8 , NE)	224	68 (30.4)	19.1 (13.8 , NE)	1.4546 (1.0667 , 1.9834) 0.0178	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	23 (37.1)	NE (5.8 , NE)	52	12 (23.1)	NE (9.0 , NE)	1.6384 (0.8105 , 3.3122) 0.1666	0.9124
No	199	96 (48.2)	15.2 (6.8 , NE)	211	66 (31.3)	19.1 (12.7 , NE)	1.4931 (1.0893 , 2.0465) 0.0125	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	92 (43.4)	16.8 (12.5 , NE)	206	64 (31.1)	NE (NE , NE)	1.1616 (0.8419 , 1.6026) 0.3570	0.9421
>=65	49	22 (44.9)	15.9 (10.1 , NE)	57	20 (35.1)	NE (7.3 , NE)	1.1530 (0.6279 , 2.1171) 0.6506	
Age								
<75	253	112 (44.3)	15.9 (13.1 , 22.6)	255	78 (30.6)	NE (NE , NE)	1.2267 (0.9172 , 1.6406) 0.1656	0.0180
>=75	8	2 (25.0)	NE (1.4 , NE)	8	6 (75.0)	2.8 (0.8 , 4.2)	0.2636 (0.0526 , 1.3201) 0.0820	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	66 (44.3)	16.5 (11.0 , NE)	160	48 (30.0)	NE (NE , NE)	1.3459 (0.9255 , 1.9572) 0.1192	0.4008
North America	17	8 (47.1)	22.6 (3.8 , NE)	17	6 (35.3)	NE (0.8 , NE)	0.8629 (0.2893 , 2.5739) 0.8044	
Europe	54	28 (51.9)	10.1 (5.8 , 17.1)	50	18 (36.0)	NE (7.0 , NE)	1.2478 (0.6894 , 2.2586) 0.4625	
Rest of World	41	12 (29.3)	NE (13.8 , NE)	36	12 (33.3)	NE (8.4 , NE)	0.5503 (0.2439 , 1.2418) 0.1455	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	29 (40.8)	15.7 (9.8 , NE)	72	25 (34.7)	NE (7.0 , NE)	0.8663 (0.5059 , 1.4834) 0.6033	0.6219
Black or African American	10	5 (50.0)	16.8 (1.4 , 22.6)	9	4 (44.4)	10.1 (0.8 , NE)	0.5786 (0.1432 , 2.3379) 0.4371	
Asian	152	67 (44.1)	16.5 (11.0 , NE)	162	48 (29.6)	NE (NE , NE)	1.3729 (0.9452 , 1.9940) 0.0951	
Other	28	13 (46.4)	17.1 (3.1 , NE)	20	7 (35.0)	11.3 (5.6 , NE)	1.1097 (0.4406 , 2.7950) 0.8285	
ECOG PS								
0	154	69 (44.8)	16.5 (12.5 , NE)	175	52 (29.7)	NE (NE , NE)	1.2624 (0.8790 , 1.8132) 0.2057	0.3463
1	106	45 (42.5)	15.9 (10.1 , NE)	87	32 (36.8)	NE (8.6 , NE)	0.9614 (0.6086 , 1.5186) 0.8744	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	63 (47.4)	15.7 (8.8 , 22.6)	139	44 (31.7)	NE (11.3 , NE)	1.2815 (0.8702 , 1.8873) 0.2066	0.4302
Negative	126	50 (39.7)	17.1 (11.6 , NE)	122	40 (32.8)	NE (12.6 , NE)	1.0232 (0.6733 , 1.5550) 0.9187	
Estrogen Receptors								
Positive	129	60 (46.5)	16.5 (9.8 , 22.6)	132	40 (30.3)	NE (11.3 , NE)	1.3042 (0.8718 , 1.9510) 0.1942	0.3474
Negative	130	53 (40.8)	17.1 (11.6 , NE)	128	44 (34.4)	NE (12.6 , NE)	0.9992 (0.6682 , 1.4943) 0.9946	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	39 (48.1)	15.2 (8.6 , NE)	92	25 (27.2)	NE (11.3 , NE)	1.5352 (0.9269 , 2.5429) 0.0922	0.1396
Negative	177	74 (41.8)	16.8 (12.5 , NE)	168	59 (35.1)	NE (10.1 , NE)	1.0027 (0.7107 , 1.4147) 0.9893	
Prior Treatment with Pertuzumab								
Yes	162	85 (52.5)	12.5 (8.6 , 15.9)	158	58 (36.7)	NE (10.1 , NE)	1.1433 (0.8159 , 1.6022) 0.4262	0.7001
No	99	29 (29.3)	NE (22.5 , NE)	105	26 (24.8)	NE (NE , NE)	1.1025 (0.6476 , 1.8770) 0.7294	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	84 (44.7)	15.7 (11.6 , NE)	191	65 (34.0)	NE (11.3 , NE)	1.0638 (0.7682 , 1.4732) 0.7035	0.3693
>= 3 lines	73	30 (41.1)	22.6 (11.0 , NE)	72	19 (26.4)	NE (NE , NE)	1.4992 (0.8405 , 2.6742) 0.1690	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	81 (51.9)	12.5 (8.8 , 15.9)	152	58 (38.2)	NE (8.6 , NE)	1.0922 (0.7764 , 1.5364) 0.6009	0.0357
>= 3 lines	6	4 (66.7)	8.6 (2.2 , 16.5)	6	0	NE (NE , NE)	NE (NE, NE) 0.0776	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	54 (41.5)	22.5 (15.2 , NE)	130	41 (31.5)	NE (12.6 , NE)	0.9133 (0.6033 , 1.3826) 0.6760	0.3156
Mild Impairment	92	43 (46.7)	13.8 (6.9 , NE)	104	37 (35.6)	NE (8.4 , NE)	1.3290 (0.8552 , 2.0651) 0.2052	
Moderate Impairment	30	15 (50.0)	16.5 (2.8 , NE)	22	5 (22.7)	NE (4.2 , NE)	1.9946 (0.7239 , 5.4962) 0.1739	
Hepatic Impairment								
Within Normal Range	208	99 (47.6)	15.7 (11.3 , 22.6)	212	71 (33.5)	NE (NE , NE)	1.2307 (0.9052 , 1.6733) 0.1839	0.3220
Mild Impairment	49	15 (30.6)	NE (13.1 , NE)	49	13 (26.5)	NE (6.3 , NE)	0.8114 (0.3844 , 1.7127) 0.5876	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	82 (42.1)	16.8 (13.1 , NE)	189	61 (32.3)	NE (NE , NE)	1.0882 (0.7788 , 1.5204) 0.6193	0.5222
No	66	32 (48.5)	15.3 (7.4 , NE)	74	23 (31.1)	NE (12.6 , NE)	1.3490 (0.7886 , 2.3076) 0.2710	
Baseline CNS Metastases								
Yes	43	16 (37.2)	16.8 (10.3 , NE)	39	14 (35.9)	NE (5.7 , NE)	0.7066 (0.3319 , 1.5044) 0.3649	0.3157
No	218	98 (45.0)	15.9 (12.5 , NE)	224	70 (31.3)	NE (NE , NE)	1.2354 (0.9078 , 1.6811) 0.1768	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	27 (43.5)	15.7 (6.9 , NE)	52	18 (34.6)	NE (7.0 , NE)	0.9928 (0.5375 , 1.8337) 0.9824	0.7584
No	199	87 (43.7)	16.5 (13.8 , NE)	211	66 (31.3)	NE (NE , NE)	1.1830 (0.8578 , 1.6315) 0.3032	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	40 (18.9)	NE (NE , NE)	206	25 (12.1)	NE (NE , NE)	1.1795 (0.7111 , 1.9562) 0.5229	0.5333
>=65	49	9 (18.4)	NE (NE , NE)	57	11 (19.3)	NE (NE , NE)	0.9391 (0.3884 , 2.2706) 0.8841	
Age								
<75	253	48 (19.0)	NE (NE , NE)	255	35 (13.7)	NE (NE , NE)	1.1114 (0.7161 , 1.7249) 0.6386	0.9358
>=75	8	1 (12.5)	NE (0.8 , NE)	8	1 (12.5)	NE (0.9 , NE)	1.4606 (0.0911 , 23.419) 0.7878	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	23 (15.4)	NE (NE , NE)	160	24 (15.0)	NE (NE , NE)	0.7533 (0.4218 , 1.3454) 0.3356	0.0285
North America	17	8 (47.1)	10.3 (1.5 , NE)	17	1 (5.9)	17.8 (NE , NE)	7.8547 (0.9777 , 63.106) 0.0218	
Europe	54	13 (24.1)	NE (NE , NE)	50	6 (12.0)	NE (NE , NE)	1.9195 (0.7267 , 5.0703) 0.1808	
Rest of World	41	5 (12.2)	NE (NE , NE)	36	5 (13.9)	NE (14.0 , NE)	0.6980 (0.2002 , 2.4328) 0.5702	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	15 (21.1)	NE (NE , NE)	72	8 (11.1)	NE (17.8 , NE)	1.6947 (0.7137 , 4.0240) 0.2249	0.4647
Black or African American	10	2 (20.0)	NE (1.5 , NE)	9	1 (11.1)	NE (14.0 , NE)	1.2066 (0.1078 , 13.511) 0.8787	
Asian	152	24 (15.8)	NE (NE , NE)	162	24 (14.8)	NE (NE , NE)	0.7955 (0.4486 , 1.4108) 0.4316	
Other	28	8 (28.6)	NE (10.0 , NE)	20	3 (15.0)	NE (NE , NE)	1.8183 (0.4800 , 6.8875) 0.3738	
ECOG PS								
0	154	28 (18.2)	NE (NE , NE)	175	25 (14.3)	NE (NE , NE)	0.9930 (0.5751 , 1.7146) 0.9781	0.6116
1	106	21 (19.8)	NE (NE , NE)	87	11 (12.6)	NE (15.3 , NE)	1.3159 (0.6316 , 2.7416) 0.4616	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	31 (23.3)	NE (NE , NE)	139	18 (12.9)	NE (NE , NE)	1.4881 (0.8279 , 2.6746) 0.1817	0.1504
Negative	126	18 (14.3)	NE (NE , NE)	122	18 (14.8)	NE (NE , NE)	0.7772 (0.4020 , 1.5022) 0.4510	
Estrogen Receptors								
Positive	129	30 (23.3)	NE (NE , NE)	132	18 (13.6)	NE (17.8 , NE)	1.3930 (0.7718 , 2.5142) 0.2696	0.2481
Negative	130	19 (14.6)	NE (NE , NE)	128	18 (14.1)	NE (NE , NE)	0.8358 (0.4361 , 1.6017) 0.5870	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	16 (19.8)	NE (NE , NE)	92	11 (12.0)	NE (17.8 , NE)	1.3124 (0.6042 , 2.8508) 0.4908	0.5969
Negative	177	33 (18.6)	NE (NE , NE)	168	25 (14.9)	NE (NE , NE)	1.0320 (0.6110 , 1.7429) 0.9087	
Prior Treatment with Pertuzumab								
Yes	162	31 (19.1)	NE (NE , NE)	158	19 (12.0)	NE (NE , NE)	1.2872 (0.7219 , 2.2950) 0.3921	0.5006
No	99	18 (18.2)	NE (NE , NE)	105	17 (16.2)	NE (NE , NE)	0.9177 (0.4711 , 1.7876) 0.8029	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	36 (19.1)	NE (NE , NE)	191	25 (13.1)	NE (NE , NE)	1.2666 (0.7584 , 2.1155) 0.3666	0.5490
>= 3 lines	73	13 (17.8)	NE (NE , NE)	72	11 (15.3)	NE (12.7 , NE)	0.7247 (0.3177 , 1.6532) 0.4433	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	29 (18.6)	NE (NE , NE)	152	18 (11.8)	NE (NE , NE)	1.2895 (0.7109 , 2.3392) 0.4023	0.9054
>= 3 lines	6	2 (33.3)	NE (1.4 , NE)	6	1 (16.7)	NE (6.0 , NE)	1.0718 (0.0915 , 12.552) 0.9559	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	20 (15.4)	NE (NE , NE)	130	15 (11.5)	NE (17.8 , NE)	0.8638 (0.4344 , 1.7176) 0.6760	0.5367
Mild Impairment	92	19 (20.7)	NE (NE , NE)	104	18 (17.3)	NE (NE , NE)	1.0997 (0.5763 , 2.0983) 0.7725	
Moderate Impairment	30	8 (26.7)	NE (11.2 , NE)	22	2 (9.1)	NE (NE , NE)	2.6163 (0.5544 , 12.346) 0.2080	
Hepatic Impairment								
Within Normal Range	208	42 (20.2)	NE (NE , NE)	212	29 (13.7)	NE (NE , NE)	1.1991 (0.7435 , 1.9338) 0.4570	0.3969
Mild Impairment	49	7 (14.3)	NE (NE , NE)	49	7 (14.3)	NE (12.7 , NE)	0.7586 (0.2643 , 2.1773) 0.6064	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	36 (18.5)	NE (NE , NE)	189	27 (14.3)	NE (17.8 , NE)	1.0837 (0.6550 , 1.7930) 0.7549	0.7054
No	66	13 (19.7)	NE (NE , NE)	74	9 (12.2)	NE (NE , NE)	1.2062 (0.5117 , 2.8435) 0.6700	
Baseline CNS Metastases								
Yes	43	10 (23.3)	NE (NE , NE)	39	5 (12.8)	15.3 (15.3 , NE)	1.2440 (0.4143 , 3.7355) 0.6963	0.6032
No	218	39 (17.9)	NE (NE , NE)	224	31 (13.8)	NE (NE , NE)	1.0671 (0.6634 , 1.7165) 0.7895	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	15 (24.2)	NE (NE , NE)	52	4 (7.7)	NE (NE , NE)	2.5223 (0.8281 , 7.6833) 0.0923	0.0698
No	199	34 (17.1)	NE (NE , NE)	211	32 (15.2)	NE (NE , NE)	0.9082 (0.5581 , 1.4780) 0.6980	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	48 (22.6)	NE (23.5 , NE)	206	51 (24.8)	NE (15.2 , NE)	0.6428 (0.4300 , 0.9609) 0.0296	0.6441
>=65	49	10 (20.4)	24.0 (24.0 , NE)	57	13 (22.8)	NE (12.7 , NE)	0.7537 (0.3290 , 1.7266) 0.5016	
Age								
<75	253	56 (22.1)	NE (24.0 , NE)	255	62 (24.3)	NE (17.8 , NE)	0.6650 (0.4610 , 0.9593) 0.0277	0.6005
>=75	8	2 (25.0)	NE (1.4 , NE)	8	2 (25.0)	10.3 (6.2 , NE)	1.2763 (0.1763 , 9.2396) 0.8087	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	39 (26.2)	NE (23.5 , NE)	160	38 (23.8)	NE (15.2 , NE)	0.8141 (0.5171 , 1.2818) 0.3703	0.5199
North America	17	4 (23.5)	NE (3.8 , NE)	17	4 (23.5)	17.8 (4.4 , 17.8)	0.8316 (0.2041 , 3.3885) 0.7967	
Europe	54	4 (7.4)	24.0 (24.0 , NE)	50	8 (16.0)	NE (NE , NE)	0.3554 (0.1063 , 1.1881) 0.0795	
Rest of World	41	11 (26.8)	NE (15.2 , NE)	36	14 (38.9)	NE (7.1 , NE)	0.4635 (0.2087 , 1.0297) 0.0528	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	12 (16.9)	NE (NE , NE)	72	19 (26.4)	NE (12.7 , NE)	0.4963 (0.2397 , 1.0275) 0.0538	0.6762
Black or African American	10	3 (30.0)	NE (1.6 , NE)	9	3 (33.3)	NE (1.4 , NE)	0.6857 (0.1377 , 3.4132) 0.6430	
Asian	152	39 (25.7)	NE (23.5 , NE)	162	38 (23.5)	NE (15.2 , NE)	0.8182 (0.5198 , 1.2879) 0.3817	
Other	28	4 (14.3)	24.0 (24.0 , NE)	20	4 (20.0)	NE (9.8 , NE)	0.3006 (0.0653 , 1.3830) 0.1036	
ECOG PS								
0	154	31 (20.1)	NE (NE , NE)	175	41 (23.4)	NE (17.8 , NE)	0.6123 (0.3818 , 0.9819) 0.0395	0.7111
1	106	27 (25.5)	24.0 (23.5 , NE)	87	23 (26.4)	NE (11.1 , NE)	0.7182 (0.4073 , 1.2665) 0.2489	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	24 (18.0)	NE (NE , NE)	139	33 (23.7)	NE (15.2 , NE)	0.5686 (0.3345 , 0.9666) 0.0345	0.3306
Negative	126	34 (27.0)	24.0 (23.5 , NE)	122	30 (24.6)	NE (13.9 , NE)	0.7842 (0.4739 , 1.2977) 0.3398	
Estrogen Receptors								
Positive	129	23 (17.8)	NE (NE , NE)	132	32 (24.2)	NE (15.2 , NE)	0.5404 (0.3146 , 0.9284) 0.0236	0.2518
Negative	130	35 (26.9)	24.0 (23.5 , NE)	128	31 (24.2)	NE (13.9 , NE)	0.8045 (0.4902 , 1.3204) 0.3840	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	10 (12.3)	NE (NE , NE)	92	21 (22.8)	NE (15.2 , NE)	0.3725 (0.1740 , 0.7978) 0.0083	0.0823
Negative	177	48 (27.1)	NE (23.5 , NE)	168	42 (25.0)	NE (NE , NE)	0.8192 (0.5376 , 1.2483) 0.3497	
Prior Treatment with Pertuzumab								
Yes	162	31 (19.1)	NE (24.0 , NE)	158	35 (22.2)	NE (13.9 , NE)	0.5664 (0.3459 , 0.9275) 0.0221	0.4843
No	99	27 (27.3)	NE (18.2 , NE)	105	29 (27.6)	NE (15.2 , NE)	0.8361 (0.4934 , 1.4167) 0.5017	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	39 (20.7)	NE (24.0 , NE)	191	54 (28.3)	NE (13.9 , NE)	0.5190 (0.3416 , 0.7886) 0.0018	0.0143
>= 3 lines	73	19 (26.0)	23.5 (23.5 , NE)	72	10 (13.9)	NE (NE , NE)	1.6103 (0.7436 , 3.4871) 0.2244	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	30 (19.2)	NE (24.0 , NE)	152	34 (22.4)	NE (13.9 , NE)	0.5722 (0.3467 , 0.9443) 0.0270	0.9365
>= 3 lines	6	1 (16.7)	NE (11.5 , NE)	6	1 (16.7)	NE (4.4 , NE)	0.4714 (0.0283 , 7.8580) 0.5924	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	29 (22.3)	NE (23.5 , NE)	130	26 (20.0)	NE (13.9 , NE)	0.7836 (0.4555 , 1.3483) 0.3756	0.6918
Mild Impairment	92	21 (22.8)	NE (18.2 , NE)	104	34 (32.7)	NE (12.7 , NE)	0.5624 (0.3251 , 0.9731) 0.0364	
Moderate Impairment	30	7 (23.3)	24.0 (14.5 , 24.0)	22	4 (18.2)	NE (10.3 , NE)	0.6881 (0.1923 , 2.4616) 0.5632	
Hepatic Impairment								
Within Normal Range	208	46 (22.1)	NE (24.0 , NE)	212	54 (25.5)	NE (17.8 , NE)	0.6418 (0.4306 , 0.9566) 0.0279	0.6065
Mild Impairment	49	12 (24.5)	NE (NE , NE)	49	10 (20.4)	NE (9.0 , NE)	0.8296 (0.3558 , 1.9344) 0.6667	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	45 (23.1)	NE (NE , NE)	189	46 (24.3)	NE (17.8 , NE)	0.7004 (0.4616 , 1.0629) 0.0916	0.6835
No	66	13 (19.7)	NE (23.5 , NE)	74	18 (24.3)	NE (13.9 , NE)	0.5646 (0.2726 , 1.1694) 0.1188	
Baseline CNS Metastases								
Yes	43	9 (20.9)	NE (18.2 , NE)	39	8 (20.5)	NE (NE , NE)	0.6697 (0.2518 , 1.7811) 0.4219	0.9138
No	218	49 (22.5)	NE (24.0 , NE)	224	56 (25.0)	NE (17.8 , NE)	0.6709 (0.4551 , 0.9892) 0.0420	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 52 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	15 (24.2)	NE (18.2 , NE)	52	10 (19.2)	NE (NE , NE)	0.8865 (0.3883 , 2.0238) 0.7738	0.3931
No	199	43 (21.6)	NE (24.0 , NE)	211	54 (25.6)	NE (17.8 , NE)	0.6243 (0.4163 , 0.9364) 0.0213	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	71 (33.5)	23.7 (19.4 , NE)	206	44 (21.4)	NE (NE , NE)	1.2099 (0.8274 , 1.7691) 0.3266	0.5228
>=65	49	12 (24.5)	NE (17.6 , NE)	57	13 (22.8)	25.4 (15.2 , 25.4)	0.9910 (0.4435 , 2.2145) 0.9822	
Age								
<75	253	82 (32.4)	23.7 (19.4 , NE)	255	56 (22.0)	25.4 (NE , NE)	1.1550 (0.8201 , 1.6267) 0.4107	0.8628
>=75	8	1 (12.5)	NE (0.8 , NE)	8	1 (12.5)	NE (10.3 , NE)	0.9354 (0.0575 , 15.210) 0.9626	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	47 (31.5)	NE (17.6 , NE)	160	33 (20.6)	25.4 (NE , NE)	1.1776 (0.7508 , 1.8473) 0.4788	0.7359
North America	17	3 (17.6)	NE (NE , NE)	17	2 (11.8)	NE (NE , NE)	1.2560 (0.2096 , 7.5266) 0.8026	
Europe	54	18 (33.3)	20.2 (15.2 , NE)	50	9 (18.0)	NE (NE , NE)	1.4454 (0.6445 , 3.2420) 0.3681	
Rest of World	41	15 (36.6)	16.8 (13.6 , NE)	36	13 (36.1)	NE (7.1 , NE)	0.8341 (0.3961 , 1.7565) 0.6283	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	21 (29.6)	NE (16.1 , NE)	72	20 (27.8)	NE (10.3 , NE)	0.8313 (0.4491 , 1.5385) 0.5555	0.4000
Black or African American	10	4 (40.0)	16.8 (1.6 , 16.8)	9	1 (11.1)	NE (1.5 , NE)	3.8443 (0.4146 , 35.645) 0.2053	
Asian	152	48 (31.6)	NE (17.6 , NE)	162	33 (20.4)	25.4 (NE , NE)	1.2025 (0.7681 , 1.8824) 0.4219	
Other	28	10 (35.7)	20.2 (15.2 , NE)	20	3 (15.0)	NE (NE , NE)	1.7447 (0.4690 , 6.4910) 0.4028	
ECOG PS								
0	154	50 (32.5)	23.7 (16.8 , NE)	175	39 (22.3)	25.4 (NE , NE)	1.1077 (0.7259 , 1.6903) 0.6346	0.9218
1	106	33 (31.1)	NE (NE , NE)	87	18 (20.7)	NE (NE , NE)	1.2432 (0.6975 , 2.2156) 0.4605	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	39 (29.3)	23.7 (17.6 , NE)	139	31 (22.3)	25.4 (NE , NE)	0.9940 (0.6179 , 1.5991) 0.9806	0.3252
Negative	126	44 (34.9)	NE (14.5 , NE)	122	25 (20.5)	NE (NE , NE)	1.4314 (0.8730 , 2.3470) 0.1544	
Estrogen Receptors								
Positive	129	37 (28.7)	23.7 (17.6 , NE)	132	29 (22.0)	25.4 (NE , NE)	0.9826 (0.6020 , 1.6039) 0.9452	0.3230
Negative	130	46 (35.4)	NE (14.5 , NE)	128	27 (21.1)	NE (NE , NE)	1.3981 (0.8659 , 2.2575) 0.1701	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	25 (30.9)	NE (15.2 , NE)	92	21 (22.8)	25.4 (NE , NE)	1.1062 (0.6118 , 2.0000) 0.7384	0.7795
Negative	177	58 (32.8)	23.7 (17.6 , NE)	168	35 (20.8)	NE (NE , NE)	1.2355 (0.8083 , 1.8886) 0.3287	
Prior Treatment with Pertuzumab								
Yes	162	58 (35.8)	20.2 (16.8 , NE)	158	27 (17.1)	25.4 (NE , NE)	1.6969 (1.0638 , 2.7067) 0.0248	0.0084
No	99	25 (25.3)	NE (23.7 , NE)	105	30 (28.6)	NE (14.1 , NE)	0.6818 (0.3988 , 1.1656) 0.1577	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	60 (31.9)	NE (19.4 , NE)	191	40 (20.9)	25.4 (NE , NE)	1.1933 (0.7969 , 1.7869) 0.3929	0.7857
>= 3 lines	73	23 (31.5)	20.2 (17.6 , NE)	72	17 (23.6)	NE (11.8 , NE)	1.0772 (0.5726 , 2.0265) 0.8158	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	54 (34.6)	20.2 (16.8 , NE)	152	26 (17.1)	25.4 (NE , NE)	1.6456 (1.0192 , 2.6568) 0.0395	0.7344
>= 3 lines	6	4 (66.7)	8.6 (1.4 , NE)	6	1 (16.7)	NE (0.7 , NE)	1.8365 (0.2009 , 16.785) 0.5848	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	41 (31.5)	23.7 (19.4 , NE)	130	26 (20.0)	NE (NE , NE)	1.1198 (0.6754 , 1.8568) 0.6631	0.1399
Mild Impairment	92	30 (32.6)	NE (16.5 , NE)	104	30 (28.8)	25.4 (15.2 , 25.4)	0.9681 (0.5829 , 1.6077) 0.9003	
Moderate Impairment	30	10 (33.3)	17.6 (14.5 , NE)	22	1 (4.5)	NE (10.3 , NE)	5.5811 (0.7128 , 43.699) 0.0650	
Hepatic Impairment								
Within Normal Range	208	67 (32.2)	NE (19.4 , NE)	212	45 (21.2)	25.4 (NE , NE)	1.1882 (0.8109 , 1.7410) 0.3769	0.7100
Mild Impairment	49	16 (32.7)	20.2 (11.1 , NE)	49	12 (24.5)	NE (9.0 , NE)	0.9942 (0.4693 , 2.1062) 0.9863	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	60 (30.8)	23.7 (17.6 , NE)	189	36 (19.0)	25.4 (NE , NE)	1.2721 (0.8382 , 1.9304) 0.2588	0.3633
No	66	23 (34.8)	NE (16.1 , NE)	74	21 (28.4)	NE (15.2 , NE)	0.9406 (0.5182 , 1.7071) 0.8434	
Baseline CNS Metastases								
Yes	43	15 (34.9)	19.4 (12.8 , NE)	39	9 (23.1)	NE (NE , NE)	1.0463 (0.4501 , 2.4323) 0.9154	0.9065
No	218	68 (31.2)	NE (20.2 , NE)	224	48 (21.4)	25.4 (NE , NE)	1.1574 (0.7976 , 1.6795) 0.4430	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	19 (30.6)	19.4 (14.5 , NE)	52	10 (19.2)	NE (14.1 , NE)	1.0938 (0.4970 , 2.4072) 0.8226	0.8995
No	199	64 (32.2)	NE (20.2 , NE)	211	47 (22.3)	25.4 (NE , NE)	1.1480 (0.7858 , 1.6773) 0.4768	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	51 (24.1)	NE (NE , NE)	206	46 (22.3)	NE (NE , NE)	0.8559 (0.5727 , 1.2791) 0.4478	0.1966
>=65	49	6 (12.2)	NE (NE , NE)	57	3 (5.3)	NE (NE , NE)	2.2229 (0.5548 , 8.9063) 0.2464	
Age								
<75	253	56 (22.1)	NE (NE , NE)	255	48 (18.8)	NE (NE , NE)	0.9745 (0.6613 , 1.4362) 0.8962	0.8309
>=75	8	1 (12.5)	NE (2.1 , NE)	8	1 (12.5)	NE (1.4 , NE)	0.7454 (0.0464 , 11.968) 0.8350	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	20 (13.4)	NE (NE , NE)	160	26 (16.3)	NE (NE , NE)	0.6408 (0.3558 , 1.1541) 0.1353	0.1055
North America	17	7 (41.2)	NE (1.5 , NE)	17	3 (17.6)	NE (5.7 , NE)	2.3421 (0.6050 , 9.0670) 0.2037	
Europe	54	16 (29.6)	NE (10.8 , NE)	50	7 (14.0)	NE (NE , NE)	1.8934 (0.7768 , 4.6153) 0.1521	
Rest of World	41	14 (34.1)	NE (8.6 , NE)	36	13 (36.1)	14.8 (1.5 , NE)	0.7635 (0.3579 , 1.6288) 0.4933	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	28 (39.4)	17.5 (5.8 , NE)	72	15 (20.8)	NE (14.8 , NE)	1.7977 (0.9596 , 3.3678) 0.0615	0.0148
Black or African American	10	1 (10.0)	NE (1.4 , NE)	9	4 (44.4)	NE (0.8 , NE)	0.1481 (0.0164 , 1.3381) 0.0486	
Asian	152	20 (13.2)	NE (NE , NE)	162	26 (16.0)	NE (NE , NE)	0.6423 (0.3566 , 1.1568) 0.1374	
Other	28	8 (28.6)	NE (7.7 , NE)	20	4 (20.0)	NE (9.5 , NE)	1.0635 (0.3104 , 3.6435) 0.9204	
ECOG PS								
0	154	37 (24.0)	NE (NE , NE)	175	36 (20.6)	NE (NE , NE)	0.9683 (0.6104 , 1.5362) 0.8935	0.9749
1	106	20 (18.9)	NE (NE , NE)	87	13 (14.9)	NE (NE , NE)	1.0452 (0.5182 , 2.1083) 0.9005	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	29 (21.8)	NE (NE , NE)	139	33 (23.7)	NE (14.9 , NE)	0.7198 (0.4354 , 1.1898) 0.1992	0.0735
Negative	126	28 (22.2)	NE (NE , NE)	122	16 (13.1)	NE (NE , NE)	1.4891 (0.8036 , 2.7594) 0.2039	
Estrogen Receptors								
Positive	129	28 (21.7)	NE (NE , NE)	132	30 (22.7)	NE (14.9 , NE)	0.7575 (0.4509 , 1.2723) 0.2950	0.1235
Negative	130	29 (22.3)	NE (NE , NE)	128	18 (14.1)	NE (NE , NE)	1.3769 (0.7626 , 2.4860) 0.2885	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	21 (25.9)	NE (NE , NE)	92	26 (28.3)	NE (14.8 , NE)	0.7893 (0.4430 , 1.4061) 0.4226	0.2535
Negative	177	36 (20.3)	NE (NE , NE)	168	23 (13.7)	NE (NE , NE)	1.2106 (0.7152 , 2.0493) 0.4774	
Prior Treatment with Pertuzumab								
Yes	162	36 (22.2)	NE (NE , NE)	158	23 (14.6)	NE (NE , NE)	1.2746 (0.7534 , 2.1565) 0.3652	0.1401
No	99	21 (21.2)	NE (NE , NE)	105	26 (24.8)	NE (14.8 , NE)	0.7031 (0.3938 , 1.2553) 0.2325	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	40 (21.3)	NE (NE , NE)	191	33 (17.3)	NE (NE , NE)	0.9970 (0.6273 , 1.5847) 0.9960	0.8467
>= 3 lines	73	17 (23.3)	NE (NE , NE)	72	16 (22.2)	NE (NE , NE)	0.9074 (0.4555 , 1.8077) 0.7765	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	36 (23.1)	NE (NE , NE)	152	23 (15.1)	NE (NE , NE)	1.2876 (0.7611 , 2.1785) 0.3454	0.9999
>= 3 lines	6	0	NE (NE , NE)	6	0	NE (NE , NE)	NE (NE , NE) NE	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	33 (25.4)	NE (NE , NE)	130	34 (26.2)	NE (14.8 , NE)	0.7214 (0.4432 , 1.1742) 0.1870	0.1570
Mild Impairment	92	15 (16.3)	NE (NE , NE)	104	14 (13.5)	NE (NE , NE)	1.0408 (0.5005 , 2.1644) 0.9131	
Moderate Impairment	30	7 (23.3)	NE (NE , NE)	22	1 (4.5)	NE (NE , NE)	4.1869 (0.5147 , 34.059) 0.1417	
Hepatic Impairment								
Within Normal Range	208	53 (25.5)	NE (NE , NE)	212	41 (19.3)	NE (NE , NE)	1.1056 (0.7335 , 1.6664) 0.6283	0.0699
Mild Impairment	49	4 (8.2)	NE (NE , NE)	49	8 (16.3)	NE (NE , NE)	0.3844 (0.1154 , 1.2807) 0.1068	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	47 (24.1)	NE (NE , NE)	189	37 (19.6)	NE (NE , NE)	1.0269 (0.6658 , 1.5840) 0.8996	0.5191
No	66	10 (15.2)	NE (NE , NE)	74	12 (16.2)	NE (NE , NE)	0.7529 (0.3236 , 1.7513) 0.5066	
Baseline CNS Metastases								
Yes	43	10 (23.3)	NE (19.4 , NE)	39	7 (17.9)	NE (NE , NE)	0.9661 (0.3577 , 2.6092) 0.9435	0.9034
No	218	47 (21.6)	NE (NE , NE)	224	42 (18.8)	NE (NE , NE)	0.9673 (0.6371 , 1.4687) 0.8785	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	13 (21.0)	NE (19.4 , NE)	52	7 (13.5)	NE (NE , NE)	1.2376 (0.4850 , 3.1580) 0.6543	0.5200
No	199	44 (22.1)	NE (NE , NE)	211	42 (19.9)	NE (NE , NE)	0.9276 (0.6068 , 1.4181) 0.7296	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	16 (7.5)	19.4 (11.6 , NE)	206	7 (3.4)	NE (18.0 , NE)	2.1993 (0.8976 , 5.3885) 0.0774	0.9997
>=65	49	0	NE (NE , NE)	57	0	NE (NE , NE)	NE (NE , NE) NE	
Age								
<75	253	16 (6.3)	NE (13.4 , NE)	255	7 (2.7)	NE (18.0 , NE)	2.2440 (0.9183 , 5.4832) 0.0688	NE
>=75	8	0	NE (NE , NE)	8	0	NE (NE , NE)	NE (NE , NE) NE	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	3 (2.0)	NE (13.4 , NE)	160	2 (1.3)	NE (NE , NE)	2.2961 (0.3711 , 14.206) 0.3592	0.2386
North America	17	1 (5.9)	NE (0.9 , NE)	17	3 (17.6)	8.7 (1.4 , NE)	0.6702 (0.0694 , 6.4698) 0.7275	
Europe	54	4 (7.4)	19.4 (11.6 , 19.4)	50	0	NE (NE , NE)	NE (NE, NE) 0.0789	
Rest of World	41	8 (19.5)	7.2 (1.4 , NE)	36	2 (5.6)	18.0 (1.4 , NE)	3.4902 (0.7370 , 16.528) 0.0905	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	8 (11.3)	NE (1.6 , NE)	72	2 (2.8)	NE (8.7 , NE)	3.3020 (0.7002 , 15.571) 0.1079	0.5012
Black or African American	10	1 (10.0)	NE (1.4 , NE)	9	3 (33.3)	18.0 (1.4 , NE)	1.0199 (0.1032 , 10.079) 0.9866	
Asian	152	3 (2.0)	NE (13.4 , NE)	162	2 (1.2)	NE (NE , NE)	2.1603 (0.3505 , 13.317) 0.3961	
Other	28	4 (14.3)	19.4 (1.6 , 19.4)	20	0	NE (NE , NE)	NE (NE, NE) 0.1534	
ECOG PS								
0	154	11 (7.1)	NE (13.4 , NE)	175	7 (4.0)	NE (18.0 , NE)	1.3173 (0.5006 , 3.4659) 0.5773	0.0142
1	106	5 (4.7)	NE (1.4 , NE)	87	0	NE (NE , NE)	NE (NE, NE) 0.0105	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	9 (6.8)	NE (1.6 , NE)	139	4 (2.9)	NE (18.0 , NE)	3.8389 (1.1782 , 12.508) 0.0162	0.2106
Negative	126	7 (5.6)	19.4 (19.4 , NE)	122	3 (2.5)	NE (8.7 , NE)	1.0840 (0.2702 , 4.3487) 0.9146	
Estrogen Receptors								
Positive	129	9 (7.0)	NE (1.6 , NE)	132	4 (3.0)	NE (18.0 , NE)	3.6428 (1.1153 , 11.897) 0.0219	0.2780
Negative	130	7 (5.4)	19.4 (19.4 , NE)	128	3 (2.3)	NE (8.7 , NE)	1.1881 (0.2959 , 4.7711) 0.8124	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	7 (8.6)	NE (1.6 , NE)	92	4 (4.3)	NE (18.0 , NE)	2.7411 (0.7996 , 9.3965) 0.0942	0.8019
Negative	177	9 (5.1)	NE (13.4 , NE)	168	3 (1.8)	NE (NE , NE)	2.0647 (0.5445 , 7.8285) 0.2807	
Prior Treatment with Pertuzumab								
Yes	162	8 (4.9)	NE (19.4 , NE)	158	4 (2.5)	NE (NE , NE)	1.2709 (0.3749 , 4.3081) 0.6997	0.1779
No	99	8 (8.1)	9.7 (1.4 , NE)	105	3 (2.9)	NE (18.0 , NE)	4.7390 (1.2548 , 17.898) 0.0112	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	13 (6.9)	19.4 (11.6 , NE)	191	7 (3.7)	NE (18.0 , NE)	1.6489 (0.6532 , 4.1624) 0.2851	0.0790
>= 3 lines	73	3 (4.1)	NE (1.4 , NE)	72	0	NE (NE , NE)	NE (NE, NE) 0.0335	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	8 (5.1)	NE (19.4 , NE)	152	4 (2.6)	NE (NE , NE)	1.1929 (0.3510 , 4.0542) 0.7772	NE
>= 3 lines	6	0	NE (NE , NE)	6	0	NE (NE , NE)	NE (NE , NE) NE	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	11 (8.5)	19.4 (9.7 , NE)	130	4 (3.1)	18.0 (18.0 , NE)	2.4587 (0.7606 , 7.9479) 0.1223	0.7971
Mild Impairment	92	4 (4.3)	NE (1.4 , NE)	104	3 (2.9)	NE (1.5 , NE)	1.3611 (0.3042 , 6.0903) 0.6843	
Moderate Impairment	30	0	NE (NE , NE)	22	0	NE (NE , NE)	NE (NE , NE) NE	
Hepatic Impairment								
Within Normal Range	208	15 (7.2)	NE (13.4 , NE)	212	5 (2.4)	NE (18.0 , NE)	2.6881 (0.9713 , 7.4389) 0.0479	0.5803
Mild Impairment	49	1 (2.0)	NE (1.4 , NE)	49	2 (4.1)	NE (1.4 , NE)	1.3241 (0.1197 , 14.643) 0.8184	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	12 (6.2)	19.4 (13.4 , NE)	189	6 (3.2)	NE (18.0 , NE)	1.8521 (0.6893 , 4.9767) 0.2146	0.4356
No	66	4 (6.1)	NE (1.4 , NE)	74	1 (1.4)	NE (8.7 , NE)	4.5291 (0.5015 , 40.906) 0.1409	
Baseline CNS Metastases								
Yes	43	3 (7.0)	19.4 (1.6 , 19.4)	39	1 (2.6)	NE (1.5 , NE)	1.7660 (0.1598 , 19.521) 0.6382	0.9633
No	218	13 (6.0)	NE (11.6 , NE)	224	6 (2.7)	NE (18.0 , NE)	2.3099 (0.8751 , 6.0969) 0.0822	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	3 (4.8)	19.4 (1.6 , NE)	52	1 (1.9)	NE (1.5 , NE)	1.2120 (0.1070 , 13.729) 0.8764	0.7651
No	199	13 (6.5)	NE (11.6 , NE)	211	6 (2.8)	NE (18.0 , NE)	2.5061 (0.9499 , 6.6116) 0.0549	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	53 (25.0)	NE (22.3 , NE)	206	37 (18.0)	NE (17.2 , NE)	0.9642 (0.6252 , 1.4869) 0.8719	0.1318
>=65	49	7 (14.3)	NE (NE , NE)	57	14 (24.6)	21.2 (15.2 , NE)	0.4657 (0.1871 , 1.1590) 0.0914	
Age								
<75	253	59 (23.3)	NE (24.3 , NE)	255	50 (19.6)	NE (21.2 , NE)	0.8358 (0.5684 , 1.2291) 0.3628	0.8990
>=75	8	1 (12.5)	NE (1.4 , NE)	8	1 (12.5)	NE (5.3 , NE)	1.4142 (0.0848 , 23.573) 0.8084	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	38 (25.5)	NE (22.3 , NE)	160	33 (20.6)	21.2 (17.2 , NE)	0.8561 (0.5301 , 1.3825) 0.5232	0.3783
North America	17	5 (29.4)	NE (3.0 , NE)	17	1 (5.9)	NE (NE , NE)	4.7021 (0.5487 , 40.296) 0.1175	
Europe	54	11 (20.4)	NE (19.4 , NE)	50	10 (20.0)	NE (15.2 , NE)	0.7035 (0.2951 , 1.6769) 0.4258	
Rest of World	41	6 (14.6)	NE (19.4 , NE)	36	7 (19.4)	NE (NE , NE)	0.5803 (0.1914 , 1.7595) 0.3301	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	16 (22.5)	NE (19.4 , NE)	72	15 (20.8)	NE (15.2 , NE)	0.8729 (0.4284 , 1.7789) 0.7070	0.9831
Black or African American	10	2 (20.0)	NE (3.0 , NE)	9	1 (11.1)	NE (1.4 , NE)	1.1739 (0.1027 , 13.416) 0.8973	
Asian	152	38 (25.0)	NE (22.3 , NE)	162	33 (20.4)	21.2 (17.2 , NE)	0.8575 (0.5310 , 1.3849) 0.5279	
Other	28	4 (14.3)	NE (19.4 , NE)	20	2 (10.0)	NE (NE , NE)	0.7810 (0.1350 , 4.5167) 0.7930	
ECOG PS								
0	154	39 (25.3)	24.3 (22.1 , NE)	175	31 (17.7)	NE (21.2 , NE)	0.9871 (0.6083 , 1.6018) 0.9572	0.1833
1	106	21 (19.8)	NE (NE , NE)	87	20 (23.0)	NE (15.2 , NE)	0.6426 (0.3455 , 1.1951) 0.1600	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	29 (21.8)	NE (24.3 , NE)	139	33 (23.7)	NE (21.2 , NE)	0.6306 (0.3783 , 1.0513) 0.0748	0.0635
Negative	126	31 (24.6)	22.3 (19.4 , NE)	122	18 (14.8)	NE (17.2 , NE)	1.2204 (0.6742 , 2.2091) 0.5111	
Estrogen Receptors								
Positive	129	28 (21.7)	NE (24.3 , NE)	132	31 (23.5)	21.2 (21.2 , NE)	0.6391 (0.3785 , 1.0791) 0.0915	0.0845
Negative	130	32 (24.6)	22.3 (19.4 , NE)	128	20 (15.6)	NE (17.2 , NE)	1.1307 (0.6384 , 2.0029) 0.6743	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	18 (22.2)	NE (NE , NE)	92	23 (25.0)	NE (15.2 , NE)	0.6313 (0.3374 , 1.1813) 0.1466	0.1811
Negative	177	42 (23.7)	NE (22.3 , NE)	168	28 (16.7)	21.2 (17.2 , NE)	1.0135 (0.6208 , 1.6546) 0.9577	
Prior Treatment with Pertuzumab								
Yes	162	34 (21.0)	NE (22.3 , NE)	158	26 (16.5)	21.2 (16.7 , 21.2)	0.8697 (0.5123 , 1.4763) 0.6066	0.9259
No	99	26 (26.3)	24.3 (19.4 , NE)	105	25 (23.8)	NE (17.2 , NE)	0.8097 (0.4625 , 1.4176) 0.4600	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	41 (21.8)	NE (22.3 , NE)	191	37 (19.4)	21.2 (21.2 , NE)	0.7618 (0.4819 , 1.2044) 0.2434	0.5409
>= 3 lines	73	19 (26.0)	NE (19.4 , NE)	72	14 (19.4)	NE (15.2 , NE)	1.0489 (0.5189 , 2.1206) 0.8904	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	33 (21.2)	NE (22.3 , NE)	152	26 (17.1)	21.2 (16.7 , 21.2)	0.8432 (0.4946 , 1.4376) 0.5322	0.3318
>= 3 lines	6	1 (16.7)	NE (3.1 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.4142	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	32 (24.6)	24.3 (22.1 , NE)	130	20 (15.4)	NE (NE , NE)	1.0423 (0.5809 , 1.8700) 0.8900	0.6471
Mild Impairment	92	22 (23.9)	NE (NE , NE)	104	27 (26.0)	21.2 (15.2 , NE)	0.7492 (0.4247 , 1.3217) 0.3209	
Moderate Impairment	30	5 (16.7)	NE (15.2 , NE)	22	3 (13.6)	NE (17.2 , NE)	0.8627 (0.2039 , 3.6506) 0.8409	
Hepatic Impairment								
Within Normal Range	208	51 (24.5)	NE (24.3 , NE)	212	41 (19.3)	21.2 (21.2 , NE)	0.9010 (0.5908 , 1.3740) 0.6314	0.3544
Mild Impairment	49	9 (18.4)	NE (19.4 , NE)	49	10 (20.4)	NE (8.4 , NE)	0.5704 (0.2290 , 1.4210) 0.2224	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	46 (23.6)	NE (24.3 , NE)	189	38 (20.1)	21.2 (21.2 , NE)	0.8350 (0.5375 , 1.2972) 0.4229	0.9684
No	66	14 (21.2)	NE (22.1 , NE)	74	13 (17.6)	NE (17.2 , NE)	0.8194 (0.3775 , 1.7786) 0.6175	
Baseline CNS Metastases								
Yes	43	13 (30.2)	19.4 (14.8 , NE)	39	4 (10.3)	NE (NE , NE)	2.1443 (0.6846 , 6.7159) 0.1800	0.0549
No	218	47 (21.6)	NE (24.3 , NE)	224	47 (21.0)	NE (21.2 , NE)	0.7251 (0.4792 , 1.0972) 0.1274	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	16 (25.8)	19.4 (15.7 , NE)	52	7 (13.5)	NE (NE , NE)	1.3630 (0.5488 , 3.3852) 0.5022	0.1924
No	199	44 (22.1)	NE (24.3 , NE)	211	44 (20.9)	NE (21.2 , NE)	0.7473 (0.4868 , 1.1471) 0.1822	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	50 (23.6)	NE (NE , NE)	206	36 (17.5)	NE (NE , NE)	1.0660 (0.6902 , 1.6465) 0.7744	0.7964
>=65	49	15 (30.6)	NE (14.8 , NE)	57	14 (24.6)	21.2 (12.7 , NE)	1.1565 (0.5571 , 2.4010) 0.6947	
Age								
<75	253	62 (24.5)	NE (NE , NE)	255	49 (19.2)	NE (21.2 , NE)	1.0225 (0.7003 , 1.4930) 0.9100	0.2902
>=75	8	3 (37.5)	14.8 (0.8 , NE)	8	1 (12.5)	NE (2.8 , NE)	2.2396 (0.2027 , 24.739) 0.4991	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	40 (26.8)	NE (NE , NE)	160	31 (19.4)	NE (21.2 , NE)	1.0929 (0.6798 , 1.7570) 0.7143	0.7459
North America	17	4 (23.5)	22.3 (22.3 , NE)	17	2 (11.8)	13.8 (13.8 , NE)	1.2293 (0.2005 , 7.5357) 0.8231	
Europe	54	13 (24.1)	NE (16.4 , NE)	50	8 (16.0)	NE (NE , NE)	1.2796 (0.5281 , 3.1008) 0.5816	
Rest of World	41	8 (19.5)	NE (NE , NE)	36	9 (25.0)	NE (11.7 , NE)	0.6746 (0.2596 , 1.7527) 0.4135	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	18 (25.4)	22.3 (22.3 , NE)	72	11 (15.3)	NE (13.8 , NE)	1.4637 (0.6890 , 3.1092) 0.3209	0.3811
Black or African American	10	2 (20.0)	NE (1.5 , NE)	9	2 (22.2)	NE (1.5 , NE)	0.7615 (0.1069 , 5.4232) 0.7846	
Asian	152	40 (26.3)	NE (NE , NE)	162	31 (19.1)	NE (21.2 , NE)	1.0947 (0.6809 , 1.7599) 0.7093	
Other	28	5 (17.9)	NE (16.4 , NE)	20	6 (30.0)	NE (8.3 , NE)	0.4386 (0.1324 , 1.4530) 0.1675	
ECOG PS								
0	154	36 (23.4)	NE (NE , NE)	175	34 (19.4)	NE (21.2 , NE)	0.8951 (0.5568 , 1.4389) 0.6477	0.5916
1	106	29 (27.4)	NE (NE , NE)	87	16 (18.4)	NE (NE , NE)	1.2985 (0.7027 , 2.3996) 0.3987	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	34 (25.6)	NE (22.3 , NE)	139	24 (17.3)	NE (21.2 , NE)	1.1932 (0.7033 , 2.0244) 0.5132	0.5412
Negative	126	31 (24.6)	NE (NE , NE)	122	25 (20.5)	NE (15.2 , NE)	0.9737 (0.5725 , 1.6560) 0.9218	
Estrogen Receptors								
Positive	129	32 (24.8)	NE (22.3 , NE)	132	22 (16.7)	NE (21.2 , NE)	1.1933 (0.6885 , 2.0683) 0.5294	0.5600
Negative	130	33 (25.4)	NE (NE , NE)	128	27 (21.1)	NE (15.2 , NE)	0.9715 (0.5819 , 1.6222) 0.9123	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	20 (24.7)	NE (22.3 , NE)	92	17 (18.5)	NE (13.8 , NE)	1.0527 (0.5484 , 2.0205) 0.8764	0.9771
Negative	177	45 (25.4)	NE (NE , NE)	168	32 (19.0)	21.2 (21.2 , NE)	1.0951 (0.6928 , 1.7311) 0.6983	
Prior Treatment with Pertuzumab								
Yes	162	42 (25.9)	NE (NE , NE)	158	26 (16.5)	21.2 (21.2 , NE)	1.1785 (0.7170 , 1.9369) 0.5134	0.3931
No	99	23 (23.2)	NE (NE , NE)	105	24 (22.9)	NE (13.8 , NE)	0.9093 (0.5114 , 1.6166) 0.7355	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	47 (25.0)	NE (NE , NE)	191	42 (22.0)	21.2 (21.2 , NE)	0.8847 (0.5805 , 1.3483) 0.5688	0.1092
>= 3 lines	73	18 (24.7)	NE (NE , NE)	72	8 (11.1)	NE (13.8 , NE)	1.9719 (0.8512 , 4.5680) 0.1067	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	40 (25.6)	NE (NE , NE)	152	26 (17.1)	21.2 (21.2 , NE)	1.1199 (0.6776 , 1.8508) 0.6544	0.1647
>= 3 lines	6	2 (33.3)	NE (1.5 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.2807	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	26 (20.0)	NE (NE , NE)	130	23 (17.7)	NE (NE , NE)	0.8267 (0.4646 , 1.4710) 0.5145	0.4286
Mild Impairment	92	29 (31.5)	NE (16.4 , NE)	104	22 (21.2)	21.2 (15.2 , NE)	1.3137 (0.7525 , 2.2933) 0.3364	
Moderate Impairment	30	9 (30.0)	NE (15.2 , NE)	22	4 (18.2)	NE (9.1 , NE)	1.3617 (0.4182 , 4.4341) 0.6068	
Hepatic Impairment								
Within Normal Range	208	55 (26.4)	NE (NE , NE)	212	43 (20.3)	NE (21.2 , NE)	1.0600 (0.7079 , 1.5873) 0.7774	0.9236
Mild Impairment	49	10 (20.4)	NE (NE , NE)	49	7 (14.3)	NE (NE , NE)	1.0362 (0.3920 , 2.7391) 0.9427	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	47 (24.1)	NE (NE , NE)	189	30 (15.9)	NE (21.2 , NE)	1.2365 (0.7778 , 1.9659) 0.3708	0.2679
No	66	18 (27.3)	NE (NE , NE)	74	20 (27.0)	NE (15.2 , NE)	0.7932 (0.4180 , 1.5051) 0.4793	
Baseline CNS Metastases								
Yes	43	7 (16.3)	NE (NE , NE)	39	6 (15.4)	NE (NE , NE)	0.7607 (0.2470 , 2.3429) 0.6325	0.4656
No	218	58 (26.6)	NE (NE , NE)	224	44 (19.6)	NE (21.2 , NE)	1.1165 (0.7519 , 1.6578) 0.5845	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	11 (17.7)	NE (NE , NE)	52	7 (13.5)	NE (NE , NE)	1.0421 (0.3964 , 2.7394) 0.9358	0.8292
No	199	54 (27.1)	NE (NE , NE)	211	43 (20.4)	NE (21.2 , NE)	1.0873 (0.7257 , 1.6289) 0.6833	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	27 (12.7)	NE (NE , NE)	206	22 (10.7)	NE (NE , NE)	0.8704 (0.4923 , 1.5390) 0.6342	0.5683
>=65	49	6 (12.2)	NE (16.5 , NE)	57	10 (17.5)	NE (12.7 , NE)	0.5250 (0.1896 , 1.4540) 0.2075	
Age								
<75	253	32 (12.6)	NE (NE , NE)	255	32 (12.5)	NE (NE , NE)	0.7134 (0.4343 , 1.1718) 0.1806	0.1919
>=75	8	1 (12.5)	NE (2.9 , NE)	8	0	NE (NE , NE)	NE (NE, NE) 0.3173	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	21 (14.1)	NE (NE , NE)	160	16 (10.0)	NE (NE , NE)	0.9600 (0.4954 , 1.8604) 0.9049	0.1131
North America	17	4 (23.5)	NE (10.2 , NE)	17	1 (5.9)	NE (NE , NE)	3.2200 (0.3569 , 29.050) 0.2709	
Europe	54	3 (5.6)	NE (NE , NE)	50	7 (14.0)	NE (13.1 , NE)	0.2240 (0.0560 , 0.8960) 0.0221	
Rest of World	41	5 (12.2)	NE (NE , NE)	36	8 (22.2)	NE (NE , NE)	0.4648 (0.1519 , 1.4220) 0.1679	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	8 (11.3)	NE (NE , NE)	72	10 (13.9)	NE (NE , NE)	0.6284 (0.2470 , 1.5988) 0.3239	0.2382
Black or African American	10	2 (20.0)	NE (3.1 , NE)	9	1 (11.1)	NE (2.8 , NE)	1.4118 (0.1277 , 15.612) 0.7774	
Asian	152	21 (13.8)	NE (NE , NE)	162	16 (9.9)	NE (NE , NE)	0.9619 (0.4963 , 1.8643) 0.9096	
Other	28	2 (7.1)	NE (NE , NE)	20	5 (25.0)	NE (9.8 , NE)	0.1415 (0.0243 , 0.8239) 0.0148	
ECOG PS								
0	154	18 (11.7)	NE (NE , NE)	175	21 (12.0)	NE (NE , NE)	0.6505 (0.3429 , 1.2339) 0.1850	0.7386
1	106	15 (14.2)	NE (NE , NE)	87	11 (12.6)	NE (NE , NE)	0.8610 (0.3936 , 1.8833) 0.7088	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	20 (15.0)	NE (NE , NE)	139	17 (12.2)	NE (NE , NE)	0.8051 (0.4167 , 1.5555) 0.5187	0.6024
Negative	126	13 (10.3)	NE (NE , NE)	122	14 (11.5)	NE (NE , NE)	0.7160 (0.3354 , 1.5287) 0.3862	
Estrogen Receptors								
Positive	129	20 (15.5)	NE (NE , NE)	132	15 (11.4)	NE (NE , NE)	0.9011 (0.4558 , 1.7814) 0.7643	0.3985
Negative	130	13 (10.0)	NE (NE , NE)	128	15 (11.7)	NE (NE , NE)	0.6773 (0.3211 , 1.4285) 0.3036	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	13 (16.0)	NE (18.2 , NE)	92	13 (14.1)	NE (NE , NE)	0.6851 (0.3128 , 1.5006) 0.3422	0.9860
Negative	177	20 (11.3)	NE (NE , NE)	168	18 (10.7)	NE (NE , NE)	0.8322 (0.4381 , 1.5808) 0.5741	
Prior Treatment with Pertuzumab								
Yes	162	24 (14.8)	NE (NE , NE)	158	14 (8.9)	NE (NE , NE)	1.1865 (0.6069 , 2.3197) 0.6164	0.0273
No	99	9 (9.1)	NE (NE , NE)	105	18 (17.1)	NE (NE , NE)	0.3803 (0.1699 , 0.8514) 0.0147	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	22 (11.7)	NE (NE , NE)	191	22 (11.5)	NE (NE , NE)	0.7400 (0.4068 , 1.3462) 0.3222	0.9082
>= 3 lines	73	11 (15.1)	NE (18.2 , NE)	72	10 (13.9)	NE (NE , NE)	0.7623 (0.3203 , 1.8144) 0.5385	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	23 (14.7)	NE (NE , NE)	152	14 (9.2)	NE (NE , NE)	1.1627 (0.5916 , 2.2851) 0.6613	0.3692
>= 3 lines	6	1 (16.7)	NE (16.5 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.4795	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	17 (13.1)	NE (NE , NE)	130	13 (10.0)	NE (NE , NE)	0.9576 (0.4614 , 1.9874) 0.9085	0.8509
Mild Impairment	92	13 (14.1)	NE (NE , NE)	104	18 (17.3)	NE (NE , NE)	0.6276 (0.3054 , 1.2900) 0.2018	
Moderate Impairment	30	2 (6.7)	NE (NE , NE)	22	1 (4.5)	NE (NE , NE)	0.8665 (0.0784 , 9.5722) 0.9069	
Hepatic Impairment								
Within Normal Range	208	27 (13.0)	NE (NE , NE)	212	25 (11.8)	NE (NE , NE)	0.7971 (0.4593 , 1.3834) 0.4200	0.4807
Mild Impairment	49	6 (12.2)	NE (NE , NE)	49	7 (14.3)	NE (NE , NE)	0.5270 (0.1739 , 1.5970) 0.2501	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	27 (13.8)	NE (NE , NE)	189	20 (10.6)	NE (NE , NE)	0.9602 (0.5350 , 1.7233) 0.8919	0.1271
No	66	6 (9.1)	NE (NE , NE)	74	12 (16.2)	NE (NE , NE)	0.3661 (0.1355 , 0.9891) 0.0396	
Baseline CNS Metastases								
Yes	43	6 (14.0)	NE (NE , NE)	39	2 (5.1)	NE (NE , NE)	2.2230 (0.4465 , 11.068) 0.3154	0.2092
No	218	27 (12.4)	NE (NE , NE)	224	30 (13.4)	NE (NE , NE)	0.6551 (0.3872 , 1.1086) 0.1128	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	6 (9.7)	NE (NE , NE)	52	2 (3.8)	NE (NE , NE)	2.0631 (0.4147 , 10.263) 0.3660	0.2459
No	199	27 (13.6)	NE (NE , NE)	211	30 (14.2)	NE (NE , NE)	0.6750 (0.3989 , 1.1420) 0.1409	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	32 (15.1)	NE (NE , NE)	206	43 (20.9)	23.7 (23.7 , NE)	0.4568 (0.2861 , 0.7296) 0.0008	0.8764
>=65	49	8 (16.3)	NE (16.4 , NE)	57	14 (24.6)	NE (12.7 , NE)	0.4965 (0.2072 , 1.1898) 0.1093	
Age								
<75	253	39 (15.4)	NE (NE , NE)	255	56 (22.0)	23.7 (23.7 , NE)	0.4581 (0.3024 , 0.6940) 0.0002	0.7136
>=75	8	1 (12.5)	NE (16.4 , NE)	8	1 (12.5)	NE (4.7 , NE)	0.0000 (NE, NE) 0.3173	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	27 (18.1)	NE (NE , NE)	160	38 (23.8)	23.7 (23.7 , NE)	0.5050 (0.3061 , 0.8330) 0.0064	0.9198
North America	17	3 (17.6)	NE (14.3 , NE)	17	3 (17.6)	NE (6.9 , NE)	0.6474 (0.1259 , 3.3287) 0.6002	
Europe	54	4 (7.4)	NE (21.9 , NE)	50	8 (16.0)	NE (NE , NE)	0.3084 (0.0918 , 1.0358) 0.0446	
Rest of World	41	6 (14.6)	NE (NE , NE)	36	8 (22.2)	NE (13.8 , NE)	0.4167 (0.1415 , 1.2271) 0.1018	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	5 (7.0)	NE (NE , NE)	72	11 (15.3)	NE (NE , NE)	0.3211 (0.1103 , 0.9352) 0.0287	0.8172
Black or African American	10	3 (30.0)	NE (4.1 , NE)	9	3 (33.3)	13.8 (2.8 , NE)	0.5615 (0.1115 , 2.8280) 0.4783	
Asian	152	28 (18.4)	NE (NE , NE)	162	40 (24.7)	23.7 (23.7 , NE)	0.5004 (0.3066 , 0.8167) 0.0047	
Other	28	4 (14.3)	NE (15.2 , NE)	20	3 (15.0)	NE (9.8 , NE)	0.4503 (0.0989 , 2.0513) 0.2906	
ECOG PS								
0	154	19 (12.3)	NE (NE , NE)	175	37 (21.1)	23.7 (23.7 , NE)	0.3605 (0.2052 , 0.6334) 0.0002	0.2815
1	106	21 (19.8)	NE (21.9 , NE)	87	20 (23.0)	NE (12.8 , NE)	0.5905 (0.3175 , 1.0982) 0.0920	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	19 (14.3)	NE (NE , NE)	139	30 (21.6)	23.7 (23.7 , NE)	0.3900 (0.2172 , 0.7004) 0.0011	0.7791
Negative	126	21 (16.7)	NE (NE , NE)	122	27 (22.1)	NE (NE , NE)	0.5494 (0.3091 , 0.9768) 0.0382	
Estrogen Receptors								
Positive	129	18 (14.0)	NE (NE , NE)	132	29 (22.0)	23.7 (13.8 , NE)	0.3700 (0.2030 , 0.6743) 0.0008	0.6381
Negative	130	22 (16.9)	NE (NE , NE)	128	28 (21.9)	NE (NE , NE)	0.5561 (0.3164 , 0.9773) 0.0384	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	8 (9.9)	NE (NE , NE)	92	18 (19.6)	23.7 (13.8 , NE)	0.3035 (0.1305 , 0.7057) 0.0035	0.4106
Negative	177	32 (18.1)	NE (NE , NE)	168	39 (23.2)	NE (NE , NE)	0.5329 (0.3314 , 0.8570) 0.0083	
Prior Treatment with Pertuzumab								
Yes	162	25 (15.4)	NE (NE , NE)	158	39 (24.7)	NE (NE , NE)	0.3937 (0.2359 , 0.6572) 0.0002	0.2515
No	99	15 (15.2)	NE (21.9 , NE)	105	18 (17.1)	23.7 (NE , NE)	0.6167 (0.3083 , 1.2339) 0.1677	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	26 (13.8)	NE (NE , NE)	191	45 (23.6)	23.7 (23.7 , NE)	0.3647 (0.2230 , 0.5965) <.0001	0.0833
>= 3 lines	73	14 (19.2)	NE (NE , NE)	72	12 (16.7)	NE (NE , NE)	0.8300 (0.3791 , 1.8172) 0.6394	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	24 (15.4)	NE (NE , NE)	152	39 (25.7)	NE (12.8 , NE)	0.3750 (0.2230 , 0.6306) 0.0001	0.1279
>= 3 lines	6	1 (16.7)	NE (9.9 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.4142	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	21 (16.2)	NE (NE , NE)	130	27 (20.8)	NE (13.8 , NE)	0.4656 (0.2583 , 0.8393) 0.0094	0.9887
Mild Impairment	92	12 (13.0)	NE (21.9 , NE)	104	23 (22.1)	23.7 (23.7 , NE)	0.4145 (0.2050 , 0.8380) 0.0115	
Moderate Impairment	30	6 (20.0)	NE (15.2 , NE)	22	7 (31.8)	NE (3.9 , NE)	0.4204 (0.1407 , 1.2561) 0.1096	
Hepatic Impairment								
Within Normal Range	208	35 (16.8)	NE (NE , NE)	212	48 (22.6)	NE (NE , NE)	0.4890 (0.3139 , 0.7618) 0.0013	0.5108
Mild Impairment	49	5 (10.2)	NE (NE , NE)	49	9 (18.4)	23.7 (NE , NE)	0.3503 (0.1160 , 1.0577) 0.0522	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	30 (15.4)	NE (NE , NE)	189	39 (20.6)	23.7 (23.7 , NE)	0.4718 (0.2901 , 0.7674) 0.0020	0.6934
No	66	10 (15.2)	NE (21.9 , NE)	74	18 (24.3)	NE (NE , NE)	0.4330 (0.1979 , 0.9476) 0.0311	
Baseline CNS Metastases								
Yes	43	9 (20.9)	NE (15.4 , NE)	39	10 (25.6)	NE (9.3 , NE)	0.4917 (0.1918 , 1.2604) 0.1311	0.9746
No	218	31 (14.2)	NE (NE , NE)	224	47 (21.0)	23.7 (23.7 , NE)	0.4468 (0.2821 , 0.7075) 0.0004	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	9 (14.5)	NE (NE , NE)	52	14 (26.9)	NE (9.3 , NE)	0.3555 (0.1484 , 0.8516) 0.0157	0.4201
No	199	31 (15.6)	NE (NE , NE)	211	43 (20.4)	23.7 (23.7 , NE)	0.4923 (0.3081 , 0.7864) 0.0025	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	19 (9.0)	NE (11.8 , NE)	206	3 (1.5)	NE (NE , NE)	4.0230 (1.1856 , 13.651) 0.0156	0.2759
>=65	49	4 (8.2)	NE (2.8 , NE)	57	0	NE (NE , NE)	NE (NE, NE) 0.0907	
Age								
<75	253	22 (8.7)	NE (12.4 , NE)	255	3 (1.2)	NE (NE , NE)	4.7359 (1.4132 , 15.871) 0.0054	NE
>=75	8	1 (12.5)	1.4 (NE , NE)	8	0	NE (NE , NE)	NE (NE , NE) NE	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	14 (9.4)	NE (4.2 , NE)	160	1 (0.6)	NE (NE , NE)	11.7303 (1.5401 , 89.342) 0.002	0.5316
North America	17	2 (11.8)	NE (0.9 , NE)	17	0	NE (NE , NE)	NE (NE, NE) 0.6270	
Europe	54	3 (5.6)	18.0 (2.8 , NE)	50	1 (2.0)	NE (1.4 , NE)	1.4264 (0.1288 , 15.793) 0.7710	
Rest of World	41	4 (9.8)	NE (1.4 , NE)	36	1 (2.8)	NE (7.9 , NE)	1.9194 (0.2133 , 17.274) 0.5609	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	6 (8.5)	NE (1.4 , NE)	72	1 (1.4)	NE (7.9 , NE)	2.9156 (0.3498 , 24.301) 0.3053	0.2053
Black or African American	10	0	NE (NE , NE)	9	0	NE (NE , NE)	NE (NE , NE) NE	
Asian	152	14 (9.2)	NE (8.2 , NE)	162	1 (0.6)	NE (NE , NE)	11.7570 (1.5434 , 89.557) 0.002	
Other	28	3 (10.7)	18.0 (2.8 , 18.0)	20	1 (5.0)	NE (1.4 , NE)	0.4524 (0.0401 , 5.1100) 0.5109	
ECOG PS								
0	154	12 (7.8)	NE (11.8 , NE)	175	2 (1.1)	NE (NE , NE)	3.9740 (0.8875 , 17.795) 0.0517	0.6811
1	106	11 (10.4)	NE (1.4 , NE)	87	1 (1.1)	NE (NE , NE)	6.8514 (0.8784 , 53.441) 0.0308	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	9 (6.8)	NE (18.0 , NE)	139	0	NE (NE , NE)	NE (NE, NE) 0.0111	0.0778
Negative	126	14 (11.1)	11.8 (2.8 , NE)	122	3 (2.5)	NE (7.9 , NE)	2.6690 (0.7633 , 9.3322) 0.1103	
Estrogen Receptors								
Positive	129	8 (6.2)	NE (NE , NE)	132	0	NE (NE , NE)	NE (NE, NE) 0.0155	0.1108
Negative	130	15 (11.5)	12.4 (2.8 , NE)	128	3 (2.3)	NE (7.9 , NE)	2.8104 (0.8034 , 9.8309) 0.0918	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	8 (9.9)	18.0 (1.4 , NE)	92	0	NE (NE , NE)	NE (NE, NE) 0.0076	0.0708
Negative	177	15 (8.5)	NE (8.2 , NE)	168	3 (1.8)	NE (NE , NE)	2.7902 (0.8064 , 9.6539) 0.0906	
Prior Treatment with Pertuzumab								
Yes	162	11 (6.8)	NE (8.2 , NE)	158	3 (1.9)	NE (NE , NE)	3.0857 (0.8538 , 11.152) 0.0702	0.1184
No	99	12 (12.1)	NE (4.2 , NE)	105	0	NE (NE , NE)	NE (NE, NE) 0.0233	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	14 (7.4)	NE (8.2 , NE)	191	2 (1.0)	NE (NE , NE)	4.5384 (1.0291 , 20.014) 0.0278	0.8195
>= 3 lines	73	9 (12.3)	NE (1.5 , NE)	72	1 (1.4)	NE (7.9 , NE)	5.2607 (0.6538 , 42.330) 0.0817	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	11 (7.1)	NE (3.1 , NE)	152	3 (2.0)	NE (NE , NE)	3.3768 (0.9347 , 12.199) 0.0486	NE
>= 3 lines	6	0	NE (NE , NE)	6	0	NE (NE , NE)	NE (NE , NE) NE	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	9 (6.9)	NE (4.2 , NE)	130	2 (1.5)	NE (7.9 , NE)	2.8992 (0.6258 , 13.431) 0.1553	0.2885
Mild Impairment	92	9 (9.8)	NE (1.4 , NE)	104	1 (1.0)	NE (NE , NE)	8.7962 (1.1094 , 69.744) 0.0128	
Moderate Impairment	30	4 (13.3)	18.0 (0.9 , NE)	22	0	NE (NE , NE)	NE (NE , NE) NE	
Hepatic Impairment								
Within Normal Range	208	16 (7.7)	NE (12.4 , NE)	212	3 (1.4)	NE (NE , NE)	4.1400 (1.2003 , 14.279) 0.0147	0.3536
Mild Impairment	49	7 (14.3)	NE (2.8 , NE)	49	0	NE (NE , NE)	NE (NE, NE) 0.1442	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	21 (10.8)	18.0 (11.8 , NE)	189	2 (1.1)	NE (NE , NE)	5.8667 (1.3715 , 25.095) 0.0069	0.5027
No	66	2 (3.0)	NE (0.9 , NE)	74	1 (1.4)	NE (1.4 , NE)	2.4207 (0.2187 , 26.791) 0.4507	
Baseline CNS Metastases								
Yes	43	4 (9.3)	NE (1.4 , NE)	39	0	NE (NE , NE)	NE (NE, NE) 0.0667	0.2735
No	218	19 (8.7)	NE (11.8 , NE)	224	3 (1.3)	NE (NE , NE)	3.8995 (1.1507 , 13.214) 0.0183	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 54 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 15 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	5 (8.1)	NE (1.4 , NE)	52	0	NE (NE , NE)	NE (NE, NE) 0.0501	0.2307
No	199	18 (9.0)	NE (11.8 , NE)	211	3 (1.4)	NE (NE , NE)	3.7435 (1.0998 , 12.742) 0.0232	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 15 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 62 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 10 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	77 (36.3)	24.6 (17.9 , NE)	206	78 (37.9)	12.5 (10.3 , NE)	0.6893 (0.4996 , 0.9511) 0.0227	0.9441
>=65	49	17 (34.7)	NE (11.7 , NE)	57	25 (43.9)	10.4 (7.0 , NE)	0.6965 (0.3742 , 1.2965) 0.2461	
Age								
<75	253	91 (36.0)	24.6 (17.9 , NE)	255	100 (39.2)	12.5 (10.3 , NE)	0.6742 (0.5049 , 0.9004) 0.0071	0.4144
>=75	8	3 (37.5)	NE (0.8 , NE)	8	3 (37.5)	NE (1.4 , NE)	1.6516 (0.3292 , 8.2862) 0.5365	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 62 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 10 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	56 (37.6)	24.6 (15.0 , NE)	160	71 (44.4)	10.4 (8.4 , 14.4)	0.5867 (0.4095 , 0.8406) 0.0033	0.2365
North America	17	6 (35.3)	NE (2.9 , NE)	17	2 (11.8)	NE (NE , NE)	2.8822 (0.5784 , 14.361) 0.1765	
Europe	54	18 (33.3)	NE (14.8 , NE)	50	19 (38.0)	12.7 (7.2 , NE)	0.6996 (0.3615 , 1.3541) 0.2820	
Rest of World	41	14 (34.1)	18.3 (18.2 , NE)	36	11 (30.6)	NE (8.5 , NE)	0.8384 (0.3763 , 1.8682) 0.6617	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 62 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 10 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	27 (38.0)	19.4 (12.1 , NE)	72	25 (34.7)	NE (8.8 , NE)	0.9170 (0.5299 , 1.5869) 0.7536	0.3924
Black or African American	10	3 (30.0)	18.3 (1.4 , NE)	9	1 (11.1)	NE (8.4 , NE)	1.8278 (0.1656 , 20.180) 0.6172	
Asian	152	56 (36.8)	24.6 (15.3 , NE)	162	71 (43.8)	10.8 (8.4 , 14.4)	0.5901 (0.4118 , 0.8455) 0.0037	
Other	28	8 (28.6)	NE (15.1 , NE)	20	6 (30.0)	NE (9.8 , NE)	0.6027 (0.1977 , 1.8367) 0.3682	
ECOG PS								
0	154	59 (38.3)	19.4 (15.1 , NE)	175	67 (38.3)	13.8 (9.8 , NE)	0.7525 (0.5265 , 1.0756) 0.1153	0.3892
1	106	35 (33.0)	24.6 (17.9 , NE)	87	36 (41.4)	11.2 (7.2 , NE)	0.5980 (0.3733 , 0.9579) 0.0315	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 62 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 10 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	49 (36.8)	NE (15.2 , NE)	139	57 (41.0)	11.3 (8.5 , NE)	0.6525 (0.4418 , 0.9638) 0.0304	0.5774
Negative	126	45 (35.7)	24.6 (18.3 , NE)	122	45 (36.9)	12.7 (9.8 , NE)	0.7503 (0.4923 , 1.1437) 0.1791	
Estrogen Receptors								
Positive	129	46 (35.7)	NE (15.3 , NE)	132	56 (42.4)	10.4 (8.4 , NE)	0.5892 (0.3952 , 0.8785) 0.0087	0.2422
Negative	130	48 (36.9)	19.4 (14.8 , NE)	128	46 (35.9)	13.8 (10.8 , NE)	0.8107 (0.5368 , 1.2244) 0.3149	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 62 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 10 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	33 (40.7)	17.9 (13.6 , NE)	92	32 (34.8)	NE (9.8 , NE)	0.9248 (0.5639 , 1.5165) 0.7505	0.1342
Negative	177	61 (34.5)	24.6 (18.3 , NE)	168	70 (41.7)	12.5 (9.0 , NE)	0.6044 (0.4255 , 0.8585) 0.0046	
Prior Treatment with Pertuzumab								
Yes	162	62 (38.3)	24.6 (15.2 , NE)	158	61 (38.6)	12.7 (10.3 , NE)	0.7713 (0.5381 , 1.1055) 0.1530	0.4600
No	99	32 (32.3)	18.2 (17.9 , NE)	105	42 (40.0)	11.3 (8.4 , NE)	0.5826 (0.3652 , 0.9294) 0.0221	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 62 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 10 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	68 (36.2)	24.6 (17.9 , NE)	191	81 (42.4)	11.2 (9.8 , NE)	0.6394 (0.4605 , 0.8879) 0.0070	0.2954
>= 3 lines	73	26 (35.6)	19.4 (15.0 , NE)	72	22 (30.6)	14.4 (9.0 , NE)	0.8517 (0.4747 , 1.5280) 0.5888	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	60 (38.5)	24.6 (15.2 , NE)	152	60 (39.5)	12.7 (9.9 , NE)	0.7665 (0.5324 , 1.1035) 0.1489	0.6894
>= 3 lines	6	2 (33.3)	NE (1.4 , NE)	6	1 (16.7)	NE (4.2 , NE)	1.1535 (0.1010 , 13.168) 0.9084	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 62 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 10 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	50 (38.5)	19.4 (18.2 , NE)	130	47 (36.2)	12.4 (8.8 , NE)	0.6769 (0.4480 , 1.0228) 0.0620	0.8873
Mild Impairment	92	31 (33.7)	NE (17.9 , NE)	104	45 (43.3)	12.5 (9.9 , NE)	0.6766 (0.4262 , 1.0740) 0.0933	
Moderate Impairment	30	12 (40.0)	15.2 (10.1 , NE)	22	11 (50.0)	8.1 (2.8 , NE)	0.5129 (0.2214 , 1.1885) 0.1142	
Hepatic Impairment								
Within Normal Range	208	81 (38.9)	24.6 (15.3 , NE)	212	84 (39.6)	12.7 (10.4 , NE)	0.7529 (0.5518 , 1.0274) 0.0714	0.1317
Mild Impairment	49	13 (26.5)	NE (19.4 , NE)	49	19 (38.8)	9.8 (6.0 , NE)	0.4258 (0.2050 , 0.8844) 0.0188	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 62 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 10 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	72 (36.9)	18.3 (15.3 , NE)	189	73 (38.6)	12.5 (10.3 , NE)	0.7110 (0.5093 , 0.9926) 0.0435	0.4218
No	66	22 (33.3)	NE (15.0 , NE)	74	30 (40.5)	11.1 (8.1 , NE)	0.6097 (0.3495 , 1.0637) 0.0791	
Baseline CNS Metastases								
Yes	43	14 (32.6)	NE (9.0 , NE)	39	15 (38.5)	10.3 (6.6 , NE)	0.6708 (0.3185 , 1.4126) 0.2909	0.7500
No	218	80 (36.7)	19.4 (17.9 , NE)	224	88 (39.3)	12.5 (10.3 , NE)	0.6952 (0.5109 , 0.9459) 0.0200	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 62 Analysis of time to definitive deterioration of EQ-5D-5L VAS by pre-specified Subgroup – Threshold 10 – Full Analysis Set

EQ-5D-5L VAS

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	20 (32.3)	NE (12.2 , NE)	52	20 (38.5)	11.3 (8.4 , NE)	0.7150 (0.3791 , 1.3483) 0.2934	0.8850
No	199	74 (37.2)	19.4 (15.3 , NE)	211	83 (39.3)	12.5 (9.9 , NE)	0.6871 (0.4996 , 0.9450) 0.0204	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	82 (38.7)	19.4 (14.7 , NE)	206	76 (36.9)	16.6 (10.3 , NE)	0.8240 (0.6011 , 1.1296) 0.2256	0.3906
>=65	49	26 (53.1)	7.6 (4.9 , NE)	57	28 (49.1)	9.0 (6.2 , NE)	1.0986 (0.6426 , 1.8780) 0.7318	
Age								
<75	253	105 (41.5)	17.5 (13.6 , NE)	255	101 (39.6)	15.2 (10.0 , 20.5)	0.8620 (0.6547 , 1.1349) 0.2851	0.9453
>=75	8	3 (37.5)	6.5 (4.9 , NE)	8	3 (37.5)	NE (0.9 , NE)	1.0286 (0.2059 , 5.1376) 0.9726	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	64 (43.0)	NE (11.1 , NE)	160	72 (45.0)	10.3 (7.6 , 17.1)	0.7150 (0.5084 , 1.0057) 0.0517	0.3168
North America	17	6 (35.3)	NE (1.6 , NE)	17	4 (23.5)	NE (5.7 , NE)	1.5227 (0.4295 , 5.3991) 0.5107	
Europe	54	24 (44.4)	16.8 (4.9 , 19.4)	50	16 (32.0)	19.1 (7.3 , NE)	1.4284 (0.7549 , 2.7027) 0.2694	
Rest of World	41	14 (34.1)	NE (11.7 , NE)	36	12 (33.3)	NE (7.1 , NE)	0.9582 (0.4423 , 2.0759) 0.9122	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	27 (38.0)	17.5 (10.6 , NE)	72	25 (34.7)	19.1 (7.3 , NE)	1.0754 (0.6226 , 1.8576) 0.7950	0.1268
Black or African American	10	4 (40.0)	NE (1.6 , NE)	9	1 (11.1)	NE (4.2 , NE)	3.7188 (0.4144 , 33.373) 0.2082	
Asian	152	64 (42.1)	NE (11.1 , NE)	162	73 (45.1)	10.3 (7.6 , 17.1)	0.7046 (0.5015 , 0.9901) 0.0417	
Other	28	13 (46.4)	15.2 (4.3 , 19.4)	20	5 (25.0)	NE (7.0 , NE)	1.8422 (0.6533 , 5.1947) 0.2453	
ECOG PS								
0	154	71 (46.1)	15.7 (10.6 , NE)	175	70 (40.0)	15.2 (9.0 , NE)	0.9870 (0.7080 , 1.3760) 0.9332	0.2010
1	106	37 (34.9)	NE (13.6 , NE)	87	34 (39.1)	14.4 (7.3 , NE)	0.7063 (0.4419 , 1.1287) 0.1425	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	54 (40.6)	NE (13.6 , NE)	139	55 (39.6)	16.6 (9.1 , NE)	0.8770 (0.6011 , 1.2797) 0.4953	0.8378
Negative	126	54 (42.9)	15.2 (10.6 , NE)	122	48 (39.3)	14.4 (8.3 , NE)	0.8793 (0.5947 , 1.3002) 0.5113	
Estrogen Receptors								
Positive	129	53 (41.1)	NE (13.6 , NE)	132	51 (38.6)	17.1 (9.1 , NE)	0.9011 (0.6117 , 1.3275) 0.5981	0.9726
Negative	130	55 (42.3)	15.2 (10.6 , NE)	128	52 (40.6)	14.4 (7.6 , NE)	0.8460 (0.5779 , 1.2385) 0.3814	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	31 (38.3)	NE (11.7 , NE)	92	35 (38.0)	16.6 (7.2 , NE)	0.8487 (0.5219 , 1.3803) 0.5071	0.7302
Negative	177	77 (43.5)	16.8 (11.0 , NE)	168	67 (39.9)	15.2 (9.0 , 20.5)	0.9100 (0.6546 , 1.2652) 0.5711	
Prior Treatment with Pertuzumab								
Yes	162	68 (42.0)	19.4 (14.5 , NE)	158	58 (36.7)	19.1 (10.3 , NE)	0.9747 (0.6850 , 1.3868) 0.8837	0.3714
No	99	40 (40.4)	14.7 (11.1 , NE)	105	46 (43.8)	9.1 (6.9 , NE)	0.7262 (0.4739 , 1.1130) 0.1368	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	75 (39.9)	19.4 (14.7 , NE)	191	75 (39.3)	19.1 (10.0 , NE)	0.8093 (0.5860 , 1.1177) 0.1971	0.3386
>= 3 lines	73	33 (45.2)	11.1 (6.9 , NE)	72	29 (40.3)	14.4 (7.3 , NE)	1.0501 (0.6363 , 1.7333) 0.8516	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	64 (41.0)	19.4 (15.2 , NE)	152	56 (36.8)	19.1 (10.2 , NE)	0.9525 (0.6637 , 1.3672) 0.7907	0.4935
>= 3 lines	6	4 (66.7)	5.7 (1.5 , NE)	6	2 (33.3)	17.1 (0.8 , 17.1)	2.7813 (0.3078 , 25.130) 0.3421	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	53 (40.8)	NE (13.6 , NE)	130	46 (35.4)	16.6 (8.7 , NE)	0.8339 (0.5570 , 1.2484) 0.3727	0.9511
Mild Impairment	92	40 (43.5)	16.8 (8.7 , NE)	104	48 (46.2)	11.6 (7.0 , 20.5)	0.9163 (0.6016 , 1.3956) 0.6742	
Moderate Impairment	30	14 (46.7)	14.5 (6.5 , NE)	22	9 (40.9)	15.2 (1.9 , NE)	0.8863 (0.3806 , 2.0639) 0.7769	
Hepatic Impairment								
Within Normal Range	208	92 (44.2)	16.8 (12.5 , NE)	212	88 (41.5)	14.4 (9.1 , NE)	0.8915 (0.6640 , 1.1968) 0.4420	0.6689
Mild Impairment	49	16 (32.7)	NE (8.6 , NE)	49	16 (32.7)	16.6 (5.7 , NE)	0.7816 (0.3892 , 1.5696) 0.4891	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	77 (39.5)	19.4 (13.6 , NE)	189	74 (39.2)	14.4 (9.0 , 19.1)	0.8140 (0.5899 , 1.1233) 0.2075	0.6791
No	66	31 (47.0)	16.8 (6.8 , NE)	74	30 (40.5)	NE (5.0 , NE)	0.9914 (0.5995 , 1.6396) 0.9700	
Baseline CNS Metastases								
Yes	43	16 (37.2)	19.4 (9.7 , NE)	39	16 (41.0)	10.3 (7.0 , NE)	0.5758 (0.2806 , 1.1817) 0.1294	0.4720
No	218	92 (42.2)	17.5 (12.5 , NE)	224	88 (39.3)	16.6 (10.0 , NE)	0.9145 (0.6818 , 1.2265) 0.5478	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Global Health Status

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	26 (41.9)	15.2 (9.7 , NE)	52	18 (34.6)	11.6 (8.4 , NE)	0.8676 (0.4662 , 1.6146) 0.6472	0.5229
No	199	82 (41.2)	NE (12.5 , NE)	211	86 (40.8)	16.6 (8.7 , 20.5)	0.8495 (0.6269 , 1.1511) 0.2905	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	66 (31.1)	NE (18.7 , NE)	206	57 (27.7)	21.0 (17.2 , NE)	0.8126 (0.5663 , 1.1660) 0.2586	0.8207
>=65	49	16 (32.7)	NE (15.2 , NE)	57	18 (31.6)	NE (12.0 , NE)	0.9033 (0.4590 , 1.7775) 0.7656	
Age								
<75	253	80 (31.6)	NE (19.5 , NE)	255	73 (28.6)	21.0 (17.2 , NE)	0.8316 (0.6029 , 1.1471) 0.2595	0.9612
>=75	8	2 (25.0)	16.1 (1.4 , NE)	8	2 (25.0)	NE (0.9 , NE)	0.5418 (0.0486 , 6.0393) 0.6129	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	53 (35.6)	NE (16.5 , NE)	160	45 (28.1)	17.2 (12.0 , NE)	0.9166 (0.6109 , 1.3753) 0.6731	0.0158
North America	17	8 (47.1)	9.8 (1.6 , NE)	17	2 (11.8)	NE (NE , NE)	4.0412 (0.8569 , 19.058) 0.0553	
Europe	54	10 (18.5)	NE (NE , NE)	50	12 (24.0)	NE (NE , NE)	0.6614 (0.2852 , 1.5341) 0.3332	
Rest of World	41	11 (26.8)	NE (15.2 , NE)	36	16 (44.4)	21.0 (4.2 , 21.0)	0.3891 (0.1787 , 0.8468) 0.0138	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	21 (29.6)	NE (15.2 , NE)	72	24 (33.3)	21.0 (7.2 , NE)	0.7051 (0.3910 , 1.2715) 0.2419	0.1780
Black or African American	10	6 (60.0)	12.5 (2.7 , NE)	9	2 (22.2)	NE (1.4 , NE)	2.1721 (0.4367 , 10.803) 0.3314	
Asian	152	53 (34.9)	NE (16.5 , NE)	162	45 (27.8)	NE (12.3 , NE)	0.9185 (0.6121 , 1.3782) 0.6804	
Other	28	2 (7.1)	NE (NE , NE)	20	4 (20.0)	NE (7.1 , NE)	0.3109 (0.0569 , 1.6981) 0.1537	
ECOG PS								
0	154	50 (32.5)	NE (18.7 , NE)	175	45 (25.7)	21.0 (17.2 , NE)	0.9484 (0.6302 , 1.4274) 0.7990	0.1670
1	106	32 (30.2)	NE (16.5 , NE)	87	30 (34.5)	NE (8.4 , NE)	0.6420 (0.3872 , 1.0646) 0.0820	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	31 (23.3)	NE (NE , NE)	139	38 (27.3)	NE (13.4 , NE)	0.6239 (0.3855 , 1.0097) 0.0528	0.0639
Negative	126	51 (40.5)	16.5 (14.5 , NE)	122	36 (29.5)	21.0 (12.3 , NE)	1.1020 (0.7164 , 1.6951) 0.6631	
Estrogen Receptors								
Positive	129	30 (23.3)	NE (19.5 , NE)	132	36 (27.3)	NE (13.4 , NE)	0.6181 (0.3777 , 1.0115) 0.0535	0.0756
Negative	130	52 (40.0)	16.5 (14.5 , NE)	128	38 (29.7)	21.0 (12.3 , NE)	1.0717 (0.7023 , 1.6353) 0.7521	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	19 (23.5)	NE (19.5 , NE)	92	23 (25.0)	NE (13.4 , NE)	0.6992 (0.3782 , 1.2926) 0.2502	0.5113
Negative	177	63 (35.6)	NE (16.1 , NE)	168	50 (29.8)	21.0 (17.2 , NE)	0.9085 (0.6234 , 1.3242) 0.6150	
Prior Treatment with Pertuzumab								
Yes	162	52 (32.1)	NE (19.5 , NE)	158	39 (24.7)	21.0 (21.0 , NE)	0.9892 (0.6486 , 1.5088) 0.9585	0.2364
No	99	30 (30.3)	NE (16.5 , NE)	105	36 (34.3)	17.2 (9.9 , NE)	0.6588 (0.4033 , 1.0759) 0.0928	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	49 (26.1)	NE (NE , NE)	191	53 (27.7)	21.0 (17.2 , NE)	0.6701 (0.4512 , 0.9951) 0.0454	0.0635
>= 3 lines	73	33 (45.2)	16.5 (7.3 , NE)	72	22 (30.6)	NE (9.9 , NE)	1.2490 (0.7214 , 2.1626) 0.4280	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	51 (32.7)	NE (19.5 , NE)	152	35 (23.0)	21.0 (21.0 , NE)	1.1024 (0.7120 , 1.7068) 0.6645	0.0074
>= 3 lines	6	1 (16.7)	NE (1.5 , NE)	6	4 (66.7)	4.5 (0.7 , 7.5)	0.1155 (0.0126 , 1.0591) 0.0301	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	36 (27.7)	NE (19.5 , NE)	130	32 (24.6)	NE (NE , NE)	0.7845 (0.4807 , 1.2803) 0.3319	0.6123
Mild Impairment	92	37 (40.2)	16.1 (14.5 , NE)	104	36 (34.6)	21.0 (11.8 , NE)	0.9502 (0.5976 , 1.5108) 0.8276	
Moderate Impairment	30	9 (30.0)	NE (14.5 , NE)	22	7 (31.8)	17.2 (2.0 , NE)	0.6882 (0.2555 , 1.8532) 0.4573	
Hepatic Impairment								
Within Normal Range	208	66 (31.7)	NE (19.5 , NE)	212	61 (28.8)	21.0 (17.2 , NE)	0.8554 (0.6009 , 1.2177) 0.3835	0.6990
Mild Impairment	49	16 (32.7)	16.5 (14.5 , NE)	49	14 (28.6)	NE (7.5 , NE)	0.7024 (0.3383 , 1.4581) 0.3395	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	63 (32.3)	NE (16.5 , NE)	189	52 (27.5)	21.0 (13.4 , NE)	0.8552 (0.5872 , 1.2455) 0.4113	0.5098
No	66	19 (28.8)	NE (16.7 , NE)	74	23 (31.1)	NE (12.3 , NE)	0.7275 (0.3953 , 1.3389) 0.3044	
Baseline CNS Metastases								
Yes	43	12 (27.9)	NE (14.8 , NE)	39	14 (35.9)	21.0 (5.7 , 21.0)	0.5609 (0.2523 , 1.2471) 0.1501	0.2880
No	218	70 (32.1)	NE (18.7 , NE)	224	61 (27.2)	NE (17.2 , NE)	0.8949 (0.6322 , 1.2669) 0.5282	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Physical Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	19 (30.6)	NE (14.5 , NE)	52	16 (30.8)	21.0 (8.3 , 21.0)	0.7356 (0.3698 , 1.4630) 0.3795	0.7782
No	199	63 (31.7)	NE (18.7 , NE)	211	59 (28.0)	NE (17.2 , NE)	0.8559 (0.5975 , 1.2261) 0.3916	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	73 (34.4)	NE (19.0 , NE)	206	77 (37.4)	13.8 (10.0 , NE)	0.6586 (0.4748 , 0.9137) 0.0118	0.6062
>=65	49	21 (42.9)	16.4 (7.3 , NE)	57	27 (47.4)	13.8 (4.8 , NE)	0.7918 (0.4466 , 1.4041) 0.4258	
Age								
<75	253	90 (35.6)	NE (19.0 , NE)	255	100 (39.2)	16.7 (10.0 , 20.5)	0.6779 (0.5077 , 0.9052) 0.0080	0.7759
>=75	8	4 (50.0)	6.9 (1.8 , NE)	8	4 (50.0)	8.1 (0.9 , 13.8)	0.6904 (0.1517 , 3.1421) 0.6300	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	65 (43.6)	16.4 (12.7 , NE)	160	65 (40.6)	11.8 (8.4 , NE)	0.8009 (0.5638 , 1.1375) 0.2123	0.0010
North America	17	8 (47.1)	NE (1.4 , NE)	17	2 (11.8)	NE (8.1 , NE)	4.2334 (0.8966 , 19.989) 0.0479	
Europe	54	15 (27.8)	NE (16.1 , NE)	50	21 (42.0)	16.7 (9.0 , 19.1)	0.5088 (0.2604 , 0.9942) 0.0447	
Rest of World	41	6 (14.6)	NE (NE , NE)	36	16 (44.4)	8.7 (4.4 , NE)	0.1941 (0.0750 , 0.5025) 0.0002	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	23 (32.4)	NE (14.2 , NE)	72	27 (37.5)	16.7 (8.7 , NE)	0.6866 (0.3922 , 1.2017) 0.1872	0.1860
Black or African American	10	2 (20.0)	NE (1.4 , NE)	9	3 (33.3)	NE (1.4 , NE)	0.3811 (0.0627 , 2.3161) 0.2770	
Asian	152	65 (42.8)	19.0 (12.7 , NE)	162	66 (40.7)	11.8 (8.4 , NE)	0.7884 (0.5558 , 1.1183) 0.1802	
Other	28	4 (14.3)	NE (16.4 , NE)	20	8 (40.0)	11.3 (2.9 , NE)	0.2219 (0.0642 , 0.7668) 0.0098	
ECOG PS								
0	154	55 (35.7)	NE (19.0 , NE)	175	64 (36.6)	16.9 (11.3 , NE)	0.7456 (0.5171 , 1.0752) 0.1147	0.2637
1	106	39 (36.8)	NE (13.7 , NE)	87	40 (46.0)	9.9 (4.4 , 16.7)	0.5525 (0.3528 , 0.8653) 0.0086	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	46 (34.6)	NE (19.0 , NE)	139	56 (40.3)	11.3 (8.7 , NE)	0.6217 (0.4182 , 0.9241) 0.0178	0.4890
Negative	126	48 (38.1)	NE (13.4 , NE)	122	48 (39.3)	16.7 (8.9 , NE)	0.7537 (0.5027 , 1.1302) 0.1691	
Estrogen Receptors								
Positive	129	45 (34.9)	NE (19.0 , NE)	132	56 (42.4)	11.3 (8.4 , NE)	0.5821 (0.3900 , 0.8687) 0.0074	0.3037
Negative	130	49 (37.7)	NE (13.7 , NE)	128	48 (37.5)	16.7 (9.0 , NE)	0.7843 (0.5242 , 1.1734) 0.2351	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	28 (34.6)	NE (14.1 , NE)	92	36 (39.1)	11.3 (8.4 , NE)	0.6578 (0.3987 , 1.0854) 0.0998	0.8697
Negative	177	66 (37.3)	NE (16.1 , NE)	168	67 (39.9)	16.7 (9.0 , 20.5)	0.7001 (0.4957 , 0.9889) 0.0418	
Prior Treatment with Pertuzumab								
Yes	162	68 (42.0)	NE (11.7 , NE)	158	59 (37.3)	16.7 (10.1 , NE)	0.8949 (0.6284 , 1.2745) 0.5361	0.0246
No	99	26 (26.3)	NE (19.0 , NE)	105	45 (42.9)	11.3 (7.1 , NE)	0.4084 (0.2500 , 0.6671) 0.0002	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	68 (36.2)	NE (16.4 , NE)	191	82 (42.9)	11.3 (8.4 , 19.1)	0.6033 (0.4351 , 0.8367) 0.0022	0.1661
>= 3 lines	73	26 (35.6)	NE (12.3 , NE)	72	22 (30.6)	NE (10.1 , NE)	0.9604 (0.5400 , 1.7079) 0.8902	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	65 (41.7)	NE (12.7 , NE)	152	56 (36.8)	19.1 (10.2 , NE)	0.9107 (0.6338 , 1.3086) 0.6129	0.5889
>= 3 lines	6	3 (50.0)	9.9 (1.4 , NE)	6	3 (50.0)	7.2 (0.8 , NE)	0.6811 (0.1362 , 3.4044) 0.6379	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	40 (30.8)	NE (NE , NE)	130	44 (33.8)	NE (9.9 , NE)	0.6394 (0.4103 , 0.9963) 0.0457	0.5019
Mild Impairment	92	42 (45.7)	16.1 (10.9 , NE)	104	48 (46.2)	13.8 (7.1 , 20.5)	0.8496 (0.5607 , 1.2873) 0.4438	
Moderate Impairment	30	12 (40.0)	14.5 (9.7 , NE)	22	10 (45.5)	11.3 (4.2 , NE)	0.6226 (0.2687 , 1.4428) 0.2630	
Hepatic Impairment								
Within Normal Range	208	81 (38.9)	NE (16.1 , NE)	212	88 (41.5)	13.8 (10.0 , 20.5)	0.7093 (0.5220 , 0.9637) 0.0275	0.4068
Mild Impairment	49	13 (26.5)	NE (NE , NE)	49	16 (32.7)	10.1 (5.8 , NE)	0.5349 (0.2538 , 1.1270) 0.0942	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	71 (36.4)	NE (14.5 , NE)	189	68 (36.0)	16.7 (10.3 , 20.5)	0.7924 (0.5654 , 1.1105) 0.1754	0.1188
No	66	23 (34.8)	NE (16.4 , NE)	74	36 (48.6)	9.9 (4.7 , NE)	0.4694 (0.2759 , 0.7985) 0.0044	
Baseline CNS Metastases								
Yes	43	18 (41.9)	13.1 (8.6 , NE)	39	11 (28.2)	NE (5.8 , NE)	1.1007 (0.5102 , 2.3747) 0.8050	0.1064
No	218	76 (34.9)	NE (19.0 , NE)	224	93 (41.5)	13.8 (8.9 , 19.1)	0.6200 (0.4557 , 0.8434) 0.0021	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Role Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	25 (40.3)	14.5 (11.5 , NE)	52	18 (34.6)	11.8 (8.1 , NE)	0.7750 (0.4125 , 1.4561) 0.4263	0.3019
No	199	69 (34.7)	NE (19.0 , NE)	211	86 (40.8)	13.8 (9.9 , 20.5)	0.6380 (0.4627 , 0.8797) 0.0057	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	65 (30.7)	25.6 (19.4 , NE)	206	53 (25.7)	NE (15.2 , NE)	0.7646 (0.5261 , 1.1112) 0.1593	0.3767
>=65	49	15 (30.6)	NE (12.4 , NE)	57	14 (24.6)	NE (12.0 , NE)	1.0326 (0.4968 , 2.1466) 0.9332	
Age								
<75	253	78 (30.8)	25.6 (19.9 , NE)	255	67 (26.3)	NE (14.1 , NE)	0.7871 (0.5637 , 1.0992) 0.1599	0.0830
>=75	8	2 (25.0)	16.4 (3.2 , NE)	8	0	NE (NE , NE)	NE (NE, NE) 0.3173	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	49 (32.9)	25.6 (16.7 , NE)	160	40 (25.0)	NE (13.8 , NE)	0.8266 (0.5376 , 1.2710) 0.3856	0.0109
North America	17	9 (52.9)	12.2 (1.4 , NE)	17	1 (5.9)	NE (NE , NE)	7.8289 (0.9857 , 62.179) 0.0215	
Europe	54	14 (25.9)	NE (19.4 , NE)	50	13 (26.0)	15.2 (12.7 , NE)	0.6454 (0.2958 , 1.4082) 0.2692	
Rest of World	41	8 (19.5)	NE (NE , NE)	36	13 (36.1)	NE (8.4 , NE)	0.4058 (0.1674 , 0.9837) 0.0393	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	18 (25.4)	NE (19.9 , NE)	72	20 (27.8)	NE (12.7 , NE)	0.7288 (0.3821 , 1.3899) 0.3323	0.7241
Black or African American	10	4 (40.0)	NE (1.4 , NE)	9	2 (22.2)	NE (8.4 , NE)	1.6738 (0.3058 , 9.1636) 0.5482	
Asian	152	50 (32.9)	25.6 (16.7 , NE)	162	40 (24.7)	NE (13.8 , NE)	0.8445 (0.5505 , 1.2957) 0.4392	
Other	28	8 (28.6)	NE (15.0 , NE)	20	5 (25.0)	14.1 (12.0 , NE)	0.5590 (0.1763 , 1.7723) 0.3175	
ECOG PS								
0	154	43 (27.9)	25.6 (19.9 , NE)	175	42 (24.0)	NE (15.2 , NE)	0.7571 (0.4890 , 1.1723) 0.2109	0.8728
1	106	37 (34.9)	NE (15.0 , NE)	87	25 (28.7)	15.2 (12.0 , NE)	0.8303 (0.4952 , 1.3924) 0.4815	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	41 (30.8)	26.4 (18.8 , NE)	139	33 (23.7)	NE (15.2 , NE)	0.8703 (0.5453 , 1.3890) 0.5626	0.8916
Negative	126	39 (31.0)	25.6 (16.7 , NE)	122	33 (27.0)	NE (12.7 , NE)	0.7873 (0.4894 , 1.2667) 0.3221	
Estrogen Receptors								
Positive	129	38 (29.5)	26.4 (18.8 , NE)	132	31 (23.5)	NE (15.2 , NE)	0.8376 (0.5159 , 1.3600) 0.4752	0.9250
Negative	130	42 (32.3)	25.6 (16.4 , NE)	128	35 (27.3)	15.2 (12.7 , NE)	0.8026 (0.5065 , 1.2717) 0.3476	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	26 (32.1)	19.9 (16.2 , NE)	92	19 (20.7)	NE (15.2 , NE)	1.0414 (0.5716 , 1.8972) 0.8909	0.2932
Negative	177	54 (30.5)	25.6 (19.4 , NE)	168	47 (28.0)	NE (12.7 , NE)	0.7467 (0.5000 , 1.1152) 0.1518	
Prior Treatment with Pertuzumab								
Yes	162	51 (31.5)	NE (18.8 , NE)	158	35 (22.2)	NE (15.2 , NE)	0.9237 (0.5947 , 1.4347) 0.7275	0.2960
No	99	29 (29.3)	25.6 (16.7 , 26.4)	105	32 (30.5)	14.1 (12.0 , NE)	0.6645 (0.3954 , 1.1165) 0.1200	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	51 (27.1)	26.4 (19.9 , NE)	191	50 (26.2)	NE (14.1 , NE)	0.6740 (0.4524 , 1.0041) 0.0512	0.0879
>= 3 lines	73	29 (39.7)	25.6 (12.2 , 25.6)	72	17 (23.6)	15.2 (12.0 , NE)	1.2565 (0.6803 , 2.3206) 0.4657	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	49 (31.4)	NE (18.8 , NE)	152	35 (23.0)	NE (15.2 , NE)	0.8921 (0.5719 , 1.3917) 0.6183	0.1407
>= 3 lines	6	2 (33.3)	15.0 (7.8 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.2945	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	35 (26.9)	26.4 (NE , NE)	130	31 (23.8)	NE (12.0 , NE)	0.6774 (0.4091 , 1.1216) 0.1278	0.0224
Mild Impairment	92	32 (34.8)	25.6 (14.3 , NE)	104	34 (32.7)	NE (12.7 , NE)	0.8212 (0.5029 , 1.3411) 0.4328	
Moderate Impairment	30	12 (40.0)	15.2 (11.7 , NE)	22	1 (4.5)	NE (13.8 , NE)	5.5331 (0.7166 , 42.724) 0.0650	
Hepatic Impairment								
Within Normal Range	208	66 (31.7)	26.4 (19.4 , NE)	212	59 (27.8)	NE (14.1 , NE)	0.7896 (0.5513 , 1.1307) 0.1974	0.4993
Mild Impairment	49	14 (28.6)	25.6 (14.5 , 25.6)	49	8 (16.3)	NE (11.1 , NE)	0.9886 (0.4050 , 2.4131) 0.9836	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	61 (31.3)	25.6 (18.8 , 26.4)	189	46 (24.3)	NE (12.7 , NE)	0.8663 (0.5850 , 1.2828) 0.4746	0.4756
No	66	19 (28.8)	NE (NE , NE)	74	21 (28.4)	NE (13.8 , NE)	0.6890 (0.3675 , 1.2919) 0.2454	
Baseline CNS Metastases								
Yes	43	12 (27.9)	19.4 (14.3 , NE)	39	12 (30.8)	12.7 (6.9 , NE)	0.4233 (0.1776 , 1.0093) 0.0478	0.2021
No	218	68 (31.2)	25.6 (19.9 , NE)	224	55 (24.6)	NE (15.2 , NE)	0.8927 (0.6212 , 1.2829) 0.5403	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Emotional Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	21 (33.9)	16.5 (14.3 , NE)	52	15 (28.8)	12.7 (10.1 , NE)	0.5531 (0.2706 , 1.1308) 0.1027	0.7487
No	199	59 (29.6)	25.6 (25.6 , NE)	211	52 (24.6)	NE (15.2 , NE)	0.8465 (0.5785 , 1.2385) 0.3918	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	76 (35.8)	19.6 (16.4 , NE)	206	80 (38.8)	14.1 (10.1 , 20.7)	0.5956 (0.4319 , 0.8213) 0.0014	0.3498
>=65	49	21 (42.9)	15.3 (8.3 , NE)	57	24 (42.1)	11.8 (5.1 , NE)	0.8837 (0.4911 , 1.5903) 0.6774	
Age								
<75	253	94 (37.2)	19.6 (15.4 , NE)	255	100 (39.2)	14.1 (10.1 , 20.7)	0.6466 (0.4856 , 0.8610) 0.0027	0.7296
>=75	8	3 (37.5)	20.7 (1.4 , 20.7)	8	4 (50.0)	2.8 (0.9 , NE)	0.3710 (0.0663 , 2.0756) 0.2414	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	62 (41.6)	NE (13.6 , NE)	160	64 (40.0)	12.9 (9.7 , 21.2)	0.7128 (0.4990 , 1.0182) 0.0616	0.2063
North America	17	6 (35.3)	19.6 (1.7 , NE)	17	3 (17.6)	NE (NE , NE)	1.8149 (0.4335 , 7.5989) 0.4077	
Europe	54	17 (31.5)	19.4 (18.8 , NE)	50	22 (44.0)	13.4 (4.2 , NE)	0.4547 (0.2379 , 0.8690) 0.0149	
Rest of World	41	12 (29.3)	NE (15.4 , NE)	36	15 (41.7)	18.0 (4.2 , NE)	0.4527 (0.2104 , 0.9741) 0.0383	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	21 (29.6)	19.9 (19.6 , NE)	72	28 (38.9)	15.2 (6.8 , NE)	0.5579 (0.3149 , 0.9884) 0.0428	0.0367
Black or African American	10	6 (60.0)	13.8 (1.4 , NE)	9	2 (22.2)	18.0 (1.5 , NE)	5.4556 (0.6516 , 45.681) 0.0795	
Asian	152	62 (40.8)	NE (13.6 , NE)	162	64 (39.5)	12.9 (10.1 , 21.2)	0.7168 (0.5019 , 1.0239) 0.0661	
Other	28	8 (28.6)	19.4 (15.2 , NE)	20	10 (50.0)	7.7 (1.4 , NE)	0.2175 (0.0729 , 0.6485) 0.0029	
ECOG PS								
0	154	57 (37.0)	19.6 (15.4 , NE)	175	64 (36.6)	18.0 (11.8 , NE)	0.6796 (0.4728 , 0.9770) 0.0361	0.3416
1	106	40 (37.7)	20.7 (14.1 , NE)	87	40 (46.0)	10.3 (4.8 , 14.1)	0.5591 (0.3578 , 0.8738) 0.0098	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	47 (35.3)	19.6 (15.4 , NE)	139	60 (43.2)	11.8 (9.8 , 15.2)	0.4954 (0.3353 , 0.7318) 0.0003	0.1032
Negative	126	50 (39.7)	19.4 (13.8 , NE)	122	43 (35.2)	20.7 (9.7 , NE)	0.8943 (0.5924 , 1.3501) 0.5977	
Estrogen Receptors								
Positive	129	46 (35.7)	19.6 (15.4 , NE)	132	54 (40.9)	12.9 (10.1 , 18.0)	0.5338 (0.3573 , 0.7974) 0.0019	0.2725
Negative	130	51 (39.2)	19.4 (13.8 , NE)	128	48 (37.5)	20.7 (9.0 , NE)	0.8172 (0.5485 , 1.2175) 0.3211	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	25 (30.9)	19.6 (15.2 , 20.7)	92	37 (40.2)	11.8 (8.7 , NE)	0.4521 (0.2688 , 0.7603) 0.0022	0.1993
Negative	177	72 (40.7)	19.4 (13.6 , NE)	168	65 (38.7)	14.1 (9.7 , NE)	0.7791 (0.5548 , 1.0940) 0.1502	
Prior Treatment with Pertuzumab								
Yes	162	64 (39.5)	19.6 (14.8 , NE)	158	60 (38.0)	13.4 (10.1 , NE)	0.7074 (0.4932 , 1.0146) 0.0595	0.3716
No	99	33 (33.3)	NE (14.8 , NE)	105	44 (41.9)	14.1 (8.4 , 20.7)	0.5531 (0.3500 , 0.8742) 0.0101	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	68 (36.2)	19.6 (15.3 , NE)	191	77 (40.3)	14.1 (9.8 , 20.7)	0.5818 (0.4168 , 0.8120) 0.0013	0.3592
>= 3 lines	73	29 (39.7)	18.8 (9.6 , NE)	72	27 (37.5)	14.1 (7.6 , NE)	0.8248 (0.4859 , 1.4002) 0.4769	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	62 (39.7)	19.6 (14.8 , NE)	152	58 (38.2)	13.4 (9.8 , NE)	0.7218 (0.5002 , 1.0415) 0.0811	0.5996
>= 3 lines	6	2 (33.3)	NE (8.3 , NE)	6	2 (33.3)	10.1 (0.8 , NE)	0.5462 (0.0761 , 3.9214) 0.5417	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	43 (33.1)	NE (18.8 , NE)	130	48 (36.9)	12.9 (9.8 , 18.0)	0.5317 (0.3450 , 0.8195) 0.0037	0.4815
Mild Impairment	92	39 (42.4)	15.3 (10.7 , NE)	104	48 (46.2)	11.8 (8.3 , 21.2)	0.6967 (0.4548 , 1.0673) 0.0967	
Moderate Impairment	30	14 (46.7)	14.5 (10.3 , 20.7)	22	8 (36.4)	20.7 (2.0 , NE)	1.0158 (0.4211 , 2.4500) 0.9713	
Hepatic Impairment								
Within Normal Range	208	81 (38.9)	19.6 (15.2 , NE)	212	88 (41.5)	14.1 (10.1 , 20.7)	0.6383 (0.4694 , 0.8681) 0.0039	0.9876
Mild Impairment	49	16 (32.7)	18.8 (10.3 , NE)	49	16 (32.7)	14.1 (6.8 , NE)	0.6539 (0.3236 , 1.3211) 0.2350	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	78 (40.0)	16.4 (14.5 , 20.7)	189	72 (38.1)	14.1 (10.1 , 21.2)	0.7211 (0.5199 , 1.0002) 0.0497	0.0718
No	66	19 (28.8)	NE (18.8 , NE)	74	32 (43.2)	12.9 (7.1 , NE)	0.4377 (0.2466 , 0.7769) 0.0038	
Baseline CNS Metastases								
Yes	43	19 (44.2)	14.8 (5.9 , NE)	39	13 (33.3)	14.1 (8.3 , NE)	0.9388 (0.4502 , 1.9578) 0.8659	0.1597
No	218	78 (35.8)	20.7 (18.8 , NE)	224	91 (40.6)	13.4 (9.8 , 20.7)	0.5976 (0.4397 , 0.8122) 0.0009	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Cognitive Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	24 (38.7)	19.4 (10.7 , NE)	52	17 (32.7)	14.1 (10.3 , NE)	0.8660 (0.4535 , 1.6538) 0.6623	0.2283
No	199	73 (36.7)	19.9 (16.4 , NE)	211	87 (41.2)	13.4 (9.7 , 21.2)	0.5927 (0.4323 , 0.8125) 0.0010	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	81 (38.2)	19.4 (15.7 , NE)	206	76 (36.9)	14.4 (10.5 , NE)	0.7617 (0.5540 , 1.0473) 0.0919	0.0345
>=65	49	25 (51.0)	11.0 (3.5 , NE)	57	20 (35.1)	NE (10.3 , NE)	1.6169 (0.8967 , 2.9155) 0.1081	
Age								
<75	253	103 (40.7)	18.2 (15.1 , NE)	255	93 (36.5)	15.2 (11.7 , NE)	0.8891 (0.6696 , 1.1804) 0.4115	0.6964
>=75	8	3 (37.5)	NE (1.4 , NE)	8	3 (37.5)	NE (3.1 , NE)	1.6706 (0.3286 , 8.4943) 0.5321	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	64 (43.0)	18.2 (13.6 , NE)	160	60 (37.5)	12.5 (10.3 , NE)	0.9034 (0.6320 , 1.2913) 0.5735	0.6550
North America	17	9 (52.9)	13.1 (1.4 , NE)	17	5 (29.4)	NE (2.8 , NE)	1.5809 (0.5221 , 4.7870) 0.4089	
Europe	54	21 (38.9)	17.5 (11.3 , NE)	50	18 (36.0)	16.7 (9.8 , NE)	0.9797 (0.5198 , 1.8465) 0.9470	
Rest of World	41	12 (29.3)	NE (15.2 , NE)	36	13 (36.1)	15.2 (7.9 , NE)	0.6122 (0.2777 , 1.3496) 0.2159	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	25 (35.2)	NE (13.6 , NE)	72	26 (36.1)	16.7 (8.5 , NE)	0.8183 (0.4701 , 1.4243) 0.4723	0.8782
Black or African American	10	5 (50.0)	10.5 (1.4 , NE)	9	4 (44.4)	NE (0.8 , NE)	0.8801 (0.2331 , 3.3229) 0.8736	
Asian	152	64 (42.1)	18.2 (13.6 , NE)	162	60 (37.0)	12.5 (10.3 , NE)	0.9067 (0.6344 , 1.2959) 0.5871	
Other	28	12 (42.9)	16.4 (11.3 , NE)	20	6 (30.0)	NE (7.1 , NE)	1.1568 (0.4304 , 3.1096) 0.7689	
ECOG PS								
0	154	60 (39.0)	19.4 (15.1 , NE)	175	64 (36.6)	16.6 (10.3 , NE)	0.7918 (0.5542 , 1.1313) 0.1982	0.4376
1	106	46 (43.4)	16.4 (6.9 , NE)	87	32 (36.8)	14.4 (10.3 , NE)	1.0327 (0.6540 , 1.6307) 0.9012	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	56 (42.1)	16.4 (13.6 , NE)	139	51 (36.7)	11.8 (10.3 , NE)	0.8510 (0.5787 , 1.2515) 0.4099	0.8740
Negative	126	50 (39.7)	19.4 (14.5 , NE)	122	44 (36.1)	16.6 (12.0 , NE)	0.9600 (0.6380 , 1.4443) 0.8375	
Estrogen Receptors								
Positive	129	54 (41.9)	16.8 (13.6 , NE)	132	48 (36.4)	11.8 (10.3 , NE)	0.8509 (0.5728 , 1.2640) 0.4211	0.8739
Negative	130	52 (40.0)	19.4 (14.5 , NE)	128	47 (36.7)	15.2 (12.0 , NE)	0.9365 (0.6289 , 1.3944) 0.7383	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	34 (42.0)	15.7 (12.8 , NE)	92	34 (37.0)	11.7 (10.2 , NE)	0.8370 (0.5160 , 1.3578) 0.4721	0.9319
Negative	177	72 (40.7)	19.4 (14.5 , NE)	168	60 (35.7)	16.7 (12.0 , NE)	0.9628 (0.6815 , 1.3603) 0.8228	
Prior Treatment with Pertuzumab								
Yes	162	66 (40.7)	19.4 (14.5 , NE)	158	54 (34.2)	16.7 (11.3 , NE)	0.8946 (0.6208 , 1.2891) 0.5495	0.8885
No	99	40 (40.4)	18.2 (13.6 , NE)	105	42 (40.0)	12.0 (8.4 , NE)	0.9091 (0.5882 , 1.4053) 0.6540	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	70 (37.2)	19.4 (16.4 , NE)	191	76 (39.8)	12.5 (10.2 , NE)	0.6918 (0.4979 , 0.9614) 0.0273	0.0040
>= 3 lines	73	36 (49.3)	12.8 (5.6 , NE)	72	20 (27.8)	NE (11.8 , NE)	1.7872 (1.0310 , 3.0981) 0.0371	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	64 (41.0)	17.5 (14.5 , NE)	152	53 (34.9)	16.7 (11.3 , NE)	0.8829 (0.6096 , 1.2787) 0.5096	0.7886
>= 3 lines	6	2 (33.3)	NE (1.5 , NE)	6	1 (16.7)	NE (0.8 , NE)	1.1724 (0.1059 , 12.978) 0.8967	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	48 (36.9)	NE (16.8 , NE)	130	44 (33.8)	15.2 (10.2 , NE)	0.8113 (0.5339 , 1.2329) 0.3227	0.6298
Mild Impairment	92	43 (46.7)	15.2 (11.1 , NE)	104	43 (41.3)	14.4 (10.3 , NE)	1.0022 (0.6552 , 1.5330) 0.9926	
Moderate Impairment	30	14 (46.7)	15.1 (4.9 , NE)	22	8 (36.4)	11.3 (5.3 , NE)	1.1533 (0.4820 , 2.7594) 0.7485	
Hepatic Impairment								
Within Normal Range	208	85 (40.9)	18.2 (15.2 , NE)	212	82 (38.7)	14.4 (11.3 , NE)	0.8385 (0.6165 , 1.1406) 0.2581	0.3781
Mild Impairment	49	21 (42.9)	14.5 (5.6 , NE)	49	14 (28.6)	15.2 (8.4 , NE)	1.2041 (0.6113 , 2.3717) 0.5898	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	81 (41.5)	16.8 (14.5 , NE)	189	69 (36.5)	15.2 (10.2 , NE)	0.8910 (0.6431 , 1.2345) 0.4822	0.8239
No	66	25 (37.9)	NE (12.5 , NE)	74	27 (36.5)	16.6 (10.5 , NE)	0.8607 (0.4976 , 1.4890) 0.5903	
Baseline CNS Metastases								
Yes	43	20 (46.5)	15.7 (5.6 , 19.4)	39	11 (28.2)	11.8 (10.3 , NE)	1.3528 (0.6351 , 2.8815) 0.4326	0.2203
No	218	86 (39.4)	NE (15.1 , NE)	224	85 (37.9)	15.2 (11.3 , NE)	0.8353 (0.6173 , 1.1303) 0.2403	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Social Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	28 (45.2)	15.7 (5.6 , NE)	52	16 (30.8)	11.8 (8.4 , NE)	1.2373 (0.6582 , 2.3261) 0.5072	0.2191
No	199	78 (39.2)	NE (15.2 , NE)	211	80 (37.9)	15.2 (11.3 , NE)	0.8170 (0.5965 , 1.1191) 0.2045	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	95 (44.8)	15.9 (12.5 , NE)	206	92 (44.7)	11.3 (6.5 , 16.7)	0.7956 (0.5953 , 1.0634) 0.1222	0.6810
>=65	49	24 (49.0)	16.7 (5.6 , 20.7)	57	27 (47.4)	10.4 (4.2 , NE)	0.8665 (0.4949 , 1.5173) 0.6113	
Age								
<75	253	115 (45.5)	16.0 (13.1 , 24.0)	255	117 (45.9)	10.4 (6.5 , 16.7)	0.7896 (0.6085 , 1.0246) 0.0751	0.3275
>=75	8	4 (50.0)	12.8 (1.4 , 20.7)	8	2 (25.0)	NE (0.9 , NE)	1.5628 (0.2600 , 9.3924) 0.6228	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	70 (47.0)	15.9 (11.8 , NE)	160	74 (46.3)	10.4 (5.7 , NE)	0.7984 (0.5730 , 1.1125) 0.1803	0.1281
North America	17	9 (52.9)	10.2 (0.9 , NE)	17	3 (17.6)	NE (5.2 , NE)	2.7704 (0.7431 , 10.329) 0.1128	
Europe	54	23 (42.6)	19.4 (5.7 , 24.0)	50	22 (44.0)	11.7 (4.2 , NE)	0.7740 (0.4260 , 1.4062) 0.4018	
Rest of World	41	17 (41.5)	19.8 (5.6 , NE)	36	20 (55.6)	6.9 (1.4 , NE)	0.5569 (0.2911 , 1.0656) 0.0728	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	34 (47.9)	15.0 (4.4 , 20.7)	72	34 (47.2)	8.3 (5.1 , 16.7)	0.8803 (0.5451 , 1.4217) 0.6095	0.3996
Black or African American	10	5 (50.0)	NE (1.4 , NE)	9	2 (22.2)	NE (4.9 , NE)	2.3481 (0.4520 , 12.199) 0.2958	
Asian	152	70 (46.1)	15.9 (11.9 , NE)	162	74 (45.7)	11.3 (5.7 , NE)	0.8005 (0.5746 , 1.1153) 0.1854	
Other	28	10 (35.7)	19.4 (15.2 , 24.0)	20	9 (45.0)	NE (1.4 , NE)	0.4696 (0.1853 , 1.1900) 0.1057	
ECOG PS								
0	154	75 (48.7)	15.2 (8.4 , 19.4)	175	77 (44.0)	11.7 (7.9 , NE)	0.9365 (0.6797 , 1.2902) 0.6909	0.0882
1	106	44 (41.5)	19.8 (13.1 , NE)	87	42 (48.3)	5.7 (2.8 , NE)	0.6031 (0.3894 , 0.9341) 0.0214	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	61 (45.9)	19.8 (11.8 , NE)	139	64 (46.0)	10.4 (5.7 , NE)	0.7886 (0.5528 , 1.1249) 0.1908	0.7319
Negative	126	57 (45.2)	14.8 (10.2 , 24.0)	122	54 (44.3)	11.3 (5.5 , NE)	0.8363 (0.5737 , 1.2191) 0.3452	
Estrogen Receptors								
Positive	129	59 (45.7)	19.8 (11.8 , NE)	132	62 (47.0)	10.4 (5.5 , NE)	0.7550 (0.5258 , 1.0841) 0.1285	0.5314
Negative	130	59 (45.4)	15.2 (12.0 , 24.0)	128	56 (43.8)	11.3 (5.5 , NE)	0.8551 (0.5905 , 1.2380) 0.3975	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	38 (46.9)	15.2 (5.7 , NE)	92	40 (43.5)	11.8 (5.7 , NE)	0.9197 (0.5878 , 1.4390) 0.7168	0.5175
Negative	177	79 (44.6)	16.4 (13.1 , 24.0)	168	78 (46.4)	9.6 (5.5 , 20.5)	0.7589 (0.5528 , 1.0420) 0.0862	
Prior Treatment with Pertuzumab								
Yes	162	76 (46.9)	16.4 (12.5 , 20.7)	158	73 (46.2)	10.4 (7.1 , 20.5)	0.7767 (0.5596 , 1.0779) 0.1288	0.8613
No	99	43 (43.4)	15.9 (8.9 , NE)	105	46 (43.8)	11.8 (4.9 , NE)	0.8154 (0.5362 , 1.2402) 0.3375	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	84 (44.7)	16.4 (14.5 , 20.7)	191	91 (47.6)	8.6 (5.3 , 16.7)	0.7243 (0.5361 , 0.9787) 0.0355	0.1927
>= 3 lines	73	35 (47.9)	12.0 (5.6 , NE)	72	28 (38.9)	12.7 (5.8 , NE)	1.0874 (0.6589 , 1.7943) 0.7520	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	73 (46.8)	16.4 (12.5 , 20.7)	152	71 (46.7)	10.4 (7.1 , 16.7)	0.7721 (0.5529 , 1.0782) 0.1272	0.9917
>= 3 lines	6	3 (50.0)	8.3 (1.4 , NE)	6	2 (33.3)	NE (0.7 , NE)	0.7792 (0.1276 , 4.7589) 0.7948	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	55 (42.3)	19.4 (15.0 , NE)	130	57 (43.8)	12.7 (5.5 , NE)	0.7088 (0.4850 , 1.0360) 0.0739	0.2233
Mild Impairment	92	46 (50.0)	13.1 (7.0 , 16.7)	104	53 (51.0)	10.4 (4.9 , 20.5)	0.9050 (0.6085 , 1.3459) 0.6164	
Moderate Impairment	30	16 (53.3)	15.2 (4.1 , 24.0)	22	6 (27.3)	NE (2.0 , NE)	1.4329 (0.5547 , 3.7018) 0.4482	
Hepatic Impairment								
Within Normal Range	208	100 (48.1)	15.9 (12.1 , 19.8)	212	100 (47.2)	10.4 (6.5 , 16.7)	0.8103 (0.6112 , 1.0742) 0.1433	0.7282
Mild Impairment	49	19 (38.8)	NE (7.3 , NE)	49	19 (38.8)	12.7 (2.8 , NE)	0.7425 (0.3926 , 1.4043) 0.3623	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	88 (45.1)	16.0 (12.5 , 20.7)	189	82 (43.4)	11.8 (6.2 , NE)	0.8589 (0.6339 , 1.1638) 0.3238	0.4343
No	66	31 (47.0)	16.7 (8.3 , NE)	74	37 (50.0)	8.1 (3.3 , NE)	0.6873 (0.4222 , 1.1187) 0.1301	
Baseline CNS Metastases								
Yes	43	17 (39.5)	19.4 (8.4 , NE)	39	19 (48.7)	8.3 (3.6 , NE)	0.6080 (0.3075 , 1.2023) 0.1471	0.4985
No	218	102 (46.8)	15.3 (11.9 , 24.0)	224	100 (44.6)	11.7 (6.9 , 20.5)	0.8397 (0.6355 , 1.1095) 0.2221	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Fatigue

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	23 (37.1)	19.4 (13.1 , NE)	52	25 (48.1)	9.6 (4.2 , NE)	0.5807 (0.3223 , 1.0463) 0.0646	0.3310
No	199	96 (48.2)	15.0 (10.2 , 24.0)	211	94 (44.5)	11.7 (6.2 , NE)	0.8668 (0.6504 , 1.1551) 0.3321	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	120 (56.6)	7.0 (4.2 , 12.5)	206	60 (29.1)	NE (NE , NE)	2.0968 (1.5357 , 2.8629) <.0001	0.4685
>=65	49	25 (51.0)	11.1 (2.9 , NE)	57	12 (21.1)	NE (NE , NE)	2.6790 (1.3441 , 5.3396) 0.0036	
Age								
<75	253	141 (55.7)	7.9 (4.4 , 12.5)	255	72 (28.2)	NE (NE , NE)	2.1397 (1.6097 , 2.8443) <.0001	0.0417
>=75	8	4 (50.0)	5.2 (0.8 , NE)	8	0	NE (NE , NE)	NE (NE, NE) 0.0228	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	85 (57.0)	7.9 (4.3 , 12.5)	160	46 (28.8)	NE (11.3 , NE)	2.1477 (1.4988 , 3.0774) <.0001	0.9151
North America	17	9 (52.9)	3.8 (0.9 , NE)	17	3 (17.6)	NE (5.7 , NE)	3.4528 (0.9328 , 12.780) 0.0476	
Europe	54	26 (48.1)	15.2 (2.8 , NE)	50	11 (22.0)	NE (NE , NE)	2.3087 (1.1363 , 4.6907) 0.0171	
Rest of World	41	25 (61.0)	4.4 (1.4 , 18.7)	36	12 (33.3)	NE (7.2 , NE)	1.9649 (0.9845 , 3.9213) 0.0552	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	42 (59.2)	4.2 (1.5 , 14.3)	72	15 (20.8)	NE (NE , NE)	3.5023 (1.9385 , 6.3276) <.0001	0.1629
Black or African American	10	4 (40.0)	NE (1.4 , NE)	9	3 (33.3)	NE (0.8 , NE)	0.9235 (0.2035 , 4.1905) 0.9197	
Asian	152	85 (55.9)	8.2 (4.3 , 12.5)	162	47 (29.0)	NE (11.3 , NE)	2.0925 (1.4640 , 2.9908) <.0001	
Other	28	14 (50.0)	17.8 (1.7 , NE)	20	7 (35.0)	NE (8.3 , NE)	1.2692 (0.5073 , 3.1757) 0.6126	
ECOG PS								
0	154	86 (55.8)	8.2 (4.4 , 15.2)	175	51 (29.1)	NE (NE , NE)	2.0792 (1.4687 , 2.9435) <.0001	0.5285
1	106	59 (55.7)	5.6 (3.2 , 16.8)	87	21 (24.1)	NE (11.7 , NE)	2.4941 (1.5142 , 4.1083) 0.0002	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	83 (62.4)	5.1 (3.0 , 8.8)	139	40 (28.8)	NE (NE , NE)	2.4791 (1.6984 , 3.6187) <.0001	0.4672
Negative	126	62 (49.2)	11.1 (4.7 , NE)	122	32 (26.2)	NE (12.0 , NE)	1.9719 (1.2853 , 3.0254) 0.0016	
Estrogen Receptors								
Positive	129	80 (62.0)	5.1 (3.0 , 8.8)	132	36 (27.3)	NE (NE , NE)	2.5790 (1.7385 , 3.8259) <.0001	0.2931
Negative	130	65 (50.0)	11.1 (4.4 , NE)	128	36 (28.1)	NE (11.7 , NE)	1.8705 (1.2428 , 2.8151) 0.0024	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	55 (67.9)	4.1 (1.5 , 7.2)	92	29 (31.5)	NE (9.7 , NE)	2.6727 (1.7021 , 4.1967) <.0001	0.4783
Negative	177	89 (50.3)	12.5 (6.0 , 19.4)	168	42 (25.0)	NE (NE , NE)	2.0948 (1.4495 , 3.0275) <.0001	
Prior Treatment with Pertuzumab								
Yes	162	92 (56.8)	7.0 (4.1 , 14.3)	158	40 (25.3)	NE (NE , NE)	2.5536 (1.7600 , 3.7050) <.0001	0.3162
No	99	53 (53.5)	9.8 (4.4 , 17.8)	105	32 (30.5)	NE (11.2 , NE)	1.8364 (1.1834 , 2.8498) 0.0065	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	103 (54.8)	7.9 (4.3 , 17.8)	191	52 (27.2)	NE (NE , NE)	2.2268 (1.5933 , 3.1121) <.0001	0.9905
>= 3 lines	73	42 (57.5)	8.2 (3.8 , 12.5)	72	20 (27.8)	NE (10.8 , NE)	2.1601 (1.2669 , 3.6833) 0.0037	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	87 (55.8)	7.1 (4.1 , 15.2)	152	39 (25.7)	NE (NE , NE)	2.4888 (1.7041 , 3.6349) <.0001	0.5468
>= 3 lines	6	5 (83.3)	3.0 (0.8 , NE)	6	1 (16.7)	NE (0.8 , NE)	3.9892 (0.4636 , 34.327) 0.1735	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	72 (55.4)	8.5 (4.2 , 19.4)	130	39 (30.0)	NE (11.3 , NE)	1.8485 (1.2468 , 2.7404) 0.0020	0.3404
Mild Impairment	92	56 (60.9)	6.0 (2.0 , 11.1)	104	30 (28.8)	NE (11.7 , NE)	2.5250 (1.6191 , 3.9378) <.0001	
Moderate Impairment	30	13 (43.3)	15.2 (3.1 , NE)	22	2 (9.1)	NE (NE , NE)	4.3864 (0.9885 , 19.464) 0.0332	
Hepatic Impairment								
Within Normal Range	208	121 (58.2)	7.2 (4.3 , 12.5)	212	57 (26.9)	NE (NE , NE)	2.4262 (1.7692 , 3.3272) <.0001	0.1754
Mild Impairment	49	24 (49.0)	11.1 (2.9 , NE)	49	15 (30.6)	NE (6.6 , NE)	1.4752 (0.7730 , 2.8155) 0.2384	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	108 (55.4)	7.9 (4.4 , 12.5)	189	49 (25.9)	NE (NE , NE)	2.3256 (1.6579 , 3.2624) <.0001	0.5609
No	66	37 (56.1)	7.0 (2.8 , NE)	74	23 (31.1)	NE (9.7 , NE)	1.9687 (1.1682 , 3.3180) 0.0097	
Baseline CNS Metastases								
Yes	43	25 (58.1)	4.6 (3.1 , 16.8)	39	10 (25.6)	NE (9.0 , NE)	2.4935 (1.1904 , 5.2233) 0.0126	0.7101
No	218	120 (55.0)	8.3 (4.3 , 15.2)	224	62 (27.7)	NE (NE , NE)	2.1675 (1.5941 , 2.9471) <.0001	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Nausea and Vomiting

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	28 (45.2)	16.8 (4.4 , NE)	52	12 (23.1)	NE (9.6 , NE)	1.9427 (0.9811 , 3.8469) 0.0531	0.7120
No	199	117 (58.8)	7.0 (3.2 , 9.8)	211	60 (28.4)	NE (NE , NE)	2.3086 (1.6900 , 3.1535) <.0001	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	79 (37.3)	24.6 (16.6 , NE)	206	78 (37.9)	12.9 (9.9 , 21.0)	0.6994 (0.5087 , 0.9616) 0.0270	0.0031
>=65	49	24 (49.0)	10.7 (3.5 , NE)	57	15 (26.3)	NE (10.3 , NE)	2.0107 (1.0538 , 3.8363) 0.0310	
Age								
<75	253	100 (39.5)	18.5 (16.4 , NE)	255	91 (35.7)	21.0 (11.1 , NE)	0.8617 (0.6470 , 1.1476) 0.3082	0.3854
>=75	8	3 (37.5)	8.3 (0.8 , NE)	8	2 (25.0)	NE (8.1 , NE)	2.0448 (0.3403 , 12.285) 0.4246	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	64 (43.0)	17.3 (11.9 , NE)	160	60 (37.5)	11.9 (9.1 , NE)	0.8693 (0.6084 , 1.2420) 0.4403	0.2163
North America	17	9 (52.9)	10.2 (3.0 , NE)	17	3 (17.6)	NE (NE , NE)	2.7143 (0.7298 , 10.095) 0.1209	
Europe	54	17 (31.5)	NE (16.4 , NE)	50	15 (30.0)	NE (8.9 , NE)	0.8453 (0.4179 , 1.7098) 0.6408	
Rest of World	41	13 (31.7)	NE (11.7 , NE)	36	15 (41.7)	21.0 (5.6 , 21.0)	0.6107 (0.2902 , 1.2848) 0.1875	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	24 (33.8)	NE (11.7 , NE)	72	23 (31.9)	21.0 (10.3 , 21.0)	0.9003 (0.5071 , 1.5983) 0.7162	0.1084
Black or African American	10	7 (70.0)	6.5 (3.0 , NE)	9	2 (22.2)	NE (2.8 , NE)	3.5901 (0.7367 , 17.496) 0.0919	
Asian	152	65 (42.8)	17.3 (11.9 , NE)	162	60 (37.0)	12.9 (9.8 , NE)	0.8938 (0.6265 , 1.2750) 0.5353	
Other	28	7 (25.0)	NE (16.4 , NE)	20	8 (40.0)	9.9 (1.4 , NE)	0.4069 (0.1453 , 1.1394) 0.0782	
ECOG PS								
0	154	56 (36.4)	NE (16.6 , NE)	175	68 (38.9)	13.8 (9.1 , NE)	0.7155 (0.5009 , 1.0219) 0.0644	0.0455
1	106	47 (44.3)	16.4 (10.2 , NE)	87	25 (28.7)	NE (10.3 , NE)	1.2350 (0.7542 , 2.0224) 0.4011	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	50 (37.6)	NE (16.4 , NE)	139	49 (35.3)	NE (9.9 , NE)	0.8238 (0.5541 , 1.2249) 0.3389	0.5122
Negative	126	53 (42.1)	18.2 (12.4 , NE)	122	43 (35.2)	21.0 (10.1 , NE)	0.9525 (0.6334 , 1.4323) 0.8117	
Estrogen Receptors								
Positive	129	48 (37.2)	NE (16.4 , NE)	132	47 (35.6)	NE (8.9 , NE)	0.7883 (0.5254 , 1.1826) 0.2506	0.3850
Negative	130	55 (42.3)	18.2 (12.0 , NE)	128	45 (35.2)	21.0 (10.1 , NE)	0.9751 (0.6542 , 1.4535) 0.8968	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	27 (33.3)	NE (11.9 , NE)	92	30 (32.6)	NE (8.5 , NE)	0.7478 (0.4426 , 1.2634) 0.2742	0.4971
Negative	177	76 (42.9)	17.3 (13.0 , NE)	168	62 (36.9)	21.0 (10.1 , NE)	0.9401 (0.6699 , 1.3193) 0.7213	
Prior Treatment with Pertuzumab								
Yes	162	71 (43.8)	18.5 (10.8 , NE)	158	58 (36.7)	12.9 (10.1 , NE)	0.9556 (0.6731 , 1.3566) 0.7972	0.3856
No	99	32 (32.3)	NE (16.4 , NE)	105	35 (33.3)	NE (8.5 , NE)	0.7540 (0.4655 , 1.2212) 0.2489	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	76 (40.4)	18.5 (14.5 , NE)	191	74 (38.7)	12.9 (9.9 , NE)	0.8072 (0.5844 , 1.1149) 0.1920	0.2929
>= 3 lines	73	27 (37.0)	NE (12.0 , NE)	72	19 (26.4)	NE (11.8 , NE)	1.1627 (0.6433 , 2.1016) 0.6175	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	69 (44.2)	16.6 (10.8 , NE)	152	58 (38.2)	11.9 (10.0 , NE)	0.9385 (0.6594 , 1.3358) 0.7222	0.1531
>= 3 lines	6	2 (33.3)	NE (8.6 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.3431	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	48 (36.9)	24.6 (16.6 , NE)	130	48 (36.9)	12.9 (9.8 , NE)	0.6706 (0.4448 , 1.0109) 0.0545	0.0847
Mild Impairment	92	41 (44.6)	16.4 (10.2 , NE)	104	39 (37.5)	21.0 (8.9 , NE)	1.1213 (0.7228 , 1.7394) 0.6097	
Moderate Impairment	30	14 (46.7)	14.5 (5.6 , NE)	22	5 (22.7)	NE (8.1 , NE)	1.7145 (0.6169 , 4.7648) 0.2955	
Hepatic Impairment								
Within Normal Range	208	87 (41.8)	18.5 (14.5 , NE)	212	79 (37.3)	21.0 (10.7 , NE)	0.9073 (0.6669 , 1.2344) 0.5345	0.6208
Mild Impairment	49	16 (32.7)	NE (10.2 , NE)	49	14 (28.6)	NE (6.6 , NE)	0.7479 (0.3639 , 1.5371) 0.4292	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	81 (41.5)	17.3 (12.0 , NE)	189	69 (36.5)	13.8 (9.9 , NE)	0.9216 (0.6669 , 1.2736) 0.6204	0.4569
No	66	22 (33.3)	NE (18.5 , NE)	74	24 (32.4)	NE (11.1 , NE)	0.7401 (0.4115 , 1.3311) 0.3150	
Baseline CNS Metastases								
Yes	43	20 (46.5)	13.1 (4.2 , NE)	39	14 (35.9)	10.7 (6.6 , 21.0)	1.0097 (0.5005 , 2.0372) 0.9828	0.5646
No	218	83 (38.1)	24.6 (16.4 , NE)	224	79 (35.3)	NE (11.1 , NE)	0.8527 (0.6252 , 1.1629) 0.3149	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Pain

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	26 (41.9)	16.6 (10.7 , NE)	52	20 (38.5)	10.1 (6.9 , 21.0)	0.7737 (0.4216 , 1.4199) 0.3992	0.9537
No	199	77 (38.7)	24.6 (16.4 , NE)	211	73 (34.6)	NE (11.8 , NE)	0.8900 (0.6448 , 1.2282) 0.4816	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	50 (23.6)	NE (NE , NE)	206	51 (24.8)	NE (16.1 , NE)	0.6903 (0.4639 , 1.0272) 0.0662	0.0354
>=65	49	19 (38.8)	17.7 (11.3 , NE)	57	13 (22.8)	20.5 (13.8 , NE)	1.6022 (0.7881 , 3.2572) 0.1922	
Age								
<75	253	64 (25.3)	NE (NE , NE)	255	62 (24.3)	NE (16.6 , NE)	0.7748 (0.5435 , 1.1046) 0.1570	0.0727
>=75	8	5 (62.5)	9.8 (0.8 , 17.7)	8	2 (25.0)	12.8 (11.7 , 13.8)	1.5416 (0.2508 , 9.4764) 0.6380	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	43 (28.9)	NE (NE , NE)	160	38 (23.8)	20.5 (18.0 , NE)	0.9166 (0.5880 , 1.4288) 0.6997	0.0724
North America	17	9 (52.9)	12.2 (3.0 , NE)	17	4 (23.5)	NE (1.9 , NE)	1.7200 (0.5272 , 5.6109) 0.3628	
Europe	54	13 (24.1)	NE (17.7 , NE)	50	11 (22.0)	NE (13.8 , NE)	0.6823 (0.2952 , 1.5772) 0.3684	
Rest of World	41	4 (9.8)	NE (NE , NE)	36	11 (30.6)	16.6 (11.7 , NE)	0.2447 (0.0773 , 0.7746) 0.0096	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	19 (26.8)	NE (17.7 , NE)	72	20 (27.8)	16.6 (13.8 , NE)	0.6701 (0.3526 , 1.2736) 0.2195	0.8334
Black or African American	10	2 (20.0)	NE (3.1 , NE)	9	2 (22.2)	NE (0.8 , NE)	0.6219 (0.0866 , 4.4667) 0.6337	
Asian	152	43 (28.3)	NE (NE , NE)	162	38 (23.5)	20.5 (18.0 , NE)	0.9167 (0.5880 , 1.4291) 0.7000	
Other	28	5 (17.9)	NE (18.5 , NE)	20	4 (20.0)	NE (7.0 , NE)	0.6792 (0.1778 , 2.5942) 0.5697	
ECOG PS								
0	154	36 (23.4)	NE (NE , NE)	175	37 (21.1)	NE (16.6 , NE)	0.8287 (0.5197 , 1.3214) 0.4288	0.7753
1	106	33 (31.1)	18.5 (16.4 , NE)	87	27 (31.0)	NE (10.3 , NE)	0.6837 (0.4045 , 1.1557) 0.1518	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	36 (27.1)	NE (18.6 , NE)	139	36 (25.9)	20.5 (15.2 , NE)	0.7897 (0.4942 , 1.2619) 0.3225	0.9341
Negative	126	32 (25.4)	NE (18.5 , NE)	122	27 (22.1)	NE (18.0 , NE)	0.8334 (0.4942 , 1.4055) 0.4905	
Estrogen Receptors								
Positive	129	35 (27.1)	NE (18.6 , NE)	132	32 (24.2)	20.5 (14.8 , NE)	0.8315 (0.5109 , 1.3534) 0.4572	0.7441
Negative	130	33 (25.4)	NE (18.5 , NE)	128	31 (24.2)	NE (16.6 , NE)	0.7654 (0.4641 , 1.2623) 0.2895	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	23 (28.4)	NE (17.7 , NE)	92	20 (21.7)	16.6 (14.8 , NE)	1.0402 (0.5670 , 1.9084) 0.8970	0.2758
Negative	177	45 (25.4)	NE (NE , NE)	168	43 (25.6)	20.5 (18.0 , NE)	0.7139 (0.4664 , 1.0927) 0.1187	
Prior Treatment with Pertuzumab								
Yes	162	46 (28.4)	NE (NE , NE)	158	40 (25.3)	18.0 (14.8 , NE)	0.7823 (0.5048 , 1.2122) 0.2702	0.8492
No	99	23 (23.2)	NE (NE , NE)	105	24 (22.9)	NE (16.1 , NE)	0.8054 (0.4525 , 1.4336) 0.4587	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	46 (24.5)	NE (NE , NE)	191	51 (26.7)	20.5 (16.1 , NE)	0.6589 (0.4393 , 0.9883) 0.0421	0.0561
>= 3 lines	73	23 (31.5)	NE (15.8 , NE)	72	13 (18.1)	NE (15.2 , NE)	1.3978 (0.6996 , 2.7927) 0.3416	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	44 (28.2)	NE (18.6 , NE)	152	38 (25.0)	18.0 (14.8 , NE)	0.7853 (0.5009 , 1.2310) 0.2903	0.5600
>= 3 lines	6	2 (33.3)	NE (1.5 , NE)	6	2 (33.3)	NE (0.7 , NE)	0.5319 (0.0742 , 3.8112) 0.5232	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	27 (20.8)	NE (NE , NE)	130	33 (25.4)	16.6 (14.0 , NE)	0.5336 (0.3154 , 0.9026) 0.0174	0.0209
Mild Impairment	92	31 (33.7)	18.6 (16.1 , NE)	104	28 (26.9)	20.5 (14.8 , NE)	1.0834 (0.6477 , 1.8120) 0.7598	
Moderate Impairment	30	10 (33.3)	18.5 (14.5 , NE)	22	2 (9.1)	NE (NE , NE)	3.0522 (0.6674 , 13.959) 0.1301	
Hepatic Impairment								
Within Normal Range	208	62 (29.8)	NE (18.6 , NE)	212	52 (24.5)	20.5 (15.2 , NE)	0.9047 (0.6211 , 1.3178) 0.5994	0.0902
Mild Impairment	49	7 (14.3)	NE (NE , NE)	49	12 (24.5)	NE (16.6 , NE)	0.4192 (0.1642 , 1.0699) 0.0610	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	51 (26.2)	NE (NE , NE)	189	41 (21.7)	NE (16.1 , NE)	0.9263 (0.6101 , 1.4063) 0.7191	0.2544
No	66	18 (27.3)	NE (18.5 , NE)	74	23 (31.1)	18.0 (13.8 , NE)	0.5959 (0.3176 , 1.1179) 0.1034	
Baseline CNS Metastases								
Yes	43	7 (16.3)	NE (NE , NE)	39	12 (30.8)	NE (6.3 , NE)	0.3015 (0.1110 , 0.8188) 0.0136	0.0509
No	218	62 (28.4)	NE (NE , NE)	224	52 (23.2)	20.5 (16.6 , NE)	0.9304 (0.6402 , 1.3522) 0.7035	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Dyspnoea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	15 (24.2)	NE (15.6 , NE)	52	14 (26.9)	NE (11.7 , NE)	0.5673 (0.2623 , 1.2269) 0.1449	0.4959
No	199	54 (27.1)	NE (NE , NE)	211	50 (23.7)	20.5 (16.6 , NE)	0.8648 (0.5855 , 1.2773) 0.4634	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	61 (28.8)	NE (NE , NE)	206	62 (30.1)	NE (12.7 , NE)	0.7110 (0.4971 , 1.0169) 0.0608	0.5823
>=65	49	9 (18.4)	NE (19.7 , NE)	57	15 (26.3)	NE (11.7 , NE)	0.5687 (0.2479 , 1.3045) 0.1775	
Age								
<75	253	69 (27.3)	NE (NE , NE)	255	77 (30.2)	NE (NE , NE)	0.6753 (0.4863 , 0.9377) 0.0184	0.1765
>=75	8	1 (12.5)	NE (2.9 , NE)	8	0	NE (NE , NE)	NE (NE, NE) 0.3173	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	37 (24.8)	NE (NE , NE)	160	49 (30.6)	NE (12.6 , NE)	0.5849 (0.3795 , 0.9016) 0.0141	0.4586
North America	17	7 (41.2)	NE (2.5 , NE)	17	4 (23.5)	NE (4.4 , NE)	1.4108 (0.4114 , 4.8377) 0.5805	
Europe	54	16 (29.6)	NE (14.3 , NE)	50	13 (26.0)	NE (11.4 , NE)	0.8951 (0.4265 , 1.8786) 0.7678	
Rest of World	41	10 (24.4)	NE (NE , NE)	36	11 (30.6)	NE (9.6 , NE)	0.6587 (0.2791 , 1.5547) 0.3367	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	22 (31.0)	NE (14.3 , NE)	72	22 (30.6)	NE (11.4 , NE)	0.8255 (0.4560 , 1.4947) 0.5239	0.5715
Black or African American	10	4 (40.0)	NE (1.4 , NE)	9	2 (22.2)	NE (8.4 , NE)	1.7885 (0.3271 , 9.7778) 0.4963	
Asian	152	38 (25.0)	NE (NE , NE)	162	49 (30.2)	NE (NE , NE)	0.6081 (0.3959 , 0.9341) 0.0218	
Other	28	6 (21.4)	NE (19.4 , NE)	20	4 (20.0)	NE (8.4 , NE)	0.7518 (0.2072 , 2.7276) 0.6643	
ECOG PS								
0	154	42 (27.3)	NE (19.7 , NE)	175	54 (30.9)	NE (12.7 , NE)	0.6428 (0.4273 , 0.9670) 0.0326	0.6779
1	106	28 (26.4)	NE (NE , NE)	87	23 (26.4)	NE (NE , NE)	0.7922 (0.4550 , 1.3791) 0.4092	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	35 (26.3)	NE (NE , NE)	139	44 (31.7)	NE (12.5 , NE)	0.6066 (0.3875 , 0.9494) 0.0273	0.3798
Negative	126	35 (27.8)	NE (19.4 , NE)	122	32 (26.2)	NE (NE , NE)	0.8411 (0.5180 , 1.3657) 0.4847	
Estrogen Receptors								
Positive	129	35 (27.1)	NE (NE , NE)	132	42 (31.8)	NE (12.5 , NE)	0.6160 (0.3916 , 0.9692) 0.0346	0.4920
Negative	130	35 (26.9)	NE (19.4 , NE)	128	34 (26.6)	NE (NE , NE)	0.8033 (0.4984 , 1.2949) 0.3680	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	24 (29.6)	NE (NE , NE)	92	25 (27.2)	NE (12.7 , NE)	0.8904 (0.5067 , 1.5647) 0.6876	0.3230
Negative	177	46 (26.0)	NE (19.7 , NE)	168	51 (30.4)	NE (NE , NE)	0.6216 (0.4152 , 0.9307) 0.0200	
Prior Treatment with Pertuzumab								
Yes	162	49 (30.2)	NE (19.7 , NE)	158	46 (29.1)	NE (NE , NE)	0.7466 (0.4952 , 1.1258) 0.1622	0.3757
No	99	21 (21.2)	NE (NE , NE)	105	31 (29.5)	NE (12.7 , NE)	0.5664 (0.3244 , 0.9890) 0.0423	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	50 (26.6)	NE (NE , NE)	191	58 (30.4)	NE (NE , NE)	0.6547 (0.4468 , 0.9594) 0.0286	0.5958
>= 3 lines	73	20 (27.4)	NE (19.7 , NE)	72	19 (26.4)	NE (12.7 , NE)	0.8053 (0.4261 , 1.5218) 0.5034	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	49 (31.4)	NE (19.4 , NE)	152	44 (28.9)	NE (NE , NE)	0.7946 (0.5244 , 1.2038) 0.2772	0.0320
>= 3 lines	6	0	NE (NE , NE)	6	2 (33.3)	NE (1.4 , NE)	0.0000 (NE, NE) 0.0624	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	29 (22.3)	NE (NE , NE)	130	40 (30.8)	NE (12.6 , NE)	0.4984 (0.3058 , 0.8125) 0.0044	0.1438
Mild Impairment	92	31 (33.7)	NE (14.5 , NE)	104	33 (31.7)	NE (12.5 , NE)	0.8639 (0.5280 , 1.4137) 0.5644	
Moderate Impairment	30	7 (23.3)	NE (19.7 , NE)	22	3 (13.6)	NE (NE , NE)	1.3772 (0.3550 , 5.3429) 0.6452	
Hepatic Impairment								
Within Normal Range	208	60 (28.8)	NE (NE , NE)	212	67 (31.6)	NE (NE , NE)	0.6940 (0.4880 , 0.9869) 0.0410	0.9406
Mild Impairment	49	10 (20.4)	NE (NE , NE)	49	10 (20.4)	NE (12.5 , NE)	0.7002 (0.2890 , 1.6966) 0.4274	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	51 (26.2)	NE (NE , NE)	189	53 (28.0)	NE (12.7 , NE)	0.7223 (0.4898 , 1.0654) 0.0991	0.6575
No	66	19 (28.8)	NE (19.4 , NE)	74	24 (32.4)	NE (11.7 , NE)	0.6211 (0.3377 , 1.1424) 0.1233	
Baseline CNS Metastases								
Yes	43	11 (25.6)	NE (19.4 , NE)	39	14 (35.9)	NE (3.7 , NE)	0.5212 (0.2330 , 1.1658) 0.1069	0.3189
No	218	59 (27.1)	NE (NE , NE)	224	63 (28.1)	NE (NE , NE)	0.7346 (0.5134 , 1.0510) 0.0904	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Insomnia

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	17 (27.4)	NE (19.4 , NE)	52	21 (40.4)	11.3 (4.8 , NE)	0.4871 (0.2538 , 0.9347) 0.0271	0.2410
No	199	53 (26.6)	NE (NE , NE)	211	56 (26.5)	NE (NE , NE)	0.7625 (0.5219 , 1.1139) 0.1597	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	101 (47.6)	15.2 (6.9 , NE)	206	60 (29.1)	19.1 (13.8 , NE)	1.5919 (1.1538 , 2.1963) 0.0044	0.3720
>=65	49	18 (36.7)	20.1 (5.6 , NE)	57	18 (31.6)	20.5 (10.1 , NE)	1.1662 (0.6052 , 2.2470) 0.6503	
Age								
<75	253	115 (45.5)	16.4 (9.9 , NE)	255	75 (29.4)	19.1 (13.8 , NE)	1.4893 (1.1112 , 1.9961) 0.0076	0.6954
>=75	8	4 (50.0)	1.6 (0.8 , NE)	8	3 (37.5)	NE (0.9 , NE)	1.8651 (0.4114 , 8.4562) 0.4294	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	73 (49.0)	15.6 (5.6 , NE)	160	51 (31.9)	19.1 (12.4 , NE)	1.5045 (1.0498 , 2.1562) 0.0258	0.3793
North America	17	10 (58.8)	3.0 (1.5 , NE)	17	3 (17.6)	NE (11.3 , NE)	4.1137 (1.1275 , 15.009) 0.0206	
Europe	54	17 (31.5)	NE (15.1 , NE)	50	12 (24.0)	NE (12.6 , NE)	1.1388 (0.5390 , 2.4061) 0.7373	
Rest of World	41	19 (46.3)	NE (2.9 , NE)	36	12 (33.3)	16.7 (9.0 , NE)	1.4402 (0.6978 , 2.9725) 0.3268	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	29 (40.8)	NE (4.4 , NE)	72	20 (27.8)	16.1 (12.6 , NE)	1.5250 (0.8603 , 2.7031) 0.1493	0.9865
Black or African American	10	6 (60.0)	5.0 (1.5 , NE)	9	3 (33.3)	16.7 (0.8 , NE)	2.1593 (0.5244 , 8.8907) 0.2758	
Asian	152	73 (48.0)	15.6 (5.6 , NE)	162	51 (31.5)	20.5 (12.4 , NE)	1.5001 (1.0466 , 2.1500) 0.0270	
Other	28	11 (39.3)	NE (5.6 , NE)	20	4 (20.0)	NE (5.6 , NE)	1.5811 (0.4956 , 5.0444) 0.4358	
ECOG PS								
0	154	71 (46.1)	16.4 (9.8 , NE)	175	50 (28.6)	19.1 (13.8 , NE)	1.5650 (1.0867 , 2.2536) 0.0158	0.4089
1	106	48 (45.3)	NE (4.4 , NE)	87	28 (32.2)	NE (11.7 , NE)	1.3577 (0.8506 , 2.1670) 0.1974	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	66 (49.6)	15.2 (4.3 , NE)	139	42 (30.2)	20.5 (13.8 , NE)	1.6454 (1.1142 , 2.4300) 0.0118	0.5283
Negative	126	53 (42.1)	16.4 (7.4 , NE)	122	36 (29.5)	19.1 (11.7 , NE)	1.3633 (0.8908 , 2.0865) 0.1537	
Estrogen Receptors								
Positive	129	63 (48.8)	19.0 (4.3 , NE)	132	39 (29.5)	16.7 (13.8 , NE)	1.6445 (1.0991 , 2.4604) 0.0150	0.5108
Negative	130	56 (43.1)	15.6 (7.4 , NE)	128	39 (30.5)	19.1 (11.7 , NE)	1.3465 (0.8927 , 2.0311) 0.1565	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	47 (58.0)	4.4 (2.8 , 15.2)	92	33 (35.9)	16.1 (11.3 , NE)	1.7696 (1.1315 , 2.7675) 0.0117	0.5086
Negative	177	72 (40.7)	20.1 (15.5 , NE)	168	45 (26.8)	20.5 (19.1 , NE)	1.4269 (0.9804 , 2.0768) 0.0631	
Prior Treatment with Pertuzumab								
Yes	162	72 (44.4)	20.1 (9.9 , NE)	158	46 (29.1)	19.1 (12.6 , NE)	1.4273 (0.9813 , 2.0762) 0.0627	0.6498
No	99	47 (47.5)	15.5 (5.5 , NE)	105	32 (30.5)	NE (13.8 , NE)	1.6443 (1.0485 , 2.5786) 0.0295	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	81 (43.1)	19.0 (12.2 , NE)	191	57 (29.8)	19.1 (12.7 , NE)	1.3690 (0.9732 , 1.9256) 0.0718	0.3709
>= 3 lines	73	38 (52.1)	6.9 (3.2 , NE)	72	21 (29.2)	16.7 (13.8 , NE)	1.8898 (1.1051 , 3.2319) 0.0183	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	68 (43.6)	20.1 (12.2 , NE)	152	46 (30.3)	19.1 (12.4 , NE)	1.3309 (0.9105 , 1.9453) 0.1408	0.0278
>= 3 lines	6	4 (66.7)	3.0 (0.8 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.0532	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	60 (46.2)	19.0 (6.8 , NE)	130	38 (29.2)	16.7 (13.8 , NE)	1.4509 (0.9617 , 2.1889) 0.0761	0.8742
Mild Impairment	92	43 (46.7)	15.5 (4.5 , NE)	104	33 (31.7)	20.5 (11.7 , NE)	1.6040 (1.0172 , 2.5294) 0.0420	
Moderate Impairment	30	12 (40.0)	20.1 (5.6 , NE)	22	5 (22.7)	NE (4.2 , NE)	1.4128 (0.4955 , 4.0280) 0.5092	
Hepatic Impairment								
Within Normal Range	208	97 (46.6)	16.4 (9.8 , NE)	212	64 (30.2)	19.1 (13.8 , NE)	1.5083 (1.0968 , 2.0742) 0.0114	0.7418
Mild Impairment	49	22 (44.9)	15.5 (3.2 , NE)	49	14 (28.6)	NE (6.6 , NE)	1.3695 (0.7001 , 2.6790) 0.3588	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	92 (47.2)	15.2 (6.8 , 20.1)	189	52 (27.5)	20.5 (13.8 , NE)	1.7261 (1.2257 , 2.4308) 0.0016	0.0884
No	66	27 (40.9)	NE (5.6 , NE)	74	26 (35.1)	19.1 (12.6 , NE)	1.0444 (0.6075 , 1.7957) 0.8802	
Baseline CNS Metastases								
Yes	43	19 (44.2)	15.6 (3.0 , NE)	39	10 (25.6)	NE (7.0 , NE)	1.7909 (0.8265 , 3.8807) 0.1367	0.6721
No	218	100 (45.9)	16.4 (9.8 , NE)	224	68 (30.4)	19.1 (13.8 , NE)	1.4546 (1.0667 , 1.9834) 0.0178	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Appetite Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	23 (37.1)	NE (5.8 , NE)	52	12 (23.1)	NE (9.0 , NE)	1.6384 (0.8105 , 3.3122) 0.1666	0.9124
No	199	96 (48.2)	15.2 (6.8 , NE)	211	66 (31.3)	19.1 (12.7 , NE)	1.4931 (1.0893 , 2.0465) 0.0125	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	92 (43.4)	16.8 (12.5 , NE)	206	64 (31.1)	NE (NE , NE)	1.1616 (0.8419 , 1.6026) 0.3570	0.9421
>=65	49	22 (44.9)	15.9 (10.1 , NE)	57	20 (35.1)	NE (7.3 , NE)	1.1530 (0.6279 , 2.1171) 0.6506	
Age								
<75	253	112 (44.3)	15.9 (13.1 , 22.6)	255	78 (30.6)	NE (NE , NE)	1.2267 (0.9172 , 1.6406) 0.1656	0.0180
>=75	8	2 (25.0)	NE (1.4 , NE)	8	6 (75.0)	2.8 (0.8 , 4.2)	0.2636 (0.0526 , 1.3201) 0.0820	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	66 (44.3)	16.5 (11.0 , NE)	160	48 (30.0)	NE (NE , NE)	1.3459 (0.9255 , 1.9572) 0.1192	0.4008
North America	17	8 (47.1)	22.6 (3.8 , NE)	17	6 (35.3)	NE (0.8 , NE)	0.8629 (0.2893 , 2.5739) 0.8044	
Europe	54	28 (51.9)	10.1 (5.8 , 17.1)	50	18 (36.0)	NE (7.0 , NE)	1.2478 (0.6894 , 2.2586) 0.4625	
Rest of World	41	12 (29.3)	NE (13.8 , NE)	36	12 (33.3)	NE (8.4 , NE)	0.5503 (0.2439 , 1.2418) 0.1455	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	29 (40.8)	15.7 (9.8 , NE)	72	25 (34.7)	NE (7.0 , NE)	0.8663 (0.5059 , 1.4834) 0.6033	0.6219
Black or African American	10	5 (50.0)	16.8 (1.4 , 22.6)	9	4 (44.4)	10.1 (0.8 , NE)	0.5786 (0.1432 , 2.3379) 0.4371	
Asian	152	67 (44.1)	16.5 (11.0 , NE)	162	48 (29.6)	NE (NE , NE)	1.3729 (0.9452 , 1.9940) 0.0951	
Other	28	13 (46.4)	17.1 (3.1 , NE)	20	7 (35.0)	11.3 (5.6 , NE)	1.1097 (0.4406 , 2.7950) 0.8285	
ECOG PS								
0	154	69 (44.8)	16.5 (12.5 , NE)	175	52 (29.7)	NE (NE , NE)	1.2624 (0.8790 , 1.8132) 0.2057	0.3463
1	106	45 (42.5)	15.9 (10.1 , NE)	87	32 (36.8)	NE (8.6 , NE)	0.9614 (0.6086 , 1.5186) 0.8744	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	63 (47.4)	15.7 (8.8 , 22.6)	139	44 (31.7)	NE (11.3 , NE)	1.2815 (0.8702 , 1.8873) 0.2066	0.4302
Negative	126	50 (39.7)	17.1 (11.6 , NE)	122	40 (32.8)	NE (12.6 , NE)	1.0232 (0.6733 , 1.5550) 0.9187	
Estrogen Receptors								
Positive	129	60 (46.5)	16.5 (9.8 , 22.6)	132	40 (30.3)	NE (11.3 , NE)	1.3042 (0.8718 , 1.9510) 0.1942	0.3474
Negative	130	53 (40.8)	17.1 (11.6 , NE)	128	44 (34.4)	NE (12.6 , NE)	0.9992 (0.6682 , 1.4943) 0.9946	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	39 (48.1)	15.2 (8.6 , NE)	92	25 (27.2)	NE (11.3 , NE)	1.5352 (0.9269 , 2.5429) 0.0922	0.1396
Negative	177	74 (41.8)	16.8 (12.5 , NE)	168	59 (35.1)	NE (10.1 , NE)	1.0027 (0.7107 , 1.4147) 0.9893	
Prior Treatment with Pertuzumab								
Yes	162	85 (52.5)	12.5 (8.6 , 15.9)	158	58 (36.7)	NE (10.1 , NE)	1.1433 (0.8159 , 1.6022) 0.4262	0.7001
No	99	29 (29.3)	NE (22.5 , NE)	105	26 (24.8)	NE (NE , NE)	1.1025 (0.6476 , 1.8770) 0.7294	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	84 (44.7)	15.7 (11.6 , NE)	191	65 (34.0)	NE (11.3 , NE)	1.0638 (0.7682 , 1.4732) 0.7035	0.3693
>= 3 lines	73	30 (41.1)	22.6 (11.0 , NE)	72	19 (26.4)	NE (NE , NE)	1.4992 (0.8405 , 2.6742) 0.1690	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	81 (51.9)	12.5 (8.8 , 15.9)	152	58 (38.2)	NE (8.6 , NE)	1.0922 (0.7764 , 1.5364) 0.6009	0.0357
>= 3 lines	6	4 (66.7)	8.6 (2.2 , 16.5)	6	0	NE (NE , NE)	NE (NE, NE) 0.0776	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	54 (41.5)	22.5 (15.2 , NE)	130	41 (31.5)	NE (12.6 , NE)	0.9133 (0.6033 , 1.3826) 0.6760	0.3156
Mild Impairment	92	43 (46.7)	13.8 (6.9 , NE)	104	37 (35.6)	NE (8.4 , NE)	1.3290 (0.8552 , 2.0651) 0.2052	
Moderate Impairment	30	15 (50.0)	16.5 (2.8 , NE)	22	5 (22.7)	NE (4.2 , NE)	1.9946 (0.7239 , 5.4962) 0.1739	
Hepatic Impairment								
Within Normal Range	208	99 (47.6)	15.7 (11.3 , 22.6)	212	71 (33.5)	NE (NE , NE)	1.2307 (0.9052 , 1.6733) 0.1839	0.3220
Mild Impairment	49	15 (30.6)	NE (13.1 , NE)	49	13 (26.5)	NE (6.3 , NE)	0.8114 (0.3844 , 1.7127) 0.5876	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	82 (42.1)	16.8 (13.1 , NE)	189	61 (32.3)	NE (NE , NE)	1.0882 (0.7788 , 1.5204) 0.6193	0.5222
No	66	32 (48.5)	15.3 (7.4 , NE)	74	23 (31.1)	NE (12.6 , NE)	1.3490 (0.7886 , 2.3076) 0.2710	
Baseline CNS Metastases								
Yes	43	16 (37.2)	16.8 (10.3 , NE)	39	14 (35.9)	NE (5.7 , NE)	0.7066 (0.3319 , 1.5044) 0.3649	0.3157
No	218	98 (45.0)	15.9 (12.5 , NE)	224	70 (31.3)	NE (NE , NE)	1.2354 (0.9078 , 1.6811) 0.1768	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Constipation

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	27 (43.5)	15.7 (6.9 , NE)	52	18 (34.6)	NE (7.0 , NE)	0.9928 (0.5375 , 1.8337) 0.9824	0.7584
No	199	87 (43.7)	16.5 (13.8 , NE)	211	66 (31.3)	NE (NE , NE)	1.1830 (0.8578 , 1.6315) 0.3032	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	40 (18.9)	NE (NE , NE)	206	25 (12.1)	NE (NE , NE)	1.1795 (0.7111 , 1.9562) 0.5229	0.5333
>=65	49	9 (18.4)	NE (NE , NE)	57	11 (19.3)	NE (NE , NE)	0.9391 (0.3884 , 2.2706) 0.8841	
Age								
<75	253	48 (19.0)	NE (NE , NE)	255	35 (13.7)	NE (NE , NE)	1.1114 (0.7161 , 1.7249) 0.6386	0.9358
>=75	8	1 (12.5)	NE (0.8 , NE)	8	1 (12.5)	NE (0.9 , NE)	1.4606 (0.0911 , 23.419) 0.7878	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	23 (15.4)	NE (NE , NE)	160	24 (15.0)	NE (NE , NE)	0.7533 (0.4218 , 1.3454) 0.3356	0.0285
North America	17	8 (47.1)	10.3 (1.5 , NE)	17	1 (5.9)	17.8 (NE , NE)	7.8547 (0.9777 , 63.106) 0.0218	
Europe	54	13 (24.1)	NE (NE , NE)	50	6 (12.0)	NE (NE , NE)	1.9195 (0.7267 , 5.0703) 0.1808	
Rest of World	41	5 (12.2)	NE (NE , NE)	36	5 (13.9)	NE (14.0 , NE)	0.6980 (0.2002 , 2.4328) 0.5702	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	15 (21.1)	NE (NE , NE)	72	8 (11.1)	NE (17.8 , NE)	1.6947 (0.7137 , 4.0240) 0.2249	0.4647
Black or African American	10	2 (20.0)	NE (1.5 , NE)	9	1 (11.1)	NE (14.0 , NE)	1.2066 (0.1078 , 13.511) 0.8787	
Asian	152	24 (15.8)	NE (NE , NE)	162	24 (14.8)	NE (NE , NE)	0.7955 (0.4486 , 1.4108) 0.4316	
Other	28	8 (28.6)	NE (10.0 , NE)	20	3 (15.0)	NE (NE , NE)	1.8183 (0.4800 , 6.8875) 0.3738	
ECOG PS								
0	154	28 (18.2)	NE (NE , NE)	175	25 (14.3)	NE (NE , NE)	0.9930 (0.5751 , 1.7146) 0.9781	0.6116
1	106	21 (19.8)	NE (NE , NE)	87	11 (12.6)	NE (15.3 , NE)	1.3159 (0.6316 , 2.7416) 0.4616	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	31 (23.3)	NE (NE , NE)	139	18 (12.9)	NE (NE , NE)	1.4881 (0.8279 , 2.6746) 0.1817	0.1504
Negative	126	18 (14.3)	NE (NE , NE)	122	18 (14.8)	NE (NE , NE)	0.7772 (0.4020 , 1.5022) 0.4510	
Estrogen Receptors								
Positive	129	30 (23.3)	NE (NE , NE)	132	18 (13.6)	NE (17.8 , NE)	1.3930 (0.7718 , 2.5142) 0.2696	0.2481
Negative	130	19 (14.6)	NE (NE , NE)	128	18 (14.1)	NE (NE , NE)	0.8358 (0.4361 , 1.6017) 0.5870	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	16 (19.8)	NE (NE , NE)	92	11 (12.0)	NE (17.8 , NE)	1.3124 (0.6042 , 2.8508) 0.4908	0.5969
Negative	177	33 (18.6)	NE (NE , NE)	168	25 (14.9)	NE (NE , NE)	1.0320 (0.6110 , 1.7429) 0.9087	
Prior Treatment with Pertuzumab								
Yes	162	31 (19.1)	NE (NE , NE)	158	19 (12.0)	NE (NE , NE)	1.2872 (0.7219 , 2.2950) 0.3921	0.5006
No	99	18 (18.2)	NE (NE , NE)	105	17 (16.2)	NE (NE , NE)	0.9177 (0.4711 , 1.7876) 0.8029	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	36 (19.1)	NE (NE , NE)	191	25 (13.1)	NE (NE , NE)	1.2666 (0.7584 , 2.1155) 0.3666	0.5490
>= 3 lines	73	13 (17.8)	NE (NE , NE)	72	11 (15.3)	NE (12.7 , NE)	0.7247 (0.3177 , 1.6532) 0.4433	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	29 (18.6)	NE (NE , NE)	152	18 (11.8)	NE (NE , NE)	1.2895 (0.7109 , 2.3392) 0.4023	0.9054
>= 3 lines	6	2 (33.3)	NE (1.4 , NE)	6	1 (16.7)	NE (6.0 , NE)	1.0718 (0.0915 , 12.552) 0.9559	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	20 (15.4)	NE (NE , NE)	130	15 (11.5)	NE (17.8 , NE)	0.8638 (0.4344 , 1.7176) 0.6760	0.5367
Mild Impairment	92	19 (20.7)	NE (NE , NE)	104	18 (17.3)	NE (NE , NE)	1.0997 (0.5763 , 2.0983) 0.7725	
Moderate Impairment	30	8 (26.7)	NE (11.2 , NE)	22	2 (9.1)	NE (NE , NE)	2.6163 (0.5544 , 12.346) 0.2080	
Hepatic Impairment								
Within Normal Range	208	42 (20.2)	NE (NE , NE)	212	29 (13.7)	NE (NE , NE)	1.1991 (0.7435 , 1.9338) 0.4570	0.3969
Mild Impairment	49	7 (14.3)	NE (NE , NE)	49	7 (14.3)	NE (12.7 , NE)	0.7586 (0.2643 , 2.1773) 0.6064	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	36 (18.5)	NE (NE , NE)	189	27 (14.3)	NE (17.8 , NE)	1.0837 (0.6550 , 1.7930) 0.7549	0.7054
No	66	13 (19.7)	NE (NE , NE)	74	9 (12.2)	NE (NE , NE)	1.2062 (0.5117 , 2.8435) 0.6700	
Baseline CNS Metastases								
Yes	43	10 (23.3)	NE (NE , NE)	39	5 (12.8)	15.3 (15.3 , NE)	1.2440 (0.4143 , 3.7355) 0.6963	0.6032
No	218	39 (17.9)	NE (NE , NE)	224	31 (13.8)	NE (NE , NE)	1.0671 (0.6634 , 1.7165) 0.7895	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Diarrhea

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	15 (24.2)	NE (NE , NE)	52	4 (7.7)	NE (NE , NE)	2.5223 (0.8281 , 7.6833) 0.0923	0.0698
No	199	34 (17.1)	NE (NE , NE)	211	32 (15.2)	NE (NE , NE)	0.9082 (0.5581 , 1.4780) 0.6980	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	48 (22.6)	NE (23.5 , NE)	206	51 (24.8)	NE (15.2 , NE)	0.6428 (0.4300 , 0.9609) 0.0296	0.6441
>=65	49	10 (20.4)	24.0 (24.0 , NE)	57	13 (22.8)	NE (12.7 , NE)	0.7537 (0.3290 , 1.7266) 0.5016	
Age								
<75	253	56 (22.1)	NE (24.0 , NE)	255	62 (24.3)	NE (17.8 , NE)	0.6650 (0.4610 , 0.9593) 0.0277	0.6005
>=75	8	2 (25.0)	NE (1.4 , NE)	8	2 (25.0)	10.3 (6.2 , NE)	1.2763 (0.1763 , 9.2396) 0.8087	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	39 (26.2)	NE (23.5 , NE)	160	38 (23.8)	NE (15.2 , NE)	0.8141 (0.5171 , 1.2818) 0.3703	0.5199
North America	17	4 (23.5)	NE (3.8 , NE)	17	4 (23.5)	17.8 (4.4 , 17.8)	0.8316 (0.2041 , 3.3885) 0.7967	
Europe	54	4 (7.4)	24.0 (24.0 , NE)	50	8 (16.0)	NE (NE , NE)	0.3554 (0.1063 , 1.1881) 0.0795	
Rest of World	41	11 (26.8)	NE (15.2 , NE)	36	14 (38.9)	NE (7.1 , NE)	0.4635 (0.2087 , 1.0297) 0.0528	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	12 (16.9)	NE (NE , NE)	72	19 (26.4)	NE (12.7 , NE)	0.4963 (0.2397 , 1.0275) 0.0538	0.6762
Black or African American	10	3 (30.0)	NE (1.6 , NE)	9	3 (33.3)	NE (1.4 , NE)	0.6857 (0.1377 , 3.4132) 0.6430	
Asian	152	39 (25.7)	NE (23.5 , NE)	162	38 (23.5)	NE (15.2 , NE)	0.8182 (0.5198 , 1.2879) 0.3817	
Other	28	4 (14.3)	24.0 (24.0 , NE)	20	4 (20.0)	NE (9.8 , NE)	0.3006 (0.0653 , 1.3830) 0.1036	
ECOG PS								
0	154	31 (20.1)	NE (NE , NE)	175	41 (23.4)	NE (17.8 , NE)	0.6123 (0.3818 , 0.9819) 0.0395	0.7111
1	106	27 (25.5)	24.0 (23.5 , NE)	87	23 (26.4)	NE (11.1 , NE)	0.7182 (0.4073 , 1.2665) 0.2489	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	24 (18.0)	NE (NE , NE)	139	33 (23.7)	NE (15.2 , NE)	0.5686 (0.3345 , 0.9666) 0.0345	0.3306
Negative	126	34 (27.0)	24.0 (23.5 , NE)	122	30 (24.6)	NE (13.9 , NE)	0.7842 (0.4739 , 1.2977) 0.3398	
Estrogen Receptors								
Positive	129	23 (17.8)	NE (NE , NE)	132	32 (24.2)	NE (15.2 , NE)	0.5404 (0.3146 , 0.9284) 0.0236	0.2518
Negative	130	35 (26.9)	24.0 (23.5 , NE)	128	31 (24.2)	NE (13.9 , NE)	0.8045 (0.4902 , 1.3204) 0.3840	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	10 (12.3)	NE (NE , NE)	92	21 (22.8)	NE (15.2 , NE)	0.3725 (0.1740 , 0.7978) 0.0083	0.0823
Negative	177	48 (27.1)	NE (23.5 , NE)	168	42 (25.0)	NE (NE , NE)	0.8192 (0.5376 , 1.2483) 0.3497	
Prior Treatment with Pertuzumab								
Yes	162	31 (19.1)	NE (24.0 , NE)	158	35 (22.2)	NE (13.9 , NE)	0.5664 (0.3459 , 0.9275) 0.0221	0.4843
No	99	27 (27.3)	NE (18.2 , NE)	105	29 (27.6)	NE (15.2 , NE)	0.8361 (0.4934 , 1.4167) 0.5017	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	39 (20.7)	NE (24.0 , NE)	191	54 (28.3)	NE (13.9 , NE)	0.5190 (0.3416 , 0.7886) 0.0018	0.0143
>= 3 lines	73	19 (26.0)	23.5 (23.5 , NE)	72	10 (13.9)	NE (NE , NE)	1.6103 (0.7436 , 3.4871) 0.2244	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	30 (19.2)	NE (24.0 , NE)	152	34 (22.4)	NE (13.9 , NE)	0.5722 (0.3467 , 0.9443) 0.0270	0.9365
>= 3 lines	6	1 (16.7)	NE (11.5 , NE)	6	1 (16.7)	NE (4.4 , NE)	0.4714 (0.0283 , 7.8580) 0.5924	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	29 (22.3)	NE (23.5 , NE)	130	26 (20.0)	NE (13.9 , NE)	0.7836 (0.4555 , 1.3483) 0.3756	0.6918
Mild Impairment	92	21 (22.8)	NE (18.2 , NE)	104	34 (32.7)	NE (12.7 , NE)	0.5624 (0.3251 , 0.9731) 0.0364	
Moderate Impairment	30	7 (23.3)	24.0 (14.5 , 24.0)	22	4 (18.2)	NE (10.3 , NE)	0.6881 (0.1923 , 2.4616) 0.5632	
Hepatic Impairment								
Within Normal Range	208	46 (22.1)	NE (24.0 , NE)	212	54 (25.5)	NE (17.8 , NE)	0.6418 (0.4306 , 0.9566) 0.0279	0.6065
Mild Impairment	49	12 (24.5)	NE (NE , NE)	49	10 (20.4)	NE (9.0 , NE)	0.8296 (0.3558 , 1.9344) 0.6667	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	45 (23.1)	NE (NE , NE)	189	46 (24.3)	NE (17.8 , NE)	0.7004 (0.4616 , 1.0629) 0.0916	0.6835
No	66	13 (19.7)	NE (23.5 , NE)	74	18 (24.3)	NE (13.9 , NE)	0.5646 (0.2726 , 1.1694) 0.1188	
Baseline CNS Metastases								
Yes	43	9 (20.9)	NE (18.2 , NE)	39	8 (20.5)	NE (NE , NE)	0.6697 (0.2518 , 1.7811) 0.4219	0.9138
No	218	49 (22.5)	NE (24.0 , NE)	224	56 (25.0)	NE (17.8 , NE)	0.6709 (0.4551 , 0.9892) 0.0420	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 58 Analysis of time to definitive deterioration of EORTC QLQ-C30 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Common Symptoms/Financial Difficulties

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	15 (24.2)	NE (18.2 , NE)	52	10 (19.2)	NE (NE , NE)	0.8865 (0.3883 , 2.0238) 0.7738	0.3931
No	199	43 (21.6)	NE (24.0 , NE)	211	54 (25.6)	NE (17.8 , NE)	0.6243 (0.4163 , 0.9364) 0.0213	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	71 (33.5)	23.7 (19.4 , NE)	206	44 (21.4)	NE (NE , NE)	1.2099 (0.8274 , 1.7691) 0.3266	0.5228
>=65	49	12 (24.5)	NE (17.6 , NE)	57	13 (22.8)	25.4 (15.2 , 25.4)	0.9910 (0.4435 , 2.2145) 0.9822	
Age								
<75	253	82 (32.4)	23.7 (19.4 , NE)	255	56 (22.0)	25.4 (NE , NE)	1.1550 (0.8201 , 1.6267) 0.4107	0.8628
>=75	8	1 (12.5)	NE (0.8 , NE)	8	1 (12.5)	NE (10.3 , NE)	0.9354 (0.0575 , 15.210) 0.9626	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	47 (31.5)	NE (17.6 , NE)	160	33 (20.6)	25.4 (NE , NE)	1.1776 (0.7508 , 1.8473) 0.4788	0.7359
North America	17	3 (17.6)	NE (NE , NE)	17	2 (11.8)	NE (NE , NE)	1.2560 (0.2096 , 7.5266) 0.8026	
Europe	54	18 (33.3)	20.2 (15.2 , NE)	50	9 (18.0)	NE (NE , NE)	1.4454 (0.6445 , 3.2420) 0.3681	
Rest of World	41	15 (36.6)	16.8 (13.6 , NE)	36	13 (36.1)	NE (7.1 , NE)	0.8341 (0.3961 , 1.7565) 0.6283	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	21 (29.6)	NE (16.1 , NE)	72	20 (27.8)	NE (10.3 , NE)	0.8313 (0.4491 , 1.5385) 0.5555	0.4000
Black or African American	10	4 (40.0)	16.8 (1.6 , 16.8)	9	1 (11.1)	NE (1.5 , NE)	3.8443 (0.4146 , 35.645) 0.2053	
Asian	152	48 (31.6)	NE (17.6 , NE)	162	33 (20.4)	25.4 (NE , NE)	1.2025 (0.7681 , 1.8824) 0.4219	
Other	28	10 (35.7)	20.2 (15.2 , NE)	20	3 (15.0)	NE (NE , NE)	1.7447 (0.4690 , 6.4910) 0.4028	
ECOG PS								
0	154	50 (32.5)	23.7 (16.8 , NE)	175	39 (22.3)	25.4 (NE , NE)	1.1077 (0.7259 , 1.6903) 0.6346	0.9218
1	106	33 (31.1)	NE (NE , NE)	87	18 (20.7)	NE (NE , NE)	1.2432 (0.6975 , 2.2156) 0.4605	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	39 (29.3)	23.7 (17.6 , NE)	139	31 (22.3)	25.4 (NE , NE)	0.9940 (0.6179 , 1.5991) 0.9806	0.3252
Negative	126	44 (34.9)	NE (14.5 , NE)	122	25 (20.5)	NE (NE , NE)	1.4314 (0.8730 , 2.3470) 0.1544	
Estrogen Receptors								
Positive	129	37 (28.7)	23.7 (17.6 , NE)	132	29 (22.0)	25.4 (NE , NE)	0.9826 (0.6020 , 1.6039) 0.9452	0.3230
Negative	130	46 (35.4)	NE (14.5 , NE)	128	27 (21.1)	NE (NE , NE)	1.3981 (0.8659 , 2.2575) 0.1701	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	25 (30.9)	NE (15.2 , NE)	92	21 (22.8)	25.4 (NE , NE)	1.1062 (0.6118 , 2.0000) 0.7384	0.7795
Negative	177	58 (32.8)	23.7 (17.6 , NE)	168	35 (20.8)	NE (NE , NE)	1.2355 (0.8083 , 1.8886) 0.3287	
Prior Treatment with Pertuzumab								
Yes	162	58 (35.8)	20.2 (16.8 , NE)	158	27 (17.1)	25.4 (NE , NE)	1.6969 (1.0638 , 2.7067) 0.0248	0.0084
No	99	25 (25.3)	NE (23.7 , NE)	105	30 (28.6)	NE (14.1 , NE)	0.6818 (0.3988 , 1.1656) 0.1577	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	60 (31.9)	NE (19.4 , NE)	191	40 (20.9)	25.4 (NE , NE)	1.1933 (0.7969 , 1.7869) 0.3929	0.7857
>= 3 lines	73	23 (31.5)	20.2 (17.6 , NE)	72	17 (23.6)	NE (11.8 , NE)	1.0772 (0.5726 , 2.0265) 0.8158	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	54 (34.6)	20.2 (16.8 , NE)	152	26 (17.1)	25.4 (NE , NE)	1.6456 (1.0192 , 2.6568) 0.0395	0.7344
>= 3 lines	6	4 (66.7)	8.6 (1.4 , NE)	6	1 (16.7)	NE (0.7 , NE)	1.8365 (0.2009 , 16.785) 0.5848	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	41 (31.5)	23.7 (19.4 , NE)	130	26 (20.0)	NE (NE , NE)	1.1198 (0.6754 , 1.8568) 0.6631	0.1399
Mild Impairment	92	30 (32.6)	NE (16.5 , NE)	104	30 (28.8)	25.4 (15.2 , 25.4)	0.9681 (0.5829 , 1.6077) 0.9003	
Moderate Impairment	30	10 (33.3)	17.6 (14.5 , NE)	22	1 (4.5)	NE (10.3 , NE)	5.5811 (0.7128 , 43.699) 0.0650	
Hepatic Impairment								
Within Normal Range	208	67 (32.2)	NE (19.4 , NE)	212	45 (21.2)	25.4 (NE , NE)	1.1882 (0.8109 , 1.7410) 0.3769	0.7100
Mild Impairment	49	16 (32.7)	20.2 (11.1 , NE)	49	12 (24.5)	NE (9.0 , NE)	0.9942 (0.4693 , 2.1062) 0.9863	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	60 (30.8)	23.7 (17.6 , NE)	189	36 (19.0)	25.4 (NE , NE)	1.2721 (0.8382 , 1.9304) 0.2588	0.3633
No	66	23 (34.8)	NE (16.1 , NE)	74	21 (28.4)	NE (15.2 , NE)	0.9406 (0.5182 , 1.7071) 0.8434	
Baseline CNS Metastases								
Yes	43	15 (34.9)	19.4 (12.8 , NE)	39	9 (23.1)	NE (NE , NE)	1.0463 (0.4501 , 2.4323) 0.9154	0.9065
No	218	68 (31.2)	NE (20.2 , NE)	224	48 (21.4)	25.4 (NE , NE)	1.1574 (0.7976 , 1.6795) 0.4430	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Body Image

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	19 (30.6)	19.4 (14.5 , NE)	52	10 (19.2)	NE (14.1 , NE)	1.0938 (0.4970 , 2.4072) 0.8226	0.8995
No	199	64 (32.2)	NE (20.2 , NE)	211	47 (22.3)	25.4 (NE , NE)	1.1480 (0.7858 , 1.6773) 0.4768	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	51 (24.1)	NE (NE , NE)	206	46 (22.3)	NE (NE , NE)	0.8559 (0.5727 , 1.2791) 0.4478	0.1966
>=65	49	6 (12.2)	NE (NE , NE)	57	3 (5.3)	NE (NE , NE)	2.2229 (0.5548 , 8.9063) 0.2464	
Age								
<75	253	56 (22.1)	NE (NE , NE)	255	48 (18.8)	NE (NE , NE)	0.9745 (0.6613 , 1.4362) 0.8962	0.8309
>=75	8	1 (12.5)	NE (2.1 , NE)	8	1 (12.5)	NE (1.4 , NE)	0.7454 (0.0464 , 11.968) 0.8350	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	20 (13.4)	NE (NE , NE)	160	26 (16.3)	NE (NE , NE)	0.6408 (0.3558 , 1.1541) 0.1353	0.1055
North America	17	7 (41.2)	NE (1.5 , NE)	17	3 (17.6)	NE (5.7 , NE)	2.3421 (0.6050 , 9.0670) 0.2037	
Europe	54	16 (29.6)	NE (10.8 , NE)	50	7 (14.0)	NE (NE , NE)	1.8934 (0.7768 , 4.6153) 0.1521	
Rest of World	41	14 (34.1)	NE (8.6 , NE)	36	13 (36.1)	14.8 (1.5 , NE)	0.7635 (0.3579 , 1.6288) 0.4933	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	28 (39.4)	17.5 (5.8 , NE)	72	15 (20.8)	NE (14.8 , NE)	1.7977 (0.9596 , 3.3678) 0.0615	0.0148
Black or African American	10	1 (10.0)	NE (1.4 , NE)	9	4 (44.4)	NE (0.8 , NE)	0.1481 (0.0164 , 1.3381) 0.0486	
Asian	152	20 (13.2)	NE (NE , NE)	162	26 (16.0)	NE (NE , NE)	0.6423 (0.3566 , 1.1568) 0.1374	
Other	28	8 (28.6)	NE (7.7 , NE)	20	4 (20.0)	NE (9.5 , NE)	1.0635 (0.3104 , 3.6435) 0.9204	
ECOG PS								
0	154	37 (24.0)	NE (NE , NE)	175	36 (20.6)	NE (NE , NE)	0.9683 (0.6104 , 1.5362) 0.8935	0.9749
1	106	20 (18.9)	NE (NE , NE)	87	13 (14.9)	NE (NE , NE)	1.0452 (0.5182 , 2.1083) 0.9005	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	29 (21.8)	NE (NE , NE)	139	33 (23.7)	NE (14.9 , NE)	0.7198 (0.4354 , 1.1898) 0.1992	0.0735
Negative	126	28 (22.2)	NE (NE , NE)	122	16 (13.1)	NE (NE , NE)	1.4891 (0.8036 , 2.7594) 0.2039	
Estrogen Receptors								
Positive	129	28 (21.7)	NE (NE , NE)	132	30 (22.7)	NE (14.9 , NE)	0.7575 (0.4509 , 1.2723) 0.2950	0.1235
Negative	130	29 (22.3)	NE (NE , NE)	128	18 (14.1)	NE (NE , NE)	1.3769 (0.7626 , 2.4860) 0.2885	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	21 (25.9)	NE (NE , NE)	92	26 (28.3)	NE (14.8 , NE)	0.7893 (0.4430 , 1.4061) 0.4226	0.2535
Negative	177	36 (20.3)	NE (NE , NE)	168	23 (13.7)	NE (NE , NE)	1.2106 (0.7152 , 2.0493) 0.4774	
Prior Treatment with Pertuzumab								
Yes	162	36 (22.2)	NE (NE , NE)	158	23 (14.6)	NE (NE , NE)	1.2746 (0.7534 , 2.1565) 0.3652	0.1401
No	99	21 (21.2)	NE (NE , NE)	105	26 (24.8)	NE (14.8 , NE)	0.7031 (0.3938 , 1.2553) 0.2325	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	40 (21.3)	NE (NE , NE)	191	33 (17.3)	NE (NE , NE)	0.9970 (0.6273 , 1.5847) 0.9960	0.8467
>= 3 lines	73	17 (23.3)	NE (NE , NE)	72	16 (22.2)	NE (NE , NE)	0.9074 (0.4555 , 1.8077) 0.7765	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	36 (23.1)	NE (NE , NE)	152	23 (15.1)	NE (NE , NE)	1.2876 (0.7611 , 2.1785) 0.3454	0.9999
>= 3 lines	6	0	NE (NE , NE)	6	0	NE (NE , NE)	NE (NE , NE) NE	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	33 (25.4)	NE (NE , NE)	130	34 (26.2)	NE (14.8 , NE)	0.7214 (0.4432 , 1.1742) 0.1870	0.1570
Mild Impairment	92	15 (16.3)	NE (NE , NE)	104	14 (13.5)	NE (NE , NE)	1.0408 (0.5005 , 2.1644) 0.9131	
Moderate Impairment	30	7 (23.3)	NE (NE , NE)	22	1 (4.5)	NE (NE , NE)	4.1869 (0.5147 , 34.059) 0.1417	
Hepatic Impairment								
Within Normal Range	208	53 (25.5)	NE (NE , NE)	212	41 (19.3)	NE (NE , NE)	1.1056 (0.7335 , 1.6664) 0.6283	0.0699
Mild Impairment	49	4 (8.2)	NE (NE , NE)	49	8 (16.3)	NE (NE , NE)	0.3844 (0.1154 , 1.2807) 0.1068	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	47 (24.1)	NE (NE , NE)	189	37 (19.6)	NE (NE , NE)	1.0269 (0.6658 , 1.5840) 0.8996	0.5191
No	66	10 (15.2)	NE (NE , NE)	74	12 (16.2)	NE (NE , NE)	0.7529 (0.3236 , 1.7513) 0.5066	
Baseline CNS Metastases								
Yes	43	10 (23.3)	NE (19.4 , NE)	39	7 (17.9)	NE (NE , NE)	0.9661 (0.3577 , 2.6092) 0.9435	0.9034
No	218	47 (21.6)	NE (NE , NE)	224	42 (18.8)	NE (NE , NE)	0.9673 (0.6371 , 1.4687) 0.8785	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Functioning

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	13 (21.0)	NE (19.4 , NE)	52	7 (13.5)	NE (NE , NE)	1.2376 (0.4850 , 3.1580) 0.6543	0.5200
No	199	44 (22.1)	NE (NE , NE)	211	42 (19.9)	NE (NE , NE)	0.9276 (0.6068 , 1.4181) 0.7296	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	16 (7.5)	19.4 (11.6 , NE)	206	7 (3.4)	NE (18.0 , NE)	2.1993 (0.8976 , 5.3885) 0.0774	0.9997
>=65	49	0	NE (NE , NE)	57	0	NE (NE , NE)	NE (NE , NE) NE	
Age								
<75	253	16 (6.3)	NE (13.4 , NE)	255	7 (2.7)	NE (18.0 , NE)	2.2440 (0.9183 , 5.4832) 0.0688	NE
>=75	8	0	NE (NE , NE)	8	0	NE (NE , NE)	NE (NE , NE) NE	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	3 (2.0)	NE (13.4 , NE)	160	2 (1.3)	NE (NE , NE)	2.2961 (0.3711 , 14.206) 0.3592	0.2386
North America	17	1 (5.9)	NE (0.9 , NE)	17	3 (17.6)	8.7 (1.4 , NE)	0.6702 (0.0694 , 6.4698) 0.7275	
Europe	54	4 (7.4)	19.4 (11.6 , 19.4)	50	0	NE (NE , NE)	NE (NE, NE) 0.0789	
Rest of World	41	8 (19.5)	7.2 (1.4 , NE)	36	2 (5.6)	18.0 (1.4 , NE)	3.4902 (0.7370 , 16.528) 0.0905	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	8 (11.3)	NE (1.6 , NE)	72	2 (2.8)	NE (8.7 , NE)	3.3020 (0.7002 , 15.571) 0.1079	0.5012
Black or African American	10	1 (10.0)	NE (1.4 , NE)	9	3 (33.3)	18.0 (1.4 , NE)	1.0199 (0.1032 , 10.079) 0.9866	
Asian	152	3 (2.0)	NE (13.4 , NE)	162	2 (1.2)	NE (NE , NE)	2.1603 (0.3505 , 13.317) 0.3961	
Other	28	4 (14.3)	19.4 (1.6 , 19.4)	20	0	NE (NE , NE)	NE (NE, NE) 0.1534	
ECOG PS								
0	154	11 (7.1)	NE (13.4 , NE)	175	7 (4.0)	NE (18.0 , NE)	1.3173 (0.5006 , 3.4659) 0.5773	0.0142
1	106	5 (4.7)	NE (1.4 , NE)	87	0	NE (NE , NE)	NE (NE, NE) 0.0105	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	9 (6.8)	NE (1.6 , NE)	139	4 (2.9)	NE (18.0 , NE)	3.8389 (1.1782 , 12.508) 0.0162	0.2106
Negative	126	7 (5.6)	19.4 (19.4 , NE)	122	3 (2.5)	NE (8.7 , NE)	1.0840 (0.2702 , 4.3487) 0.9146	
Estrogen Receptors								
Positive	129	9 (7.0)	NE (1.6 , NE)	132	4 (3.0)	NE (18.0 , NE)	3.6428 (1.1153 , 11.897) 0.0219	0.2780
Negative	130	7 (5.4)	19.4 (19.4 , NE)	128	3 (2.3)	NE (8.7 , NE)	1.1881 (0.2959 , 4.7711) 0.8124	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	7 (8.6)	NE (1.6 , NE)	92	4 (4.3)	NE (18.0 , NE)	2.7411 (0.7996 , 9.3965) 0.0942	0.8019
Negative	177	9 (5.1)	NE (13.4 , NE)	168	3 (1.8)	NE (NE , NE)	2.0647 (0.5445 , 7.8285) 0.2807	
Prior Treatment with Pertuzumab								
Yes	162	8 (4.9)	NE (19.4 , NE)	158	4 (2.5)	NE (NE , NE)	1.2709 (0.3749 , 4.3081) 0.6997	0.1779
No	99	8 (8.1)	9.7 (1.4 , NE)	105	3 (2.9)	NE (18.0 , NE)	4.7390 (1.2548 , 17.898) 0.0112	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	13 (6.9)	19.4 (11.6 , NE)	191	7 (3.7)	NE (18.0 , NE)	1.6489 (0.6532 , 4.1624) 0.2851	0.0790
>= 3 lines	73	3 (4.1)	NE (1.4 , NE)	72	0	NE (NE , NE)	NE (NE, NE) 0.0335	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	8 (5.1)	NE (19.4 , NE)	152	4 (2.6)	NE (NE , NE)	1.1929 (0.3510 , 4.0542) 0.7772	NE
>= 3 lines	6	0	NE (NE , NE)	6	0	NE (NE , NE)	NE (NE , NE) NE	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	11 (8.5)	19.4 (9.7 , NE)	130	4 (3.1)	18.0 (18.0 , NE)	2.4587 (0.7606 , 7.9479) 0.1223	0.7971
Mild Impairment	92	4 (4.3)	NE (1.4 , NE)	104	3 (2.9)	NE (1.5 , NE)	1.3611 (0.3042 , 6.0903) 0.6843	
Moderate Impairment	30	0	NE (NE , NE)	22	0	NE (NE , NE)	NE (NE , NE) NE	
Hepatic Impairment								
Within Normal Range	208	15 (7.2)	NE (13.4 , NE)	212	5 (2.4)	NE (18.0 , NE)	2.6881 (0.9713 , 7.4389) 0.0479	0.5803
Mild Impairment	49	1 (2.0)	NE (1.4 , NE)	49	2 (4.1)	NE (1.4 , NE)	1.3241 (0.1197 , 14.643) 0.8184	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	12 (6.2)	19.4 (13.4 , NE)	189	6 (3.2)	NE (18.0 , NE)	1.8521 (0.6893 , 4.9767) 0.2146	0.4356
No	66	4 (6.1)	NE (1.4 , NE)	74	1 (1.4)	NE (8.7 , NE)	4.5291 (0.5015 , 40.906) 0.1409	
Baseline CNS Metastases								
Yes	43	3 (7.0)	19.4 (1.6 , 19.4)	39	1 (2.6)	NE (1.5 , NE)	1.7660 (0.1598 , 19.521) 0.6382	0.9633
No	218	13 (6.0)	NE (11.6 , NE)	224	6 (2.7)	NE (18.0 , NE)	2.3099 (0.8751 , 6.0969) 0.0822	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Sexual Enjoyment

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	3 (4.8)	19.4 (1.6 , NE)	52	1 (1.9)	NE (1.5 , NE)	1.2120 (0.1070 , 13.729) 0.8764	0.7651
No	199	13 (6.5)	NE (11.6 , NE)	211	6 (2.8)	NE (18.0 , NE)	2.5061 (0.9499 , 6.6116) 0.0549	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	53 (25.0)	NE (22.3 , NE)	206	37 (18.0)	NE (17.2 , NE)	0.9642 (0.6252 , 1.4869) 0.8719	0.1318
>=65	49	7 (14.3)	NE (NE , NE)	57	14 (24.6)	21.2 (15.2 , NE)	0.4657 (0.1871 , 1.1590) 0.0914	
Age								
<75	253	59 (23.3)	NE (24.3 , NE)	255	50 (19.6)	NE (21.2 , NE)	0.8358 (0.5684 , 1.2291) 0.3628	0.8990
>=75	8	1 (12.5)	NE (1.4 , NE)	8	1 (12.5)	NE (5.3 , NE)	1.4142 (0.0848 , 23.573) 0.8084	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	38 (25.5)	NE (22.3 , NE)	160	33 (20.6)	21.2 (17.2 , NE)	0.8561 (0.5301 , 1.3825) 0.5232	0.3783
North America	17	5 (29.4)	NE (3.0 , NE)	17	1 (5.9)	NE (NE , NE)	4.7021 (0.5487 , 40.296) 0.1175	
Europe	54	11 (20.4)	NE (19.4 , NE)	50	10 (20.0)	NE (15.2 , NE)	0.7035 (0.2951 , 1.6769) 0.4258	
Rest of World	41	6 (14.6)	NE (19.4 , NE)	36	7 (19.4)	NE (NE , NE)	0.5803 (0.1914 , 1.7595) 0.3301	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	16 (22.5)	NE (19.4 , NE)	72	15 (20.8)	NE (15.2 , NE)	0.8729 (0.4284 , 1.7789) 0.7070	0.9831
Black or African American	10	2 (20.0)	NE (3.0 , NE)	9	1 (11.1)	NE (1.4 , NE)	1.1739 (0.1027 , 13.416) 0.8973	
Asian	152	38 (25.0)	NE (22.3 , NE)	162	33 (20.4)	21.2 (17.2 , NE)	0.8575 (0.5310 , 1.3849) 0.5279	
Other	28	4 (14.3)	NE (19.4 , NE)	20	2 (10.0)	NE (NE , NE)	0.7810 (0.1350 , 4.5167) 0.7930	
ECOG PS								
0	154	39 (25.3)	24.3 (22.1 , NE)	175	31 (17.7)	NE (21.2 , NE)	0.9871 (0.6083 , 1.6018) 0.9572	0.1833
1	106	21 (19.8)	NE (NE , NE)	87	20 (23.0)	NE (15.2 , NE)	0.6426 (0.3455 , 1.1951) 0.1600	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	29 (21.8)	NE (24.3 , NE)	139	33 (23.7)	NE (21.2 , NE)	0.6306 (0.3783 , 1.0513) 0.0748	0.0635
Negative	126	31 (24.6)	22.3 (19.4 , NE)	122	18 (14.8)	NE (17.2 , NE)	1.2204 (0.6742 , 2.2091) 0.5111	
Estrogen Receptors								
Positive	129	28 (21.7)	NE (24.3 , NE)	132	31 (23.5)	21.2 (21.2 , NE)	0.6391 (0.3785 , 1.0791) 0.0915	0.0845
Negative	130	32 (24.6)	22.3 (19.4 , NE)	128	20 (15.6)	NE (17.2 , NE)	1.1307 (0.6384 , 2.0029) 0.6743	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	18 (22.2)	NE (NE , NE)	92	23 (25.0)	NE (15.2 , NE)	0.6313 (0.3374 , 1.1813) 0.1466	0.1811
Negative	177	42 (23.7)	NE (22.3 , NE)	168	28 (16.7)	21.2 (17.2 , NE)	1.0135 (0.6208 , 1.6546) 0.9577	
Prior Treatment with Pertuzumab								
Yes	162	34 (21.0)	NE (22.3 , NE)	158	26 (16.5)	21.2 (16.7 , 21.2)	0.8697 (0.5123 , 1.4763) 0.6066	0.9259
No	99	26 (26.3)	24.3 (19.4 , NE)	105	25 (23.8)	NE (17.2 , NE)	0.8097 (0.4625 , 1.4176) 0.4600	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	41 (21.8)	NE (22.3 , NE)	191	37 (19.4)	21.2 (21.2 , NE)	0.7618 (0.4819 , 1.2044) 0.2434	0.5409
>= 3 lines	73	19 (26.0)	NE (19.4 , NE)	72	14 (19.4)	NE (15.2 , NE)	1.0489 (0.5189 , 2.1206) 0.8904	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	33 (21.2)	NE (22.3 , NE)	152	26 (17.1)	21.2 (16.7 , 21.2)	0.8432 (0.4946 , 1.4376) 0.5322	0.3318
>= 3 lines	6	1 (16.7)	NE (3.1 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.4142	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	32 (24.6)	24.3 (22.1 , NE)	130	20 (15.4)	NE (NE , NE)	1.0423 (0.5809 , 1.8700) 0.8900	0.6471
Mild Impairment	92	22 (23.9)	NE (NE , NE)	104	27 (26.0)	21.2 (15.2 , NE)	0.7492 (0.4247 , 1.3217) 0.3209	
Moderate Impairment	30	5 (16.7)	NE (15.2 , NE)	22	3 (13.6)	NE (17.2 , NE)	0.8627 (0.2039 , 3.6506) 0.8409	
Hepatic Impairment								
Within Normal Range	208	51 (24.5)	NE (24.3 , NE)	212	41 (19.3)	21.2 (21.2 , NE)	0.9010 (0.5908 , 1.3740) 0.6314	0.3544
Mild Impairment	49	9 (18.4)	NE (19.4 , NE)	49	10 (20.4)	NE (8.4 , NE)	0.5704 (0.2290 , 1.4210) 0.2224	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	46 (23.6)	NE (24.3 , NE)	189	38 (20.1)	21.2 (21.2 , NE)	0.8350 (0.5375 , 1.2972) 0.4229	0.9684
No	66	14 (21.2)	NE (22.1 , NE)	74	13 (17.6)	NE (17.2 , NE)	0.8194 (0.3775 , 1.7786) 0.6175	
Baseline CNS Metastases								
Yes	43	13 (30.2)	19.4 (14.8 , NE)	39	4 (10.3)	NE (NE , NE)	2.1443 (0.6846 , 6.7159) 0.1800	0.0549
No	218	47 (21.6)	NE (24.3 , NE)	224	47 (21.0)	NE (21.2 , NE)	0.7251 (0.4792 , 1.0972) 0.1274	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Functional Scales/Future Perspective

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	16 (25.8)	19.4 (15.7 , NE)	52	7 (13.5)	NE (NE , NE)	1.3630 (0.5488 , 3.3852) 0.5022	0.1924
No	199	44 (22.1)	NE (24.3 , NE)	211	44 (20.9)	NE (21.2 , NE)	0.7473 (0.4868 , 1.1471) 0.1822	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	75 (35.4)	NE (17.4 , NE)	206	63 (30.6)	16.7 (13.8 , NE)	0.9302 (0.6620 , 1.3071) 0.6715	0.4573
>=65	49	20 (40.8)	18.5 (7.3 , NE)	57	18 (31.6)	NE (10.4 , NE)	1.1890 (0.6276 , 2.2525) 0.5900	
Age								
<75	253	92 (36.4)	NE (17.4 , NE)	255	80 (31.4)	16.7 (13.9 , NE)	0.9401 (0.6941 , 1.2732) 0.6858	0.1649
>=75	8	3 (37.5)	NE (0.8 , NE)	8	1 (12.5)	NE (2.8 , NE)	4.3445 (0.4472 , 42.206) 0.1678	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	59 (39.6)	NE (14.5 , NE)	160	49 (30.6)	15.3 (13.9 , NE)	1.0840 (0.7376 , 1.5930) 0.6889	0.8941
North America	17	4 (23.5)	NE (2.9 , NE)	17	4 (23.5)	13.8 (7.2 , NE)	0.8942 (0.2216 , 3.6082) 0.8753	
Europe	54	19 (35.2)	18.5 (12.5 , NE)	50	16 (32.0)	16.7 (8.3 , NE)	0.8110 (0.4122 , 1.5955) 0.5536	
Rest of World	41	13 (31.7)	NE (7.2 , NE)	36	12 (33.3)	NE (9.7 , NE)	0.8472 (0.3863 , 1.8578) 0.6770	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	27 (38.0)	NE (10.6 , NE)	72	23 (31.9)	16.7 (11.7 , NE)	1.0484 (0.6000 , 1.8319) 0.8659	0.6036
Black or African American	10	2 (20.0)	NE (1.5 , NE)	9	2 (22.2)	NE (1.5 , NE)	0.7615 (0.1069 , 5.4232) 0.7846	
Asian	152	59 (38.8)	NE (14.5 , NE)	162	49 (30.2)	15.3 (13.9 , NE)	1.0843 (0.7378 , 1.5936) 0.6876	
Other	28	7 (25.0)	NE (16.4 , NE)	20	7 (35.0)	NE (7.0 , NE)	0.4760 (0.1645 , 1.3778) 0.1637	
ECOG PS								
0	154	51 (33.1)	NE (NE , NE)	175	57 (32.6)	14.3 (11.7 , NE)	0.7977 (0.5441 , 1.1697) 0.2439	0.1356
1	106	44 (41.5)	18.5 (12.5 , NE)	87	24 (27.6)	16.7 (15.3 , NE)	1.2887 (0.7791 , 2.1316) 0.3177	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	49 (36.8)	NE (16.4 , NE)	139	42 (30.2)	15.3 (11.7 , NE)	1.0076 (0.6637 , 1.5299) 0.9728	0.9751
Negative	126	46 (36.5)	NE (14.5 , NE)	122	38 (31.1)	16.7 (13.8 , NE)	0.9700 (0.6284 , 1.4972) 0.8862	
Estrogen Receptors								
Positive	129	47 (36.4)	NE (17.4 , NE)	132	39 (29.5)	15.3 (11.7 , NE)	1.0077 (0.6552 , 1.5499) 0.9716	0.9680
Negative	130	48 (36.9)	NE (14.5 , NE)	128	41 (32.0)	16.7 (13.8 , NE)	0.9590 (0.6294 , 1.4612) 0.8389	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	30 (37.0)	NE (15.2 , NE)	92	29 (31.5)	NE (11.7 , NE)	0.9872 (0.5895 , 1.6534) 0.9621	0.7950
Negative	177	65 (36.7)	NE (16.4 , NE)	168	51 (30.4)	16.7 (13.9 , NE)	1.0000 (0.6902 , 1.4489) 0.9953	
Prior Treatment with Pertuzumab								
Yes	162	59 (36.4)	NE (17.4 , NE)	158	46 (29.1)	15.3 (13.9 , NE)	0.9471 (0.6388 , 1.4042) 0.7891	0.9960
No	99	36 (36.4)	NE (15.6 , NE)	105	35 (33.3)	NE (9.7 , NE)	1.0117 (0.6339 , 1.6149) 0.9784	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	68 (36.2)	NE (17.4 , NE)	191	66 (34.6)	14.3 (13.8 , NE)	0.8277 (0.5871 , 1.1669) 0.2764	0.1003
>= 3 lines	73	27 (37.0)	NE (10.6 , NE)	72	15 (20.8)	NE (NE , NE)	1.6482 (0.8734 , 3.1104) 0.1194	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	56 (35.9)	NE (17.4 , NE)	152	46 (30.3)	15.3 (13.9 , NE)	0.8933 (0.5991 , 1.3320) 0.5810	0.0567
>= 3 lines	6	3 (50.0)	NE (1.5 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.1619	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	39 (30.0)	NE (NE , NE)	130	35 (26.9)	NE (15.3 , NE)	0.8691 (0.5463 , 1.3826) 0.5506	0.2992
Mild Impairment	92	44 (47.8)	14.5 (6.9 , NE)	104	39 (37.5)	14.1 (11.7 , 17.0)	1.2165 (0.7879 , 1.8781) 0.3802	
Moderate Impairment	30	11 (36.7)	18.5 (9.0 , NE)	22	4 (18.2)	NE (8.4 , NE)	1.6827 (0.5345 , 5.2974) 0.3670	
Hepatic Impairment								
Within Normal Range	208	83 (39.9)	NE (15.6 , NE)	212	71 (33.5)	15.3 (13.8 , NE)	0.9968 (0.7229 , 1.3744) 0.9806	0.7631
Mild Impairment	49	12 (24.5)	NE (NE , NE)	49	10 (20.4)	NE (9.0 , NE)	0.8754 (0.3757 , 2.0400) 0.7558	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	67 (34.4)	NE (17.4 , NE)	189	55 (29.1)	15.3 (13.8 , NE)	0.9648 (0.6718 , 1.3855) 0.8363	0.9093
No	66	28 (42.4)	NE (10.6 , NE)	74	26 (35.1)	17.0 (8.5 , NE)	0.9982 (0.5822 , 1.7115) 0.9982	
Baseline CNS Metastases								
Yes	43	13 (30.2)	NE (15.6 , NE)	39	14 (35.9)	15.3 (6.6 , NE)	0.5481 (0.2492 , 1.2057) 0.1290	0.1799
No	218	82 (37.6)	NE (17.4 , NE)	224	67 (29.9)	17.0 (13.9 , NE)	1.0658 (0.7693 , 1.4768) 0.7047	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Systemic Therapy Side Effects

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	17 (27.4)	NE (15.6 , NE)	52	15 (28.8)	NE (8.3 , NE)	0.7495 (0.3681 , 1.5260) 0.4227	0.3680
No	199	78 (39.2)	NE (16.4 , NE)	211	66 (31.3)	16.7 (13.9 , NE)	1.0467 (0.7515 , 1.4578) 0.7901	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	27 (12.7)	NE (NE , NE)	206	22 (10.7)	NE (NE , NE)	0.8704 (0.4923 , 1.5390) 0.6342	0.5683
>=65	49	6 (12.2)	NE (16.5 , NE)	57	10 (17.5)	NE (12.7 , NE)	0.5250 (0.1896 , 1.4540) 0.2075	
Age								
<75	253	32 (12.6)	NE (NE , NE)	255	32 (12.5)	NE (NE , NE)	0.7134 (0.4343 , 1.1718) 0.1806	0.1919
>=75	8	1 (12.5)	NE (2.9 , NE)	8	0	NE (NE , NE)	NE (NE, NE) 0.3173	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	21 (14.1)	NE (NE , NE)	160	16 (10.0)	NE (NE , NE)	0.9600 (0.4954 , 1.8604) 0.9049	0.1131
North America	17	4 (23.5)	NE (10.2 , NE)	17	1 (5.9)	NE (NE , NE)	3.2200 (0.3569 , 29.050) 0.2709	
Europe	54	3 (5.6)	NE (NE , NE)	50	7 (14.0)	NE (13.1 , NE)	0.2240 (0.0560 , 0.8960) 0.0221	
Rest of World	41	5 (12.2)	NE (NE , NE)	36	8 (22.2)	NE (NE , NE)	0.4648 (0.1519 , 1.4220) 0.1679	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	8 (11.3)	NE (NE , NE)	72	10 (13.9)	NE (NE , NE)	0.6284 (0.2470 , 1.5988) 0.3239	0.2382
Black or African American	10	2 (20.0)	NE (3.1 , NE)	9	1 (11.1)	NE (2.8 , NE)	1.4118 (0.1277 , 15.612) 0.7774	
Asian	152	21 (13.8)	NE (NE , NE)	162	16 (9.9)	NE (NE , NE)	0.9619 (0.4963 , 1.8643) 0.9096	
Other	28	2 (7.1)	NE (NE , NE)	20	5 (25.0)	NE (9.8 , NE)	0.1415 (0.0243 , 0.8239) 0.0148	
ECOG PS								
0	154	18 (11.7)	NE (NE , NE)	175	21 (12.0)	NE (NE , NE)	0.6505 (0.3429 , 1.2339) 0.1850	0.7386
1	106	15 (14.2)	NE (NE , NE)	87	11 (12.6)	NE (NE , NE)	0.8610 (0.3936 , 1.8833) 0.7088	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	20 (15.0)	NE (NE , NE)	139	17 (12.2)	NE (NE , NE)	0.8051 (0.4167 , 1.5555) 0.5187	0.6024
Negative	126	13 (10.3)	NE (NE , NE)	122	14 (11.5)	NE (NE , NE)	0.7160 (0.3354 , 1.5287) 0.3862	
Estrogen Receptors								
Positive	129	20 (15.5)	NE (NE , NE)	132	15 (11.4)	NE (NE , NE)	0.9011 (0.4558 , 1.7814) 0.7643	0.3985
Negative	130	13 (10.0)	NE (NE , NE)	128	15 (11.7)	NE (NE , NE)	0.6773 (0.3211 , 1.4285) 0.3036	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	13 (16.0)	NE (18.2 , NE)	92	13 (14.1)	NE (NE , NE)	0.6851 (0.3128 , 1.5006) 0.3422	0.9860
Negative	177	20 (11.3)	NE (NE , NE)	168	18 (10.7)	NE (NE , NE)	0.8322 (0.4381 , 1.5808) 0.5741	
Prior Treatment with Pertuzumab								
Yes	162	24 (14.8)	NE (NE , NE)	158	14 (8.9)	NE (NE , NE)	1.1865 (0.6069 , 2.3197) 0.6164	0.0273
No	99	9 (9.1)	NE (NE , NE)	105	18 (17.1)	NE (NE , NE)	0.3803 (0.1699 , 0.8514) 0.0147	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	22 (11.7)	NE (NE , NE)	191	22 (11.5)	NE (NE , NE)	0.7400 (0.4068 , 1.3462) 0.3222	0.9082
>= 3 lines	73	11 (15.1)	NE (18.2 , NE)	72	10 (13.9)	NE (NE , NE)	0.7623 (0.3203 , 1.8144) 0.5385	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	23 (14.7)	NE (NE , NE)	152	14 (9.2)	NE (NE , NE)	1.1627 (0.5916 , 2.2851) 0.6613	0.3692
>= 3 lines	6	1 (16.7)	NE (16.5 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.4795	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	17 (13.1)	NE (NE , NE)	130	13 (10.0)	NE (NE , NE)	0.9576 (0.4614 , 1.9874) 0.9085	0.8509
Mild Impairment	92	13 (14.1)	NE (NE , NE)	104	18 (17.3)	NE (NE , NE)	0.6276 (0.3054 , 1.2900) 0.2018	
Moderate Impairment	30	2 (6.7)	NE (NE , NE)	22	1 (4.5)	NE (NE , NE)	0.8665 (0.0784 , 9.5722) 0.9069	
Hepatic Impairment								
Within Normal Range	208	27 (13.0)	NE (NE , NE)	212	25 (11.8)	NE (NE , NE)	0.7971 (0.4593 , 1.3834) 0.4200	0.4807
Mild Impairment	49	6 (12.2)	NE (NE , NE)	49	7 (14.3)	NE (NE , NE)	0.5270 (0.1739 , 1.5970) 0.2501	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	27 (13.8)	NE (NE , NE)	189	20 (10.6)	NE (NE , NE)	0.9602 (0.5350 , 1.7233) 0.8919	0.1271
No	66	6 (9.1)	NE (NE , NE)	74	12 (16.2)	NE (NE , NE)	0.3661 (0.1355 , 0.9891) 0.0396	
Baseline CNS Metastases								
Yes	43	6 (14.0)	NE (NE , NE)	39	2 (5.1)	NE (NE , NE)	2.2230 (0.4465 , 11.068) 0.3154	0.2092
No	218	27 (12.4)	NE (NE , NE)	224	30 (13.4)	NE (NE , NE)	0.6551 (0.3872 , 1.1086) 0.1128	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Breast Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	6 (9.7)	NE (NE , NE)	52	2 (3.8)	NE (NE , NE)	2.0631 (0.4147 , 10.263) 0.3660	0.2459
No	199	27 (13.6)	NE (NE , NE)	211	30 (14.2)	NE (NE , NE)	0.6750 (0.3989 , 1.1420) 0.1409	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	78 (36.8)	25.0 (18.7 , NE)	206	84 (40.8)	18.2 (8.4 , 24.9)	0.6318 (0.4616 , 0.8648) 0.0038	0.4961
>=65	49	17 (34.7)	15.9 (12.5 , NE)	57	20 (35.1)	NE (6.7 , NE)	0.7571 (0.3955 , 1.4495) 0.4017	
Age								
<75	253	92 (36.4)	20.1 (18.7 , NE)	255	103 (40.4)	18.2 (8.5 , NE)	0.6430 (0.4840 , 0.8543) 0.0021	0.1438
>=75	8	3 (37.5)	14.8 (4.6 , 15.9)	8	1 (12.5)	NE (2.8 , NE)	0.9128 (0.0569 , 14.635) 0.9486	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	65 (43.6)	18.7 (10.6 , NE)	160	66 (41.3)	20.7 (6.7 , NE)	0.7948 (0.5629 , 1.1224) 0.1892	0.1763
North America	17	8 (47.1)	14.3 (4.3 , NE)	17	5 (29.4)	NE (3.0 , NE)	0.9971 (0.3102 , 3.2052) 0.9969	
Europe	54	8 (14.8)	NE (NE , NE)	50	15 (30.0)	24.9 (11.1 , 24.9)	0.3548 (0.1472 , 0.8551) 0.0162	
Rest of World	41	14 (34.1)	19.6 (19.4 , NE)	36	18 (50.0)	9.7 (5.6 , 18.2)	0.4070 (0.1944 , 0.8520) 0.0131	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	18 (25.4)	19.6 (19.4 , NE)	72	27 (37.5)	18.2 (7.9 , 24.9)	0.4481 (0.2425 , 0.8278) 0.0087	0.1164
Black or African American	10	7 (70.0)	5.6 (1.4 , NE)	9	3 (33.3)	NE (1.4 , NE)	1.9282 (0.4956 , 7.5022) 0.3445	
Asian	152	66 (43.4)	18.7 (10.3 , NE)	162	68 (42.0)	12.4 (6.7 , NE)	0.7835 (0.5570 , 1.1020) 0.1585	
Other	28	4 (14.3)	NE (15.2 , NE)	20	6 (30.0)	NE (7.1 , NE)	0.2720 (0.0736 , 1.0053) 0.0384	
ECOG PS								
0	154	53 (34.4)	20.1 (18.7 , NE)	175	68 (38.9)	18.2 (8.4 , NE)	0.5987 (0.4159 , 0.8620) 0.0054	0.6063
1	106	42 (39.6)	25.0 (11.1 , NE)	87	36 (41.4)	24.9 (5.6 , 24.9)	0.7260 (0.4630 , 1.1383) 0.1570	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	47 (35.3)	20.1 (15.9 , NE)	139	54 (38.8)	20.7 (8.4 , NE)	0.6548 (0.4412 , 0.9719) 0.0344	0.9758
Negative	126	47 (37.3)	19.6 (14.8 , NE)	122	49 (40.2)	18.2 (7.9 , NE)	0.6638 (0.4421 , 0.9966) 0.0457	
Estrogen Receptors								
Positive	129	45 (34.9)	25.0 (18.7 , NE)	132	50 (37.9)	20.7 (8.4 , NE)	0.6755 (0.4500 , 1.0140) 0.0569	0.8974
Negative	130	49 (37.7)	19.6 (14.8 , NE)	128	52 (40.6)	12.4 (7.9 , NE)	0.6526 (0.4389 , 0.9703) 0.0331	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	23 (28.4)	25.0 (15.9 , 25.0)	92	36 (39.1)	20.7 (6.9 , NE)	0.5198 (0.3057 , 0.8838) 0.0142	0.2871
Negative	177	71 (40.1)	19.4 (14.8 , NE)	168	67 (39.9)	18.2 (8.4 , NE)	0.7307 (0.5211 , 1.0247) 0.0669	
Prior Treatment with Pertuzumab								
Yes	162	64 (39.5)	20.1 (15.2 , NE)	158	63 (39.9)	18.2 (7.9 , NE)	0.6891 (0.4841 , 0.9810) 0.0380	0.7917
No	99	31 (31.3)	19.4 (16.7 , NE)	105	41 (39.0)	12.4 (8.4 , NE)	0.6272 (0.3926 , 1.0022) 0.0479	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	67 (35.6)	25.0 (18.7 , NE)	191	79 (41.4)	12.4 (8.4 , NE)	0.5789 (0.4165 , 0.8047) 0.0010	0.1476
>= 3 lines	73	28 (38.4)	19.4 (11.1 , NE)	72	25 (34.7)	24.9 (7.0 , 24.9)	0.9806 (0.5691 , 1.6895) 0.9197	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	63 (40.4)	20.1 (14.8 , NE)	152	63 (41.4)	18.2 (6.9 , NE)	0.6764 (0.4744 , 0.9645) 0.0301	0.2228
>= 3 lines	6	1 (16.7)	NE (8.5 , NE)	6	0	NE (NE , NE)	NE (NE, NE) 0.4795	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	50 (38.5)	19.6 (18.7 , NE)	130	50 (38.5)	NE (7.0 , NE)	0.6668 (0.4457 , 0.9976) 0.0470	0.5194
Mild Impairment	92	34 (37.0)	NE (11.1 , NE)	104	43 (41.3)	18.2 (8.4 , NE)	0.7376 (0.4695 , 1.1588) 0.1848	
Moderate Impairment	30	10 (33.3)	20.1 (12.5 , NE)	22	10 (45.5)	5.3 (2.8 , NE)	0.3876 (0.1587 , 0.9466) 0.0322	
Hepatic Impairment								
Within Normal Range	208	77 (37.0)	20.1 (18.7 , NE)	212	90 (42.5)	12.4 (7.9 , NE)	0.6221 (0.4572 , 0.8466) 0.0023	0.3830
Mild Impairment	49	18 (36.7)	19.4 (9.5 , NE)	49	14 (28.6)	20.7 (8.4 , NE)	0.9075 (0.4491 , 1.8338) 0.7820	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	72 (36.9)	19.4 (15.9 , NE)	189	71 (37.6)	18.2 (8.5 , NE)	0.6879 (0.4935 , 0.9589) 0.0263	0.3612
No	66	23 (34.8)	25.0 (19.6 , NE)	74	33 (44.6)	12.4 (4.2 , 24.9)	0.5571 (0.3228 , 0.9612) 0.0329	
Baseline CNS Metastases								
Yes	43	18 (41.9)	NE (5.6 , NE)	39	17 (43.6)	18.2 (3.7 , 18.2)	0.7400 (0.3790 , 1.4449) 0.3722	0.8366
No	218	77 (35.3)	20.1 (18.7 , NE)	224	87 (38.8)	20.7 (8.6 , NE)	0.6436 (0.4721 , 0.8776) 0.0050	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Arm Symptoms

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	23 (37.1)	19.6 (8.3 , NE)	52	25 (48.1)	8.4 (3.3 , 18.2)	0.5607 (0.3139 , 1.0016) 0.0470	0.4843
No	199	72 (36.2)	25.0 (18.7 , NE)	211	79 (37.4)	20.7 (10.6 , NE)	0.6829 (0.4945 , 0.9430) 0.0197	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Age								
<65	212	19 (9.0)	NE (11.8 , NE)	206	3 (1.5)	NE (NE , NE)	4.0230 (1.1856 , 13.651) 0.0156	0.2759
>=65	49	4 (8.2)	NE (2.8 , NE)	57	0	NE (NE , NE)	NE (NE, NE) 0.0907	
Age								
<75	253	22 (8.7)	NE (12.4 , NE)	255	3 (1.2)	NE (NE , NE)	4.7359 (1.4132 , 15.871) 0.0054	NE
>=75	8	1 (12.5)	1.4 (NE , NE)	8	0	NE (NE , NE)	NE (NE , NE) NE	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Region								
Asia	149	14 (9.4)	NE (4.2 , NE)	160	1 (0.6)	NE (NE , NE)	11.7303 (1.5401 , 89.342) 0.002	0.5316
North America	17	2 (11.8)	NE (0.9 , NE)	17	0	NE (NE , NE)	NE (NE, NE) 0.6270	
Europe	54	3 (5.6)	18.0 (2.8 , NE)	50	1 (2.0)	NE (1.4 , NE)	1.4264 (0.1288 , 15.793) 0.7710	
Rest of World	41	4 (9.8)	NE (1.4 , NE)	36	1 (2.8)	NE (7.9 , NE)	1.9194 (0.2133 , 17.274) 0.5609	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Race								
White	71	6 (8.5)	NE (1.4 , NE)	72	1 (1.4)	NE (7.9 , NE)	2.9156 (0.3498 , 24.301) 0.3053	0.2053
Black or African American	10	0	NE (NE , NE)	9	0	NE (NE , NE)	NE (NE , NE) NE	
Asian	152	14 (9.2)	NE (8.2 , NE)	162	1 (0.6)	NE (NE , NE)	11.7570 (1.5434 , 89.557) 0.002	
Other	28	3 (10.7)	18.0 (2.8 , 18.0)	20	1 (5.0)	NE (1.4 , NE)	0.4524 (0.0401 , 5.1100) 0.5109	
ECOG PS								
0	154	12 (7.8)	NE (11.8 , NE)	175	2 (1.1)	NE (NE , NE)	3.9740 (0.8875 , 17.795) 0.0517	0.6811
1	106	11 (10.4)	NE (1.4 , NE)	87	1 (1.1)	NE (NE , NE)	6.8514 (0.8784 , 53.441) 0.0308	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Hormone Receptor Status								
Positive	133	9 (6.8)	NE (18.0 , NE)	139	0	NE (NE , NE)	NE (NE, NE) 0.0111	0.0778
Negative	126	14 (11.1)	11.8 (2.8 , NE)	122	3 (2.5)	NE (7.9 , NE)	2.6690 (0.7633 , 9.3322) 0.1103	
Estrogen Receptors								
Positive	129	8 (6.2)	NE (NE , NE)	132	0	NE (NE , NE)	NE (NE, NE) 0.0155	0.1108
Negative	130	15 (11.5)	12.4 (2.8 , NE)	128	3 (2.3)	NE (7.9 , NE)	2.8104 (0.8034 , 9.8309) 0.0918	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Progesterone Receptors								
Positive	81	8 (9.9)	18.0 (1.4 , NE)	92	0	NE (NE , NE)	NE (NE, NE) 0.0076	0.0708
Negative	177	15 (8.5)	NE (8.2 , NE)	168	3 (1.8)	NE (NE , NE)	2.7902 (0.8064 , 9.6539) 0.0906	
Prior Treatment with Pertuzumab								
Yes	162	11 (6.8)	NE (8.2 , NE)	158	3 (1.9)	NE (NE , NE)	3.0857 (0.8538 , 11.152) 0.0702	0.1184
No	99	12 (12.1)	NE (4.2 , NE)	105	0	NE (NE , NE)	NE (NE, NE) 0.0233	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Lines of Prior Systemic Therapy Not Including Hormone Therapy								
< 3 lines	188	14 (7.4)	NE (8.2 , NE)	191	2 (1.0)	NE (NE , NE)	4.5384 (1.0291 , 20.014) 0.0278	0.8195
>= 3 lines	73	9 (12.3)	NE (1.5 , NE)	72	1 (1.4)	NE (7.9 , NE)	5.2607 (0.6538 , 42.330) 0.0817	
Lines of Systemic Therapy Prior to Pertuzumab Treatment								
< 3 lines	156	11 (7.1)	NE (3.1 , NE)	152	3 (2.0)	NE (NE , NE)	3.3768 (0.9347 , 12.199) 0.0486	NE
>= 3 lines	6	0	NE (NE , NE)	6	0	NE (NE , NE)	NE (NE , NE) NE	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Renal Impairment at Baseline								
Within Normal Range	130	9 (6.9)	NE (4.2 , NE)	130	2 (1.5)	NE (7.9 , NE)	2.8992 (0.6258 , 13.431) 0.1553	0.2885
Mild Impairment	92	9 (9.8)	NE (1.4 , NE)	104	1 (1.0)	NE (NE , NE)	8.7962 (1.1094 , 69.744) 0.0128	
Moderate Impairment	30	4 (13.3)	18.0 (0.9 , NE)	22	0	NE (NE , NE)	NE (NE , NE) NE	
Hepatic Impairment								
Within Normal Range	208	16 (7.7)	NE (12.4 , NE)	212	3 (1.4)	NE (NE , NE)	4.1400 (1.2003 , 14.279) 0.0147	0.3536
Mild Impairment	49	7 (14.3)	NE (2.8 , NE)	49	0	NE (NE , NE)	NE (NE, NE) 0.1442	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
Baseline Visceral Disease								
Yes	195	21 (10.8)	18.0 (11.8 , NE)	189	2 (1.1)	NE (NE , NE)	5.8667 (1.3715 , 25.095) 0.0069	0.5027
No	66	2 (3.0)	NE (0.9 , NE)	74	1 (1.4)	NE (1.4 , NE)	2.4207 (0.2187 , 26.791) 0.4507	
Baseline CNS Metastases								
Yes	43	4 (9.3)	NE (1.4 , NE)	39	0	NE (NE , NE)	NE (NE, NE) 0.0667	0.2735
No	218	19 (8.7)	NE (11.8 , NE)	224	3 (1.3)	NE (NE , NE)	3.8995 (1.1507 , 13.214) 0.0183	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 60 Analysis of time to definitive deterioration of EORTC QLQ-BR23 by pre-specified Subgroup – Threshold 10 – Full Analysis Set

Symptom Scales/Upset by Hair Loss

	T-DXd (N=261)			T-DM1 (N=263)			T-DXd vs T-DM1	Interaction
Subgroup	n	No. of Events (%)	Median (95% CI) [a] (months)	n	No. of Events (%)	Median (95% CI) [a] (months)	Hazard Ratio (95% CI) p-value[b]	p-value [c]
History of CNS Metastases								
Yes	62	5 (8.1)	NE (1.4 , NE)	52	0	NE (NE , NE)	NE (NE, NE) 0.0501	0.2307
No	199	18 (9.0)	NE (11.8 , NE)	211	3 (1.4)	NE (NE , NE)	3.7435 (1.0998 , 12.742) 0.0232	

Notes: Time to definitive deterioration is defined as the time from randomization until the date of the first symptom deterioration, out of the two consecutive visits for which a deterioration should be observed. Deterioration is defined as an increase of 10 or more points each scale.
[a] Median is from Kaplan-Meier analysis. Confidence Interval (CI) for median was computed using the Brookmeyer-Crowley method.
[b] Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. P-value from unstratified log-rank test.
[c] P-value for interaction term is from unstratified Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
<65	T-DXd (N=209)	208 (99.5)	10.72 (1.36, 84.54)	1.05 (1.01, 1.08)	0.044 (0.013, 0.075)	1.46 (1.19, 1.78)	0.8396
	T-DM1 (N=204)	194 (95.1)				<.0001	
>=65	T-DXd (N=48)	48 (100)	NE (NE, NE)	1.04 (0.99, 1.09)	0.035 (-0.013, 0.083)	1.67 (1.12, 2.49)	
	T-DM1 (N=57)	55 (96.5)				0.0064	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Serious TEAE							
<65	T-DXd (N=209)	31 (14.8)	1.19 (0.68, 2.09)	1.16 (0.72, 1.89)	0.021 (-0.046, 0.087)	0.87 (0.51, 1.48)	0.9513
	T-DM1 (N=204)	26 (12.7)				0.6008	
>=65	T-DXd (N=48)	18 (37.5)	1.03 (0.46, 2.28)	1.02 (0.62, 1.68)	0.007 (-0.179, 0.192)	0.73 (0.39, 1.38)	
	T-DM1 (N=57)	21 (36.8)				0.3309	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with Study Drug Discontinuation							
<65	T-DXd (N=209)	26 (12.4)	2.49 (1.20, 5.19)	2.31 (1.17, 4.55)	0.070 (0.016, 0.125)	1.31 (0.64, 2.67)	0.6419
	T-DM1 (N=204)	11 (5.4)				0.4576	
>=65	T-DXd (N=48)	9 (18.8)	1.41 (0.50, 4.00)	1.34 (0.56, 3.19)	0.047 (-0.095, 0.190)	1.00 (0.39, 2.61)	
	T-DM1 (N=57)	8 (14.0)				0.9992	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Severe TEAE (CTCAE Grade >=3)							
<65	T-DXd (N=209)	102 (48.8)	1.14 (0.77, 1.67)	1.07 (0.87, 1.31)	0.032 (-0.064, 0.128)	0.78 (0.59, 1.03)	0.3327
	T-DM1 (N=204)	93 (45.6)				0.0983	
>=65	T-DXd (N=48)	32 (66.7)	1.45 (0.65, 3.23)	1.15 (0.85, 1.55)	0.088 (-0.097, 0.273)	0.96 (0.58, 1.56)	
	T-DM1 (N=57)	33 (57.9)				0.9128	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with an Outcome of Death							
<65	T-DXd (N=209)	2 (1.0)	0.48 (0.09, 2.67)	0.49 (0.09, 2.64)	-0.010 (-0.033, 0.013)	0.39 (0.07, 2.14)	0.1431
	T-DM1 (N=204)	4 (2.0)				0.2614	
>=65	T-DXd (N=48)	3 (6.3)	3.73 (0.38, 37.10)	3.56 (0.38, 33.14)	0.045 (-0.032, 0.121)	2.73 (0.28, 26.74)	
	T-DM1 (N=57)	1 (1.8)				0.3702	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
<75	T-DXd (N=250)	249 (99.6)	12.40 (1.60, 96.08)	1.05 (1.02, 1.08)	0.043 (0.016, 0.071)	1.50 (1.25, 1.80)	0.9675
	T-DM1 (N=253)	241 (95.3)				<.0001	
>=75	T-DXd (N=7)	7 (100)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	1.68 (0.56, 5.05)	
	T-DM1 (N=8)	8 (100)				0.3311	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Serious TEAE							
<75	T-DXd (N=250)	46 (18.4)	1.04 (0.66, 1.64)	1.03 (0.71, 1.50)	0.006 (-0.061, 0.073)	0.71 (0.47, 1.09)	0.4613
	T-DM1 (N=253)	45 (17.8)				0.1133	
>=75	T-DXd (N=7)	3 (42.9)	2.25 (0.25, 20.13)	1.71 (0.39, 7.48)	0.179 (-0.295, 0.652)	1.57 (0.26, 9.42)	
	T-DM1 (N=8)	2 (25.0)				0.6220	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with Study Drug Discontinuation							
<75	T-DXd (N=250)	34 (13.6)	2.06 (1.13, 3.75)	1.91 (1.11, 3.29)	0.065 (0.012, 0.118)	1.14 (0.64, 2.02)	0.6746
	T-DM1 (N=253)	18 (7.1)				0.6637	
>=75	T-DXd (N=7)	1 (14.3)	1.17 (0.06, 22.94)	1.14 (0.09, 15.08)	0.018 (-0.328, 0.364)	0.90 (0.06, 14.72)	
	T-DM1 (N=8)	1 (12.5)				0.9432	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Severe TEAE (CTCAE Grade >=3)							
<75	T-DXd (N=250)	130 (52.0)	1.13 (0.79, 1.60)	1.06 (0.89, 1.26)	0.030 (-0.057, 0.117)	0.77 (0.60, 0.98)	0.1577
	T-DM1 (N=253)	124 (49.0)				0.0459	
>=75	T-DXd (N=7)	4 (57.1)	4.00 (0.45, 35.79)	2.29 (0.59, 8.91)	0.321 (-0.152, 0.795)	2.36 (0.43, 12.89)	
	T-DM1 (N=8)	2 (25.0)				0.2882	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with an Outcome of Death							
<75	T-DXd (N=250)	5 (2.0)	1.01 (0.29, 3.54)	1.01 (0.30, 3.45)	0.000 (-0.024, 0.025)	0.76 (0.22, 2.67)	0.9999
	T-DM1 (N=253)	5 (2.0)				0.6662	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Region	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
Asia	T-DXd (N=147)	146 (99.3)	8.76 (1.10, 69.97)	1.05 (1.01, 1.10)	0.050 (0.012, 0.088)	1.53 (1.22, 1.94)	0.5060
	T-DM1 (N=159)	150 (94.3)				<.0001	
North America	T-DXd (N=17)	17 (100)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.94 (0.47, 1.88)	
	T-DM1 (N=17)	17 (100)				0.8767	
Europe	T-DXd (N=52)	52 (100)	NE (NE, NE)	1.07 (0.99, 1.14)	0.061 (-0.006, 0.128)	1.56 (1.04, 2.34)	
	T-DM1 (N=49)	46 (93.9)				0.0318	
Rest of World	T-DXd (N=41)	41 (100)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	1.36 (0.86, 2.17)	
	T-DM1 (N=36)	36 (100)				0.1802	
Serious TEAE							
Asia	T-DXd (N=147)	27 (18.4)	0.93 (0.52, 1.65)	0.94 (0.59, 1.50)	-0.011 (-0.099, 0.077)	0.60 (0.36, 1.03)	0.7117

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Region							
	T-DM1 (N=159)	31 (19.5)				0.0622	
North America	T-DXd (N=17)	1 (5.9)	1.00 (0.06, 17.41)	1.00 (0.07, 14.72)	0.000 (-0.158, 0.158)	0.80 (0.05, 13.07)	
	T-DM1 (N=17)	1 (5.9)				0.8782	
Europe	T-DXd (N=52)	11 (21.2)	1.61 (0.57, 4.56)	1.48 (0.62, 3.51)	0.069 (-0.079, 0.217)	1.10 (0.42, 2.90)	
	T-DM1 (N=49)	7 (14.3)				0.8500	
Rest of World	T-DXd (N=41)	10 (24.4)	1.13 (0.39, 3.26)	1.10 (0.49, 2.48)	0.022 (-0.167, 0.211)	0.91 (0.35, 2.31)	
	T-DM1 (N=36)	8 (22.2)				0.8321	
TEAE associated with Study Drug Discontinuation							
Asia	T-DXd (N=147)	22 (15.0)	1.98 (0.96, 4.09)	1.83 (0.96, 3.50)	0.068 (-0.004, 0.140)	0.96 (0.48, 1.92)	0.8767
	T-DM1 (N=159)	13 (8.2)				0.9063	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Region							
North America	T-DXd (N=17)	1 (5.9)	1.00 (0.06, 17.41)	1.00 (0.07, 14.72)	0.000 (-0.158, 0.158)	0.60 (0.04, 9.60)	
	T-DM1 (N=17)	1 (5.9)				0.7148	
Europe	T-DXd (N=52)	6 (11.5)	2.00 (0.47, 8.48)	1.88 (0.50, 7.12)	0.054 (-0.056, 0.164)	1.48 (0.37, 5.92)	
	T-DM1 (N=49)	3 (6.1)				0.5822	
Rest of World	T-DXd (N=41)	6 (14.6)	2.91 (0.55, 15.46)	2.63 (0.57, 12.24)	0.091 (-0.041, 0.222)	1.94 (0.39, 9.67)	
	T-DM1 (N=36)	2 (5.6)				0.4105	
Severe TEAE (CTCAE Grade >=3)							
Asia	T-DXd (N=147)	79 (53.7)	1.04 (0.66, 1.63)	1.02 (0.82, 1.25)	0.009 (-0.103, 0.121)	0.68 (0.50, 0.93)	0.1700
	T-DM1 (N=159)	84 (52.8)				0.0234	
North America	T-DXd (N=17)	9 (52.9)	5.25 (1.09, 25.21)	3.00 (0.98, 9.20)	0.353 (0.054, 0.651)	2.91 (0.79, 10.77)	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
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Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Region							
	T-DM1 (N=17)	3 (17.6)				0.0931	
Europe	T-DXd (N=52)	25 (48.1)	1.23 (0.56, 2.71)	1.12 (0.73, 1.72)	0.052 (-0.142, 0.246)	0.91 (0.51, 1.64)	
	T-DM1 (N=49)	21 (42.9)				0.7657	
Rest of World	T-DXd (N=41)	21 (51.2)	1.05 (0.43, 2.57)	1.02 (0.66, 1.59)	0.012 (-0.212, 0.236)	0.81 (0.43, 1.52)	
	T-DM1 (N=36)	18 (50.0)				0.5090	
TEAE associated with an Outcome of Death							
Asia	T-DXd (N=147)	2 (1.4)	1.08 (0.15, 7.79)	1.08 (0.15, 7.58)	0.001 (-0.024, 0.027)	0.83 (0.11, 6.21)	0.9858
	T-DM1 (N=159)	2 (1.3)				0.8569	
North America	T-DXd (N=17)	1 (5.9)	NE (NE, NE)	NE (NE, NE)	0.059 (-0.053, 0.171)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.4212	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Europe	T-DXd (N=52)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=49)	0				NE	
Rest of World	T-DXd (N=41)	2 (4.9)	0.56 (0.09, 3.58)	0.59 (0.10, 3.31)	-0.035 (-0.146, 0.077)	0.47 (0.08, 2.83)	
	T-DM1 (N=36)	3 (8.3)				0.3987	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Race							
Treatment-Emergent Adverse Events (TEAE)							
White	T-DXd (N=71)	71 (100)	NE (NE, NE)	1.03 (0.99, 1.07)	0.028 (-0.010, 0.067)	1.52 (1.08, 2.14)	0.7681
	T-DM1 (N=71)	69 (97.2)				0.0141	
Black or African American	T-DXd (N=10)	10 (100)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	1.96 (0.72, 5.32)	
	T-DM1 (N=9)	9 (100)				0.1544	
Asian	T-DXd (N=149)	148 (99.3)	8.76 (1.10, 69.99)	1.05 (1.01, 1.09)	0.049 (0.011, 0.087)	1.54 (1.22, 1.93)	
	T-DM1 (N=161)	152 (94.4)				<.0001	
Other	T-DXd (N=27)	27 (100)	NE (NE, NE)	1.05 (0.95, 1.16)	0.050 (-0.046, 0.146)	1.09 (0.60, 1.98)	
	T-DM1 (N=20)	19 (95.0)				0.8560	
Serious TEAE							
White	T-DXd (N=71)	13 (18.3)	1.10 (0.46, 2.62)	1.08 (0.53, 2.21)	0.014 (-0.111, 0.139)	0.83 (0.38, 1.84)	0.7127

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Race							
	T-DM1 (N=71)	12 (16.9)				0.6519	
Black or African American	T-DXd (N=10)	1 (10.0)	0.89 (0.05, 16.66)	0.90 (0.07, 12.38)	-0.011 (-0.288, 0.266)	0.95 (0.06, 15.18)	
	T-DM1 (N=9)	1 (11.1)				0.9703	
Asian	T-DXd (N=149)	27 (18.1)	0.93 (0.52, 1.64)	0.94 (0.59, 1.50)	-0.011 (-0.098, 0.075)	0.61 (0.36, 1.03)	
	T-DM1 (N=161)	31 (19.3)				0.0639	
Other	T-DXd (N=27)	8 (29.6)	2.39 (0.54, 10.48)	1.98 (0.60, 6.52)	0.146 (-0.086, 0.379)	1.42 (0.37, 5.52)	
	T-DM1 (N=20)	3 (15.0)				0.6072	
TEAE associated with Study Drug Discontinuation							
White	T-DXd (N=71)	6 (8.5)	1.22 (0.35, 4.19)	1.20 (0.38, 3.75)	0.014 (-0.074, 0.102)	0.85 (0.26, 2.80)	0.8010
	T-DM1 (N=71)	5 (7.0)				0.7881	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Race							
Black or African American	T-DXd (N=10)	1 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.086, 0.286)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.4561	
Asian	T-DXd (N=149)	22 (14.8)	1.97 (0.95, 4.07)	1.83 (0.96, 3.50)	0.067 (-0.004, 0.138)	0.96 (0.48, 1.93)	
	T-DM1 (N=161)	13 (8.1)				0.9133	
Other	T-DXd (N=27)	6 (22.2)	5.43 (0.60, 49.29)	4.44 (0.58, 34.06)	0.172 (-0.011, 0.356)	3.41 (0.41, 28.33)	
	T-DM1 (N=20)	1 (5.0)				0.2275	
Severe TEAE (CTCAE Grade >=3)							
White	T-DXd (N=71)	34 (47.9)	1.41 (0.73, 2.75)	1.21 (0.83, 1.77)	0.085 (-0.078, 0.247)	1.00 (0.61, 1.66)	0.4430
	T-DM1 (N=71)	28 (39.4)				0.9820	
Black or African American	T-DXd (N=10)	6 (60.0)	1.87 (0.30, 11.63)	1.35 (0.56, 3.28)	0.156 (-0.289, 0.600)	1.31 (0.37, 4.68)	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
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Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Race							
	T-DM1 (N=9)	4 (44.4)				0.6833	
Asian	T-DXd (N=149)	80 (53.7)	1.04 (0.66, 1.62)	1.02 (0.83, 1.25)	0.009 (-0.102, 0.120)	0.68 (0.50, 0.93)	
	T-DM1 (N=161)	85 (52.8)				0.0243	
Other	T-DXd (N=27)	14 (51.9)	1.32 (0.41, 4.20)	1.15 (0.63, 2.11)	0.069 (-0.220, 0.357)	0.87 (0.37, 2.06)	
	T-DM1 (N=20)	9 (45.0)				0.7656	
TEAE associated with an Outcome of Death							
White	T-DXd (N=71)	3 (4.2)	1.52 (0.25, 9.39)	1.50 (0.26, 8.71)	0.014 (-0.047, 0.075)	1.15 (0.19, 6.91)	0.9923
	T-DM1 (N=71)	2 (2.8)				0.8799	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	-0.111 (-0.316, 0.094)	NE (NE, NE)	
	T-DM1 (N=9)	1 (11.1)				0.2918	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Asian	T-DXd (N=149)	2 (1.3)	1.08 (0.15, 7.78)	1.08 (0.15, 7.57)	0.001 (-0.024, 0.026)	0.83 (0.11, 6.23)	
	T-DM1 (N=161)	2 (1.2)				0.8601	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=20)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
0	T-DXd (N=152)	151 (99.3)	8.23 (1.03, 65.75)	1.05 (1.01, 1.09)	0.045 (0.010, 0.080)	1.42 (1.14, 1.78)	0.5715
	T-DM1 (N=174)	165 (94.8)				0.0010	
1	T-DXd (N=105)	105 (100)	NE (NE, NE)	1.04 (1.00, 1.08)	0.034 (-0.004, 0.073)	1.65 (1.22, 2.22)	
	T-DM1 (N=87)	84 (96.6)				0.0004	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Serious TEAE							
0	T-DXd (N=152)	25 (16.4)	1.29 (0.70, 2.39)	1.24 (0.74, 2.10)	0.032 (-0.045, 0.110)	0.79 (0.45, 1.42)	0.4660
	T-DM1 (N=174)	23 (13.2)				0.4366	
1	T-DXd (N=105)	24 (22.9)	0.78 (0.40, 1.50)	0.83 (0.51, 1.35)	-0.047 (-0.171, 0.076)	0.63 (0.36, 1.13)	
	T-DM1 (N=87)	24 (27.6)				0.1203	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with Study Drug Discontinuation							
0	T-DXd (N=152)	19 (12.5)	2.12 (0.97, 4.60)	1.98 (0.97, 4.02)	0.062 (-0.002, 0.126)	1.12 (0.53, 2.37)	0.7914
	T-DM1 (N=174)	11 (6.3)				0.7730	
1	T-DXd (N=105)	16 (15.2)	1.78 (0.72, 4.37)	1.66 (0.74, 3.69)	0.060 (-0.031, 0.152)	1.07 (0.45, 2.51)	
	T-DM1 (N=87)	8 (9.2)				0.8847	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Severe TEAE (CTCAE Grade >=3)							
0	T-DXd (N=152)	74 (48.7)	1.17 (0.75, 1.81)	1.09 (0.86, 1.37)	0.039 (-0.070, 0.147)	0.77 (0.56, 1.06)	0.9218
	T-DM1 (N=174)	78 (44.8)				0.1316	
1	T-DXd (N=105)	60 (57.1)	1.08 (0.61, 1.92)	1.04 (0.81, 1.33)	0.020 (-0.121, 0.161)	0.79 (0.54, 1.16)	
	T-DM1 (N=87)	48 (55.2)				0.2424	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with an Outcome of Death							
0	T-DXd (N=152)	2 (1.3)	0.76 (0.13, 4.61)	0.76 (0.13, 4.51)	-0.004 (-0.031, 0.022)	0.51 (0.08, 3.18)	0.6646
	T-DM1 (N=174)	3 (1.7)				0.4600	
1	T-DXd (N=105)	3 (2.9)	1.25 (0.20, 7.65)	1.24 (0.21, 7.27)	0.006 (-0.039, 0.050)	0.99 (0.16, 5.99)	
	T-DM1 (N=87)	2 (2.3)				0.9946	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
Positive	T-DXd (N=133)	133 (100)	NE (NE, NE)	1.05 (1.01, 1.08)	0.043 (0.009, 0.077)	1.46 (1.14, 1.87)	0.8257
	T-DM1 (N=139)	133 (95.7)				0.0011	
Negative	T-DXd (N=123)	122 (99.2)	6.37 (0.75, 53.68)	1.04 (1.00, 1.09)	0.041 (0.000, 0.083)	1.52 (1.17, 1.97)	
	T-DM1 (N=121)	115 (95.0)				0.0006	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Serious TEAE							
Positive	T-DXd (N=133)	21 (15.8)	0.90 (0.47, 1.71)	0.91 (0.54, 1.56)	-0.015 (-0.103, 0.073)	0.64 (0.35, 1.15)	0.4667
	T-DM1 (N=139)	24 (17.3)				0.1343	
Negative	T-DXd (N=123)	28 (22.8)	1.26 (0.68, 2.33)	1.20 (0.73, 1.96)	0.038 (-0.064, 0.139)	0.85 (0.48, 1.49)	
	T-DM1 (N=121)	23 (19.0)				0.5603	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with Study Drug Discontinuation							
Positive	T-DXd (N=133)	17 (12.8)	2.40 (1.00, 5.77)	2.22 (0.99, 4.97)	0.070 (0.002, 0.139)	1.37 (0.58, 3.19)	0.6147
	T-DM1 (N=139)	8 (5.8)				0.4699	
Negative	T-DXd (N=123)	18 (14.6)	1.71 (0.77, 3.80)	1.61 (0.79, 3.26)	0.055 (-0.025, 0.136)	0.96 (0.45, 2.05)	
	T-DM1 (N=121)	11 (9.1)				0.9173	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Severe TEAE (CTCAE Grade >=3)							
Positive	T-DXd (N=133)	74 (55.6)	1.39 (0.86, 2.24)	1.17 (0.93, 1.48)	0.082 (-0.037, 0.200)	0.88 (0.63, 1.24)	0.3844
	T-DM1 (N=139)	66 (47.5)				0.5028	
Negative	T-DXd (N=123)	60 (48.8)	0.97 (0.59, 1.60)	0.98 (0.76, 1.27)	-0.008 (-0.134, 0.117)	0.71 (0.49, 1.02)	
	T-DM1 (N=121)	60 (49.6)				0.0789	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with an Outcome of Death							
Positive	T-DXd (N=133)	3 (2.3)	1.05 (0.21, 5.28)	1.05 (0.21, 5.09)	0.001 (-0.034, 0.036)	0.69 (0.14, 3.48)	0.9737
	T-DM1 (N=139)	3 (2.2)				0.6472	
Negative	T-DXd (N=123)	2 (1.6)	0.98 (0.14, 7.10)	0.98 (0.14, 6.87)	0.000 (-0.032, 0.032)	0.91 (0.13, 6.47)	
	T-DM1 (N=121)	2 (1.7)				0.9233	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
Positive	T-DXd (N=129)	129 (100)	NE (NE, NE)	1.05 (1.01, 1.09)	0.045 (0.010, 0.081)	1.53 (1.19, 1.97)	0.7950
	T-DM1 (N=132)	126 (95.5)				0.0004	
Negative	T-DXd (N=127)	126 (99.2)	6.25 (0.74, 52.66)	1.04 (1.00, 1.09)	0.039 (-0.001, 0.079)	1.46 (1.13, 1.87)	
	T-DM1 (N=127)	121 (95.3)				0.0017	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Serious TEAE							
Positive	T-DXd (N=129)	20 (15.5)	0.83 (0.43, 1.58)	0.85 (0.50, 1.47)	-0.027 (-0.118, 0.064)	0.59 (0.32, 1.08)	0.3098
	T-DM1 (N=132)	24 (18.2)				0.0833	
Negative	T-DXd (N=127)	29 (22.8)	1.34 (0.72, 2.47)	1.26 (0.77, 2.06)	0.047 (-0.052, 0.146)	0.89 (0.51, 1.56)	
	T-DM1 (N=127)	23 (18.1)				0.6790	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with Study Drug Discontinuation							
Positive	T-DXd (N=129)	16 (12.4)	2.19 (0.90, 5.32)	2.05 (0.91, 4.62)	0.063 (-0.007, 0.133)	1.25 (0.53, 2.94)	0.7917
	T-DM1 (N=132)	8 (6.1)				0.6152	
Negative	T-DXd (N=127)	19 (15.0)	1.86 (0.84, 4.08)	1.73 (0.86, 3.48)	0.063 (-0.016, 0.142)	1.03 (0.48, 2.18)	
	T-DM1 (N=127)	11 (8.7)				0.9463	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Severe TEAE (CTCAE Grade >=3)							
Positive	T-DXd (N=129)	71 (55.0)	1.22 (0.75, 1.99)	1.10 (0.87, 1.39)	0.050 (-0.071, 0.171)	0.81 (0.57, 1.13)	0.8514
	T-DM1 (N=132)	66 (50.0)				0.2333	
Negative	T-DXd (N=127)	63 (49.6)	1.10 (0.67, 1.80)	1.05 (0.81, 1.35)	0.024 (-0.099, 0.147)	0.77 (0.54, 1.11)	
	T-DM1 (N=127)	60 (47.2)				0.1876	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with an Outcome of Death							
Positive	T-DXd (N=129)	3 (2.3)	1.02 (0.20, 5.17)	1.02 (0.21, 4.98)	0.001 (-0.036, 0.037)	0.67 (0.13, 3.41)	0.9934
	T-DM1 (N=132)	3 (2.3)				0.6285	
Negative	T-DXd (N=127)	2 (1.6)	1.00 (0.14, 7.21)	1.00 (0.14, 6.99)	0.000 (-0.031, 0.031)	0.92 (0.13, 6.54)	
	T-DM1 (N=127)	2 (1.6)				0.9315	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
Positive	T-DXd (N=81)	81 (100)	NE (NE, NE)	1.03 (1.00, 1.07)	0.033 (-0.004, 0.069)	1.30 (0.96, 1.77)	0.2570
	T-DM1 (N=92)	89 (96.7)				0.0583	
Negative	T-DXd (N=174)	173 (99.4)	9.85 (1.23, 78.59)	1.05 (1.01, 1.09)	0.048 (0.012, 0.084)	1.62 (1.30, 2.02)	
	T-DM1 (N=167)	158 (94.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Serious TEAE							
Positive	T-DXd (N=81)	9 (11.1)	0.76 (0.31, 1.88)	0.79 (0.35, 1.74)	-0.030 (-0.129, 0.069)	0.58 (0.25, 1.38)	0.4335
	T-DM1 (N=92)	13 (14.1)				0.2169	
Negative	T-DXd (N=174)	40 (23.0)	1.17 (0.70, 1.96)	1.13 (0.75, 1.69)	0.026 (-0.061, 0.114)	0.78 (0.49, 1.24)	
	T-DM1 (N=167)	34 (20.4)				0.2911	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with Study Drug Discontinuation							
Positive	T-DXd (N=81)	8 (9.9)	1.57 (0.52, 4.73)	1.51 (0.55, 4.18)	0.034 (-0.049, 0.116)	0.96 (0.33, 2.78)	0.5422
	T-DM1 (N=92)	6 (6.5)				0.9335	
Negative	T-DXd (N=174)	27 (15.5)	2.18 (1.08, 4.38)	1.99 (1.07, 3.73)	0.077 (0.010, 0.145)	1.21 (0.62, 2.35)	
	T-DM1 (N=167)	13 (7.8)				0.5810	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Severe TEAE (CTCAE Grade >=3)							
Positive	T-DXd (N=81)	43 (53.1)	1.23 (0.68, 2.24)	1.11 (0.83, 1.49)	0.053 (-0.096, 0.202)	0.80 (0.52, 1.22)	0.9817
	T-DM1 (N=92)	44 (47.8)				0.3157	
Negative	T-DXd (N=174)	91 (52.3)	1.14 (0.74, 1.74)	1.07 (0.86, 1.31)	0.032 (-0.074, 0.138)	0.80 (0.59, 1.08)	
	T-DM1 (N=167)	82 (49.1)				0.1778	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with an Outcome of Death							
Positive	T-DXd (N=81)	2 (2.5)	0.75 (0.12, 4.61)	0.76 (0.13, 4.42)	-0.008 (-0.058, 0.042)	0.52 (0.09, 3.18)	0.5916
	T-DM1 (N=92)	3 (3.3)				0.4720	
Negative	T-DXd (N=174)	3 (1.7)	1.45 (0.24, 8.77)	1.44 (0.24, 8.51)	0.005 (-0.020, 0.031)	1.14 (0.19, 6.99)	
	T-DM1 (N=167)	2 (1.2)				0.8891	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
Yes	T-DXd (N=160)	159 (99.4)	5.23 (0.60, 45.28)	1.03 (1.00, 1.06)	0.026 (-0.004, 0.056)	1.59 (1.27, 2.00)	0.5428
	T-DM1 (N=157)	152 (96.8)				<.0001	
No	T-DXd (N=97)	97 (100)	NE (NE, NE)	1.07 (1.02, 1.13)	0.067 (0.019, 0.115)	1.40 (1.05, 1.86)	
	T-DM1 (N=104)	97 (93.3)				0.0123	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Serious TEAE							
Yes	T-DXd (N=160)	24 (15.0)	0.98 (0.53, 1.81)	0.98 (0.58, 1.65)	-0.003 (-0.082, 0.076)	0.63 (0.35, 1.13)	0.5271
	T-DM1 (N=157)	24 (15.3)				0.1206	
No	T-DXd (N=97)	25 (25.8)	1.22 (0.64, 2.34)	1.17 (0.71, 1.91)	0.037 (-0.081, 0.155)	0.85 (0.48, 1.51)	
	T-DM1 (N=104)	23 (22.1)				0.5823	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with Study Drug Discontinuation							
Yes	T-DXd (N=160)	17 (10.6)	1.44 (0.66, 3.12)	1.39 (0.69, 2.81)	0.030 (-0.033, 0.093)	0.76 (0.36, 1.62)	0.1575
	T-DM1 (N=157)	12 (7.6)				0.4795	
No	T-DXd (N=97)	18 (18.6)	3.16 (1.26, 7.94)	2.76 (1.20, 6.31)	0.118 (0.027, 0.209)	1.80 (0.75, 4.32)	
	T-DM1 (N=104)	7 (6.7)				0.1842	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Severe TEAE (CTCAE Grade >=3)							
Yes	T-DXd (N=160)	75 (46.9)	0.99 (0.64, 1.54)	0.99 (0.79, 1.26)	-0.003 (-0.112, 0.107)	0.71 (0.52, 0.99)	0.2377
	T-DM1 (N=157)	74 (47.1)				0.0516	
No	T-DXd (N=97)	59 (60.8)	1.55 (0.89, 2.72)	1.22 (0.95, 1.56)	0.108 (-0.028, 0.245)	0.94 (0.64, 1.37)	
	T-DM1 (N=104)	52 (50.0)				0.7882	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with an Outcome of Death							
Yes	T-DXd (N=160)	2 (1.3)	0.65 (0.11, 3.94)	0.65 (0.11, 3.86)	-0.007 (-0.034, 0.021)	0.50 (0.08, 3.01)	0.4819
	T-DM1 (N=157)	3 (1.9)				0.4366	
No	T-DXd (N=97)	3 (3.1)	1.63 (0.27, 9.96)	1.61 (0.27, 9.42)	0.012 (-0.032, 0.055)	1.22 (0.20, 7.49)	
	T-DM1 (N=104)	2 (1.9)				0.8289	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
< 3 lines	T-DXd (N=186)	185 (99.5)	7.11 (0.87, 58.40)	1.03 (1.00, 1.06)	0.032 (0.003, 0.061)	1.49 (1.21, 1.83)	0.6584
	T-DM1 (N=189)	182 (96.3)				<.0001	
>= 3 lines	T-DXd (N=71)	71 (100)	NE (NE, NE)	1.07 (1.01, 1.14)	0.069 (0.011, 0.128)	1.54 (1.09, 2.17)	
	T-DM1 (N=72)	67 (93.1)				0.0078	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Serious TEAE							
< 3 lines	T-DXd (N=186)	29 (15.6)	0.91 (0.52, 1.57)	0.92 (0.58, 1.46)	-0.013 (-0.088, 0.061)	0.63 (0.38, 1.05)	0.4030
	T-DM1 (N=189)	32 (16.9)				0.0761	
>= 3 lines	T-DXd (N=71)	20 (28.2)	1.49 (0.69, 3.21)	1.35 (0.75, 2.42)	0.073 (-0.067, 0.214)	0.91 (0.46, 1.83)	
	T-DM1 (N=72)	15 (20.8)				0.8001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with Study Drug Discontinuation							
< 3 lines	T-DXd (N=186)	25 (13.4)	2.10 (1.04, 4.25)	1.95 (1.03, 3.70)	0.066 (0.005, 0.126)	1.19 (0.60, 2.33)	0.6666
	T-DM1 (N=189)	13 (6.9)				0.6228	
>= 3 lines	T-DXd (N=71)	10 (14.1)	1.80 (0.62, 5.26)	1.69 (0.65, 4.40)	0.058 (-0.046, 0.161)	0.99 (0.35, 2.77)	
	T-DM1 (N=72)	6 (8.3)				0.9765	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Severe TEAE (CTCAE Grade >=3)							
< 3 lines	T-DXd (N=186)	89 (47.8)	1.01 (0.67, 1.51)	1.00 (0.81, 1.24)	0.002 (-0.099, 0.103)	0.74 (0.55, 0.99)	0.3277
	T-DM1 (N=189)	90 (47.6)				0.0524	
>= 3 lines	T-DXd (N=71)	45 (63.4)	1.73 (0.89, 3.38)	1.27 (0.95, 1.70)	0.134 (-0.027, 0.295)	0.89 (0.57, 1.40)	
	T-DM1 (N=72)	36 (50.0)				0.6420	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with an Outcome of Death							
< 3 lines	T-DXd (N=186)	3 (1.6)	3.08 (0.32, 29.89)	3.05 (0.32, 29.04)	0.011 (-0.010, 0.032)	2.20 (0.23, 21.40)	0.1952
	T-DM1 (N=189)	1 (0.5)				0.4859	
>= 3 lines	T-DXd (N=71)	2 (2.8)	0.49 (0.09, 2.78)	0.51 (0.10, 2.68)	-0.027 (-0.093, 0.038)	0.36 (0.06, 2.11)	
	T-DM1 (N=72)	4 (5.6)				0.2437	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
< 3 lines	T-DXd (N=154)	153 (99.4)	4.16 (0.46, 37.69)	1.02 (0.99, 1.05)	0.020 (-0.009, 0.049)	1.60 (1.27, 2.01)	0.8906
	T-DM1 (N=151)	147 (97.4)				<.0001	
>= 3 lines	T-DXd (N=6)	6 (100)	NE (NE, NE)	1.20 (0.84, 1.72)	0.167 (-0.132, 0.465)	1.61 (0.41, 6.32)	
	T-DM1 (N=6)	5 (83.3)				0.6256	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Serious TEAE							
< 3 lines	T-DXd (N=154)	21 (13.6)	0.88 (0.46, 1.67)	0.90 (0.52, 1.55)	-0.016 (-0.095, 0.063)	0.56 (0.30, 1.03)	0.2910
	T-DM1 (N=151)	23 (15.2)				0.0591	
>= 3 lines	T-DXd (N=6)	3 (50.0)	5.00 (0.34, 72.76)	3.00 (0.42, 21.30)	0.333 (-0.166, 0.832)	2.33 (0.24, 22.56)	
	T-DM1 (N=6)	1 (16.7)				0.4513	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with Study Drug Discontinuation							
< 3 lines	T-DXd (N=154)	17 (11.0)	1.75 (0.77, 3.96)	1.67 (0.79, 3.52)	0.044 (-0.019, 0.108)	0.92 (0.41, 2.03)	0.9903
	T-DM1 (N=151)	10 (6.6)				0.8308	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	-0.333 (-0.711, 0.044)	NE (NE, NE)	
	T-DM1 (N=6)	2 (33.3)				0.0896	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Severe TEAE (CTCAE Grade >=3)							
< 3 lines	T-DXd (N=154)	70 (45.5)	0.96 (0.61, 1.51)	0.98 (0.77, 1.25)	-0.009 (-0.121, 0.103)	0.70 (0.50, 0.99)	0.5070
	T-DM1 (N=151)	70 (46.4)				0.0483	
>= 3 lines	T-DXd (N=6)	5 (83.3)	2.50 (0.16, 38.60)	1.25 (0.64, 2.44)	0.167 (-0.314, 0.647)	0.71 (0.16, 3.23)	
	T-DM1 (N=6)	4 (66.7)				0.6703	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with an Outcome of Death							
< 3 lines	T-DXd (N=154)	1 (0.6)	0.49 (0.04, 5.43)	0.49 (0.04, 5.35)	-0.007 (-0.029, 0.015)	0.40 (0.04, 4.43)	0.7423
	T-DM1 (N=151)	2 (1.3)				0.4398	
>= 3 lines	T-DXd (N=6)	1 (16.7)	1.00 (0.05, 20.83)	1.00 (0.08, 12.56)	0.000 (-0.422, 0.422)	0.63 (0.04, 10.88)	
	T-DM1 (N=6)	1 (16.7)				0.7505	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
Within Normal Range	T-DXd (N=130)	130 (100)	NE (NE, NE)	1.06 (1.01, 1.10)	0.054 (0.015, 0.093)	1.65 (1.28, 2.12)	0.2097
	T-DM1 (N=130)	123 (94.6)				0.0001	
Mild Impairment	T-DXd (N=92)	92 (100)	NE (NE, NE)	1.05 (1.01, 1.10)	0.048 (0.007, 0.089)	1.55 (1.16, 2.08)	
	T-DM1 (N=104)	99 (95.2)				0.0008	
Moderate Impairment	T-DXd (N=30)	29 (96.7)	0.00 (0.00, NE)	0.97 (0.90, 1.03)	-0.033 (-0.098, 0.031)	0.95 (0.53, 1.70)	
	T-DM1 (N=22)	22 (100)				0.9916	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Serious TEAE							
Within Normal Range	T-DXd (N=130)	22 (16.9)	1.69 (0.82, 3.47)	1.57 (0.84, 2.93)	0.062 (-0.022, 0.145)	1.08 (0.54, 2.15)	0.3860
	T-DM1 (N=130)	14 (10.8)				0.8351	
Mild Impairment	T-DXd (N=92)	16 (17.4)	0.67 (0.33, 1.34)	0.72 (0.41, 1.27)	-0.066 (-0.179, 0.046)	0.53 (0.28, 1.01)	
	T-DM1 (N=104)	25 (24.0)				0.0492	
Moderate Impairment	T-DXd (N=30)	10 (33.3)	0.87 (0.28, 2.77)	0.92 (0.43, 1.94)	-0.030 (-0.293, 0.232)	0.65 (0.26, 1.67)	
	T-DM1 (N=22)	8 (36.4)				0.3740	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with Study Drug Discontinuation							
Within Normal Range	T-DXd (N=130)	16 (12.3)	4.42 (1.44, 13.61)	4.00 (1.37, 11.64)	0.092 (0.029, 0.156)	1.96 (0.65, 5.99)	0.2525
	T-DM1 (N=130)	4 (3.1)				0.2260	
Mild Impairment	T-DXd (N=92)	10 (10.9)	0.93 (0.38, 2.28)	0.94 (0.43, 2.08)	-0.007 (-0.095, 0.082)	0.63 (0.27, 1.47)	
	T-DM1 (N=104)	12 (11.5)				0.2824	
Moderate Impairment	T-DXd (N=30)	8 (26.7)	2.30 (0.53, 9.94)	1.96 (0.58, 6.54)	0.130 (-0.083, 0.344)	1.30 (0.34, 4.93)	
	T-DM1 (N=22)	3 (13.6)				0.7004	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Severe TEAE (CTCAE Grade >=3)							
Within Normal Range	T-DXd (N=130)	66 (50.8)	1.41 (0.86, 2.29)	1.20 (0.92, 1.56)	0.085 (-0.036, 0.205)	0.84 (0.58, 1.20)	0.8361
	T-DM1 (N=130)	55 (42.3)				0.3854	
Mild Impairment	T-DXd (N=92)	52 (56.5)	1.16 (0.66, 2.04)	1.07 (0.83, 1.38)	0.036 (-0.103, 0.176)	0.82 (0.56, 1.20)	
	T-DM1 (N=104)	55 (52.9)				0.3403	
Moderate Impairment	T-DXd (N=30)	15 (50.0)	0.69 (0.23, 2.10)	0.85 (0.51, 1.39)	-0.091 (-0.363, 0.182)	0.65 (0.31, 1.41)	
	T-DM1 (N=22)	13 (59.1)				0.2901	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with an Outcome of Death							
Within Normal Range	T-DXd (N=130)	2 (1.5)	1.00 (0.14, 7.21)	1.00 (0.14, 6.99)	0.000 (-0.030, 0.030)	0.62 (0.08, 4.66)	0.8852
	T-DM1 (N=130)	2 (1.5)				0.6373	
Mild Impairment	T-DXd (N=92)	3 (3.3)	1.72 (0.28, 10.52)	1.70 (0.29, 9.93)	0.013 (-0.031, 0.058)	1.37 (0.23, 8.29)	
	T-DM1 (N=104)	2 (1.9)				0.7304	
Moderate Impairment	T-DXd (N=30)	0	NE (NE, NE)	NE (NE, NE)	-0.045 (-0.132, 0.042)	NE (NE, NE)	
	T-DM1 (N=22)	1 (4.5)				0.2429	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
Within Normal Range	T-DXd (N=208)	207 (99.5)	10.25 (1.30, 80.78)	1.04 (1.01, 1.08)	0.042 (0.012, 0.072)	1.46 (1.20, 1.78)	0.3521
	T-DM1 (N=212)	202 (95.3)				<.0001	
Mild Impairment	T-DXd (N=49)	49 (100)	NE (NE, NE)	1.04 (0.98, 1.10)	0.041 (-0.015, 0.096)	1.77 (1.17, 2.67)	
	T-DM1 (N=49)	47 (95.9)				0.0050	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Serious TEAE							
Within Normal Range	T-DXd (N=208)	32 (15.4)	0.95 (0.56, 1.61)	0.96 (0.62, 1.49)	-0.007 (-0.076, 0.063)	0.60 (0.37, 0.99)	0.3260
	T-DM1 (N=212)	34 (16.0)				0.0438	
Mild Impairment	T-DXd (N=49)	17 (34.7)	1.47 (0.62, 3.49)	1.31 (0.71, 2.39)	0.082 (-0.100, 0.263)	1.18 (0.57, 2.44)	
	T-DM1 (N=49)	13 (26.5)				0.6685	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with Study Drug Discontinuation							
Within Normal Range	T-DXd (N=208)	27 (13.0)	1.83 (0.95, 3.50)	1.72 (0.96, 3.10)	0.054 (-0.004, 0.112)	1.04 (0.55, 1.94)	0.6881
	T-DM1 (N=212)	16 (7.5)				0.9119	
Mild Impairment	T-DXd (N=49)	8 (16.3)	2.99 (0.74, 12.04)	2.67 (0.75, 9.46)	0.102 (-0.021, 0.225)	1.42 (0.37, 5.43)	
	T-DM1 (N=49)	3 (6.1)				0.6106	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Severe TEAE (CTCAE Grade >=3)							
Within Normal Range	T-DXd (N=208)	99 (47.6)	0.98 (0.67, 1.44)	0.99 (0.81, 1.21)	-0.005 (-0.101, 0.090)	0.70 (0.53, 0.93)	0.0922
	T-DM1 (N=212)	102 (48.1)				0.0176	
Mild Impairment	T-DXd (N=49)	35 (71.4)	2.60 (1.13, 6.00)	1.46 (1.04, 2.04)	0.224 (0.036, 0.413)	1.20 (0.71, 2.03)	
	T-DM1 (N=49)	24 (49.0)				0.4618	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with an Outcome of Death							
Within Normal Range	T-DXd (N=208)	3 (1.4)	1.02 (0.20, 5.11)	1.02 (0.21, 4.99)	0.000 (-0.022, 0.023)	0.74 (0.15, 3.73)	0.9277
	T-DM1 (N=212)	3 (1.4)				0.7131	
Mild Impairment	T-DXd (N=49)	2 (4.1)	1.00 (0.14, 7.40)	1.00 (0.15, 6.82)	0.000 (-0.078, 0.078)	0.80 (0.11, 5.91)	
	T-DM1 (N=49)	2 (4.1)				0.8289	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
Yes	T-DXd (N=192)	191 (99.5)	9.60 (1.20, 76.50)	1.04 (1.01, 1.08)	0.043 (0.010, 0.075)	1.47 (1.20, 1.81)	0.6672
	T-DM1 (N=188)	179 (95.2)				0.0001	
No	T-DXd (N=65)	65 (100)	NE (NE, NE)	1.04 (0.99, 1.09)	0.041 (-0.004, 0.087)	1.61 (1.14, 2.27)	
	T-DM1 (N=73)	70 (95.9)				0.0034	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Serious TEAE							
Yes	T-DXd (N=192)	38 (19.8)	1.16 (0.69, 1.94)	1.13 (0.74, 1.72)	0.022 (-0.056, 0.101)	0.80 (0.50, 1.29)	0.5773
	T-DM1 (N=188)	33 (17.6)				0.3603	
No	T-DXd (N=65)	11 (16.9)	0.86 (0.36, 2.05)	0.88 (0.43, 1.80)	-0.023 (-0.151, 0.106)	0.58 (0.26, 1.30)	
	T-DM1 (N=73)	14 (19.2)				0.1817	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with Study Drug Discontinuation							
Yes	T-DXd (N=192)	26 (13.5)	2.11 (1.05, 4.24)	1.96 (1.04, 3.69)	0.066 (0.006, 0.127)	1.12 (0.57, 2.20)	0.8848
	T-DM1 (N=188)	13 (6.9)				0.7431	
No	T-DXd (N=65)	9 (13.8)	1.79 (0.60, 5.35)	1.68 (0.63, 4.48)	0.056 (-0.049, 0.161)	1.11 (0.39, 3.16)	
	T-DM1 (N=73)	6 (8.2)				0.8427	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Severe TEAE (CTCAE Grade >=3)							
Yes	T-DXd (N=192)	99 (51.6)	1.24 (0.83, 1.85)	1.11 (0.91, 1.37)	0.053 (-0.048, 0.153)	0.85 (0.64, 1.14)	0.5476
	T-DM1 (N=188)	87 (46.3)				0.3270	
No	T-DXd (N=65)	35 (53.8)	1.02 (0.52, 1.99)	1.01 (0.74, 1.38)	0.004 (-0.162, 0.171)	0.68 (0.43, 1.08)	
	T-DM1 (N=73)	39 (53.4)				0.1091	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with an Outcome of Death							
Yes	T-DXd (N=192)	5 (2.6)	1.23 (0.33, 4.65)	1.22 (0.33, 4.49)	0.005 (-0.026, 0.035)	0.88 (0.23, 3.33)	0.9925
	T-DM1 (N=188)	4 (2.1)				0.8458	
No	T-DXd (N=65)	0	NE (NE, NE)	NE (NE, NE)	-0.014 (-0.040, 0.013)	NE (NE, NE)	
	T-DM1 (N=73)	1 (1.4)				0.3454	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
Yes	T-DXd (N=41)	41 (100)	NE (NE, NE)	1.03 (0.98, 1.08)	0.026 (-0.024, 0.075)	1.26 (0.80, 1.98)	0.4565
	T-DM1 (N=39)	38 (97.4)				0.1940	
No	T-DXd (N=216)	215 (99.5)	11.21 (1.43, 87.58)	1.05 (1.01, 1.08)	0.045 (0.015, 0.075)	1.53 (1.26, 1.86)	
	T-DM1 (N=222)	211 (95.0)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Serious TEAE							
Yes	T-DXd (N=41)	14 (34.1)	1.50 (0.57, 3.95)	1.33 (0.67, 2.64)	0.085 (-0.115, 0.285)	0.83 (0.35, 1.94)	0.7005
	T-DM1 (N=39)	10 (25.6)				0.6630	
No	T-DXd (N=216)	35 (16.2)	0.97 (0.58, 1.60)	0.97 (0.64, 1.48)	-0.005 (-0.074, 0.065)	0.68 (0.42, 1.09)	
	T-DM1 (N=222)	37 (16.7)				0.1069	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with Study Drug Discontinuation							
Yes	T-DXd (N=41)	9 (22.0)	5.20 (1.05, 25.86)	4.28 (0.99, 18.58)	0.168 (0.024, 0.313)	1.60 (0.33, 7.72)	0.4291
	T-DM1 (N=39)	2 (5.1)				0.5521	
No	T-DXd (N=216)	26 (12.0)	1.65 (0.87, 3.14)	1.57 (0.88, 2.81)	0.044 (-0.012, 0.100)	1.00 (0.54, 1.86)	
	T-DM1 (N=222)	17 (7.7)				0.9939	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Severe TEAE (CTCAE Grade >=3)							
Yes	T-DXd (N=41)	21 (51.2)	1.51 (0.62, 3.65)	1.25 (0.77, 2.02)	0.102 (-0.115, 0.319)	0.84 (0.43, 1.64)	0.8517
	T-DM1 (N=39)	16 (41.0)				0.6171	
No	T-DXd (N=216)	113 (52.3)	1.12 (0.77, 1.62)	1.06 (0.88, 1.27)	0.028 (-0.066, 0.121)	0.79 (0.61, 1.03)	
	T-DM1 (N=222)	110 (49.5)				0.0974	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with an Outcome of Death							
Yes	T-DXd (N=41)	1 (2.4)	NE (NE, NE)	NE (NE, NE)	0.024 (-0.023, 0.072)	NE (NE, NE)	0.9922
	T-DM1 (N=39)	0				0.7180	
No	T-DXd (N=216)	4 (1.9)	0.82 (0.22, 3.09)	0.82 (0.22, 3.02)	-0.004 (-0.031, 0.023)	0.68 (0.18, 2.55)	
	T-DM1 (N=222)	5 (2.3)				0.5634	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Treatment-Emergent Adverse Events (TEAE)							
Yes	T-DXd (N=60)	59 (98.3)	1.16 (0.07, 18.97)	1.00 (0.95, 1.05)	0.003 (-0.047, 0.052)	1.08 (0.74, 1.58)	0.0538
	T-DM1 (N=52)	51 (98.1)				0.6026	
No	T-DXd (N=197)	197 (100)	NE (NE, NE)	1.06 (1.02, 1.09)	0.053 (0.022, 0.083)	1.65 (1.35, 2.02)	
	T-DM1 (N=209)	198 (94.7)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Serious TEAE							
Yes	T-DXd (N=60)	20 (33.3)	1.86 (0.79, 4.38)	1.58 (0.83, 2.97)	0.122 (-0.041, 0.285)	0.98 (0.46, 2.10)	0.2041
	T-DM1 (N=52)	11 (21.2)				0.9533	
No	T-DXd (N=197)	29 (14.7)	0.83 (0.49, 1.41)	0.85 (0.55, 1.34)	-0.025 (-0.096, 0.046)	0.60 (0.37, 0.99)	
	T-DM1 (N=209)	36 (17.2)				0.0435	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with Study Drug Discontinuation							
Yes	T-DXd (N=60)	12 (20.0)	4.08 (1.08, 15.37)	3.47 (1.03, 11.62)	0.142 (0.023, 0.262)	1.66 (0.45, 6.05)	0.3870
	T-DM1 (N=52)	3 (5.8)				0.4391	
No	T-DXd (N=197)	23 (11.7)	1.59 (0.82, 3.12)	1.53 (0.83, 2.80)	0.040 (-0.017, 0.098)	0.95 (0.50, 1.82)	
	T-DM1 (N=209)	16 (7.7)				0.8842	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Severe TEAE (CTCAE Grade >=3)							
Yes	T-DXd (N=60)	33 (55.0)	1.80 (0.85, 3.83)	1.36 (0.91, 2.04)	0.146 (-0.037, 0.330)	0.94 (0.53, 1.64)	0.2768
	T-DM1 (N=52)	21 (40.4)				0.8251	
No	T-DXd (N=197)	101 (51.3)	1.04 (0.71, 1.54)	1.02 (0.84, 1.24)	0.010 (-0.087, 0.108)	0.76 (0.57, 1.00)	
	T-DM1 (N=209)	105 (50.2)				0.0604	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 30 Overall Summary of Treatment-Emergent Adverse Events by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
TEAE associated with an Outcome of Death							
Yes	T-DXd (N=60)	3 (5.0)	NE (NE, NE)	NE (NE, NE)	0.050 (-0.005, 0.105)	NE (NE, NE)	0.9909
	T-DM1 (N=52)	0				0.2715	
No	T-DXd (N=197)	2 (1.0)	0.42 (0.08, 2.18)	0.42 (0.08, 2.16)	-0.014 (-0.039, 0.011)	0.36 (0.07, 1.88)	
	T-DM1 (N=209)	5 (2.4)				0.2078	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
<65	T-DXd (N=209)	198 (94.7)	14.21 (7.29, 27.69)	1.70 (1.49, 1.92)	0.389 (0.314, 0.463)	3.11 (2.46, 3.94)	0.0649
	T-DM1 (N=204)	114 (55.9)				<.0001	
>=65	T-DXd (N=48)	39 (81.3)	2.17 (0.87, 5.38)	1.22 (0.97, 1.53)	0.146 (-0.019, 0.311)	2.02 (1.28, 3.17)	
	T-DM1 (N=57)	38 (66.7)				0.0024	
Nausea							
<65	T-DXd (N=209)	164 (78.5)	7.79 (5.01, 12.13)	2.46 (1.99, 3.05)	0.466 (0.381, 0.551)	3.68 (2.76, 4.91)	0.9953
	T-DM1 (N=204)	65 (31.9)				<.0001	
>=65	T-DXd (N=48)	31 (64.6)	5.60 (2.41, 13.04)	2.63 (1.59, 4.34)	0.400 (0.225, 0.576)	3.80 (2.02, 7.16)	
	T-DM1 (N=57)	14 (24.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
<65	T-DXd (N=209)	105 (50.2)	9.83 (5.70, 16.95)	5.39 (3.44, 8.45)	0.409 (0.331, 0.488)	5.90 (3.62, 9.63)	0.4712
	T-DM1 (N=204)	19 (9.3)				<.0001	
>=65	T-DXd (N=48)	21 (43.8)	5.55 (2.10, 14.73)	3.56 (1.66, 7.65)	0.315 (0.151, 0.479)	4.19 (1.78, 9.88)	
	T-DM1 (N=57)	7 (12.3)				0.0004	
Constipation							
<65	T-DXd (N=209)	74 (35.4)	2.56 (1.62, 4.04)	2.01 (1.42, 2.84)	0.178 (0.094, 0.261)	1.74 (1.16, 2.59)	0.2862
	T-DM1 (N=204)	36 (17.6)				0.0063	
>=65	T-DXd (N=48)	14 (29.2)	1.15 (0.49, 2.72)	1.11 (0.60, 2.06)	0.029 (-0.144, 0.201)	1.04 (0.50, 2.16)	
	T-DM1 (N=57)	15 (26.3)				0.9132	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
<65	T-DXd (N=209)	62 (29.7)	6.20 (3.28, 11.70)	4.66 (2.64, 8.20)	0.233 (0.163, 0.303)	4.55 (2.50, 8.29)	0.5841
	T-DM1 (N=204)	13 (6.4)				<.0001	
>=65	T-DXd (N=48)	13 (27.1)	3.86 (1.26, 11.80)	3.09 (1.19, 8.04)	0.183 (0.038, 0.329)	3.30 (1.17, 9.26)	
	T-DM1 (N=57)	5 (8.8)				0.0161	
Stomatitis							
<65	T-DXd (N=209)	28 (13.4)	7.73 (2.66, 22.48)	6.83 (2.44, 19.13)	0.114 (0.064, 0.164)	5.54 (1.94, 15.86)	0.2427
	T-DM1 (N=204)	4 (2.0)				0.0003	
>=65	T-DXd (N=48)	12 (25.0)	2.83 (0.97, 8.25)	2.38 (0.96, 5.85)	0.145 (-0.001, 0.291)	2.30 (0.86, 6.14)	
	T-DM1 (N=57)	6 (10.5)				0.0869	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
<65	T-DXd (N=209)	24 (11.5)	8.69 (2.57, 29.34)	7.81 (2.39, 25.53)	0.100 (0.054, 0.146)	5.62 (1.68, 18.78)	0.4454
	T-DM1 (N=204)	3 (1.5)				0.0017	
>=65	T-DXd (N=48)	5 (10.4)	3.20 (0.59, 17.29)	2.97 (0.60, 14.62)	0.069 (-0.030, 0.168)	2.54 (0.49, 13.18)	
	T-DM1 (N=57)	2 (3.5)				0.2487	
Investigations							
Any PT							
<65	T-DXd (N=209)	127 (60.8)	0.68 (0.45, 1.02)	0.87 (0.76, 1.01)	-0.088 (-0.180, 0.003)	0.55 (0.43, 0.70)	0.0642
	T-DM1 (N=204)	142 (69.6)				<.0001	
>=65	T-DXd (N=48)	35 (72.9)	1.46 (0.63, 3.36)	1.12 (0.87, 1.45)	0.080 (-0.096, 0.257)	0.92 (0.58, 1.46)	
	T-DM1 (N=57)	37 (64.9)				0.8216	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
<65	T-DXd (N=209)	55 (26.3)	4.20 (2.31, 7.61)	3.36 (1.99, 5.66)	0.185 (0.115, 0.255)	3.02 (1.73, 5.27)	0.9902
	T-DM1 (N=204)	16 (7.8)				<.0001	
>=65	T-DXd (N=48)	20 (41.7)	3.81 (1.53, 9.51)	2.64 (1.33, 5.24)	0.259 (0.090, 0.427)	2.96 (1.35, 6.50)	
	T-DM1 (N=57)	9 (15.8)				0.0047	
Aspartate aminotransferase increased							
<65	T-DXd (N=209)	58 (27.8)	0.57 (0.38, 0.86)	0.69 (0.52, 0.91)	-0.124 (-0.215, -0.034)	0.47 (0.33, 0.66)	0.3376
	T-DM1 (N=204)	82 (40.2)				<.0001	
>=65	T-DXd (N=48)	8 (16.7)	0.30 (0.12, 0.75)	0.41 (0.20, 0.84)	-0.237 (-0.402, -0.072)	0.31 (0.14, 0.69)	
	T-DM1 (N=57)	23 (40.4)				0.0026	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
<65	T-DXd (N=209)	45 (21.5)	4.81 (2.41, 9.61)	3.99 (2.13, 7.50)	0.161 (0.098, 0.225)	3.38 (1.74, 6.55)	0.5378
	T-DM1 (N=204)	11 (5.4)				0.0001	
>=65	T-DXd (N=48)	13 (27.1)	6.69 (1.78, 25.16)	5.15 (1.56, 17.00)	0.218 (0.080, 0.357)	5.07 (1.44, 17.81)	
	T-DM1 (N=57)	3 (5.3)				0.0049	
Alanine aminotransferase increased							
<65	T-DXd (N=209)	50 (23.9)	0.74 (0.48, 1.14)	0.80 (0.58, 1.10)	-0.060 (-0.145, 0.026)	0.61 (0.42, 0.89)	0.2862
	T-DM1 (N=204)	61 (29.9)				0.0106	
>=65	T-DXd (N=48)	6 (12.5)	0.37 (0.13, 1.03)	0.45 (0.19, 1.05)	-0.156 (-0.305, -0.006)	0.36 (0.14, 0.93)	
	T-DM1 (N=57)	16 (28.1)				0.0284	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
<65	T-DXd (N=209)	40 (19.1)	0.32 (0.21, 0.51)	0.45 (0.33, 0.63)	-0.230 (-0.316, -0.144)	0.29 (0.20, 0.43)	0.2391
	T-DM1 (N=204)	86 (42.2)				<.0001	
>=65	T-DXd (N=48)	14 (29.2)	0.49 (0.22, 1.11)	0.64 (0.38, 1.08)	-0.164 (-0.347, 0.018)	0.47 (0.25, 0.91)	
	T-DM1 (N=57)	26 (45.6)				0.0249	
Weight decreased							
<65	T-DXd (N=209)	36 (17.2)	4.04 (1.95, 8.37)	3.51 (1.79, 6.89)	0.123 (0.064, 0.182)	2.64 (1.30, 5.34)	0.2293
	T-DM1 (N=204)	10 (4.9)				0.0051	
>=65	T-DXd (N=48)	7 (14.6)	1.45 (0.45, 4.65)	1.39 (0.50, 3.84)	0.041 (-0.087, 0.168)	1.17 (0.39, 3.49)	
	T-DM1 (N=57)	6 (10.5)				0.7788	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
<65	T-DXd (N=209)	13 (6.2)	0.40 (0.20, 0.79)	0.44 (0.23, 0.82)	-0.080 (-0.138, -0.022)	0.32 (0.17, 0.63)	0.3341
	T-DM1 (N=204)	29 (14.2)				0.0005	
>=65	T-DXd (N=48)	4 (8.3)	0.77 (0.20, 2.92)	0.79 (0.24, 2.64)	-0.022 (-0.134, 0.090)	0.69 (0.19, 2.45)	
	T-DM1 (N=57)	6 (10.5)				0.5598	
General disorders and administration site conditions							
Any PT							
<65	T-DXd (N=209)	132 (63.2)	1.78 (1.20, 2.64)	1.29 (1.08, 1.53)	0.141 (0.047, 0.236)	1.12 (0.86, 1.46)	0.3130
	T-DM1 (N=204)	100 (49.0)				0.3866	
>=65	T-DXd (N=48)	27 (56.3)	0.94 (0.43, 2.03)	0.97 (0.70, 1.36)	-0.016 (-0.207, 0.174)	0.76 (0.45, 1.26)	
	T-DM1 (N=57)	33 (57.9)				0.2905	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
<65	T-DXd (N=209)	26 (12.4)	3.48 (1.54, 7.88)	3.17 (1.47, 6.84)	0.085 (0.033, 0.137)	2.78 (1.25, 6.18)	0.5953
	T-DM1 (N=204)	8 (3.9)				0.0088	
>=65	T-DXd (N=48)	3 (6.3)	1.83 (0.29, 11.45)	1.78 (0.31, 10.22)	0.027 (-0.056, 0.111)	1.75 (0.29, 10.50)	
	T-DM1 (N=57)	2 (3.5)				0.5328	
Pyrexia							
<65	T-DXd (N=209)	22 (10.5)	0.81 (0.44, 1.47)	0.83 (0.48, 1.41)	-0.022 (-0.084, 0.040)	0.55 (0.31, 0.99)	0.5175
	T-DM1 (N=204)	26 (12.7)				0.0426	
>=65	T-DXd (N=48)	5 (10.4)	0.39 (0.13, 1.20)	0.46 (0.18, 1.19)	-0.124 (-0.263, 0.015)	0.30 (0.11, 0.84)	
	T-DM1 (N=57)	13 (22.8)				0.0158	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
<65	T-DXd (N=209)	111 (53.1)	3.07 (2.03, 4.63)	1.97 (1.52, 2.55)	0.261 (0.170, 0.353)	2.03 (1.47, 2.82)	0.7828
	T-DM1 (N=204)	55 (27.0)				<.0001	
>=65	T-DXd (N=48)	28 (58.3)	2.59 (1.17, 5.71)	1.66 (1.09, 2.55)	0.232 (0.046, 0.419)	1.83 (1.03, 3.26)	
	T-DM1 (N=57)	20 (35.1)				0.0369	
Alopecia							
<65	T-DXd (N=209)	79 (37.8)	24.19 (9.54, 61.33)	15.42 (6.38, 37.29)	0.353 (0.284, 0.423)	17.14 (6.94, 42.33)	0.2640
	T-DM1 (N=204)	5 (2.5)				<.0001	
>=65	T-DXd (N=48)	16 (33.3)	9.00 (2.43, 33.30)	6.33 (1.96, 20.44)	0.281 (0.135, 0.426)	7.05 (2.05, 24.21)	
	T-DM1 (N=57)	3 (5.3)				0.0003	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
<65	T-DXd (N=209)	101 (48.3)	2.35 (1.57, 3.54)	1.70 (1.31, 2.20)	0.199 (0.107, 0.291)	1.73 (1.25, 2.40)	0.2074
	T-DM1 (N=204)	58 (28.4)				0.0008	
>=65	T-DXd (N=48)	21 (43.8)	1.24 (0.57, 2.70)	1.13 (0.72, 1.79)	0.052 (-0.137, 0.240)	1.08 (0.59, 1.97)	
	T-DM1 (N=57)	22 (38.6)				0.8058	
Decreased appetite							
<65	T-DXd (N=209)	62 (29.7)	2.55 (1.56, 4.16)	2.09 (1.40, 3.10)	0.154 (0.076, 0.233)	2.06 (1.33, 3.21)	0.0902
	T-DM1 (N=204)	29 (14.2)				0.0011	
>=65	T-DXd (N=48)	13 (27.1)	1.04 (0.44, 2.48)	1.03 (0.54, 1.94)	0.008 (-0.162, 0.178)	0.94 (0.44, 1.97)	
	T-DM1 (N=57)	15 (26.3)				0.8593	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
<65	T-DXd (N=209)	93 (44.5)	1.17 (0.79, 1.73)	1.09 (0.87, 1.37)	0.038 (-0.057, 0.133)	0.78 (0.58, 1.05)	0.0185
	T-DM1 (N=204)	83 (40.7)				0.1077	
>=65	T-DXd (N=48)	23 (47.9)	2.58 (1.14, 5.83)	1.82 (1.08, 3.08)	0.216 (0.034, 0.398)	1.87 (0.98, 3.59)	
	T-DM1 (N=57)	15 (26.3)				0.0544	
Infections and infestations							
Any PT							
<65	T-DXd (N=209)	88 (42.1)	1.56 (1.04, 2.33)	1.32 (1.02, 1.71)	0.102 (0.010, 0.195)	0.98 (0.71, 1.36)	0.4664
	T-DM1 (N=204)	65 (31.9)				0.9209	
>=65	T-DXd (N=48)	24 (50.0)	1.85 (0.84, 4.06)	1.43 (0.91, 2.24)	0.149 (-0.039, 0.337)	1.16 (0.64, 2.11)	
	T-DM1 (N=57)	20 (35.1)				0.6325	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
<65	T-DXd (N=209)	81 (38.8)	1.56 (1.03, 2.35)	1.34 (1.02, 1.76)	0.098 (0.008, 0.189)	0.91 (0.65, 1.28)	0.3641
	T-DM1 (N=204)	59 (28.9)				0.5866	
>=65	T-DXd (N=48)	26 (54.2)	2.19 (1.00, 4.80)	1.54 (1.00, 2.39)	0.191 (0.003, 0.378)	1.19 (0.66, 2.15)	
	T-DM1 (N=57)	20 (35.1)				0.5581	
Epistaxis							
<65	T-DXd (N=209)	22 (10.5)	0.66 (0.37, 1.18)	0.69 (0.42, 1.15)	-0.047 (-0.111, 0.018)	0.40 (0.23, 0.70)	0.7178
	T-DM1 (N=204)	31 (15.2)				0.0009	
>=65	T-DXd (N=48)	7 (14.6)	0.71 (0.25, 2.01)	0.76 (0.32, 1.80)	-0.047 (-0.190, 0.096)	0.45 (0.17, 1.21)	
	T-DM1 (N=57)	11 (19.3)				0.1072	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
<65	T-DXd (N=209)	83 (39.7)	1.78 (1.18, 2.70)	1.47 (1.11, 1.95)	0.128 (0.037, 0.218)	1.19 (0.85, 1.68)	0.7974
	T-DM1 (N=204)	55 (27.0)				0.3107	
>=65	T-DXd (N=48)	20 (41.7)	1.32 (0.60, 2.91)	1.19 (0.73, 1.93)	0.066 (-0.121, 0.252)	1.11 (0.59, 2.06)	
	T-DM1 (N=57)	20 (35.1)				0.7399	
Anaemia							
<65	T-DXd (N=209)	66 (31.6)	2.39 (1.49, 3.84)	1.95 (1.35, 2.83)	0.154 (0.073, 0.235)	1.61 (1.05, 2.45)	0.7776
	T-DM1 (N=204)	33 (16.2)				0.0263	
>=65	T-DXd (N=48)	17 (35.4)	2.29 (0.95, 5.55)	1.84 (0.95, 3.53)	0.161 (-0.009, 0.331)	1.84 (0.86, 3.94)	
	T-DM1 (N=57)	11 (19.3)				0.1114	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
<65	T-DXd (N=209)	37 (17.7)	7.10 (2.93, 17.23)	6.02 (2.60, 13.95)	0.148 (0.091, 0.204)	4.38 (1.84, 10.45)	0.9427
	T-DM1 (N=204)	6 (2.9)				0.0003	
>=65	T-DXd (N=48)	4 (8.3)	5.09 (0.55, 47.18)	4.75 (0.55, 41.08)	0.066 (-0.020, 0.151)	4.61 (0.51, 41.29)	
	T-DM1 (N=57)	1 (1.8)				0.1333	
Thrombocytopenia							
<65	T-DXd (N=209)	12 (5.7)	0.48 (0.23, 0.99)	0.51 (0.26, 1.00)	-0.055 (-0.109, -0.002)	0.35 (0.17, 0.72)	0.2962
	T-DM1 (N=204)	23 (11.3)				0.0029	
>=65	T-DXd (N=48)	1 (2.1)	0.13 (0.02, 1.08)	0.15 (0.02, 1.15)	-0.120 (-0.218, -0.021)	0.13 (0.02, 1.07)	
	T-DM1 (N=57)	8 (14.0)				0.0249	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
<65	T-DXd (N=209)	78 (37.3)	1.09 (0.73, 1.63)	1.06 (0.82, 1.37)	0.020 (-0.072, 0.113)	0.73 (0.53, 1.01)	0.2818
	T-DM1 (N=204)	72 (35.3)				0.0597	
>=65	T-DXd (N=48)	16 (33.3)	1.40 (0.60, 3.25)	1.27 (0.70, 2.29)	0.070 (-0.105, 0.246)	1.12 (0.55, 2.28)	
	T-DM1 (N=57)	15 (26.3)				0.7474	
Vascular disorders							
Any PT							
<65	T-DXd (N=209)	32 (15.3)	2.66 (1.35, 5.22)	2.40 (1.30, 4.44)	0.089 (0.030, 0.149)	1.80 (0.94, 3.47)	0.9721
	T-DM1 (N=204)	13 (6.4)				0.0738	
>=65	T-DXd (N=48)	13 (27.1)	2.27 (0.85, 6.07)	1.93 (0.87, 4.26)	0.130 (-0.024, 0.285)	1.68 (0.69, 4.06)	
	T-DM1 (N=57)	8 (14.0)				0.2484	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
<65	T-DXd (N=209)	32 (15.3)	1.36 (0.77, 2.39)	1.30 (0.80, 2.13)	0.035 (-0.030, 0.101)	0.79 (0.46, 1.36)	0.3237
	T-DM1 (N=204)	24 (11.8)				0.3928	
>=65	T-DXd (N=48)	9 (18.8)	1.96 (0.64, 5.98)	1.78 (0.68, 4.65)	0.082 (-0.054, 0.218)	1.51 (0.54, 4.26)	
	T-DM1 (N=57)	6 (10.5)				0.4301	
Psychiatric disorders							
Any PT							
<65	T-DXd (N=209)	34 (16.3)	1.17 (0.68, 2.01)	1.14 (0.73, 1.81)	0.021 (-0.049, 0.090)	0.77 (0.47, 1.28)	0.9633
	T-DM1 (N=204)	29 (14.2)				0.3099	
>=65	T-DXd (N=48)	5 (10.4)	0.99 (0.28, 3.46)	0.99 (0.32, 3.04)	-0.001 (-0.119, 0.116)	0.81 (0.25, 2.67)	
	T-DM1 (N=57)	6 (10.5)				0.7302	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
<65	T-DXd (N=209)	28 (13.4)	1.70 (0.90, 3.22)	1.61 (0.91, 2.85)	0.051 (-0.009, 0.110)	1.03 (0.56, 1.90)	0.1061
	T-DM1 (N=204)	17 (8.3)				0.9245	
>=65	T-DXd (N=48)	4 (8.3)	0.43 (0.12, 1.46)	0.48 (0.16, 1.42)	-0.092 (-0.218, 0.034)	0.36 (0.11, 1.16)	
	T-DM1 (N=57)	10 (17.5)				0.0743	
Hepatobiliary disorders							
Any PT							
<65	T-DXd (N=209)	14 (6.7)	0.54 (0.27, 1.07)	0.57 (0.30, 1.07)	-0.051 (-0.106, 0.005)	0.44 (0.22, 0.85)	0.1149
	T-DM1 (N=204)	24 (11.8)				0.0132	
>=65	T-DXd (N=48)	6 (12.5)	1.49 (0.42, 5.21)	1.43 (0.46, 4.38)	0.037 (-0.082, 0.156)	1.12 (0.34, 3.71)	
	T-DM1 (N=57)	5 (8.8)				0.8475	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
<75	T-DXd (N=250)	230 (92.0)	8.29 (4.93, 13.96)	1.58 (1.42, 1.77)	0.339 (0.269, 0.408)	2.86 (2.31, 3.53)	0.9235
	T-DM1 (N=253)	147 (58.1)				<.0001	
>=75	T-DXd (N=7)	7 (100)	NE (NE, NE)	1.60 (0.94, 2.74)	0.375 (0.040, 0.710)	2.57 (0.78, 8.40)	
	T-DM1 (N=8)	5 (62.5)				0.0944	
Nausea							
<75	T-DXd (N=250)	189 (75.6)	7.22 (4.86, 10.70)	2.52 (2.06, 3.08)	0.456 (0.378, 0.533)	3.74 (2.86, 4.89)	0.8785
	T-DM1 (N=253)	76 (30.0)				<.0001	
>=75	T-DXd (N=7)	6 (85.7)	10.00 (0.78, 128.77)	2.29 (0.89, 5.88)	0.482 (0.058, 0.906)	3.50 (0.86, 14.23)	
	T-DM1 (N=8)	3 (37.5)				0.0541	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
<75	T-DXd (N=250)	123 (49.2)	8.46 (5.26, 13.60)	4.79 (3.26, 7.04)	0.389 (0.317, 0.462)	5.30 (3.47, 8.10)	0.9795
	T-DM1 (N=253)	26 (10.3)				<.0001	
>=75	T-DXd (N=7)	3 (42.9)	NE (NE, NE)	NE (NE, NE)	0.429 (0.062, 0.795)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.0442	
Constipation							
<75	T-DXd (N=250)	85 (34.0)	2.14 (1.43, 3.22)	1.76 (1.29, 2.38)	0.146 (0.070, 0.223)	1.53 (1.07, 2.18)	0.8712
	T-DM1 (N=253)	49 (19.4)				0.0178	
>=75	T-DXd (N=7)	3 (42.9)	2.25 (0.25, 20.13)	1.71 (0.39, 7.48)	0.179 (-0.295, 0.652)	1.78 (0.30, 10.71)	
	T-DM1 (N=8)	2 (25.0)				0.5205	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
<75	T-DXd (N=250)	73 (29.2)	5.73 (3.26, 10.05)	4.35 (2.64, 7.15)	0.225 (0.161, 0.289)	4.34 (2.56, 7.36)	0.5777
	T-DM1 (N=253)	17 (6.7)				<.0001	
>=75	T-DXd (N=7)	2 (28.6)	2.80 (0.20, 40.06)	2.29 (0.26, 20.13)	0.161 (-0.245, 0.566)	2.20 (0.20, 24.32)	
	T-DM1 (N=8)	1 (12.5)				0.5084	
Stomatitis							
<75	T-DXd (N=250)	39 (15.6)	4.49 (2.19, 9.22)	3.95 (2.01, 7.73)	0.116 (0.065, 0.167)	3.31 (1.65, 6.65)	0.9885
	T-DM1 (N=253)	10 (4.0)				0.0004	
>=75	T-DXd (N=7)	1 (14.3)	NE (NE, NE)	NE (NE, NE)	0.143 (-0.116, 0.402)	NE (NE, NE)	
	T-DM1 (N=8)	0				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
<75	T-DXd (N=250)	28 (11.2)	6.26 (2.37, 16.48)	5.67 (2.22, 14.44)	0.092 (0.050, 0.135)	4.30 (1.65, 11.18)	0.9909
	T-DM1 (N=253)	5 (2.0)				0.0012	
>=75	T-DXd (N=7)	1 (14.3)	NE (NE, NE)	NE (NE, NE)	0.143 (-0.116, 0.402)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.3711	
Investigations							
Any PT							
<75	T-DXd (N=250)	159 (63.6)	0.81 (0.56, 1.17)	0.93 (0.82, 1.05)	-0.048 (-0.131, 0.035)	0.62 (0.50, 0.77)	0.4170
	T-DM1 (N=253)	173 (68.4)				<.0001	
>=75	T-DXd (N=7)	3 (42.9)	0.25 (0.03, 2.24)	0.57 (0.22, 1.47)	-0.321 (-0.795, 0.152)	0.34 (0.08, 1.36)	
	T-DM1 (N=8)	6 (75.0)				0.1197	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
<75	T-DXd (N=250)	73 (29.2)	3.93 (2.38, 6.50)	3.08 (2.01, 4.72)	0.197 (0.130, 0.264)	2.85 (1.80, 4.53)	0.8808
	T-DM1 (N=253)	24 (9.5)				<.0001	
>=75	T-DXd (N=7)	2 (28.6)	2.80 (0.20, 40.06)	2.29 (0.26, 20.13)	0.161 (-0.245, 0.566)	2.50 (0.22, 27.90)	
	T-DM1 (N=8)	1 (12.5)				0.4420	
Aspartate aminotransferase increased							
<75	T-DXd (N=250)	66 (26.4)	0.55 (0.38, 0.80)	0.67 (0.52, 0.86)	-0.131 (-0.213, -0.050)	0.47 (0.34, 0.64)	0.9734
	T-DM1 (N=253)	100 (39.5)				<.0001	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	-0.625 (-0.960, -0.290)	NE (NE, NE)	
	T-DM1 (N=8)	5 (62.5)				0.0047	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
<75	T-DXd (N=250)	58 (23.2)	5.16 (2.79, 9.53)	4.19 (2.40, 7.32)	0.177 (0.117, 0.236)	3.67 (2.04, 6.58)	0.9994
	T-DM1 (N=253)	14 (5.5)				<.0001	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	
Alanine aminotransferase increased							
<75	T-DXd (N=250)	56 (22.4)	0.71 (0.48, 1.06)	0.78 (0.57, 1.05)	-0.065 (-0.141, 0.012)	0.60 (0.42, 0.86)	0.9765
	T-DM1 (N=253)	73 (28.9)				0.0049	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	-0.500 (-0.846, -0.154)	NE (NE, NE)	
	T-DM1 (N=8)	4 (50.0)				0.0292	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
<75	T-DXd (N=250)	54 (21.6)	0.36 (0.25, 0.54)	0.50 (0.38, 0.66)	-0.215 (-0.294, -0.135)	0.33 (0.24, 0.46)	0.9772
	T-DM1 (N=253)	109 (43.1)				<.0001	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	-0.375 (-0.710, -0.040)	NE (NE, NE)	
	T-DM1 (N=8)	3 (37.5)				0.0801	
Weight decreased							
<75	T-DXd (N=250)	43 (17.2)	3.30 (1.78, 6.11)	2.90 (1.66, 5.08)	0.113 (0.058, 0.168)	2.24 (1.24, 4.04)	0.9837
	T-DM1 (N=253)	15 (5.9)				0.0062	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	-0.125 (-0.354, 0.104)	NE (NE, NE)	
	T-DM1 (N=8)	1 (12.5)				0.3173	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
<75	T-DXd (N=250)	17 (6.8)	0.45 (0.25, 0.83)	0.49 (0.28, 0.85)	-0.070 (-0.123, -0.018)	0.37 (0.21, 0.67)	0.9996
	T-DM1 (N=253)	35 (13.8)				0.0007	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	
General disorders and administration site conditions							
Any PT							
<75	T-DXd (N=250)	154 (61.6)	1.54 (1.08, 2.20)	1.21 (1.03, 1.41)	0.106 (0.020, 0.192)	1.02 (0.81, 1.29)	0.5492
	T-DM1 (N=253)	129 (51.0)				0.8534	
>=75	T-DXd (N=7)	5 (71.4)	2.50 (0.29, 21.39)	1.43 (0.62, 3.30)	0.214 (-0.267, 0.696)	1.53 (0.41, 5.73)	
	T-DM1 (N=8)	4 (50.0)				0.5221	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
<75	T-DXd (N=250)	29 (11.6)	3.19 (1.52, 6.69)	2.93 (1.46, 5.89)	0.076 (0.030, 0.123)	2.64 (1.28, 5.43)	0.9996
	T-DM1 (N=253)	10 (4.0)				0.0064	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	
Pyrexia							
<75	T-DXd (N=250)	26 (10.4)	0.66 (0.39, 1.12)	0.69 (0.43, 1.10)	-0.046 (-0.104, 0.012)	0.44 (0.26, 0.72)	0.6566
	T-DM1 (N=253)	38 (15.0)				0.0011	
>=75	T-DXd (N=7)	1 (14.3)	1.17 (0.06, 22.94)	1.14 (0.09, 15.08)	0.018 (-0.328, 0.364)	0.99 (0.06, 15.94)	
	T-DM1 (N=8)	1 (12.5)				0.9942	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
<75	T-DXd (N=250)	137 (54.8)	2.99 (2.07, 4.32)	1.90 (1.52, 2.38)	0.259 (0.176, 0.343)	1.98 (1.49, 2.64)	0.5660
	T-DM1 (N=253)	73 (28.9)				<.0001	
>=75	T-DXd (N=7)	2 (28.6)	1.20 (0.12, 11.87)	1.14 (0.21, 6.11)	0.036 (-0.414, 0.485)	1.37 (0.19, 9.79)	
	T-DM1 (N=8)	2 (25.0)				0.7507	
Alopecia							
<75	T-DXd (N=250)	93 (37.2)	18.14 (8.57, 38.38)	11.76 (5.84, 23.71)	0.340 (0.277, 0.404)	13.15 (6.38, 27.08)	0.9854
	T-DM1 (N=253)	8 (3.2)				<.0001	
>=75	T-DXd (N=7)	2 (28.6)	NE (NE, NE)	NE (NE, NE)	0.286 (-0.049, 0.620)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.1159	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
<75	T-DXd (N=250)	120 (48.0)	2.15 (1.49, 3.10)	1.60 (1.27, 2.01)	0.180 (0.096, 0.263)	1.61 (1.21, 2.15)	0.2084
	T-DM1 (N=253)	76 (30.0)				0.0011	
>=75	T-DXd (N=7)	2 (28.6)	0.40 (0.05, 3.42)	0.57 (0.15, 2.23)	-0.214 (-0.696, 0.267)	0.57 (0.10, 3.12)	
	T-DM1 (N=8)	4 (50.0)				0.5123	
Decreased appetite							
<75	T-DXd (N=250)	74 (29.6)	2.17 (1.41, 3.34)	1.83 (1.30, 2.56)	0.134 (0.061, 0.206)	1.79 (1.22, 2.62)	0.1633
	T-DM1 (N=253)	41 (16.2)				0.0028	
>=75	T-DXd (N=7)	1 (14.3)	0.28 (0.02, 3.58)	0.38 (0.05, 2.88)	-0.232 (-0.656, 0.192)	0.38 (0.04, 3.70)	
	T-DM1 (N=8)	3 (37.5)				0.3897	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
<75	T-DXd (N=250)	114 (45.6)	1.37 (0.96, 1.96)	1.20 (0.98, 1.48)	0.077 (-0.009, 0.163)	0.94 (0.71, 1.23)	0.9372
	T-DM1 (N=253)	96 (37.9)				0.6392	
>=75	T-DXd (N=7)	2 (28.6)	1.20 (0.12, 11.87)	1.14 (0.21, 6.11)	0.036 (-0.414, 0.485)	0.98 (0.14, 6.97)	
	T-DM1 (N=8)	2 (25.0)				0.9822	
Infections and infestations							
Any PT							
<75	T-DXd (N=250)	110 (44.0)	1.58 (1.10, 2.27)	1.33 (1.06, 1.66)	0.108 (0.023, 0.193)	1.00 (0.75, 1.33)	0.6977
	T-DM1 (N=253)	84 (33.2)				0.9954	
>=75	T-DXd (N=7)	2 (28.6)	2.80 (0.20, 40.06)	2.29 (0.26, 20.13)	0.161 (-0.245, 0.566)	2.58 (0.23, 28.48)	
	T-DM1 (N=8)	1 (12.5)				0.4228	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
<75	T-DXd (N=250)	105 (42.0)	1.62 (1.13, 2.34)	1.36 (1.08, 1.72)	0.112 (0.028, 0.195)	0.95 (0.70, 1.27)	0.5657
	T-DM1 (N=253)	78 (30.8)				0.7204	
>=75	T-DXd (N=7)	2 (28.6)	2.80 (0.20, 40.06)	2.29 (0.26, 20.13)	0.161 (-0.245, 0.566)	1.91 (0.17, 21.23)	
	T-DM1 (N=8)	1 (12.5)				0.5922	
Epistaxis							
<75	T-DXd (N=250)	29 (11.6)	0.66 (0.40, 1.10)	0.70 (0.45, 1.08)	-0.050 (-0.111, 0.011)	0.41 (0.25, 0.67)	0.9996
	T-DM1 (N=253)	42 (16.6)				0.0002	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
<75	T-DXd (N=250)	102 (40.8)	1.70 (1.17, 2.46)	1.41 (1.11, 1.81)	0.119 (0.037, 0.202)	1.19 (0.88, 1.60)	0.3788
	T-DM1 (N=253)	73 (28.9)				0.2642	
>=75	T-DXd (N=7)	1 (14.3)	0.50 (0.04, 7.10)	0.57 (0.06, 5.03)	-0.107 (-0.504, 0.289)	0.44 (0.04, 4.91)	
	T-DM1 (N=8)	2 (25.0)				0.4896	
Anaemia							
<75	T-DXd (N=250)	82 (32.8)	2.38 (1.56, 3.63)	1.93 (1.39, 2.67)	0.158 (0.084, 0.232)	1.66 (1.14, 2.41)	0.6320
	T-DM1 (N=253)	43 (17.0)				0.0069	
>=75	T-DXd (N=7)	1 (14.3)	1.17 (0.06, 22.94)	1.14 (0.09, 15.08)	0.018 (-0.328, 0.364)	0.96 (0.06, 15.46)	
	T-DM1 (N=8)	1 (12.5)				0.9748	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
<75	T-DXd (N=250)	41 (16.4)	6.89 (3.03, 15.69)	5.93 (2.71, 12.96)	0.136 (0.086, 0.186)	4.58 (2.05, 10.26)	0.9994
	T-DM1 (N=253)	7 (2.8)				<.0001	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	
Thrombocytopenia							
<75	T-DXd (N=250)	13 (5.2)	0.39 (0.20, 0.77)	0.42 (0.23, 0.79)	-0.071 (-0.119, -0.022)	0.31 (0.16, 0.60)	0.9996
	T-DM1 (N=253)	31 (12.3)				0.0002	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
<75	T-DXd (N=250)	92 (36.8)	1.11 (0.77, 1.60)	1.07 (0.85, 1.35)	0.024 (-0.060, 0.108)	0.77 (0.57, 1.03)	0.9730
	T-DM1 (N=253)	87 (34.4)				0.0816	
>=75	T-DXd (N=7)	2 (28.6)	NE (NE, NE)	NE (NE, NE)	0.286 (-0.049, 0.620)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.1286	
Vascular disorders							
Any PT							
<75	T-DXd (N=250)	42 (16.8)	2.23 (1.28, 3.89)	2.02 (1.24, 3.32)	0.085 (0.028, 0.142)	1.52 (0.89, 2.58)	0.9841
	T-DM1 (N=253)	21 (8.3)				0.1215	
>=75	T-DXd (N=7)	3 (42.9)	NE (NE, NE)	NE (NE, NE)	0.429 (0.062, 0.795)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.0537	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Age							
Eye disorders							
Any PT							
<75	T-DXd (N=250)	40 (16.0)	1.47 (0.88, 2.46)	1.40 (0.89, 2.18)	0.045 (-0.015, 0.105)	0.91 (0.56, 1.49)	0.9708
	T-DM1 (N=253)	29 (11.5)				0.7172	
>=75	T-DXd (N=7)	1 (14.3)	1.17 (0.06, 22.94)	1.14 (0.09, 15.08)	0.018 (-0.328, 0.364)	1.15 (0.07, 18.46)	
	T-DM1 (N=8)	1 (12.5)				0.9189	
Psychiatric disorders							
Any PT							
<75	T-DXd (N=250)	39 (15.6)	1.19 (0.72, 1.96)	1.16 (0.76, 1.78)	0.022 (-0.040, 0.083)	0.82 (0.52, 1.31)	0.9827
	T-DM1 (N=253)	34 (13.4)				0.4147	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	-0.125 (-0.354, 0.104)	NE (NE, NE)	
	T-DM1 (N=8)	1 (12.5)				0.1967	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
<75	T-DXd (N=250)	31 (12.4)	1.29 (0.74, 2.26)	1.25 (0.76, 2.06)	0.025 (-0.030, 0.080)	0.82 (0.48, 1.41)	0.4398
	T-DM1 (N=253)	25 (9.9)				0.4789	
>=75	T-DXd (N=7)	1 (14.3)	0.50 (0.04, 7.10)	0.57 (0.06, 5.03)	-0.107 (-0.504, 0.289)	0.37 (0.03, 4.38)	
	T-DM1 (N=8)	2 (25.0)				0.4167	
Hepatobiliary disorders							
Any PT							
<75	T-DXd (N=250)	20 (8.0)	0.67 (0.37, 1.22)	0.70 (0.41, 1.20)	-0.035 (-0.086, 0.017)	0.52 (0.29, 0.94)	0.9997
	T-DM1 (N=253)	29 (11.5)				0.0273	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Asia	T-DXd (N=147)	128 (87.1)	6.01 (3.39, 10.67)	1.65 (1.41, 1.93)	0.342 (0.248, 0.437)	2.74 (2.07, 3.62)	0.3160
	T-DM1 (N=159)	84 (52.8)				<.0001	
North America	T-DXd (N=17)	17 (100)	NE (NE, NE)	1.42 (1.04, 1.93)	0.294 (0.078, 0.511)	1.48 (0.70, 3.12)	
	T-DM1 (N=17)	12 (70.6)				0.2603	
Europe	T-DXd (N=52)	52 (100)	NE (NE, NE)	1.69 (1.34, 2.13)	0.408 (0.271, 0.546)	3.95 (2.44, 6.40)	
	T-DM1 (N=49)	29 (59.2)				<.0001	
Rest of World	T-DXd (N=41)	40 (97.6)	13.33 (1.60, 111.32)	1.30 (1.07, 1.58)	0.226 (0.076, 0.375)	3.46 (2.03, 5.90)	
	T-DM1 (N=36)	27 (75.0)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Nausea							
Asia	T-DXd (N=147)	100 (68.0)	6.12 (3.73, 10.06)	2.64 (1.98, 3.51)	0.422 (0.321, 0.524)	3.72 (2.58, 5.36)	0.1529
	T-DM1 (N=159)	41 (25.8)				<.0001	
North America	T-DXd (N=17)	15 (88.2)	5.25 (0.90, 30.61)	1.50 (0.97, 2.31)	0.294 (0.014, 0.574)	1.56 (0.70, 3.48)	
	T-DM1 (N=17)	10 (58.8)				0.2251	
Europe	T-DXd (N=52)	45 (86.5)	16.07 (5.86, 44.09)	3.03 (1.92, 4.78)	0.580 (0.423, 0.737)	5.12 (2.79, 9.40)	
	T-DM1 (N=49)	14 (28.6)				<.0001	
Rest of World	T-DXd (N=41)	35 (85.4)	9.17 (3.07, 27.39)	2.20 (1.43, 3.37)	0.465 (0.272, 0.657)	3.48 (1.86, 6.49)	
	T-DM1 (N=36)	14 (38.9)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Asia	T-DXd (N=147)	70 (47.6)	8.73 (4.68, 16.26)	5.05 (3.03, 8.41)	0.382 (0.289, 0.474)	5.49 (3.14, 9.60)	0.4459
	T-DM1 (N=159)	15 (9.4)				<.0001	
North America	T-DXd (N=17)	11 (64.7)	8.56 (1.74, 42.17)	3.67 (1.24, 10.85)	0.471 (0.180, 0.761)	3.59 (1.00, 12.87)	
	T-DM1 (N=17)	3 (17.6)				0.0339	
Europe	T-DXd (N=52)	25 (48.1)	21.76 (4.78, 99.10)	11.78 (2.94, 47.12)	0.440 (0.293, 0.587)	13.43 (3.18, 56.80)	
	T-DM1 (N=49)	2 (4.1)				<.0001	
Rest of World	T-DXd (N=41)	20 (48.8)	4.76 (1.63, 13.87)	2.93 (1.32, 6.48)	0.321 (0.126, 0.517)	3.50 (1.40, 8.73)	
	T-DM1 (N=36)	6 (16.7)				0.0043	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Constipation							
Asia	T-DXd (N=147)	50 (34.0)	2.22 (1.31, 3.74)	1.80 (1.22, 2.67)	0.151 (0.054, 0.249)	1.68 (1.06, 2.64)	0.1517
	T-DM1 (N=159)	30 (18.9)				0.0253	
North America	T-DXd (N=17)	7 (41.2)	0.79 (0.20, 3.06)	0.88 (0.41, 1.87)	-0.059 (-0.392, 0.274)	0.63 (0.22, 1.78)	
	T-DM1 (N=17)	8 (47.1)				0.3730	
Europe	T-DXd (N=52)	22 (42.3)	3.76 (1.47, 9.58)	2.59 (1.28, 5.26)	0.260 (0.090, 0.429)	2.35 (1.05, 5.28)	
	T-DM1 (N=49)	8 (16.3)				0.0331	
Rest of World	T-DXd (N=41)	9 (22.0)	1.74 (0.53, 5.79)	1.58 (0.58, 4.28)	0.081 (-0.089, 0.250)	1.19 (0.40, 3.57)	
	T-DM1 (N=36)	5 (13.9)				0.7590	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Asia	T-DXd (N=147)	35 (23.8)	7.97 (3.24, 19.59)	6.31 (2.73, 14.56)	0.200 (0.125, 0.275)	6.04 (2.54, 14.40)	0.2679
	T-DM1 (N=159)	6 (3.8)				<.0001	
North America	T-DXd (N=17)	4 (23.5)	4.92 (0.49, 49.61)	4.00 (0.50, 32.20)	0.176 (-0.054, 0.407)	4.02 (0.45, 35.99)	
	T-DM1 (N=17)	1 (5.9)				0.1789	
Europe	T-DXd (N=52)	24 (46.2)	7.54 (2.58, 22.07)	4.52 (1.87, 10.92)	0.359 (0.200, 0.519)	5.44 (2.07, 14.27)	
	T-DM1 (N=49)	5 (10.2)				0.0001	
Rest of World	T-DXd (N=41)	12 (29.3)	2.07 (0.69, 6.25)	1.76 (0.73, 4.20)	0.126 (-0.059, 0.311)	1.66 (0.62, 4.44)	
	T-DM1 (N=36)	6 (16.7)				0.3102	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Stomatitis							
Asia	T-DXd (N=147)	24 (16.3)	3.68 (1.60, 8.49)	3.24 (1.51, 6.99)	0.113 (0.044, 0.182)	2.54 (1.13, 5.69)	0.9998
	T-DM1 (N=159)	8 (5.0)				0.0190	
North America	T-DXd (N=17)	3 (17.6)	NE (NE, NE)	NE (NE, NE)	0.176 (-0.005, 0.358)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.1191	
Europe	T-DXd (N=52)	6 (11.5)	3.06 (0.59, 15.98)	2.83 (0.60, 13.35)	0.075 (-0.028, 0.178)	2.57 (0.52, 12.80)	
	T-DM1 (N=49)	2 (4.1)				0.2286	
Rest of World	T-DXd (N=41)	7 (17.1)	NE (NE, NE)	NE (NE, NE)	0.171 (0.056, 0.286)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.0187	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Asia	T-DXd (N=147)	9 (6.1)	10.30 (1.29, 82.28)	9.73 (1.25, 75.90)	0.055 (0.014, 0.096)	7.72 (0.97, 61.38)	0.5581
	T-DM1 (N=159)	1 (0.6)				0.0230	
North America	T-DXd (N=17)	4 (23.5)	2.31 (0.36, 14.72)	2.00 (0.42, 9.50)	0.118 (-0.136, 0.371)	1.32 (0.24, 7.41)	
	T-DM1 (N=17)	2 (11.8)				0.7507	
Europe	T-DXd (N=52)	8 (15.4)	8.73 (1.05, 72.60)	7.54 (0.98, 58.09)	0.133 (0.028, 0.239)	6.34 (0.79, 50.97)	
	T-DM1 (N=49)	1 (2.0)				0.0465	
Rest of World	T-DXd (N=41)	8 (19.5)	8.48 (1.01, 71.57)	7.02 (0.92, 53.49)	0.167 (0.035, 0.300)	5.14 (0.64, 41.49)	
	T-DM1 (N=36)	1 (2.8)				0.0880	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Asia	T-DXd (N=147)	100 (68.0)	0.62 (0.37, 1.03)	0.88 (0.77, 1.01)	-0.093 (-0.193, 0.006)	0.52 (0.39, 0.67)	0.0530
	T-DM1 (N=159)	123 (77.4)				<.0001	
North America	T-DXd (N=17)	11 (64.7)	4.40 (1.04, 18.60)	2.20 (0.97, 4.97)	0.353 (0.039, 0.667)	2.32 (0.80, 6.69)	
	T-DM1 (N=17)	5 (29.4)				0.1050	
Europe	T-DXd (N=52)	26 (50.0)	0.69 (0.31, 1.52)	0.84 (0.59, 1.21)	-0.092 (-0.285, 0.102)	0.59 (0.35, 1.01)	
	T-DM1 (N=49)	29 (59.2)				0.0569	
Rest of World	T-DXd (N=41)	25 (61.0)	0.99 (0.40, 2.49)	1.00 (0.70, 1.43)	-0.001 (-0.220, 0.217)	0.71 (0.40, 1.28)	
	T-DM1 (N=36)	22 (61.1)				0.2680	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
Asia	T-DXd (N=147)	62 (42.2)	4.31 (2.49, 7.47)	2.92 (1.91, 4.45)	0.277 (0.180, 0.374)	2.84 (1.76, 4.59)	0.9233
	T-DM1 (N=159)	23 (14.5)				<.0001	
North America	T-DXd (N=17)	1 (5.9)	NE (NE, NE)	NE (NE, NE)	0.059 (-0.053, 0.171)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.4008	
Europe	T-DXd (N=52)	6 (11.5)	6.26 (0.73, 54.03)	5.65 (0.71, 45.29)	0.095 (0.000, 0.190)	5.02 (0.60, 41.77)	
	T-DM1 (N=49)	1 (2.0)				0.0969	
Rest of World	T-DXd (N=41)	6 (14.6)	6.00 (0.69, 52.46)	5.27 (0.67, 41.71)	0.119 (-0.002, 0.239)	4.30 (0.52, 35.84)	
	T-DM1 (N=36)	1 (2.8)				0.1417	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
Asia	T-DXd (N=147)	38 (25.9)	0.50 (0.31, 0.82)	0.63 (0.45, 0.88)	-0.150 (-0.254, -0.046)	0.43 (0.29, 0.65)	0.9439
	T-DM1 (N=159)	65 (40.9)				<.0001	
North America	T-DXd (N=17)	1 (5.9)	0.47 (0.04, 5.72)	0.50 (0.05, 5.01)	-0.059 (-0.248, 0.131)	0.47 (0.04, 5.18)	
	T-DM1 (N=17)	2 (11.8)				0.5352	
Europe	T-DXd (N=52)	14 (26.9)	0.58 (0.25, 1.35)	0.69 (0.39, 1.23)	-0.119 (-0.301, 0.064)	0.53 (0.26, 1.06)	
	T-DM1 (N=49)	19 (38.8)				0.0706	
Rest of World	T-DXd (N=41)	13 (31.7)	0.42 (0.16, 1.05)	0.60 (0.35, 1.04)	-0.211 (-0.427, 0.006)	0.34 (0.16, 0.72)	
	T-DM1 (N=36)	19 (52.8)				0.0035	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
Asia	T-DXd (N=147)	52 (35.4)	6.15 (3.18, 11.90)	4.33 (2.46, 7.61)	0.272 (0.184, 0.360)	3.91 (2.12, 7.20)	0.7436
	T-DM1 (N=159)	13 (8.2)				<.0001	
North America	T-DXd (N=17)	1 (5.9)	1.00 (0.06, 17.41)	1.00 (0.07, 14.72)	0.000 (-0.158, 0.158)	0.83 (0.05, 13.46)	
	T-DM1 (N=17)	1 (5.9)				0.8969	
Europe	T-DXd (N=52)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=49)	0				NE	
Rest of World	T-DXd (N=41)	5 (12.2)	NE (NE, NE)	NE (NE, NE)	0.122 (0.022, 0.222)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.0572	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
Asia	T-DXd (N=147)	30 (20.4)	0.53 (0.31, 0.89)	0.62 (0.42, 0.92)	-0.123 (-0.221, -0.025)	0.46 (0.29, 0.73)	0.6852
	T-DM1 (N=159)	52 (32.7)				0.0007	
North America	T-DXd (N=17)	1 (5.9)	NE (NE, NE)	NE (NE, NE)	0.059 (-0.053, 0.171)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.3173	
Europe	T-DXd (N=52)	13 (25.0)	0.83 (0.34, 2.01)	0.88 (0.46, 1.67)	-0.036 (-0.208, 0.137)	0.71 (0.33, 1.51)	
	T-DM1 (N=49)	14 (28.6)				0.3776	
Rest of World	T-DXd (N=41)	12 (29.3)	0.94 (0.35, 2.50)	0.96 (0.48, 1.90)	-0.013 (-0.218, 0.192)	0.76 (0.33, 1.73)	
	T-DM1 (N=36)	11 (30.6)				0.5198	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Asia	T-DXd (N=147)	46 (31.3)	0.31 (0.19, 0.49)	0.52 (0.40, 0.69)	-0.285 (-0.391, -0.178)	0.30 (0.21, 0.43)	0.3951
	T-DM1 (N=159)	95 (59.7)				<.0001	
North America	T-DXd (N=17)	2 (11.8)	1.00 (0.12, 8.06)	1.00 (0.16, 6.30)	0.000 (-0.217, 0.217)	0.73 (0.10, 5.20)	
	T-DM1 (N=17)	2 (11.8)				0.7491	
Europe	T-DXd (N=52)	2 (3.8)	0.16 (0.03, 0.75)	0.19 (0.04, 0.82)	-0.166 (-0.290, -0.041)	0.16 (0.04, 0.74)	
	T-DM1 (N=49)	10 (20.4)				0.0076	
Rest of World	T-DXd (N=41)	4 (9.8)	0.67 (0.17, 2.71)	0.70 (0.20, 2.42)	-0.041 (-0.186, 0.104)	0.49 (0.13, 1.85)	
	T-DM1 (N=36)	5 (13.9)				0.2856	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
Asia	T-DXd (N=147)	30 (20.4)	3.14 (1.54, 6.40)	2.70 (1.44, 5.08)	0.129 (0.052, 0.206)	1.94 (0.99, 3.81)	0.7814
	T-DM1 (N=159)	12 (7.5)				0.0496	
North America	T-DXd (N=17)	5 (29.4)	NE (NE, NE)	NE (NE, NE)	0.294 (0.078, 0.511)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.0265	
Europe	T-DXd (N=52)	4 (7.7)	4.00 (0.43, 37.11)	3.77 (0.44, 32.56)	0.057 (-0.026, 0.139)	3.39 (0.38, 30.34)	
	T-DM1 (N=49)	1 (2.0)				0.2461	
Rest of World	T-DXd (N=41)	4 (9.8)	1.19 (0.25, 5.71)	1.17 (0.28, 4.88)	0.014 (-0.114, 0.142)	0.85 (0.19, 3.85)	
	T-DM1 (N=36)	3 (8.3)				0.8294	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
Asia	T-DXd (N=147)	11 (7.5)	0.50 (0.24, 1.08)	0.54 (0.27, 1.08)	-0.064 (-0.132, 0.005)	0.42 (0.20, 0.88)	0.9950
	T-DM1 (N=159)	22 (13.8)				0.0189	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	-0.059 (-0.171, 0.053)	NE (NE, NE)	
	T-DM1 (N=17)	1 (5.9)				0.2705	
Europe	T-DXd (N=52)	0	NE (NE, NE)	NE (NE, NE)	-0.061 (-0.128, 0.006)	NE (NE, NE)	
	T-DM1 (N=49)	3 (6.1)				0.0693	
Rest of World	T-DXd (N=41)	6 (14.6)	0.51 (0.16, 1.62)	0.59 (0.23, 1.49)	-0.104 (-0.282, 0.074)	0.40 (0.14, 1.16)	
	T-DM1 (N=36)	9 (25.0)				0.0813	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
Asia	T-DXd (N=147)	87 (59.2)	1.58 (1.01, 2.49)	1.24 (1.00, 1.53)	0.114 (0.003, 0.225)	1.03 (0.75, 1.40)	0.8282
	T-DM1 (N=159)	76 (47.8)				0.8487	
North America	T-DXd (N=17)	13 (76.5)	2.89 (0.66, 12.57)	1.44 (0.86, 2.43)	0.235 (-0.076, 0.547)	1.48 (0.63, 3.48)	
	T-DM1 (N=17)	9 (52.9)				0.3646	
Europe	T-DXd (N=52)	38 (73.1)	1.58 (0.68, 3.67)	1.16 (0.88, 1.51)	0.098 (-0.083, 0.279)	1.09 (0.68, 1.75)	
	T-DM1 (N=49)	31 (63.3)				0.7275	
Rest of World	T-DXd (N=41)	21 (51.2)	1.17 (0.48, 2.88)	1.08 (0.69, 1.71)	0.040 (-0.184, 0.264)	0.89 (0.46, 1.69)	
	T-DM1 (N=36)	17 (47.2)				0.7141	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Asia	T-DXd (N=147)	27 (18.4)	3.75 (1.70, 8.28)	3.24 (1.58, 6.67)	0.127 (0.055, 0.199)	3.03 (1.42, 6.46)	0.8487
	T-DM1 (N=159)	9 (5.7)				0.0026	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	1 (1.9)	0.94 (0.06, 15.47)	0.94 (0.06, 14.65)	-0.001 (-0.056, 0.053)	0.54 (0.03, 9.65)	
	T-DM1 (N=49)	1 (2.0)				0.6734	
Rest of World	T-DXd (N=41)	1 (2.4)	NE (NE, NE)	NE (NE, NE)	0.024 (-0.023, 0.072)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.3930	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Pyrexia							
Asia	T-DXd (N=147)	20 (13.6)	0.84 (0.45, 1.59)	0.87 (0.50, 1.49)	-0.021 (-0.100, 0.058)	0.59 (0.32, 1.07)	0.7495
	T-DM1 (N=159)	25 (15.7)				0.0780	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	4 (7.7)	0.43 (0.12, 1.52)	0.47 (0.15, 1.47)	-0.086 (-0.213, 0.040)	0.27 (0.08, 0.91)	
	T-DM1 (N=49)	8 (16.3)				0.0244	
Rest of World	T-DXd (N=41)	3 (7.3)	0.39 (0.09, 1.71)	0.44 (0.12, 1.63)	-0.093 (-0.239, 0.052)	0.30 (0.07, 1.22)	
	T-DM1 (N=36)	6 (16.7)				0.0762	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Asia	T-DXd (N=147)	84 (57.1)	3.60 (2.23, 5.81)	2.11 (1.58, 2.83)	0.301 (0.195, 0.407)	2.25 (1.55, 3.26)	0.6157
	T-DM1 (N=159)	43 (27.0)				<.0001	
North America	T-DXd (N=17)	4 (23.5)	1.44 (0.27, 7.68)	1.33 (0.35, 5.08)	0.059 (-0.212, 0.330)	1.27 (0.28, 5.69)	
	T-DM1 (N=17)	3 (17.6)				0.7550	
Europe	T-DXd (N=52)	27 (51.9)	2.23 (0.99, 5.00)	1.59 (0.98, 2.57)	0.193 (0.004, 0.382)	1.54 (0.83, 2.87)	
	T-DM1 (N=49)	16 (32.7)				0.1682	
Rest of World	T-DXd (N=41)	24 (58.5)	2.50 (0.99, 6.27)	1.62 (0.98, 2.69)	0.224 (0.007, 0.442)	1.86 (0.94, 3.66)	
	T-DM1 (N=36)	13 (36.1)				0.0695	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Alopecia							
Asia	T-DXd (N=147)	56 (38.1)	15.69 (6.50, 37.85)	10.10 (4.48, 22.73)	0.343 (0.259, 0.427)	11.24 (4.84, 26.10)	0.9986
	T-DM1 (N=159)	6 (3.8)				<.0001	
North America	T-DXd (N=17)	3 (17.6)	NE (NE, NE)	NE (NE, NE)	0.176 (-0.005, 0.358)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.0739	
Europe	T-DXd (N=52)	17 (32.7)	NE (NE, NE)	NE (NE, NE)	0.327 (0.199, 0.454)	NE (NE, NE)	
	T-DM1 (N=49)	0				<.0001	
Rest of World	T-DXd (N=41)	19 (46.3)	14.68 (3.11, 69.34)	8.34 (2.08, 33.37)	0.408 (0.238, 0.578)	9.69 (2.25, 41.62)	
	T-DM1 (N=36)	2 (5.6)				0.0002	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Asia	T-DXd (N=147)	72 (49.0)	1.87 (1.18, 2.96)	1.44 (1.10, 1.89)	0.150 (0.041, 0.259)	1.50 (1.05, 2.13)	0.9320
	T-DM1 (N=159)	54 (34.0)				0.0268	
North America	T-DXd (N=17)	10 (58.8)	3.43 (0.83, 14.21)	2.00 (0.87, 4.62)	0.294 (-0.025, 0.613)	1.98 (0.68, 5.81)	
	T-DM1 (N=17)	5 (29.4)				0.2014	
Europe	T-DXd (N=52)	21 (40.4)	2.34 (0.98, 5.59)	1.80 (0.97, 3.33)	0.179 (0.002, 0.357)	1.82 (0.88, 3.78)	
	T-DM1 (N=49)	11 (22.4)				0.1037	
Rest of World	T-DXd (N=41)	19 (46.3)	2.25 (0.87, 5.82)	1.67 (0.90, 3.11)	0.186 (-0.026, 0.397)	1.50 (0.69, 3.26)	
	T-DM1 (N=36)	10 (27.8)				0.3036	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Decreased appetite							
Asia	T-DXd (N=147)	48 (32.7)	2.17 (1.28, 3.69)	1.79 (1.20, 2.68)	0.144 (0.047, 0.241)	1.75 (1.10, 2.78)	0.9119
	T-DM1 (N=159)	29 (18.2)				0.0180	
North America	T-DXd (N=17)	3 (17.6)	1.61 (0.23, 11.09)	1.50 (0.29, 7.87)	0.059 (-0.178, 0.296)	1.41 (0.23, 8.48)	
	T-DM1 (N=17)	2 (11.8)				0.7051	
Europe	T-DXd (N=52)	12 (23.1)	1.54 (0.57, 4.16)	1.41 (0.63, 3.16)	0.068 (-0.087, 0.222)	1.38 (0.56, 3.37)	
	T-DM1 (N=49)	8 (16.3)				0.4830	
Rest of World	T-DXd (N=41)	12 (29.3)	2.57 (0.80, 8.18)	2.11 (0.82, 5.41)	0.154 (-0.026, 0.333)	2.12 (0.74, 6.02)	
	T-DM1 (N=36)	5 (13.9)				0.1536	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
Asia	T-DXd (N=147)	51 (34.7)	1.16 (0.72, 1.87)	1.10 (0.80, 1.52)	0.032 (-0.073, 0.138)	0.83 (0.56, 1.24)	0.8881
	T-DM1 (N=159)	50 (31.4)				0.3639	
North America	T-DXd (N=17)	10 (58.8)	2.62 (0.65, 10.48)	1.67 (0.78, 3.55)	0.235 (-0.091, 0.561)	1.25 (0.45, 3.47)	
	T-DM1 (N=17)	6 (35.3)				0.6688	
Europe	T-DXd (N=52)	27 (51.9)	1.33 (0.61, 2.90)	1.16 (0.77, 1.74)	0.070 (-0.124, 0.265)	0.85 (0.49, 1.50)	
	T-DM1 (N=49)	22 (44.9)				0.5932	
Rest of World	T-DXd (N=41)	28 (68.3)	1.72 (0.68, 4.37)	1.23 (0.86, 1.76)	0.127 (-0.089, 0.343)	0.94 (0.52, 1.68)	
	T-DM1 (N=36)	20 (55.6)				0.8540	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
Asia	T-DXd (N=147)	61 (41.5)	1.69 (1.05, 2.71)	1.40 (1.03, 1.91)	0.119 (0.013, 0.226)	1.02 (0.69, 1.50)	0.2707
	T-DM1 (N=159)	47 (29.6)				0.9282	
North America	T-DXd (N=17)	8 (47.1)	6.66 (1.15, 38.58)	4.00 (0.99, 16.16)	0.353 (0.071, 0.635)	4.24 (0.90, 20.01)	
	T-DM1 (N=17)	2 (11.8)				0.0468	
Europe	T-DXd (N=52)	21 (40.4)	1.17 (0.52, 2.60)	1.10 (0.67, 1.80)	0.036 (-0.153, 0.226)	0.83 (0.44, 1.58)	
	T-DM1 (N=49)	18 (36.7)				0.5718	
Rest of World	T-DXd (N=41)	22 (53.7)	1.16 (0.47, 2.84)	1.07 (0.70, 1.65)	0.037 (-0.187, 0.260)	0.81 (0.43, 1.53)	
	T-DM1 (N=36)	18 (50.0)				0.5238	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Asia	T-DXd (N=147)	60 (40.8)	1.98 (1.22, 3.22)	1.58 (1.14, 2.20)	0.150 (0.046, 0.255)	1.07 (0.72, 1.61)	0.3182
	T-DM1 (N=159)	41 (25.8)				0.7260	
North America	T-DXd (N=17)	10 (58.8)	1.27 (0.33, 4.93)	1.11 (0.61, 2.02)	0.059 (-0.274, 0.392)	0.75 (0.30, 1.86)	
	T-DM1 (N=17)	9 (52.9)				0.5342	
Europe	T-DXd (N=52)	17 (32.7)	0.84 (0.37, 1.90)	0.89 (0.52, 1.52)	-0.040 (-0.226, 0.145)	0.64 (0.32, 1.25)	
	T-DM1 (N=49)	18 (36.7)				0.1859	
Rest of World	T-DXd (N=41)	20 (48.8)	2.16 (0.85, 5.52)	1.60 (0.89, 2.86)	0.182 (-0.032, 0.397)	1.23 (0.59, 2.57)	
	T-DM1 (N=36)	11 (30.6)				0.5857	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Epistaxis							
Asia	T-DXd (N=147)	14 (9.5)	0.82 (0.39, 1.72)	0.84 (0.43, 1.63)	-0.018 (-0.086, 0.050)	0.47 (0.23, 0.96)	0.5680
	T-DM1 (N=159)	18 (11.3)				0.0355	
North America	T-DXd (N=17)	3 (17.6)	0.70 (0.13, 3.72)	0.75 (0.20, 2.86)	-0.059 (-0.330, 0.212)	0.52 (0.11, 2.39)	
	T-DM1 (N=17)	4 (23.5)				0.3947	
Europe	T-DXd (N=52)	6 (11.5)	0.33 (0.11, 0.93)	0.40 (0.17, 0.97)	-0.170 (-0.324, -0.017)	0.23 (0.08, 0.63)	
	T-DM1 (N=49)	14 (28.6)				0.0021	
Rest of World	T-DXd (N=41)	6 (14.6)	0.86 (0.25, 2.94)	0.88 (0.31, 2.48)	-0.020 (-0.183, 0.143)	0.54 (0.17, 1.71)	
	T-DM1 (N=36)	6 (16.7)				0.2921	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Asia	T-DXd (N=147)	57 (38.8)	2.09 (1.27, 3.43)	1.67 (1.18, 2.36)	0.155 (0.052, 0.258)	1.43 (0.94, 2.16)	0.2209
	T-DM1 (N=159)	37 (23.3)				0.0926	
North America	T-DXd (N=17)	6 (35.3)	2.55 (0.52, 12.55)	2.00 (0.60, 6.72)	0.176 (-0.114, 0.467)	1.18 (0.27, 5.05)	
	T-DM1 (N=17)	3 (17.6)				0.8266	
Europe	T-DXd (N=52)	13 (25.0)	0.69 (0.29, 1.63)	0.77 (0.41, 1.42)	-0.077 (-0.253, 0.100)	0.58 (0.28, 1.22)	
	T-DM1 (N=49)	16 (32.7)				0.1479	
Rest of World	T-DXd (N=41)	27 (65.9)	1.73 (0.69, 4.33)	1.25 (0.85, 1.82)	0.131 (-0.088, 0.349)	1.17 (0.65, 2.11)	
	T-DM1 (N=36)	19 (52.8)				0.5924	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
Asia	T-DXd (N=147)	51 (34.7)	2.60 (1.52, 4.44)	2.04 (1.36, 3.08)	0.177 (0.081, 0.274)	1.80 (1.13, 2.89)	0.6934
	T-DM1 (N=159)	27 (17.0)				0.0123	
North America	T-DXd (N=17)	4 (23.5)	2.31 (0.36, 14.72)	2.00 (0.42, 9.50)	0.118 (-0.136, 0.371)	0.94 (0.15, 5.74)	
	T-DM1 (N=17)	2 (11.8)				0.9471	
Europe	T-DXd (N=52)	9 (17.3)	1.26 (0.43, 3.68)	1.21 (0.49, 3.00)	0.030 (-0.112, 0.172)	0.96 (0.35, 2.60)	
	T-DM1 (N=49)	7 (14.3)				0.9377	
Rest of World	T-DXd (N=41)	19 (46.3)	3.02 (1.12, 8.19)	2.09 (1.04, 4.18)	0.241 (0.037, 0.445)	2.00 (0.87, 4.58)	
	T-DM1 (N=36)	8 (22.2)				0.0950	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
Asia	T-DXd (N=147)	11 (7.5)	6.35 (1.38, 29.15)	5.95 (1.34, 26.39)	0.062 (0.016, 0.108)	4.28 (0.94, 19.58)	0.9024
	T-DM1 (N=159)	2 (1.3)				0.0419	
North America	T-DXd (N=17)	2 (11.8)	2.13 (0.17, 26.03)	2.00 (0.20, 20.04)	0.059 (-0.131, 0.248)	1.83 (0.16, 20.38)	
	T-DM1 (N=17)	1 (5.9)				0.6164	
Europe	T-DXd (N=52)	9 (17.3)	NE (NE, NE)	NE (NE, NE)	0.173 (0.070, 0.276)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.0050	
Rest of World	T-DXd (N=41)	19 (46.3)	6.91 (2.07, 23.10)	4.17 (1.56, 11.12)	0.352 (0.168, 0.536)	3.87 (1.31, 11.40)	
	T-DM1 (N=36)	4 (11.1)				0.0082	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
Asia	T-DXd (N=147)	3 (2.0)	0.28 (0.08, 1.03)	0.29 (0.08, 1.04)	-0.049 (-0.094, -0.003)	0.25 (0.07, 0.90)	0.2774
	T-DM1 (N=159)	11 (6.9)				0.0225	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	-0.118 (-0.271, 0.036)	NE (NE, NE)	
	T-DM1 (N=17)	2 (11.8)				0.0797	
Europe	T-DXd (N=52)	1 (1.9)	0.10 (0.01, 0.84)	0.12 (0.02, 0.91)	-0.144 (-0.254, -0.034)	0.09 (0.01, 0.71)	
	T-DM1 (N=49)	8 (16.3)				0.0042	
Rest of World	T-DXd (N=41)	9 (22.0)	0.73 (0.26, 2.07)	0.79 (0.36, 1.73)	-0.058 (-0.252, 0.135)	0.60 (0.24, 1.49)	
	T-DM1 (N=36)	10 (27.8)				0.2593	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
Asia	T-DXd (N=147)	39 (26.5)	1.07 (0.64, 1.79)	1.05 (0.72, 1.54)	0.014 (-0.084, 0.112)	0.73 (0.47, 1.15)	0.7231
	T-DM1 (N=159)	40 (25.2)				0.1712	
North America	T-DXd (N=17)	11 (64.7)	2.62 (0.65, 10.48)	1.57 (0.81, 3.06)	0.235 (-0.091, 0.561)	1.23 (0.47, 3.21)	
	T-DM1 (N=17)	7 (41.2)				0.6758	
Europe	T-DXd (N=52)	23 (44.2)	1.06 (0.48, 2.32)	1.03 (0.66, 1.61)	0.014 (-0.180, 0.207)	0.72 (0.40, 1.32)	
	T-DM1 (N=49)	21 (42.9)				0.2943	
Rest of World	T-DXd (N=41)	21 (51.2)	0.94 (0.38, 2.30)	0.97 (0.63, 1.49)	-0.016 (-0.239, 0.208)	0.72 (0.39, 1.36)	
	T-DM1 (N=36)	19 (52.8)				0.3139	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
Asia	T-DXd (N=147)	20 (13.6)	4.01 (1.56, 10.30)	3.61 (1.49, 8.73)	0.098 (0.035, 0.161)	2.63 (1.05, 6.60)	0.2830
	T-DM1 (N=159)	6 (3.8)				0.0333	
North America	T-DXd (N=17)	6 (35.3)	4.09 (0.69, 24.24)	3.00 (0.70, 12.82)	0.235 (-0.039, 0.509)	3.05 (0.61, 15.17)	
	T-DM1 (N=17)	2 (11.8)				0.1539	
Europe	T-DXd (N=52)	13 (25.0)	2.00 (0.72, 5.53)	1.75 (0.76, 4.02)	0.107 (-0.046, 0.260)	1.30 (0.51, 3.32)	
	T-DM1 (N=49)	7 (14.3)				0.5817	
Rest of World	T-DXd (N=41)	6 (14.6)	0.86 (0.25, 2.94)	0.88 (0.31, 2.48)	-0.020 (-0.183, 0.143)	0.71 (0.23, 2.22)	
	T-DM1 (N=36)	6 (16.7)				0.5620	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
Asia	T-DXd (N=147)	20 (13.6)	1.32 (0.66, 2.62)	1.27 (0.69, 2.33)	0.029 (-0.044, 0.102)	0.73 (0.38, 1.42)	0.6778
	T-DM1 (N=159)	17 (10.7)				0.3558	
North America	T-DXd (N=17)	4 (23.5)	4.92 (0.49, 49.61)	4.00 (0.50, 32.20)	0.176 (-0.054, 0.407)	3.26 (0.36, 29.29)	
	T-DM1 (N=17)	1 (5.9)				0.2644	
Europe	T-DXd (N=52)	9 (17.3)	1.07 (0.38, 3.05)	1.06 (0.44, 2.53)	0.010 (-0.136, 0.156)	0.87 (0.33, 2.25)	
	T-DM1 (N=49)	8 (16.3)				0.7665	
Rest of World	T-DXd (N=41)	8 (19.5)	1.94 (0.53, 7.08)	1.76 (0.58, 5.35)	0.084 (-0.075, 0.243)	1.16 (0.34, 3.90)	
	T-DM1 (N=36)	4 (11.1)				0.8122	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
Asia	T-DXd (N=147)	19 (12.9)	0.83 (0.44, 1.60)	0.86 (0.49, 1.50)	-0.022 (-0.099, 0.056)	0.57 (0.31, 1.06)	0.2186
	T-DM1 (N=159)	24 (15.1)				0.0720	
North America	T-DXd (N=17)	1 (5.9)	1.00 (0.06, 17.41)	1.00 (0.07, 14.72)	0.000 (-0.158, 0.158)	0.69 (0.04, 11.09)	
	T-DM1 (N=17)	1 (5.9)				0.7932	
Europe	T-DXd (N=52)	10 (19.2)	3.65 (0.94, 14.17)	3.14 (0.92, 10.74)	0.131 (0.005, 0.257)	2.41 (0.66, 8.85)	
	T-DM1 (N=49)	3 (6.1)				0.1702	
Rest of World	T-DXd (N=41)	9 (22.0)	1.17 (0.38, 3.53)	1.13 (0.47, 2.72)	0.025 (-0.156, 0.206)	0.89 (0.33, 2.41)	
	T-DM1 (N=36)	7 (19.4)				0.8202	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Asia	T-DXd (N=147)	16 (10.9)	1.26 (0.59, 2.69)	1.24 (0.63, 2.44)	0.021 (-0.046, 0.088)	0.76 (0.37, 1.59)	0.7228
	T-DM1 (N=159)	14 (8.8)				0.4722	
North America	T-DXd (N=17)	4 (23.5)	4.92 (0.49, 49.61)	4.00 (0.50, 32.20)	0.176 (-0.054, 0.407)	2.51 (0.27, 22.89)	
	T-DM1 (N=17)	1 (5.9)				0.4000	
Europe	T-DXd (N=52)	8 (15.4)	0.93 (0.32, 2.71)	0.94 (0.38, 2.32)	-0.009 (-0.152, 0.133)	0.62 (0.22, 1.74)	
	T-DM1 (N=49)	8 (16.3)				0.3588	
Rest of World	T-DXd (N=41)	4 (9.8)	0.86 (0.20, 3.74)	0.88 (0.24, 3.26)	-0.014 (-0.151, 0.124)	0.63 (0.16, 2.56)	
	T-DM1 (N=36)	4 (11.1)				0.5176	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Region	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
Asia	T-DXd (N=147)	16 (10.9)	0.80 (0.40, 1.60)	0.82 (0.45, 1.52)	-0.023 (-0.096, 0.050)	0.66 (0.34, 1.27)	0.6311
	T-DM1 (N=159)	21 (13.2)				0.2182	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	-0.059 (-0.171, 0.053)	NE (NE, NE)	
	T-DM1 (N=17)	1 (5.9)				0.3173	
Europe	T-DXd (N=52)	2 (3.8)	0.29 (0.05, 1.49)	0.31 (0.07, 1.48)	-0.084 (-0.190, 0.022)	0.20 (0.04, 1.01)	
	T-DM1 (N=49)	6 (12.2)				0.0317	
Rest of World	T-DXd (N=41)	2 (4.9)	1.79 (0.16, 20.66)	1.76 (0.17, 18.57)	0.021 (-0.064, 0.106)	0.94 (0.08, 10.89)	
	T-DM1 (N=36)	1 (2.8)				0.9627	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
White	T-DXd (N=71)	71 (100)	NE (NE, NE)	1.51 (1.28, 1.78)	0.338 (0.228, 0.448)	3.42 (2.31, 5.05)	0.7249
	T-DM1 (N=71)	47 (66.2)				<.0001	
Black or African American	T-DXd (N=10)	10 (100)	NE (NE, NE)	1.80 (1.00, 3.23)	0.444 (0.120, 0.769)	4.23 (1.27, 14.10)	
	T-DM1 (N=9)	5 (55.6)				0.0111	
Asian	T-DXd (N=149)	130 (87.2)	5.97 (3.37, 10.57)	1.63 (1.40, 1.91)	0.338 (0.244, 0.432)	2.71 (2.06, 3.57)	
	T-DM1 (N=161)	86 (53.4)				<.0001	
Other	T-DXd (N=27)	26 (96.3)	11.14 (1.22, 102.02)	1.38 (1.02, 1.85)	0.263 (0.050, 0.476)	2.37 (1.22, 4.63)	
	T-DM1 (N=20)	14 (70.0)				0.0104	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Nausea							
White	T-DXd (N=71)	62 (87.3)	12.68 (5.41, 29.72)	2.48 (1.79, 3.44)	0.521 (0.386, 0.657)	3.85 (2.41, 6.16)	0.9797
	T-DM1 (N=71)	25 (35.2)				<.0001	
Black or African American	T-DXd (N=10)	10 (100)	NE (NE, NE)	2.25 (1.08, 4.67)	0.556 (0.231, 0.880)	4.53 (1.37, 14.99)	
	T-DM1 (N=9)	4 (44.4)				0.0061	
Asian	T-DXd (N=149)	102 (68.5)	5.96 (3.64, 9.73)	2.56 (1.94, 3.39)	0.417 (0.316, 0.519)	3.61 (2.52, 5.16)	
	T-DM1 (N=161)	43 (26.7)				<.0001	
Other	T-DXd (N=27)	21 (77.8)	6.50 (1.79, 23.64)	2.22 (1.18, 4.17)	0.428 (0.166, 0.689)	3.32 (1.40, 7.84)	
	T-DM1 (N=20)	7 (35.0)				0.0039	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
White	T-DXd (N=71)	38 (53.5)	7.93 (3.42, 18.38)	4.22 (2.21, 8.07)	0.408 (0.269, 0.548)	4.65 (2.25, 9.64)	0.9394
	T-DM1 (N=71)	9 (12.7)				<.0001	
Black or African American	T-DXd (N=10)	5 (50.0)	8.00 (0.71, 90.00)	4.50 (0.64, 31.60)	0.389 (0.017, 0.761)	4.99 (0.58, 42.80)	
	T-DM1 (N=9)	1 (11.1)				0.1005	
Asian	T-DXd (N=149)	72 (48.3)	9.10 (4.89, 16.94)	5.19 (3.12, 8.63)	0.390 (0.298, 0.482)	5.72 (3.28, 9.99)	
	T-DM1 (N=161)	15 (9.3)				<.0001	
Other	T-DXd (N=27)	11 (40.7)	13.06 (1.52, 112.38)	8.15 (1.14, 58.06)	0.357 (0.149, 0.566)	9.47 (1.22, 73.59)	
	T-DM1 (N=20)	1 (5.0)				0.0087	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Constipation							
White	T-DXd (N=71)	25 (35.2)	2.03 (0.96, 4.29)	1.67 (0.96, 2.89)	0.141 (-0.005, 0.287)	1.38 (0.72, 2.62)	0.9666
	T-DM1 (N=71)	15 (21.1)				0.3258	
Black or African American	T-DXd (N=10)	3 (30.0)	3.43 (0.29, 40.94)	2.70 (0.34, 21.53)	0.189 (-0.162, 0.539)	2.35 (0.24, 22.83)	
	T-DM1 (N=9)	1 (11.1)				0.4476	
Asian	T-DXd (N=149)	50 (33.6)	2.21 (1.31, 3.72)	1.80 (1.21, 2.67)	0.149 (0.052, 0.246)	1.68 (1.06, 2.65)	
	T-DM1 (N=161)	30 (18.6)				0.0248	
Other	T-DXd (N=27)	10 (37.0)	1.76 (0.49, 6.34)	1.48 (0.60, 3.66)	0.120 (-0.143, 0.383)	1.25 (0.43, 3.69)	
	T-DM1 (N=20)	5 (25.0)				0.6806	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
White	T-DXd (N=71)	27 (38.0)	4.23 (1.81, 9.87)	3.00 (1.52, 5.92)	0.254 (0.117, 0.390)	3.27 (1.54, 6.97)	0.7647
	T-DM1 (N=71)	9 (12.7)				0.0011	
Black or African American	T-DXd (N=10)	1 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.086, 0.286)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.3865	
Asian	T-DXd (N=149)	35 (23.5)	7.93 (3.23, 19.49)	6.30 (2.73, 14.55)	0.198 (0.124, 0.272)	6.04 (2.54, 14.40)	
	T-DM1 (N=161)	6 (3.7)				<.0001	
Other	T-DXd (N=27)	12 (44.4)	4.53 (1.07, 19.19)	2.96 (0.96, 9.13)	0.294 (0.050, 0.539)	3.29 (0.93, 11.69)	
	T-DM1 (N=20)	3 (15.0)				0.0512	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Stomatitis							
White	T-DXd (N=71)	10 (14.1)	11.48 (1.43, 92.23)	10.00 (1.31, 76.08)	0.127 (0.041, 0.212)	9.08 (1.16, 71.06)	0.7987
	T-DM1 (N=71)	1 (1.4)				0.0107	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	26 (17.4)	4.04 (1.77, 9.24)	3.51 (1.64, 7.51)	0.125 (0.055, 0.194)	2.78 (1.25, 6.17)	
	T-DM1 (N=161)	8 (5.0)				0.0089	
Other	T-DXd (N=27)	4 (14.8)	3.30 (0.34, 32.10)	2.96 (0.36, 24.53)	0.098 (-0.066, 0.263)	2.53 (0.28, 23.01)	
	T-DM1 (N=20)	1 (5.0)				0.3936	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
White	T-DXd (N=71)	16 (22.5)	10.04 (2.21, 45.52)	8.00 (1.91, 33.52)	0.197 (0.093, 0.302)	6.15 (1.41, 26.80)	0.8850
	T-DM1 (N=71)	2 (2.8)				0.0058	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	9 (6.0)	5.11 (1.09, 24.05)	4.86 (1.07, 22.14)	0.048 (0.006, 0.090)	3.90 (0.84, 18.24)	
	T-DM1 (N=161)	2 (1.2)				0.0625	
Other	T-DXd (N=27)	4 (14.8)	3.30 (0.34, 32.10)	2.96 (0.36, 24.53)	0.098 (-0.066, 0.263)	2.71 (0.30, 24.50)	
	T-DM1 (N=20)	1 (5.0)				0.3565	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
White	T-DXd (N=71)	39 (54.9)	1.18 (0.61, 2.29)	1.08 (0.79, 1.48)	0.042 (-0.122, 0.206)	0.82 (0.52, 1.30)	0.2213
	T-DM1 (N=71)	36 (50.7)				0.4176	
Black or African American	T-DXd (N=10)	8 (80.0)	2.00 (0.25, 15.99)	1.20 (0.69, 2.09)	0.133 (-0.262, 0.529)	0.86 (0.30, 2.51)	
	T-DM1 (N=9)	6 (66.7)				0.8253	
Asian	T-DXd (N=149)	101 (67.8)	0.61 (0.37, 1.00)	0.87 (0.76, 1.00)	-0.099 (-0.197, 0.000)	0.51 (0.39, 0.67)	
	T-DM1 (N=161)	125 (77.6)				<.0001	
Other	T-DXd (N=27)	14 (51.9)	0.72 (0.22, 2.31)	0.86 (0.52, 1.44)	-0.081 (-0.367, 0.204)	0.61 (0.28, 1.33)	
	T-DM1 (N=20)	12 (60.0)				0.2154	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
White	T-DXd (N=71)	7 (9.9)	3.77 (0.76, 18.83)	3.50 (0.75, 16.27)	0.070 (-0.009, 0.150)	2.66 (0.55, 12.87)	1.0000
	T-DM1 (N=71)	2 (2.8)				0.2055	
Black or African American	T-DXd (N=10)	2 (20.0)	NE (NE, NE)	NE (NE, NE)	0.200 (-0.048, 0.448)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.2117	
Asian	T-DXd (N=149)	63 (42.3)	4.40 (2.54, 7.60)	2.96 (1.94, 4.52)	0.280 (0.184, 0.376)	2.91 (1.80, 4.69)	
	T-DM1 (N=161)	23 (14.3)				<.0001	
Other	T-DXd (N=27)	3 (11.1)	NE (NE, NE)	NE (NE, NE)	0.111 (-0.007, 0.230)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.1540	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
White	T-DXd (N=71)	16 (22.5)	0.54 (0.26, 1.12)	0.64 (0.38, 1.09)	-0.127 (-0.274, 0.021)	0.47 (0.25, 0.89)	0.5682
	T-DM1 (N=71)	25 (35.2)				0.0195	
Black or African American	T-DXd (N=10)	3 (30.0)	0.21 (0.03, 1.49)	0.45 (0.16, 1.29)	-0.367 (-0.786, 0.052)	0.16 (0.03, 0.82)	
	T-DM1 (N=9)	6 (66.7)				0.0146	
Asian	T-DXd (N=149)	38 (25.5)	0.49 (0.30, 0.80)	0.62 (0.45, 0.87)	-0.155 (-0.258, -0.052)	0.42 (0.28, 0.64)	
	T-DM1 (N=161)	66 (41.0)				<.0001	
Other	T-DXd (N=27)	9 (33.3)	0.75 (0.23, 2.49)	0.83 (0.39, 1.78)	-0.067 (-0.345, 0.212)	0.61 (0.23, 1.60)	
	T-DM1 (N=20)	8 (40.0)				0.3217	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
White	T-DXd (N=71)	4 (5.6)	4.18 (0.46, 38.35)	4.00 (0.46, 34.91)	0.042 (-0.018, 0.102)	3.09 (0.34, 27.89)	0.9990
	T-DM1 (N=71)	1 (1.4)				0.2901	
Black or African American	T-DXd (N=10)	2 (20.0)	NE (NE, NE)	NE (NE, NE)	0.200 (-0.048, 0.448)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.2262	
Asian	T-DXd (N=149)	52 (34.9)	6.10 (3.16, 11.80)	4.32 (2.46, 7.61)	0.268 (0.181, 0.356)	3.92 (2.13, 7.21)	
	T-DM1 (N=161)	13 (8.1)				<.0001	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=20)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
White	T-DXd (N=71)	17 (23.9)	1.08 (0.50, 2.36)	1.06 (0.58, 1.93)	0.014 (-0.125, 0.153)	0.93 (0.47, 1.85)	0.3618
	T-DM1 (N=71)	16 (22.5)				0.8445	
Black or African American	T-DXd (N=10)	3 (30.0)	1.50 (0.19, 11.93)	1.35 (0.29, 6.34)	0.078 (-0.315, 0.471)	0.99 (0.16, 6.01)	
	T-DM1 (N=9)	2 (22.2)				0.9950	
Asian	T-DXd (N=149)	30 (20.1)	0.51 (0.31, 0.86)	0.61 (0.41, 0.90)	-0.128 (-0.225, -0.031)	0.45 (0.29, 0.71)	
	T-DM1 (N=161)	53 (32.9)				0.0005	
Other	T-DXd (N=27)	6 (22.2)	0.67 (0.18, 2.49)	0.74 (0.28, 1.96)	-0.078 (-0.333, 0.177)	0.54 (0.17, 1.69)	
	T-DM1 (N=20)	6 (30.0)				0.2945	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
White	T-DXd (N=71)	4 (5.6)	0.29 (0.09, 0.96)	0.33 (0.11, 0.98)	-0.113 (-0.215, -0.010)	0.24 (0.08, 0.77)	0.9794
	T-DM1 (N=71)	12 (16.9)				0.0101	
Black or African American	T-DXd (N=10)	2 (20.0)	NE (NE, NE)	NE (NE, NE)	0.200 (-0.048, 0.448)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.2183	
Asian	T-DXd (N=149)	47 (31.5)	0.30 (0.19, 0.49)	0.52 (0.40, 0.68)	-0.287 (-0.393, -0.181)	0.30 (0.21, 0.42)	
	T-DM1 (N=161)	97 (60.2)				<.0001	
Other	T-DXd (N=27)	1 (3.7)	0.22 (0.02, 2.27)	0.25 (0.03, 2.20)	-0.113 (-0.285, 0.059)	0.17 (0.02, 1.70)	
	T-DM1 (N=20)	3 (15.0)				0.0910	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
White	T-DXd (N=71)	9 (12.7)	5.01 (1.04, 24.07)	4.50 (1.01, 20.10)	0.099 (0.012, 0.185)	3.72 (0.80, 17.29)	0.8318
	T-DM1 (N=71)	2 (2.8)				0.0729	
Black or African American	T-DXd (N=10)	2 (20.0)	2.00 (0.15, 26.73)	1.80 (0.19, 16.66)	0.089 (-0.233, 0.411)	1.66 (0.15, 18.39)	
	T-DM1 (N=9)	1 (11.1)				0.6751	
Asian	T-DXd (N=149)	30 (20.1)	3.13 (1.54, 6.38)	2.70 (1.44, 5.08)	0.127 (0.051, 0.203)	1.96 (1.00, 3.84)	
	T-DM1 (N=161)	12 (7.5)				0.0471	
Other	T-DXd (N=27)	2 (7.4)	1.52 (0.13, 18.03)	1.48 (0.14, 15.22)	0.024 (-0.113, 0.161)	1.30 (0.12, 14.47)	
	T-DM1 (N=20)	1 (5.0)				0.8299	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
White	T-DXd (N=71)	4 (5.6)	0.55 (0.15, 1.95)	0.57 (0.17, 1.87)	-0.042 (-0.130, 0.045)	0.47 (0.14, 1.61)	0.9382
	T-DM1 (N=71)	7 (9.9)				0.2199	
Black or African American	T-DXd (N=10)	2 (20.0)	0.20 (0.03, 1.53)	0.36 (0.09, 1.42)	-0.356 (-0.764, 0.053)	0.19 (0.03, 1.00)	
	T-DM1 (N=9)	5 (55.6)				0.0306	
Asian	T-DXd (N=149)	11 (7.4)	0.50 (0.24, 1.08)	0.54 (0.27, 1.08)	-0.063 (-0.130, 0.005)	0.42 (0.20, 0.88)	
	T-DM1 (N=161)	22 (13.7)				0.0192	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	-0.050 (-0.146, 0.046)	NE (NE, NE)	
	T-DM1 (N=20)	1 (5.0)				0.2332	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
White	T-DXd (N=71)	46 (64.8)	1.79 (0.91, 3.51)	1.28 (0.96, 1.70)	0.141 (-0.020, 0.302)	1.12 (0.72, 1.74)	0.8044
	T-DM1 (N=71)	36 (50.7)				0.6114	
Black or African American	T-DXd (N=10)	7 (70.0)	1.87 (0.28, 12.31)	1.26 (0.62, 2.57)	0.144 (-0.287, 0.576)	1.03 (0.32, 3.27)	
	T-DM1 (N=9)	5 (55.6)				0.9829	
Asian	T-DXd (N=149)	88 (59.1)	1.54 (0.98, 2.41)	1.22 (0.99, 1.50)	0.106 (-0.004, 0.217)	1.01 (0.74, 1.38)	
	T-DM1 (N=161)	78 (48.4)				0.9269	
Other	T-DXd (N=27)	18 (66.7)	0.86 (0.25, 2.98)	0.95 (0.64, 1.41)	-0.033 (-0.302, 0.235)	0.81 (0.39, 1.65)	
	T-DM1 (N=20)	14 (70.0)				0.5341	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
White	T-DXd (N=71)	2 (2.8)	2.03 (0.18, 22.89)	2.00 (0.19, 21.56)	0.014 (-0.033, 0.061)	1.26 (0.11, 14.80)	0.9802
	T-DM1 (N=71)	1 (1.4)				0.8539	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	27 (18.1)	3.74 (1.69, 8.24)	3.24 (1.58, 6.66)	0.125 (0.054, 0.197)	3.03 (1.42, 6.46)	
	T-DM1 (N=161)	9 (5.6)				0.0027	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=20)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Pyrexia							
White	T-DXd (N=71)	3 (4.2)	0.35 (0.09, 1.37)	0.38 (0.10, 1.36)	-0.070 (-0.158, 0.017)	0.25 (0.06, 0.95)	0.6483
	T-DM1 (N=71)	8 (11.3)				0.0281	
Black or African American	T-DXd (N=10)	1 (10.0)	0.89 (0.05, 16.66)	0.90 (0.07, 12.38)	-0.011 (-0.288, 0.266)	0.67 (0.04, 11.05)	
	T-DM1 (N=9)	1 (11.1)				0.7787	
Asian	T-DXd (N=149)	20 (13.4)	0.84 (0.45, 1.59)	0.86 (0.50, 1.49)	-0.021 (-0.099, 0.057)	0.59 (0.32, 1.07)	
	T-DM1 (N=161)	25 (15.5)				0.0810	
Other	T-DXd (N=27)	3 (11.1)	0.38 (0.08, 1.80)	0.44 (0.12, 1.65)	-0.139 (-0.363, 0.085)	0.24 (0.06, 1.03)	
	T-DM1 (N=20)	5 (25.0)				0.0384	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
White	T-DXd (N=71)	29 (40.8)	1.64 (0.82, 3.30)	1.38 (0.88, 2.18)	0.113 (-0.043, 0.269)	1.41 (0.80, 2.47)	0.5467
	T-DM1 (N=71)	21 (29.6)				0.2374	
Black or African American	T-DXd (N=10)	6 (60.0)	3.00 (0.46, 19.59)	1.80 (0.63, 5.16)	0.267 (-0.166, 0.699)	1.94 (0.48, 7.77)	
	T-DM1 (N=9)	3 (33.3)				0.3403	
Asian	T-DXd (N=149)	84 (56.4)	3.44 (2.14, 5.52)	2.06 (1.55, 2.75)	0.290 (0.185, 0.396)	2.19 (1.52, 3.17)	
	T-DM1 (N=161)	44 (27.3)				<.0001	
Other	T-DXd (N=27)	20 (74.1)	5.31 (1.51, 18.69)	2.12 (1.12, 4.00)	0.391 (0.124, 0.657)	2.18 (0.92, 5.17)	
	T-DM1 (N=20)	7 (35.0)				0.0697	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Alopecia							
White	T-DXd (N=71)	24 (33.8)	NE (NE, NE)	NE (NE, NE)	0.338 (0.228, 0.448)	NE (NE, NE)	0.7872
	T-DM1 (N=71)	0				<.0001	
Black or African American	T-DXd (N=10)	3 (30.0)	3.43 (0.29, 40.94)	2.70 (0.34, 21.53)	0.189 (-0.162, 0.539)	2.93 (0.30, 28.21)	
	T-DM1 (N=9)	1 (11.1)				0.3228	
Asian	T-DXd (N=149)	56 (37.6)	13.25 (5.79, 30.28)	8.64 (4.07, 18.36)	0.332 (0.248, 0.416)	9.59 (4.37, 21.06)	
	T-DM1 (N=161)	7 (4.3)				<.0001	
Other	T-DXd (N=27)	12 (44.4)	NE (NE, NE)	NE (NE, NE)	0.444 (0.257, 0.632)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.0011	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
White	T-DXd (N=71)	31 (43.7)	2.28 (1.12, 4.65)	1.72 (1.07, 2.78)	0.183 (0.030, 0.337)	1.74 (0.97, 3.11)	0.8510
	T-DM1 (N=71)	18 (25.4)				0.0611	
Black or African American	T-DXd (N=10)	7 (70.0)	8.17 (1.03, 64.94)	3.15 (0.87, 11.42)	0.478 (0.085, 0.871)	2.26 (0.47, 10.99)	
	T-DM1 (N=9)	2 (22.2)				0.2990	
Asian	T-DXd (N=149)	72 (48.3)	1.85 (1.17, 2.93)	1.44 (1.10, 1.89)	0.148 (0.039, 0.256)	1.49 (1.05, 2.13)	
	T-DM1 (N=161)	54 (33.5)				0.0275	
Other	T-DXd (N=27)	12 (44.4)	1.87 (0.55, 6.33)	1.48 (0.67, 3.27)	0.144 (-0.130, 0.419)	1.43 (0.54, 3.83)	
	T-DM1 (N=20)	6 (30.0)				0.4740	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Decreased appetite							
White	T-DXd (N=71)	16 (22.5)	1.59 (0.68, 3.71)	1.45 (0.73, 2.91)	0.070 (-0.058, 0.199)	1.42 (0.66, 3.07)	0.8800
	T-DM1 (N=71)	11 (15.5)				0.3714	
Black or African American	T-DXd (N=10)	4 (40.0)	5.33 (0.47, 60.77)	3.60 (0.49, 26.54)	0.289 (-0.078, 0.655)	3.57 (0.40, 32.22)	
	T-DM1 (N=9)	1 (11.1)				0.2256	
Asian	T-DXd (N=149)	48 (32.2)	2.16 (1.27, 3.67)	1.79 (1.19, 2.68)	0.142 (0.046, 0.238)	1.75 (1.10, 2.78)	
	T-DM1 (N=161)	29 (18.0)				0.0182	
Other	T-DXd (N=27)	7 (25.9)	1.98 (0.44, 8.88)	1.73 (0.51, 5.87)	0.109 (-0.118, 0.337)	1.85 (0.48, 7.16)	
	T-DM1 (N=20)	3 (15.0)				0.3663	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
White	T-DXd (N=71)	42 (59.2)	1.58 (0.81, 3.06)	1.24 (0.91, 1.68)	0.113 (-0.050, 0.276)	1.00 (0.63, 1.57)	0.9850
	T-DM1 (N=71)	34 (47.9)				0.9950	
Black or African American	T-DXd (N=10)	7 (70.0)	1.87 (0.28, 12.31)	1.26 (0.62, 2.57)	0.144 (-0.287, 0.576)	0.85 (0.27, 2.69)	
	T-DM1 (N=9)	5 (55.6)				0.7945	
Asian	T-DXd (N=149)	53 (35.6)	1.23 (0.76, 1.97)	1.15 (0.84, 1.57)	0.045 (-0.060, 0.150)	0.88 (0.59, 1.30)	
	T-DM1 (N=161)	50 (31.1)				0.5145	
Other	T-DXd (N=27)	14 (51.9)	1.32 (0.41, 4.20)	1.15 (0.63, 2.11)	0.069 (-0.220, 0.357)	0.72 (0.31, 1.70)	
	T-DM1 (N=20)	9 (45.0)				0.4534	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
White	T-DXd (N=71)	33 (46.5)	1.42 (0.73, 2.76)	1.22 (0.83, 1.80)	0.085 (-0.077, 0.246)	0.92 (0.55, 1.55)	0.8854
	T-DM1 (N=71)	27 (38.0)				0.7639	
Black or African American	T-DXd (N=10)	6 (60.0)	1.87 (0.30, 11.63)	1.35 (0.56, 3.28)	0.156 (-0.289, 0.600)	1.22 (0.34, 4.35)	
	T-DM1 (N=9)	4 (44.4)				0.7564	
Asian	T-DXd (N=149)	62 (41.6)	1.73 (1.08, 2.77)	1.43 (1.05, 1.94)	0.124 (0.018, 0.230)	1.05 (0.72, 1.55)	
	T-DM1 (N=161)	47 (29.2)				0.7911	
Other	T-DXd (N=27)	11 (40.7)	1.28 (0.39, 4.23)	1.16 (0.55, 2.47)	0.057 (-0.222, 0.337)	0.86 (0.33, 2.23)	
	T-DM1 (N=20)	7 (35.0)				0.7598	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
White	T-DXd (N=71)	30 (42.3)	1.43 (0.73, 2.83)	1.25 (0.82, 1.91)	0.085 (-0.075, 0.244)	1.00 (0.58, 1.72)	0.6134
	T-DM1 (N=71)	24 (33.8)				0.9889	
Black or African American	T-DXd (N=10)	5 (50.0)	1.25 (0.21, 7.62)	1.13 (0.43, 2.93)	0.056 (-0.393, 0.504)	0.60 (0.16, 2.29)	
	T-DM1 (N=9)	4 (44.4)				0.4480	
Asian	T-DXd (N=149)	61 (40.9)	1.90 (1.18, 3.07)	1.53 (1.11, 2.11)	0.142 (0.038, 0.247)	1.04 (0.70, 1.55)	
	T-DM1 (N=161)	43 (26.7)				0.8294	
Other	T-DXd (N=27)	11 (40.7)	1.03 (0.32, 3.35)	1.02 (0.50, 2.06)	0.007 (-0.276, 0.291)	0.58 (0.22, 1.49)	
	T-DM1 (N=20)	8 (40.0)				0.2469	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Epistaxis							
White	T-DXd (N=71)	10 (14.1)	0.67 (0.27, 1.62)	0.71 (0.34, 1.50)	-0.056 (-0.179, 0.067)	0.49 (0.22, 1.12)	0.5821
	T-DM1 (N=71)	14 (19.7)				0.0833	
Black or African American	T-DXd (N=10)	1 (10.0)	0.39 (0.03, 5.21)	0.45 (0.05, 4.16)	-0.122 (-0.451, 0.207)	0.26 (0.02, 2.97)	
	T-DM1 (N=9)	2 (22.2)				0.2454	
Asian	T-DXd (N=149)	15 (10.1)	0.79 (0.39, 1.61)	0.81 (0.43, 1.52)	-0.024 (-0.094, 0.047)	0.45 (0.23, 0.90)	
	T-DM1 (N=161)	20 (12.4)				0.0216	
Other	T-DXd (N=27)	3 (11.1)	0.29 (0.06, 1.35)	0.37 (0.11, 1.31)	-0.189 (-0.422, 0.044)	0.14 (0.03, 0.70)	
	T-DM1 (N=20)	6 (30.0)				0.0057	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
White	T-DXd (N=71)	29 (40.8)	1.44 (0.73, 2.86)	1.26 (0.81, 1.95)	0.085 (-0.073, 0.242)	1.07 (0.62, 1.86)	0.3835
	T-DM1 (N=71)	23 (32.4)				0.7903	
Black or African American	T-DXd (N=10)	7 (70.0)	1.17 (0.17, 8.09)	1.05 (0.57, 1.94)	0.033 (-0.386, 0.452)	0.65 (0.21, 2.06)	
	T-DM1 (N=9)	6 (66.7)				0.4575	
Asian	T-DXd (N=149)	58 (38.9)	2.06 (1.26, 3.37)	1.65 (1.17, 2.32)	0.153 (0.051, 0.255)	1.41 (0.94, 2.13)	
	T-DM1 (N=161)	38 (23.6)				0.0964	
Other	T-DXd (N=27)	9 (33.3)	0.75 (0.23, 2.49)	0.83 (0.39, 1.78)	-0.067 (-0.345, 0.212)	0.63 (0.24, 1.66)	
	T-DM1 (N=20)	8 (40.0)				0.3489	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
White	T-DXd (N=71)	17 (23.9)	1.92 (0.81, 4.55)	1.70 (0.84, 3.45)	0.099 (-0.029, 0.227)	1.42 (0.65, 3.13)	0.8340
	T-DM1 (N=71)	10 (14.1)				0.3733	
Black or African American	T-DXd (N=10)	7 (70.0)	4.67 (0.67, 32.36)	2.10 (0.77, 5.76)	0.367 (-0.052, 0.786)	1.74 (0.43, 6.99)	
	T-DM1 (N=9)	3 (33.3)				0.4228	
Asian	T-DXd (N=149)	52 (34.9)	2.66 (1.56, 4.54)	2.08 (1.38, 3.13)	0.181 (0.085, 0.277)	1.86 (1.16, 2.96)	
	T-DM1 (N=161)	27 (16.8)				0.0084	
Other	T-DXd (N=27)	7 (25.9)	1.40 (0.35, 5.64)	1.30 (0.44, 3.83)	0.059 (-0.182, 0.300)	0.88 (0.25, 3.10)	
	T-DM1 (N=20)	4 (20.0)				0.8394	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
White	T-DXd (N=71)	22 (31.0)	10.18 (2.88, 35.91)	7.33 (2.30, 23.41)	0.268 (0.150, 0.385)	6.77 (2.02, 22.66)	0.4499
	T-DM1 (N=71)	3 (4.2)				0.0003	
Black or African American	T-DXd (N=10)	3 (30.0)	1.50 (0.19, 11.93)	1.35 (0.29, 6.34)	0.078 (-0.315, 0.471)	1.11 (0.18, 6.72)	
	T-DM1 (N=9)	2 (22.2)				0.9063	
Asian	T-DXd (N=149)	11 (7.4)	6.34 (1.38, 29.08)	5.94 (1.34, 26.37)	0.061 (0.016, 0.107)	4.31 (0.94, 19.68)	
	T-DM1 (N=161)	2 (1.2)				0.0409	
Other	T-DXd (N=27)	5 (18.5)	NE (NE, NE)	NE (NE, NE)	0.185 (0.039, 0.332)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.0536	

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[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
White	T-DXd (N=71)	8 (11.3)	0.62 (0.24, 1.63)	0.67 (0.29, 1.53)	-0.056 (-0.170, 0.058)	0.53 (0.22, 1.31)	0.4659
	T-DM1 (N=71)	12 (16.9)				0.1628	
Black or African American	T-DXd (N=10)	1 (10.0)	0.14 (0.01, 1.61)	0.23 (0.03, 1.66)	-0.344 (-0.719, 0.030)	0.09 (0.01, 0.90)	
	T-DM1 (N=9)	4 (44.4)				0.0139	
Asian	T-DXd (N=149)	3 (2.0)	0.26 (0.07, 0.92)	0.27 (0.08, 0.94)	-0.054 (-0.101, -0.008)	0.23 (0.06, 0.82)	
	T-DM1 (N=161)	12 (7.5)				0.0138	
Other	T-DXd (N=27)	1 (3.7)	0.22 (0.02, 2.27)	0.25 (0.03, 2.20)	-0.113 (-0.285, 0.059)	0.18 (0.02, 1.79)	
	T-DM1 (N=20)	3 (15.0)				0.1030	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
White	T-DXd (N=71)	37 (52.1)	1.33 (0.69, 2.57)	1.16 (0.82, 1.62)	0.070 (-0.094, 0.234)	0.90 (0.56, 1.44)	0.1526
	T-DM1 (N=71)	32 (45.1)				0.6550	
Black or African American	T-DXd (N=10)	6 (60.0)	3.00 (0.46, 19.59)	1.80 (0.63, 5.16)	0.267 (-0.166, 0.699)	1.59 (0.40, 6.39)	
	T-DM1 (N=9)	3 (33.3)				0.5032	
Asian	T-DXd (N=149)	40 (26.8)	1.11 (0.67, 1.85)	1.08 (0.74, 1.58)	0.020 (-0.078, 0.118)	0.76 (0.49, 1.19)	
	T-DM1 (N=161)	40 (24.8)				0.2317	
Other	T-DXd (N=27)	11 (40.7)	0.46 (0.14, 1.49)	0.68 (0.38, 1.21)	-0.193 (-0.476, 0.091)	0.28 (0.11, 0.72)	
	T-DM1 (N=20)	12 (60.0)				0.0053	

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[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
White	T-DXd (N=71)	14 (19.7)	1.69 (0.68, 4.21)	1.56 (0.72, 3.36)	0.070 (-0.050, 0.191)	1.31 (0.56, 3.04)	0.5385
	T-DM1 (N=71)	9 (12.7)				0.5372	
Black or African American	T-DXd (N=10)	1 (10.0)	0.89 (0.05, 16.66)	0.90 (0.07, 12.38)	-0.011 (-0.288, 0.266)	0.90 (0.06, 14.40)	
	T-DM1 (N=9)	1 (11.1)				0.9389	
Asian	T-DXd (N=149)	22 (14.8)	3.81 (1.58, 9.21)	3.40 (1.49, 7.72)	0.104 (0.039, 0.169)	2.54 (1.07, 5.98)	
	T-DM1 (N=161)	7 (4.3)				0.0281	
Other	T-DXd (N=27)	8 (29.6)	1.68 (0.43, 6.64)	1.48 (0.52, 4.24)	0.096 (-0.149, 0.342)	1.02 (0.30, 3.50)	
	T-DM1 (N=20)	4 (20.0)				0.9716	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
White	T-DXd (N=71)	14 (19.7)	1.50 (0.62, 3.64)	1.40 (0.67, 2.94)	0.056 (-0.067, 0.179)	1.05 (0.46, 2.38)	0.9252
	T-DM1 (N=71)	10 (14.1)				0.9085	
Black or African American	T-DXd (N=10)	3 (30.0)	NE (NE, NE)	NE (NE, NE)	0.300 (0.016, 0.584)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.1639	
Asian	T-DXd (N=149)	21 (14.1)	1.39 (0.70, 2.75)	1.33 (0.73, 2.43)	0.035 (-0.038, 0.109)	0.79 (0.41, 1.52)	
	T-DM1 (N=161)	17 (10.6)				0.4760	
Other	T-DXd (N=27)	3 (11.1)	0.71 (0.13, 3.94)	0.74 (0.17, 3.29)	-0.039 (-0.235, 0.157)	0.59 (0.12, 2.94)	
	T-DM1 (N=20)	3 (15.0)				0.5168	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
White	T-DXd (N=71)	13 (18.3)	2.05 (0.77, 5.49)	1.86 (0.79, 4.38)	0.085 (-0.029, 0.198)	1.43 (0.57, 3.61)	0.4392
	T-DM1 (N=71)	7 (9.9)				0.4450	
Black or African American	T-DXd (N=10)	1 (10.0)	0.89 (0.05, 16.66)	0.90 (0.07, 12.38)	-0.011 (-0.288, 0.266)	0.58 (0.03, 9.93)	
	T-DM1 (N=9)	1 (11.1)				0.7047	
Asian	T-DXd (N=149)	20 (13.4)	0.89 (0.47, 1.68)	0.90 (0.52, 1.56)	-0.015 (-0.092, 0.063)	0.61 (0.33, 1.11)	
	T-DM1 (N=161)	24 (14.9)				0.1041	
Other	T-DXd (N=27)	5 (18.5)	1.29 (0.27, 6.16)	1.23 (0.33, 4.57)	0.035 (-0.179, 0.250)	0.93 (0.22, 3.93)	
	T-DM1 (N=20)	3 (15.0)				0.9159	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
White	T-DXd (N=71)	11 (15.5)	1.12 (0.44, 2.83)	1.10 (0.50, 2.43)	0.014 (-0.103, 0.131)	0.77 (0.32, 1.82)	0.9990
	T-DM1 (N=71)	10 (14.1)				0.5456	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	-0.111 (-0.316, 0.094)	NE (NE, NE)	
	T-DM1 (N=9)	1 (11.1)				0.2059	
Asian	T-DXd (N=149)	17 (11.4)	1.35 (0.64, 2.85)	1.31 (0.67, 2.57)	0.027 (-0.040, 0.094)	0.80 (0.39, 1.66)	
	T-DM1 (N=161)	14 (8.7)				0.5558	
Other	T-DXd (N=27)	4 (14.8)	1.56 (0.26, 9.52)	1.48 (0.30, 7.31)	0.048 (-0.140, 0.236)	0.96 (0.16, 5.80)	
	T-DM1 (N=20)	2 (10.0)				0.9672	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
White	T-DXd (N=71)	3 (4.2)	1.00 (0.19, 5.13)	1.00 (0.21, 4.79)	0.000 (-0.066, 0.066)	0.61 (0.12, 3.14)	0.4370
	T-DM1 (N=71)	3 (4.2)				0.5538	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	16 (10.7)	0.80 (0.40, 1.60)	0.82 (0.45, 1.52)	-0.023 (-0.095, 0.049)	0.66 (0.34, 1.27)	
	T-DM1 (N=161)	21 (13.0)				0.2196	
Other	T-DXd (N=27)	1 (3.7)	0.12 (0.01, 1.08)	0.15 (0.02, 1.17)	-0.213 (-0.416, -0.010)	0.08 (0.01, 0.76)	
	T-DM1 (N=20)	5 (25.0)				0.0066	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
0	T-DXd (N=152)	144 (94.7)	11.83 (5.45, 25.65)	1.57 (1.38, 1.78)	0.344 (0.263, 0.425)	2.90 (2.25, 3.76)	0.8441
	T-DM1 (N=174)	105 (60.3)				<.0001	
1	T-DXd (N=105)	93 (88.6)	6.59 (3.16, 13.74)	1.64 (1.33, 2.01)	0.345 (0.224, 0.467)	2.88 (2.02, 4.11)	
	T-DM1 (N=87)	47 (54.0)				<.0001	
Nausea							
0	T-DXd (N=152)	114 (75.0)	7.24 (4.43, 11.83)	2.56 (2.00, 3.28)	0.457 (0.360, 0.553)	3.75 (2.69, 5.23)	0.9714
	T-DM1 (N=174)	51 (29.3)				<.0001	
1	T-DXd (N=105)	81 (77.1)	7.11 (3.75, 13.49)	2.40 (1.74, 3.31)	0.450 (0.323, 0.576)	3.63 (2.36, 5.60)	
	T-DM1 (N=87)	28 (32.2)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
0	T-DXd (N=152)	78 (51.3)	9.14 (5.10, 16.36)	4.96 (3.12, 7.89)	0.410 (0.318, 0.501)	5.46 (3.27, 9.13)	0.9931
	T-DM1 (N=174)	18 (10.3)				<.0001	
1	T-DXd (N=105)	48 (45.7)	8.32 (3.65, 18.93)	4.97 (2.49, 9.94)	0.365 (0.252, 0.478)	5.54 (2.62, 11.72)	
	T-DM1 (N=87)	8 (9.2)				<.0001	
Constipation							
0	T-DXd (N=152)	59 (38.8)	2.43 (1.49, 3.97)	1.88 (1.32, 2.67)	0.181 (0.083, 0.279)	1.68 (1.11, 2.56)	0.6651
	T-DM1 (N=174)	36 (20.7)				0.0132	
1	T-DXd (N=105)	29 (27.6)	1.83 (0.91, 3.69)	1.60 (0.92, 2.79)	0.104 (-0.013, 0.220)	1.34 (0.71, 2.52)	
	T-DM1 (N=87)	15 (17.2)				0.3601	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
0	T-DXd (N=152)	46 (30.3)	5.37 (2.77, 10.43)	4.05 (2.28, 7.20)	0.228 (0.145, 0.311)	3.96 (2.14, 7.35)	0.7195
	T-DM1 (N=174)	13 (7.5)				<.0001	
1	T-DXd (N=105)	29 (27.6)	6.26 (2.30, 16.99)	4.81 (1.94, 11.89)	0.219 (0.120, 0.317)	4.94 (1.91, 12.79)	
	T-DM1 (N=87)	5 (5.7)				0.0003	
Stomatitis							
0	T-DXd (N=152)	22 (14.5)	4.74 (1.87, 12.02)	4.20 (1.75, 10.08)	0.110 (0.048, 0.172)	3.64 (1.47, 9.02)	0.8860
	T-DM1 (N=174)	6 (3.4)				0.0028	
1	T-DXd (N=105)	18 (17.1)	4.29 (1.39, 13.22)	3.73 (1.31, 10.61)	0.125 (0.041, 0.210)	2.88 (0.97, 8.58)	
	T-DM1 (N=87)	4 (4.6)				0.0465	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
0	T-DXd (N=152)	17 (11.2)	7.18 (2.06, 25.00)	6.49 (1.94, 21.71)	0.095 (0.041, 0.148)	4.77 (1.39, 16.40)	0.8247
	T-DM1 (N=174)	3 (1.7)				0.0064	
1	T-DXd (N=105)	12 (11.4)	5.48 (1.19, 25.21)	4.97 (1.14, 21.62)	0.091 (0.023, 0.160)	3.88 (0.86, 17.44)	
	T-DM1 (N=87)	2 (2.3)				0.0571	
Investigations							
Any PT							
0	T-DXd (N=152)	95 (62.5)	0.71 (0.45, 1.13)	0.89 (0.76, 1.04)	-0.076 (-0.179, 0.027)	0.55 (0.42, 0.72)	0.3089
	T-DM1 (N=174)	122 (70.1)				<.0001	
1	T-DXd (N=105)	67 (63.8)	0.93 (0.51, 1.68)	0.97 (0.79, 1.20)	-0.017 (-0.153, 0.119)	0.71 (0.50, 1.01)	
	T-DM1 (N=87)	57 (65.5)				0.1050	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
0	T-DXd (N=152)	42 (27.6)	3.77 (2.02, 7.04)	3.00 (1.76, 5.12)	0.184 (0.101, 0.267)	2.68 (1.50, 4.77)	0.8290
	T-DM1 (N=174)	16 (9.2)				0.0005	
1	T-DXd (N=105)	33 (31.4)	3.97 (1.78, 8.87)	3.04 (1.54, 6.00)	0.211 (0.101, 0.320)	2.95 (1.41, 6.18)	
	T-DM1 (N=87)	9 (10.3)				0.0026	
Aspartate aminotransferase increased							
0	T-DXd (N=152)	36 (23.7)	0.46 (0.28, 0.75)	0.59 (0.42, 0.83)	-0.165 (-0.265, -0.066)	0.40 (0.26, 0.60)	0.3963
	T-DM1 (N=174)	70 (40.2)				<.0001	
1	T-DXd (N=105)	30 (28.6)	0.59 (0.33, 1.09)	0.71 (0.48, 1.06)	-0.117 (-0.251, 0.018)	0.51 (0.31, 0.83)	
	T-DM1 (N=87)	35 (40.2)				0.0069	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
0	T-DXd (N=152)	26 (17.1)	4.28 (1.87, 9.77)	3.72 (1.74, 7.97)	0.125 (0.058, 0.193)	2.97 (1.34, 6.58)	0.6011
	T-DM1 (N=174)	8 (4.6)				0.0050	
1	T-DXd (N=105)	32 (30.5)	5.92 (2.34, 14.96)	4.42 (1.94, 10.08)	0.236 (0.133, 0.339)	4.24 (1.77, 10.15)	
	T-DM1 (N=87)	6 (6.9)				0.0004	
Alanine aminotransferase increased							
0	T-DXd (N=152)	35 (23.0)	0.66 (0.40, 1.09)	0.74 (0.51, 1.07)	-0.080 (-0.176, 0.016)	0.56 (0.36, 0.86)	0.7686
	T-DM1 (N=174)	54 (31.0)				0.0080	
1	T-DXd (N=105)	21 (20.0)	0.70 (0.35, 1.37)	0.76 (0.45, 1.27)	-0.064 (-0.185, 0.056)	0.61 (0.34, 1.11)	
	T-DM1 (N=87)	23 (26.4)				0.1009	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
0	T-DXd (N=152)	22 (14.5)	0.19 (0.11, 0.33)	0.31 (0.20, 0.47)	-0.327 (-0.419, -0.234)	0.20 (0.12, 0.32)	0.0002
	T-DM1 (N=174)	82 (47.1)				<.0001	
1	T-DXd (N=105)	32 (30.5)	0.83 (0.45, 1.53)	0.88 (0.59, 1.33)	-0.040 (-0.173, 0.093)	0.64 (0.38, 1.06)	
	T-DM1 (N=87)	30 (34.5)				0.0980	
Weight decreased							
0	T-DXd (N=152)	23 (15.1)	3.27 (1.46, 7.31)	2.93 (1.40, 6.13)	0.100 (0.034, 0.165)	2.19 (1.01, 4.76)	0.8085
	T-DM1 (N=174)	9 (5.2)				0.0423	
1	T-DXd (N=105)	20 (19.0)	2.69 (1.08, 6.70)	2.37 (1.05, 5.33)	0.110 (0.016, 0.204)	1.88 (0.79, 4.47)	
	T-DM1 (N=87)	7 (8.0)				0.1480	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
0	T-DXd (N=152)	6 (3.9)	0.41 (0.15, 1.07)	0.43 (0.17, 1.07)	-0.052 (-0.105, 0.000)	0.27 (0.10, 0.71)	0.8155
	T-DM1 (N=174)	16 (9.2)				0.0050	
1	T-DXd (N=105)	11 (10.5)	0.42 (0.19, 0.94)	0.48 (0.24, 0.95)	-0.114 (-0.218, -0.009)	0.40 (0.19, 0.84)	
	T-DM1 (N=87)	19 (21.8)				0.0121	
General disorders and administration site conditions							
Any PT							
0	T-DXd (N=152)	95 (62.5)	1.67 (1.07, 2.60)	1.25 (1.03, 1.52)	0.125 (0.018, 0.232)	1.12 (0.84, 1.50)	0.4408
	T-DM1 (N=174)	87 (50.0)				0.4574	
1	T-DXd (N=105)	64 (61.0)	1.39 (0.78, 2.47)	1.15 (0.90, 1.48)	0.081 (-0.060, 0.221)	0.90 (0.61, 1.31)	
	T-DM1 (N=87)	46 (52.9)				0.5825	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
0	T-DXd (N=152)	20 (13.2)	2.48 (1.12, 5.49)	2.29 (1.11, 4.74)	0.074 (0.010, 0.138)	2.07 (0.96, 4.44)	0.9854
	T-DM1 (N=174)	10 (5.7)				0.0570	
1	T-DXd (N=105)	9 (8.6)	NE (NE, NE)	NE (NE, NE)	0.086 (0.032, 0.139)	NE (NE, NE)	
	T-DM1 (N=87)	0				0.0109	
Pyrexia							
0	T-DXd (N=152)	13 (8.6)	0.53 (0.26, 1.08)	0.57 (0.31, 1.07)	-0.064 (-0.133, 0.005)	0.35 (0.18, 0.69)	0.2761
	T-DM1 (N=174)	26 (14.9)				0.0018	
1	T-DXd (N=105)	14 (13.3)	0.88 (0.39, 1.98)	0.89 (0.44, 1.80)	-0.016 (-0.115, 0.083)	0.59 (0.27, 1.27)	
	T-DM1 (N=87)	13 (14.9)				0.1740	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
0	T-DXd (N=152)	86 (56.6)	3.23 (2.04, 5.11)	1.97 (1.50, 2.59)	0.278 (0.175, 0.382)	2.09 (1.47, 2.98)	0.5665
	T-DM1 (N=174)	50 (28.7)				<.0001	
1	T-DXd (N=105)	53 (50.5)	2.53 (1.38, 4.61)	1.76 (1.20, 2.57)	0.217 (0.083, 0.352)	1.74 (1.08, 2.81)	
	T-DM1 (N=87)	25 (28.7)				0.0217	
Alopecia							
0	T-DXd (N=152)	60 (39.5)	22.04 (8.55, 56.83)	13.74 (5.66, 33.32)	0.366 (0.284, 0.448)	15.32 (6.15, 38.18)	0.6524
	T-DM1 (N=174)	5 (2.9)				<.0001	
1	T-DXd (N=105)	35 (33.3)	13.99 (4.13, 47.43)	9.67 (3.08, 30.36)	0.299 (0.201, 0.397)	10.82 (3.33, 35.18)	
	T-DM1 (N=87)	3 (3.4)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
0	T-DXd (N=152)	67 (44.1)	2.26 (1.42, 3.60)	1.70 (1.25, 2.32)	0.182 (0.080, 0.284)	1.66 (1.14, 2.43)	0.4063
	T-DM1 (N=174)	45 (25.9)				0.0083	
1	T-DXd (N=105)	55 (52.4)	1.63 (0.92, 2.90)	1.30 (0.95, 1.78)	0.122 (-0.019, 0.262)	1.34 (0.88, 2.06)	
	T-DM1 (N=87)	35 (40.2)				0.1757	
Decreased appetite							
0	T-DXd (N=152)	48 (31.6)	2.75 (1.60, 4.74)	2.20 (1.43, 3.38)	0.172 (0.082, 0.263)	2.13 (1.31, 3.46)	0.0856
	T-DM1 (N=174)	25 (14.4)				0.0019	
1	T-DXd (N=105)	27 (25.7)	1.24 (0.63, 2.42)	1.18 (0.70, 1.97)	0.039 (-0.082, 0.159)	1.16 (0.64, 2.08)	
	T-DM1 (N=87)	19 (21.8)				0.6391	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
0	T-DXd (N=152)	66 (43.4)	1.35 (0.87, 2.11)	1.20 (0.92, 1.57)	0.072 (-0.034, 0.178)	0.90 (0.64, 1.28)	0.8262
	T-DM1 (N=174)	63 (36.2)				0.5649	
1	T-DXd (N=105)	50 (47.6)	1.35 (0.76, 2.40)	1.18 (0.85, 1.64)	0.074 (-0.067, 0.214)	0.94 (0.61, 1.46)	
	T-DM1 (N=87)	35 (40.2)				0.7943	
Infections and infestations							
Any PT							
0	T-DXd (N=152)	66 (43.4)	2.01 (1.27, 3.20)	1.57 (1.16, 2.13)	0.158 (0.055, 0.261)	1.17 (0.80, 1.71)	0.1306
	T-DM1 (N=174)	48 (27.6)				0.4104	
1	T-DXd (N=105)	46 (43.8)	1.05 (0.59, 1.87)	1.03 (0.74, 1.43)	0.013 (-0.128, 0.154)	0.78 (0.50, 1.20)	
	T-DM1 (N=87)	37 (42.5)				0.2534	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
0	T-DXd (N=152)	68 (44.7)	1.85 (1.17, 2.91)	1.47 (1.10, 1.95)	0.143 (0.038, 0.247)	0.96 (0.67, 1.39)	0.8353
	T-DM1 (N=174)	53 (30.5)				0.8417	
1	T-DXd (N=105)	39 (37.1)	1.39 (0.76, 2.54)	1.24 (0.83, 1.87)	0.073 (-0.061, 0.206)	0.95 (0.58, 1.56)	
	T-DM1 (N=87)	26 (29.9)				0.8334	
Epistaxis							
0	T-DXd (N=152)	20 (13.2)	0.73 (0.39, 1.34)	0.76 (0.45, 1.29)	-0.041 (-0.119, 0.037)	0.43 (0.24, 0.76)	0.8522
	T-DM1 (N=174)	30 (17.2)				0.0032	
1	T-DXd (N=105)	9 (8.6)	0.59 (0.23, 1.46)	0.62 (0.27, 1.41)	-0.052 (-0.142, 0.038)	0.41 (0.17, 0.97)	
	T-DM1 (N=87)	12 (13.8)				0.0372	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
0	T-DXd (N=152)	55 (36.2)	1.68 (1.04, 2.70)	1.43 (1.03, 1.99)	0.109 (0.009, 0.209)	1.13 (0.75, 1.68)	0.9303
	T-DM1 (N=174)	44 (25.3)				0.5584	
1	T-DXd (N=105)	48 (45.7)	1.52 (0.85, 2.73)	1.28 (0.90, 1.82)	0.101 (-0.038, 0.239)	1.12 (0.71, 1.76)	
	T-DM1 (N=87)	31 (35.6)				0.6234	
Anaemia							
0	T-DXd (N=152)	39 (25.7)	2.16 (1.23, 3.79)	1.86 (1.17, 2.95)	0.119 (0.032, 0.205)	1.44 (0.86, 2.41)	0.7214
	T-DM1 (N=174)	24 (13.8)				0.1599	
1	T-DXd (N=105)	44 (41.9)	2.42 (1.28, 4.55)	1.82 (1.17, 2.85)	0.189 (0.060, 0.318)	1.73 (1.02, 2.94)	
	T-DM1 (N=87)	20 (23.0)				0.0405	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
0	T-DXd (N=152)	26 (17.1)	8.77 (2.99, 25.76)	7.44 (2.66, 20.84)	0.148 (0.084, 0.212)	5.72 (1.98, 16.47)	0.4867
	T-DM1 (N=174)	4 (2.3)				0.0003	
1	T-DXd (N=105)	15 (14.3)	4.67 (1.30, 16.70)	4.14 (1.24, 13.85)	0.108 (0.031, 0.186)	3.17 (0.91, 11.08)	
	T-DM1 (N=87)	3 (3.4)				0.0564	
Thrombocytopenia							
0	T-DXd (N=152)	10 (6.6)	0.57 (0.26, 1.28)	0.60 (0.29, 1.26)	-0.043 (-0.104, 0.017)	0.42 (0.19, 0.93)	0.1647
	T-DM1 (N=174)	19 (10.9)				0.0267	
1	T-DXd (N=105)	3 (2.9)	0.18 (0.05, 0.67)	0.21 (0.06, 0.71)	-0.109 (-0.189, -0.030)	0.16 (0.05, 0.59)	
	T-DM1 (N=87)	12 (13.8)				0.0017	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
0	T-DXd (N=152)	61 (40.1)	1.38 (0.87, 2.16)	1.23 (0.92, 1.63)	0.074 (-0.031, 0.178)	0.87 (0.61, 1.26)	0.2889
	T-DM1 (N=174)	57 (32.8)				0.4716	
1	T-DXd (N=105)	33 (31.4)	0.87 (0.48, 1.59)	0.91 (0.61, 1.37)	-0.031 (-0.164, 0.103)	0.68 (0.41, 1.13)	
	T-DM1 (N=87)	30 (34.5)				0.1336	
Vascular disorders							
Any PT							
0	T-DXd (N=152)	26 (17.1)	2.79 (1.35, 5.74)	2.48 (1.30, 4.74)	0.102 (0.031, 0.173)	1.79 (0.89, 3.58)	0.5526
	T-DM1 (N=174)	12 (6.9)				0.0972	
1	T-DXd (N=105)	19 (18.1)	1.91 (0.82, 4.48)	1.75 (0.83, 3.67)	0.078 (-0.020, 0.175)	1.43 (0.64, 3.18)	
	T-DM1 (N=87)	9 (10.3)				0.3787	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
0	T-DXd (N=152)	24 (15.8)	1.73 (0.89, 3.36)	1.62 (0.90, 2.89)	0.060 (-0.013, 0.133)	1.10 (0.58, 2.06)	0.3624
	T-DM1 (N=174)	17 (9.8)				0.7726	
1	T-DXd (N=105)	17 (16.2)	1.10 (0.50, 2.41)	1.08 (0.56, 2.10)	0.012 (-0.090, 0.115)	0.66 (0.31, 1.38)	
	T-DM1 (N=87)	13 (14.9)				0.2674	
Psychiatric disorders							
Any PT							
0	T-DXd (N=152)	28 (18.4)	1.65 (0.89, 3.04)	1.53 (0.91, 2.57)	0.064 (-0.015, 0.142)	1.06 (0.60, 1.88)	0.0705
	T-DM1 (N=174)	21 (12.1)				0.8376	
1	T-DXd (N=105)	11 (10.5)	0.61 (0.26, 1.42)	0.65 (0.31, 1.36)	-0.056 (-0.153, 0.041)	0.47 (0.21, 1.03)	
	T-DM1 (N=87)	14 (16.1)				0.0543	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
0	T-DXd (N=152)	18 (11.8)	1.99 (0.91, 4.36)	1.87 (0.91, 3.84)	0.055 (-0.008, 0.118)	1.30 (0.61, 2.79)	0.0737
	T-DM1 (N=174)	11 (6.3)				0.4913	
1	T-DXd (N=105)	14 (13.3)	0.68 (0.31, 1.49)	0.73 (0.38, 1.40)	-0.051 (-0.155, 0.054)	0.42 (0.20, 0.88)	
	T-DM1 (N=87)	16 (18.4)				0.0180	
Hepatobiliary disorders							
Any PT							
0	T-DXd (N=152)	9 (5.9)	0.55 (0.24, 1.25)	0.57 (0.27, 1.24)	-0.044 (-0.103, 0.015)	0.42 (0.19, 0.96)	0.5195
	T-DM1 (N=174)	18 (10.3)				0.0340	
1	T-DXd (N=105)	11 (10.5)	0.81 (0.33, 1.97)	0.83 (0.38, 1.82)	-0.022 (-0.113, 0.069)	0.63 (0.27, 1.46)	
	T-DM1 (N=87)	11 (12.6)				0.2832	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Positive	T-DXd (N=133)	122 (91.7)	8.42 (4.17, 17.00)	1.61 (1.38, 1.88)	0.349 (0.254, 0.444)	2.89 (2.16, 3.85)	0.6544
	T-DM1 (N=139)	79 (56.8)				<.0001	
Negative	T-DXd (N=123)	114 (92.7)	8.33 (3.86, 17.99)	1.54 (1.32, 1.79)	0.324 (0.225, 0.422)	2.75 (2.04, 3.71)	
	T-DM1 (N=121)	73 (60.3)				<.0001	
Nausea							
Positive	T-DXd (N=133)	105 (78.9)	10.34 (5.90, 18.12)	2.97 (2.22, 3.96)	0.523 (0.422, 0.624)	4.62 (3.17, 6.75)	0.0885
	T-DM1 (N=139)	37 (26.6)				<.0001	
Negative	T-DXd (N=123)	89 (72.4)	4.92 (2.86, 8.49)	2.08 (1.60, 2.72)	0.376 (0.261, 0.492)	2.95 (2.04, 4.26)	
	T-DM1 (N=121)	42 (34.7)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Positive	T-DXd (N=133)	63 (47.4)	8.72 (4.49, 16.96)	5.06 (2.93, 8.76)	0.380 (0.282, 0.478)	5.61 (3.08, 10.20)	0.8514
	T-DM1 (N=139)	13 (9.4)				<.0001	
Negative	T-DXd (N=123)	62 (50.4)	8.44 (4.30, 16.59)	4.69 (2.73, 8.07)	0.397 (0.292, 0.501)	5.12 (2.81, 9.34)	
	T-DM1 (N=121)	13 (10.7)				<.0001	
Constipation							
Positive	T-DXd (N=133)	50 (37.6)	2.62 (1.51, 4.55)	2.01 (1.33, 3.03)	0.189 (0.084, 0.294)	1.73 (1.07, 2.78)	0.4208
	T-DM1 (N=139)	26 (18.7)				0.0222	
Negative	T-DXd (N=123)	38 (30.9)	1.72 (0.96, 3.08)	1.50 (0.97, 2.32)	0.102 (-0.007, 0.211)	1.36 (0.82, 2.26)	
	T-DM1 (N=121)	25 (20.7)				0.2342	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Positive	T-DXd (N=133)	42 (31.6)	5.95 (2.84, 12.48)	4.39 (2.30, 8.39)	0.244 (0.154, 0.334)	4.45 (2.23, 8.89)	0.8166
	T-DM1 (N=139)	10 (7.2)				<.0001	
Negative	T-DXd (N=123)	32 (26.0)	4.97 (2.18, 11.31)	3.93 (1.89, 8.19)	0.194 (0.105, 0.283)	3.81 (1.75, 8.29)	
	T-DM1 (N=121)	8 (6.6)				0.0003	
Stomatitis							
Positive	T-DXd (N=133)	21 (15.8)	5.02 (1.84, 13.76)	4.39 (1.70, 11.30)	0.122 (0.053, 0.191)	3.69 (1.39, 9.82)	0.8280
	T-DM1 (N=139)	5 (3.6)				0.0051	
Negative	T-DXd (N=123)	19 (15.4)	4.24 (1.53, 11.75)	3.74 (1.44, 9.69)	0.113 (0.040, 0.186)	3.04 (1.13, 8.20)	
	T-DM1 (N=121)	5 (4.1)				0.0208	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Positive	T-DXd (N=133)	17 (12.8)	20.22 (2.65, 154.26)	17.77 (2.40, 131.64)	0.121 (0.062, 0.179)	14.25 (1.89, 107.37)	0.1203
	T-DM1 (N=139)	1 (0.7)				0.0007	
Negative	T-DXd (N=123)	12 (9.8)	3.16 (0.99, 10.10)	2.95 (0.98, 8.90)	0.065 (0.003, 0.126)	2.07 (0.66, 6.48)	
	T-DM1 (N=121)	4 (3.3)				0.2047	
Investigations							
Any PT							
Positive	T-DXd (N=133)	85 (63.9)	0.69 (0.41, 1.15)	0.89 (0.75, 1.05)	-0.080 (-0.191, 0.030)	0.55 (0.41, 0.73)	0.3061
	T-DM1 (N=139)	100 (71.9)				0.0002	
Negative	T-DXd (N=123)	77 (62.6)	0.89 (0.53, 1.50)	0.96 (0.79, 1.16)	-0.027 (-0.147, 0.094)	0.69 (0.51, 0.95)	
	T-DM1 (N=121)	79 (65.3)				0.0427	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
Positive	T-DXd (N=133)	40 (30.1)	5.00 (2.44, 10.27)	3.80 (2.04, 7.09)	0.222 (0.132, 0.312)	3.60 (1.84, 7.02)	0.3233
	T-DM1 (N=139)	11 (7.9)				<.0001	
Negative	T-DXd (N=123)	35 (28.5)	3.04 (1.54, 6.01)	2.46 (1.40, 4.33)	0.169 (0.071, 0.267)	2.25 (1.21, 4.19)	
	T-DM1 (N=121)	14 (11.6)				0.0087	
Aspartate aminotransferase increased							
Positive	T-DXd (N=133)	32 (24.1)	0.38 (0.23, 0.64)	0.53 (0.37, 0.76)	-0.213 (-0.323, -0.103)	0.34 (0.22, 0.53)	0.0852
	T-DM1 (N=139)	63 (45.3)				<.0001	
Negative	T-DXd (N=123)	34 (27.6)	0.72 (0.42, 1.24)	0.80 (0.55, 1.16)	-0.071 (-0.187, 0.045)	0.60 (0.38, 0.95)	
	T-DM1 (N=121)	42 (34.7)				0.0335	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
Positive	T-DXd (N=133)	27 (20.3)	4.17 (1.82, 9.56)	3.53 (1.66, 7.48)	0.145 (0.067, 0.224)	2.89 (1.31, 6.39)	0.4404
	T-DM1 (N=139)	8 (5.8)				0.0060	
Negative	T-DXd (N=123)	31 (25.2)	6.46 (2.58, 16.14)	5.08 (2.20, 11.74)	0.202 (0.117, 0.288)	4.78 (1.99, 11.46)	
	T-DM1 (N=121)	6 (5.0)				0.0001	
Alanine aminotransferase increased							
Positive	T-DXd (N=133)	27 (20.3)	0.55 (0.32, 0.96)	0.64 (0.42, 0.97)	-0.114 (-0.217, -0.010)	0.48 (0.30, 0.79)	0.2627
	T-DM1 (N=139)	44 (31.7)				0.0029	
Negative	T-DXd (N=123)	29 (23.6)	0.82 (0.46, 1.47)	0.86 (0.56, 1.33)	-0.037 (-0.146, 0.072)	0.70 (0.42, 1.15)	
	T-DM1 (N=121)	33 (27.3)				0.1670	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Positive	T-DXd (N=133)	26 (19.5)	0.32 (0.19, 0.55)	0.45 (0.31, 0.67)	-0.236 (-0.343, -0.130)	0.30 (0.19, 0.48)	0.4743
	T-DM1 (N=139)	60 (43.2)				<.0001	
Negative	T-DXd (N=123)	28 (22.8)	0.39 (0.22, 0.68)	0.53 (0.36, 0.78)	-0.202 (-0.317, -0.087)	0.36 (0.23, 0.58)	
	T-DM1 (N=121)	52 (43.0)				<.0001	
Weight decreased							
Positive	T-DXd (N=133)	19 (14.3)	3.69 (1.43, 9.56)	3.31 (1.36, 8.03)	0.100 (0.031, 0.168)	2.68 (1.07, 6.73)	0.6130
	T-DM1 (N=139)	6 (4.3)				0.0292	
Negative	T-DXd (N=123)	24 (19.5)	2.69 (1.23, 5.90)	2.36 (1.18, 4.72)	0.112 (0.027, 0.198)	1.78 (0.84, 3.73)	
	T-DM1 (N=121)	10 (8.3)				0.1253	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
Positive	T-DXd (N=133)	8 (6.0)	0.34 (0.15, 0.79)	0.38 (0.18, 0.82)	-0.098 (-0.171, -0.025)	0.28 (0.12, 0.64)	0.2983
	T-DM1 (N=139)	22 (15.8)				0.0013	
Negative	T-DXd (N=123)	9 (7.3)	0.66 (0.27, 1.60)	0.68 (0.30, 1.53)	-0.034 (-0.106, 0.038)	0.53 (0.22, 1.25)	
	T-DM1 (N=121)	13 (10.7)				0.1432	
General disorders and administration site conditions							
Any PT							
Positive	T-DXd (N=133)	82 (61.7)	1.88 (1.16, 3.05)	1.34 (1.07, 1.68)	0.156 (0.039, 0.273)	1.16 (0.84, 1.62)	0.3397
	T-DM1 (N=139)	64 (46.0)				0.3712	
Negative	T-DXd (N=123)	76 (61.8)	1.22 (0.73, 2.03)	1.08 (0.88, 1.33)	0.048 (-0.075, 0.171)	0.92 (0.66, 1.27)	
	T-DM1 (N=121)	69 (57.0)				0.6118	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Positive	T-DXd (N=133)	13 (9.8)	3.66 (1.16, 11.51)	3.40 (1.14, 10.15)	0.069 (0.011, 0.127)	3.00 (0.97, 9.25)	0.6949
	T-DM1 (N=139)	4 (2.9)				0.0452	
Negative	T-DXd (N=123)	15 (12.2)	2.66 (1.00, 7.11)	2.46 (0.99, 6.13)	0.072 (0.003, 0.142)	2.34 (0.90, 6.04)	
	T-DM1 (N=121)	6 (5.0)				0.0712	
Pyrexia							
Positive	T-DXd (N=133)	13 (9.8)	0.68 (0.32, 1.45)	0.72 (0.37, 1.39)	-0.039 (-0.115, 0.037)	0.46 (0.23, 0.95)	0.9514
	T-DM1 (N=139)	19 (13.7)				0.0316	
Negative	T-DXd (N=123)	14 (11.4)	0.65 (0.31, 1.35)	0.69 (0.36, 1.30)	-0.051 (-0.138, 0.035)	0.43 (0.21, 0.86)	
	T-DM1 (N=121)	20 (16.5)				0.0152	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Positive	T-DXd (N=133)	78 (58.6)	4.06 (2.43, 6.78)	2.26 (1.65, 3.10)	0.327 (0.217, 0.438)	2.45 (1.65, 3.65)	0.1108
	T-DM1 (N=139)	36 (25.9)				<.0001	
Negative	T-DXd (N=123)	61 (49.6)	2.07 (1.23, 3.48)	1.54 (1.12, 2.11)	0.174 (0.052, 0.295)	1.55 (1.04, 2.33)	
	T-DM1 (N=121)	39 (32.2)				0.0318	
Alopecia							
Positive	T-DXd (N=133)	54 (40.6)	30.99 (9.38, 102.38)	18.81 (6.03, 58.70)	0.384 (0.298, 0.471)	21.25 (6.64, 67.99)	0.2531
	T-DM1 (N=139)	3 (2.2)				<.0001	
Negative	T-DXd (N=123)	41 (33.3)	11.60 (4.39, 30.61)	8.07 (3.30, 19.72)	0.292 (0.201, 0.383)	8.96 (3.54, 22.68)	
	T-DM1 (N=121)	5 (4.1)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Positive	T-DXd (N=133)	62 (46.6)	2.09 (1.27, 3.44)	1.58 (1.15, 2.17)	0.171 (0.057, 0.285)	1.64 (1.10, 2.43)	0.8093
	T-DM1 (N=139)	41 (29.5)				0.0140	
Negative	T-DXd (N=123)	59 (48.0)	1.94 (1.15, 3.26)	1.49 (1.08, 2.04)	0.157 (0.036, 0.279)	1.47 (0.98, 2.21)	
	T-DM1 (N=121)	39 (32.2)				0.0626	
Decreased appetite							
Positive	T-DXd (N=133)	42 (31.6)	2.59 (1.44, 4.68)	2.09 (1.31, 3.33)	0.165 (0.066, 0.264)	2.13 (1.26, 3.61)	0.2045
	T-DM1 (N=139)	21 (15.1)				0.0040	
Negative	T-DXd (N=123)	32 (26.0)	1.50 (0.82, 2.75)	1.37 (0.85, 2.20)	0.070 (-0.034, 0.174)	1.29 (0.75, 2.21)	
	T-DM1 (N=121)	23 (19.0)				0.3638	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
Positive	T-DXd (N=133)	59 (44.4)	1.26 (0.77, 2.03)	1.14 (0.86, 1.51)	0.055 (-0.062, 0.172)	0.85 (0.59, 1.24)	0.4637
	T-DM1 (N=139)	54 (38.8)				0.4097	
Negative	T-DXd (N=123)	57 (46.3)	1.51 (0.91, 2.52)	1.27 (0.94, 1.73)	0.100 (-0.023, 0.223)	1.05 (0.71, 1.56)	
	T-DM1 (N=121)	44 (36.4)				0.8043	
Infections and infestations							
Any PT							
Positive	T-DXd (N=133)	63 (47.4)	2.39 (1.44, 3.96)	1.73 (1.25, 2.40)	0.200 (0.088, 0.313)	1.32 (0.88, 1.98)	0.0543
	T-DM1 (N=139)	38 (27.3)				0.1825	
Negative	T-DXd (N=123)	49 (39.8)	1.04 (0.62, 1.74)	1.03 (0.75, 1.40)	0.010 (-0.113, 0.133)	0.77 (0.51, 1.16)	
	T-DM1 (N=121)	47 (38.8)				0.2170	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Positive	T-DXd (N=133)	55 (41.4)	1.52 (0.93, 2.50)	1.31 (0.95, 1.79)	0.097 (-0.017, 0.211)	0.97 (0.65, 1.44)	0.7685
	T-DM1 (N=139)	44 (31.7)				0.8637	
Negative	T-DXd (N=123)	52 (42.3)	1.80 (1.06, 3.06)	1.46 (1.03, 2.07)	0.134 (0.015, 0.252)	0.96 (0.62, 1.49)	
	T-DM1 (N=121)	35 (28.9)				0.8593	
Epistaxis							
Positive	T-DXd (N=133)	15 (11.3)	0.68 (0.33, 1.37)	0.71 (0.39, 1.31)	-0.045 (-0.127, 0.036)	0.44 (0.23, 0.85)	0.9286
	T-DM1 (N=139)	22 (15.8)				0.0129	
Negative	T-DXd (N=123)	14 (11.4)	0.65 (0.31, 1.35)	0.69 (0.36, 1.30)	-0.051 (-0.138, 0.035)	0.39 (0.19, 0.79)	
	T-DM1 (N=121)	20 (16.5)				0.0068	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Positive	T-DXd (N=133)	53 (39.8)	1.58 (0.96, 2.62)	1.35 (0.97, 1.88)	0.104 (-0.009, 0.216)	1.09 (0.72, 1.64)	0.6094
	T-DM1 (N=139)	41 (29.5)				0.6749	
Negative	T-DXd (N=123)	50 (40.7)	1.83 (1.07, 3.13)	1.49 (1.04, 2.14)	0.134 (0.016, 0.251)	1.31 (0.84, 2.03)	
	T-DM1 (N=121)	33 (27.3)				0.2275	
Anaemia							
Positive	T-DXd (N=133)	40 (30.1)	2.06 (1.16, 3.66)	1.74 (1.11, 2.72)	0.128 (0.028, 0.228)	1.41 (0.84, 2.34)	0.4899
	T-DM1 (N=139)	24 (17.3)				0.1893	
Negative	T-DXd (N=123)	43 (35.0)	2.71 (1.48, 4.98)	2.12 (1.33, 3.38)	0.184 (0.077, 0.291)	1.94 (1.14, 3.30)	
	T-DM1 (N=121)	20 (16.5)				0.0129	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
Positive	T-DXd (N=133)	24 (18.0)	7.43 (2.50, 22.06)	6.27 (2.24, 17.59)	0.152 (0.081, 0.223)	4.95 (1.71, 14.36)	0.8839
	T-DM1 (N=139)	4 (2.9)				0.0011	
Negative	T-DXd (N=123)	17 (13.8)	6.31 (1.80, 22.13)	5.57 (1.68, 18.53)	0.113 (0.046, 0.180)	4.18 (1.22, 14.39)	
	T-DM1 (N=121)	3 (2.5)				0.0139	
Thrombocytopenia							
Positive	T-DXd (N=133)	8 (6.0)	0.46 (0.19, 1.10)	0.49 (0.22, 1.10)	-0.062 (-0.130, 0.006)	0.34 (0.15, 0.80)	0.7485
	T-DM1 (N=139)	17 (12.2)				0.0099	
Negative	T-DXd (N=123)	5 (4.1)	0.35 (0.12, 1.02)	0.38 (0.14, 1.03)	-0.067 (-0.132, -0.002)	0.29 (0.10, 0.83)	
	T-DM1 (N=121)	13 (10.7)				0.0146	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
Positive	T-DXd (N=133)	50 (37.6)	1.01 (0.62, 1.65)	1.00 (0.74, 1.37)	0.002 (-0.113, 0.117)	0.74 (0.50, 1.10)	0.4060
	T-DM1 (N=139)	52 (37.4)				0.1376	
Negative	T-DXd (N=123)	44 (35.8)	1.43 (0.83, 2.45)	1.27 (0.88, 1.84)	0.077 (-0.040, 0.193)	0.91 (0.58, 1.44)	
	T-DM1 (N=121)	34 (28.1)				0.6906	
Vascular disorders							
Any PT							
Positive	T-DXd (N=133)	20 (15.0)	1.87 (0.88, 4.00)	1.74 (0.89, 3.42)	0.064 (-0.013, 0.141)	1.37 (0.66, 2.82)	0.3551
	T-DM1 (N=139)	12 (8.6)				0.4002	
Negative	T-DXd (N=123)	25 (20.3)	3.17 (1.41, 7.13)	2.73 (1.33, 5.61)	0.129 (0.044, 0.214)	2.03 (0.94, 4.40)	
	T-DM1 (N=121)	9 (7.4)				0.0666	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
Positive	T-DXd (N=133)	21 (15.8)	1.67 (0.81, 3.45)	1.57 (0.83, 2.95)	0.057 (-0.022, 0.137)	1.10 (0.55, 2.17)	0.5629
	T-DM1 (N=139)	14 (10.1)				0.7934	
Negative	T-DXd (N=123)	20 (16.3)	1.27 (0.63, 2.60)	1.23 (0.67, 2.26)	0.030 (-0.058, 0.119)	0.78 (0.40, 1.52)	
	T-DM1 (N=121)	16 (13.2)				0.4634	
Psychiatric disorders							
Any PT							
Positive	T-DXd (N=133)	19 (14.3)	0.84 (0.43, 1.63)	0.86 (0.49, 1.51)	-0.023 (-0.108, 0.063)	0.61 (0.33, 1.13)	0.1404
	T-DM1 (N=139)	23 (16.5)				0.1159	
Negative	T-DXd (N=123)	20 (16.3)	1.76 (0.82, 3.79)	1.64 (0.84, 3.20)	0.063 (-0.021, 0.148)	1.15 (0.56, 2.38)	
	T-DM1 (N=121)	12 (9.9)				0.6993	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Positive	T-DXd (N=133)	14 (10.5)	1.05 (0.48, 2.30)	1.05 (0.52, 2.11)	0.005 (-0.068, 0.077)	0.67 (0.32, 1.43)	0.5819
	T-DM1 (N=139)	14 (10.1)				0.3018	
Negative	T-DXd (N=123)	18 (14.6)	1.42 (0.66, 3.05)	1.36 (0.70, 2.66)	0.039 (-0.044, 0.122)	0.90 (0.43, 1.87)	
	T-DM1 (N=121)	13 (10.7)				0.7769	
Hepatobiliary disorders							
Any PT							
Positive	T-DXd (N=133)	15 (11.3)	0.71 (0.35, 1.45)	0.75 (0.40, 1.39)	-0.038 (-0.119, 0.042)	0.55 (0.28, 1.07)	0.5922
	T-DM1 (N=139)	21 (15.1)				0.0762	
Negative	T-DXd (N=123)	4 (3.3)	0.47 (0.14, 1.62)	0.49 (0.15, 1.59)	-0.034 (-0.088, 0.021)	0.37 (0.11, 1.27)	
	T-DM1 (N=121)	8 (6.6)				0.1029	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Positive	T-DXd (N=129)	118 (91.5)	8.67 (4.28, 17.58)	1.65 (1.41, 1.95)	0.362 (0.264, 0.459)	2.98 (2.21, 4.01)	0.4712
	T-DM1 (N=132)	73 (55.3)				<.0001	
Negative	T-DXd (N=127)	118 (92.9)	8.24 (3.83, 17.72)	1.51 (1.31, 1.75)	0.315 (0.219, 0.411)	2.69 (2.01, 3.60)	
	T-DM1 (N=127)	78 (61.4)				<.0001	
Nausea							
Positive	T-DXd (N=129)	101 (78.3)	10.00 (5.66, 17.67)	2.95 (2.19, 3.98)	0.518 (0.414, 0.621)	4.58 (3.11, 6.75)	0.1053
	T-DM1 (N=132)	35 (26.5)				<.0001	
Negative	T-DXd (N=127)	93 (73.2)	5.16 (3.02, 8.82)	2.11 (1.63, 2.74)	0.386 (0.273, 0.499)	3.00 (2.09, 4.30)	
	T-DM1 (N=127)	44 (34.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Positive	T-DXd (N=129)	61 (47.3)	8.97 (4.51, 17.83)	5.20 (2.94, 9.19)	0.382 (0.283, 0.481)	5.77 (3.10, 10.72)	0.7589
	T-DM1 (N=132)	12 (9.1)				<.0001	
Negative	T-DXd (N=127)	64 (50.4)	8.20 (4.26, 15.79)	4.57 (2.71, 7.72)	0.394 (0.291, 0.496)	4.99 (2.79, 8.91)	
	T-DM1 (N=127)	14 (11.0)				<.0001	
Constipation							
Positive	T-DXd (N=129)	48 (37.2)	2.96 (1.66, 5.29)	2.23 (1.43, 3.48)	0.205 (0.101, 0.310)	1.96 (1.18, 3.26)	0.1938
	T-DM1 (N=132)	22 (16.7)				0.0078	
Negative	T-DXd (N=127)	40 (31.5)	1.63 (0.93, 2.85)	1.43 (0.94, 2.16)	0.094 (-0.014, 0.203)	1.26 (0.78, 2.06)	
	T-DM1 (N=127)	28 (22.0)				0.3454	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Positive	T-DXd (N=129)	40 (31.0)	5.48 (2.60, 11.55)	4.09 (2.14, 7.83)	0.234 (0.143, 0.326)	4.15 (2.07, 8.30)	0.9597
	T-DM1 (N=132)	10 (7.6)				<.0001	
Negative	T-DXd (N=127)	34 (26.8)	5.44 (2.40, 12.30)	4.25 (2.05, 8.82)	0.205 (0.117, 0.293)	4.13 (1.90, 8.94)	
	T-DM1 (N=127)	8 (6.3)				<.0001	
Stomatitis							
Positive	T-DXd (N=129)	21 (16.3)	4.94 (1.80, 13.54)	4.30 (1.67, 11.05)	0.125 (0.053, 0.196)	3.63 (1.36, 9.66)	0.8572
	T-DM1 (N=132)	5 (3.8)				0.0058	
Negative	T-DXd (N=127)	19 (15.0)	4.29 (1.55, 11.89)	3.80 (1.46, 9.86)	0.110 (0.040, 0.181)	3.08 (1.14, 8.30)	
	T-DM1 (N=127)	5 (3.9)				0.0194	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Positive	T-DXd (N=129)	17 (13.2)	NE (NE, NE)	NE (NE, NE)	0.132 (0.073, 0.190)	NE (NE, NE)	0.9893
	T-DM1 (N=132)	0				0.0002	
Negative	T-DXd (N=127)	12 (9.4)	2.55 (0.87, 7.45)	2.40 (0.87, 6.61)	0.055 (-0.006, 0.116)	1.69 (0.59, 4.86)	
	T-DM1 (N=127)	5 (3.9)				0.3240	
Investigations							
Any PT							
Positive	T-DXd (N=129)	82 (63.6)	0.68 (0.40, 1.15)	0.88 (0.75, 1.05)	-0.084 (-0.197, 0.029)	0.55 (0.41, 0.74)	0.3705
	T-DM1 (N=132)	95 (72.0)				0.0002	
Negative	T-DXd (N=127)	80 (63.0)	0.87 (0.52, 1.46)	0.95 (0.79, 1.14)	-0.031 (-0.149, 0.086)	0.67 (0.49, 0.91)	
	T-DM1 (N=127)	84 (66.1)				0.0239	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
Positive	T-DXd (N=129)	39 (30.2)	4.77 (2.31, 9.82)	3.63 (1.94, 6.77)	0.219 (0.127, 0.311)	3.46 (1.77, 6.76)	0.4112
	T-DM1 (N=132)	11 (8.3)				0.0001	
Negative	T-DXd (N=127)	36 (28.3)	3.19 (1.62, 6.28)	2.57 (1.46, 4.53)	0.173 (0.078, 0.269)	2.33 (1.25, 4.32)	
	T-DM1 (N=127)	14 (11.0)				0.0059	
Aspartate aminotransferase increased							
Positive	T-DXd (N=129)	30 (23.3)	0.37 (0.22, 0.64)	0.52 (0.36, 0.75)	-0.214 (-0.326, -0.103)	0.34 (0.22, 0.53)	0.0988
	T-DM1 (N=132)	59 (44.7)				<.0001	
Negative	T-DXd (N=127)	36 (28.3)	0.70 (0.41, 1.18)	0.78 (0.55, 1.12)	-0.079 (-0.193, 0.036)	0.58 (0.37, 0.89)	
	T-DM1 (N=127)	46 (36.2)				0.0168	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
Positive	T-DXd (N=129)	26 (20.2)	4.51 (1.88, 10.81)	3.80 (1.71, 8.45)	0.149 (0.069, 0.228)	3.12 (1.35, 7.22)	0.6632
	T-DM1 (N=132)	7 (5.3)				0.0051	
Negative	T-DXd (N=127)	32 (25.2)	5.77 (2.44, 13.66)	4.57 (2.10, 9.97)	0.197 (0.112, 0.282)	4.22 (1.86, 9.58)	
	T-DM1 (N=127)	7 (5.5)				0.0002	
Alanine aminotransferase increased							
Positive	T-DXd (N=129)	26 (20.2)	0.54 (0.31, 0.95)	0.63 (0.41, 0.97)	-0.117 (-0.222, -0.011)	0.48 (0.29, 0.78)	0.2591
	T-DM1 (N=132)	42 (31.8)				0.0027	
Negative	T-DXd (N=127)	30 (23.6)	0.81 (0.46, 1.43)	0.86 (0.56, 1.31)	-0.039 (-0.147, 0.068)	0.69 (0.42, 1.13)	
	T-DM1 (N=127)	35 (27.6)				0.1453	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Positive	T-DXd (N=129)	25 (19.4)	0.33 (0.19, 0.57)	0.46 (0.30, 0.68)	-0.230 (-0.339, -0.122)	0.30 (0.18, 0.48)	0.5416
	T-DM1 (N=132)	56 (42.4)				<.0001	
Negative	T-DXd (N=127)	29 (22.8)	0.38 (0.22, 0.65)	0.52 (0.36, 0.75)	-0.213 (-0.326, -0.100)	0.35 (0.22, 0.56)	
	T-DM1 (N=127)	56 (44.1)				<.0001	
Weight decreased							
Positive	T-DXd (N=129)	18 (14.0)	4.12 (1.48, 11.46)	3.68 (1.41, 9.63)	0.102 (0.034, 0.170)	3.03 (1.12, 8.18)	0.4506
	T-DM1 (N=132)	5 (3.8)				0.0217	
Negative	T-DXd (N=127)	25 (19.7)	2.58 (1.21, 5.51)	2.27 (1.17, 4.42)	0.110 (0.026, 0.195)	1.68 (0.82, 3.44)	
	T-DM1 (N=127)	11 (8.7)				0.1485	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
Positive	T-DXd (N=129)	8 (6.2)	0.37 (0.16, 0.87)	0.41 (0.19, 0.90)	-0.089 (-0.163, -0.016)	0.31 (0.13, 0.71)	0.4823
	T-DM1 (N=132)	20 (15.2)				0.0035	
Negative	T-DXd (N=127)	9 (7.1)	0.57 (0.24, 1.35)	0.60 (0.27, 1.32)	-0.047 (-0.119, 0.024)	0.46 (0.20, 1.06)	
	T-DM1 (N=127)	15 (11.8)				0.0614	
General disorders and administration site conditions							
Any PT							
Positive	T-DXd (N=129)	79 (61.2)	1.78 (1.09, 2.92)	1.30 (1.04, 1.64)	0.143 (0.023, 0.262)	1.12 (0.80, 1.57)	0.6203
	T-DM1 (N=132)	62 (47.0)				0.5047	
Negative	T-DXd (N=127)	79 (62.2)	1.34 (0.81, 2.21)	1.13 (0.92, 1.39)	0.071 (-0.050, 0.192)	0.97 (0.70, 1.35)	
	T-DM1 (N=127)	70 (55.1)				0.8799	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Positive	T-DXd (N=129)	12 (9.3)	3.28 (1.03, 10.46)	3.07 (1.02, 9.27)	0.063 (0.005, 0.121)	2.67 (0.85, 8.33)	0.8883
	T-DM1 (N=132)	4 (3.0)				0.0795	
Negative	T-DXd (N=127)	16 (12.6)	2.91 (1.10, 7.69)	2.67 (1.08, 6.59)	0.079 (0.010, 0.147)	2.55 (0.99, 6.53)	
	T-DM1 (N=127)	6 (4.7)				0.0436	
Pyrexia							
Positive	T-DXd (N=129)	13 (10.1)	0.67 (0.31, 1.41)	0.70 (0.36, 1.36)	-0.043 (-0.122, 0.036)	0.45 (0.22, 0.92)	0.9829
	T-DM1 (N=132)	19 (14.4)				0.0259	
Negative	T-DXd (N=127)	14 (11.0)	0.66 (0.32, 1.38)	0.70 (0.37, 1.32)	-0.047 (-0.131, 0.036)	0.44 (0.22, 0.88)	
	T-DM1 (N=127)	20 (15.7)				0.0170	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Positive	T-DXd (N=129)	76 (58.9)	3.82 (2.27, 6.43)	2.16 (1.58, 2.96)	0.316 (0.202, 0.430)	2.32 (1.56, 3.46)	0.2158
	T-DM1 (N=132)	36 (27.3)				<.0001	
Negative	T-DXd (N=127)	63 (49.6)	2.22 (1.33, 3.71)	1.62 (1.18, 2.21)	0.189 (0.071, 0.307)	1.64 (1.09, 2.45)	
	T-DM1 (N=127)	39 (30.7)				0.0153	
Alopecia							
Positive	T-DXd (N=129)	53 (41.1)	29.99 (9.06, 99.28)	18.08 (5.80, 56.39)	0.388 (0.300, 0.477)	20.47 (6.39, 65.53)	0.2955
	T-DM1 (N=132)	3 (2.3)				<.0001	
Negative	T-DXd (N=127)	42 (33.1)	12.05 (4.58, 31.73)	8.40 (3.44, 20.54)	0.291 (0.203, 0.380)	9.31 (3.68, 23.54)	
	T-DM1 (N=127)	5 (3.9)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Positive	T-DXd (N=129)	59 (45.7)	2.16 (1.29, 3.62)	1.63 (1.17, 2.27)	0.177 (0.062, 0.292)	1.71 (1.13, 2.58)	0.5993
	T-DM1 (N=132)	37 (28.0)				0.0100	
Negative	T-DXd (N=127)	62 (48.8)	1.86 (1.12, 3.09)	1.44 (1.07, 1.95)	0.150 (0.030, 0.269)	1.41 (0.95, 2.09)	
	T-DM1 (N=127)	43 (33.9)				0.0865	
Decreased appetite							
Positive	T-DXd (N=129)	41 (31.8)	2.77 (1.50, 5.11)	2.21 (1.36, 3.59)	0.174 (0.074, 0.274)	2.26 (1.31, 3.91)	0.1229
	T-DM1 (N=132)	19 (14.4)				0.0026	
Negative	T-DXd (N=127)	33 (26.0)	1.43 (0.79, 2.58)	1.32 (0.84, 2.09)	0.063 (-0.040, 0.166)	1.24 (0.74, 2.09)	
	T-DM1 (N=127)	25 (19.7)				0.4339	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
Positive	T-DXd (N=129)	58 (45.0)	1.30 (0.79, 2.12)	1.16 (0.87, 1.55)	0.063 (-0.056, 0.183)	0.88 (0.60, 1.29)	0.5843
	T-DM1 (N=132)	51 (38.6)				0.5221	
Negative	T-DXd (N=127)	58 (45.7)	1.48 (0.90, 2.45)	1.26 (0.94, 1.70)	0.094 (-0.026, 0.215)	1.02 (0.69, 1.51)	
	T-DM1 (N=127)	46 (36.2)				0.9107	
Infections and infestations							
Any PT							
Positive	T-DXd (N=129)	61 (47.3)	2.30 (1.38, 3.85)	1.69 (1.21, 2.34)	0.193 (0.077, 0.308)	1.28 (0.84, 1.93)	0.0863
	T-DM1 (N=132)	37 (28.0)				0.2464	
Negative	T-DXd (N=127)	51 (40.2)	1.10 (0.67, 1.83)	1.06 (0.78, 1.45)	0.024 (-0.096, 0.144)	0.80 (0.53, 1.19)	
	T-DM1 (N=127)	48 (37.8)				0.2726	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Positive	T-DXd (N=129)	54 (41.9)	1.60 (0.96, 2.66)	1.35 (0.97, 1.87)	0.108 (-0.008, 0.224)	1.00 (0.67, 1.51)	0.9350
	T-DM1 (N=132)	41 (31.1)				0.9925	
Negative	T-DXd (N=127)	53 (41.7)	1.74 (1.04, 2.93)	1.43 (1.02, 2.01)	0.126 (0.009, 0.243)	0.95 (0.62, 1.46)	
	T-DM1 (N=127)	37 (29.1)				0.8127	
Epistaxis							
Positive	T-DXd (N=129)	15 (11.6)	0.70 (0.34, 1.42)	0.73 (0.39, 1.35)	-0.043 (-0.126, 0.041)	0.45 (0.23, 0.88)	0.8889
	T-DM1 (N=132)	21 (15.9)				0.0176	
Negative	T-DXd (N=127)	14 (11.0)	0.66 (0.32, 1.38)	0.70 (0.37, 1.32)	-0.047 (-0.131, 0.036)	0.39 (0.19, 0.80)	
	T-DM1 (N=127)	20 (15.7)				0.0076	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Positive	T-DXd (N=129)	51 (39.5)	1.62 (0.97, 2.71)	1.37 (0.97, 1.93)	0.107 (-0.007, 0.222)	1.12 (0.73, 1.71)	0.7402
	T-DM1 (N=132)	38 (28.8)				0.5918	
Negative	T-DXd (N=127)	52 (40.9)	1.75 (1.04, 2.96)	1.44 (1.02, 2.04)	0.126 (0.010, 0.242)	1.25 (0.81, 1.92)	
	T-DM1 (N=127)	36 (28.3)				0.2996	
Anaemia							
Positive	T-DXd (N=129)	38 (29.5)	2.21 (1.21, 4.02)	1.85 (1.15, 2.98)	0.135 (0.035, 0.236)	1.52 (0.89, 2.61)	0.7857
	T-DM1 (N=132)	21 (15.9)				0.1234	
Negative	T-DXd (N=127)	45 (35.4)	2.48 (1.39, 4.43)	1.96 (1.26, 3.03)	0.173 (0.066, 0.280)	1.75 (1.06, 2.90)	
	T-DM1 (N=127)	23 (18.1)				0.0272	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
Positive	T-DXd (N=129)	23 (17.8)	6.94 (2.33, 20.70)	5.88 (2.09, 16.54)	0.148 (0.076, 0.220)	4.63 (1.59, 13.45)	0.9955
	T-DM1 (N=132)	4 (3.0)				0.0020	
Negative	T-DXd (N=127)	18 (14.2)	6.83 (1.96, 23.80)	6.00 (1.81, 19.87)	0.118 (0.052, 0.184)	4.52 (1.32, 15.46)	
	T-DM1 (N=127)	3 (2.4)				0.0086	
Thrombocytopenia							
Positive	T-DXd (N=129)	8 (6.2)	0.45 (0.19, 1.08)	0.48 (0.22, 1.08)	-0.067 (-0.137, 0.004)	0.33 (0.14, 0.78)	0.7930
	T-DM1 (N=132)	17 (12.9)				0.0083	
Negative	T-DXd (N=127)	5 (3.9)	0.36 (0.12, 1.04)	0.38 (0.14, 1.05)	-0.063 (-0.126, 0.000)	0.29 (0.10, 0.84)	
	T-DM1 (N=127)	13 (10.2)				0.0161	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
Positive	T-DXd (N=129)	50 (38.8)	1.07 (0.65, 1.77)	1.04 (0.77, 1.42)	0.016 (-0.101, 0.134)	0.79 (0.53, 1.17)	0.6349
	T-DM1 (N=132)	49 (37.1)				0.2368	
Negative	T-DXd (N=127)	44 (34.6)	1.34 (0.79, 2.28)	1.22 (0.85, 1.76)	0.063 (-0.051, 0.177)	0.86 (0.55, 1.35)	
	T-DM1 (N=127)	36 (28.3)				0.5177	
Vascular disorders							
Any PT							
Positive	T-DXd (N=129)	20 (15.5)	1.83 (0.86, 3.93)	1.71 (0.87, 3.34)	0.064 (-0.015, 0.144)	1.33 (0.64, 2.75)	0.3223
	T-DM1 (N=132)	12 (9.1)				0.4419	
Negative	T-DXd (N=127)	25 (19.7)	3.21 (1.43, 7.20)	2.78 (1.35, 5.71)	0.126 (0.044, 0.208)	2.05 (0.95, 4.43)	
	T-DM1 (N=127)	9 (7.1)				0.0635	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
Positive	T-DXd (N=129)	21 (16.3)	1.64 (0.79, 3.38)	1.53 (0.82, 2.89)	0.057 (-0.026, 0.139)	1.07 (0.54, 2.13)	0.6015
	T-DM1 (N=132)	14 (10.6)				0.8390	
Negative	T-DXd (N=127)	20 (15.7)	1.30 (0.64, 2.63)	1.25 (0.68, 2.30)	0.031 (-0.054, 0.117)	0.78 (0.40, 1.53)	
	T-DM1 (N=127)	16 (12.6)				0.4748	
Psychiatric disorders							
Any PT							
Positive	T-DXd (N=129)	17 (13.2)	0.76 (0.38, 1.51)	0.79 (0.44, 1.42)	-0.035 (-0.121, 0.051)	0.57 (0.30, 1.09)	0.0827
	T-DM1 (N=132)	22 (16.7)				0.0862	
Negative	T-DXd (N=127)	22 (17.3)	1.84 (0.88, 3.83)	1.69 (0.89, 3.21)	0.071 (-0.013, 0.155)	1.15 (0.58, 2.30)	
	T-DM1 (N=127)	13 (10.2)				0.6919	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Positive	T-DXd (N=129)	14 (10.9)	1.22 (0.54, 2.74)	1.19 (0.57, 2.48)	0.018 (-0.055, 0.090)	0.75 (0.34, 1.63)	0.9776
	T-DM1 (N=132)	12 (9.1)				0.4643	
Negative	T-DXd (N=127)	18 (14.2)	1.23 (0.59, 2.57)	1.20 (0.63, 2.27)	0.024 (-0.059, 0.106)	0.80 (0.40, 1.61)	
	T-DM1 (N=127)	15 (11.8)				0.5266	
Hepatobiliary disorders							
Any PT							
Positive	T-DXd (N=129)	15 (11.6)	0.70 (0.34, 1.42)	0.73 (0.39, 1.35)	-0.043 (-0.126, 0.041)	0.53 (0.27, 1.05)	0.6278
	T-DM1 (N=132)	21 (15.9)				0.0660	
Negative	T-DXd (N=127)	4 (3.1)	0.48 (0.14, 1.65)	0.50 (0.15, 1.62)	-0.031 (-0.084, 0.021)	0.38 (0.11, 1.29)	
	T-DM1 (N=127)	8 (6.3)				0.1083	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Positive	T-DXd (N=81)	76 (93.8)	10.70 (3.95, 28.94)	1.60 (1.33, 1.91)	0.351 (0.238, 0.465)	2.86 (2.00, 4.08)	0.9627
	T-DM1 (N=92)	54 (58.7)				<.0001	
Negative	T-DXd (N=174)	159 (91.4)	7.65 (4.15, 14.11)	1.57 (1.37, 1.80)	0.333 (0.247, 0.419)	2.85 (2.20, 3.68)	
	T-DM1 (N=167)	97 (58.1)				<.0001	
Nausea							
Positive	T-DXd (N=81)	69 (85.2)	16.29 (7.55, 35.17)	3.27 (2.29, 4.66)	0.591 (0.473, 0.709)	5.46 (3.41, 8.75)	0.0784
	T-DM1 (N=92)	24 (26.1)				<.0001	
Negative	T-DXd (N=174)	124 (71.3)	5.19 (3.27, 8.23)	2.20 (1.74, 2.80)	0.389 (0.292, 0.487)	3.14 (2.28, 4.33)	
	T-DM1 (N=167)	54 (32.3)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Positive	T-DXd (N=81)	40 (49.4)	8.00 (3.64, 17.59)	4.54 (2.43, 8.49)	0.385 (0.259, 0.511)	5.01 (2.50, 10.04)	0.8130
	T-DM1 (N=92)	10 (10.9)				<.0001	
Negative	T-DXd (N=174)	85 (48.9)	9.01 (4.97, 16.34)	5.10 (3.12, 8.32)	0.393 (0.306, 0.479)	5.65 (3.31, 9.65)	
	T-DM1 (N=167)	16 (9.6)				<.0001	
Constipation							
Positive	T-DXd (N=81)	33 (40.7)	2.32 (1.20, 4.49)	1.78 (1.13, 2.82)	0.179 (0.042, 0.316)	1.42 (0.82, 2.45)	0.7725
	T-DM1 (N=92)	21 (22.8)				0.2103	
Negative	T-DXd (N=174)	55 (31.6)	2.11 (1.27, 3.51)	1.76 (1.19, 2.60)	0.136 (0.046, 0.227)	1.63 (1.04, 2.55)	
	T-DM1 (N=167)	30 (18.0)				0.0320	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Positive	T-DXd (N=81)	29 (35.8)	6.77 (2.77, 16.57)	4.71 (2.18, 10.16)	0.282 (0.164, 0.400)	4.74 (2.07, 10.83)	0.6642
	T-DM1 (N=92)	7 (7.6)				<.0001	
Negative	T-DXd (N=174)	45 (25.9)	4.95 (2.46, 9.96)	3.93 (2.10, 7.33)	0.193 (0.118, 0.268)	3.88 (2.01, 7.52)	
	T-DM1 (N=167)	11 (6.6)				<.0001	
Stomatitis							
Positive	T-DXd (N=81)	14 (17.3)	3.64 (1.25, 10.59)	3.18 (1.20, 8.44)	0.118 (0.024, 0.213)	2.82 (1.01, 7.86)	0.5021
	T-DM1 (N=92)	5 (5.4)				0.0382	
Negative	T-DXd (N=174)	26 (14.9)	5.69 (2.13, 15.21)	4.99 (1.96, 12.69)	0.119 (0.061, 0.178)	3.98 (1.52, 10.42)	
	T-DM1 (N=167)	5 (3.0)				0.0024	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Positive	T-DXd (N=81)	14 (17.3)	19.01 (2.44, 148.17)	15.90 (2.14, 118.28)	0.162 (0.077, 0.247)	13.30 (1.74, 101.46)	0.1966
	T-DM1 (N=92)	1 (1.1)				0.0012	
Negative	T-DXd (N=174)	15 (8.6)	3.84 (1.25, 11.83)	3.60 (1.22, 10.62)	0.062 (0.015, 0.110)	2.49 (0.82, 7.58)	
	T-DM1 (N=167)	4 (2.4)				0.0978	
Investigations							
Any PT							
Positive	T-DXd (N=81)	53 (65.4)	0.75 (0.39, 1.42)	0.91 (0.74, 1.12)	-0.063 (-0.202, 0.075)	0.56 (0.39, 0.81)	0.8217
	T-DM1 (N=92)	66 (71.7)				0.0048	
Negative	T-DXd (N=174)	108 (62.1)	0.78 (0.50, 1.22)	0.92 (0.78, 1.07)	-0.056 (-0.157, 0.045)	0.63 (0.48, 0.82)	
	T-DM1 (N=167)	113 (67.7)				0.0016	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
Positive	T-DXd (N=81)	22 (27.2)	3.91 (1.63, 9.39)	3.12 (1.47, 6.63)	0.185 (0.072, 0.297)	2.78 (1.24, 6.27)	0.9961
	T-DM1 (N=92)	8 (8.7)				0.0101	
Negative	T-DXd (N=174)	53 (30.5)	3.86 (2.13, 7.02)	2.99 (1.81, 4.95)	0.203 (0.120, 0.285)	2.83 (1.64, 4.90)	
	T-DM1 (N=167)	17 (10.2)				<.0001	
Aspartate aminotransferase increased							
Positive	T-DXd (N=81)	22 (27.2)	0.53 (0.28, 1.01)	0.66 (0.43, 1.01)	-0.141 (-0.281, -0.002)	0.41 (0.24, 0.70)	0.9881
	T-DM1 (N=92)	38 (41.3)				0.0010	
Negative	T-DXd (N=174)	44 (25.3)	0.51 (0.32, 0.80)	0.63 (0.46, 0.86)	-0.148 (-0.247, -0.050)	0.46 (0.31, 0.67)	
	T-DM1 (N=167)	67 (40.1)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
Positive	T-DXd (N=81)	11 (13.6)	2.25 (0.79, 6.40)	2.08 (0.81, 5.38)	0.071 (-0.019, 0.161)	1.77 (0.65, 4.83)	0.0700
	T-DM1 (N=92)	6 (6.5)				0.2556	
Negative	T-DXd (N=174)	47 (27.0)	7.36 (3.35, 16.13)	5.64 (2.75, 11.57)	0.222 (0.149, 0.296)	5.14 (2.43, 10.89)	
	T-DM1 (N=167)	8 (4.8)				<.0001	
Alanine aminotransferase increased							
Positive	T-DXd (N=81)	20 (24.7)	0.98 (0.49, 1.96)	0.99 (0.59, 1.66)	-0.003 (-0.132, 0.126)	0.76 (0.42, 1.40)	0.2112
	T-DM1 (N=92)	23 (25.0)				0.3748	
Negative	T-DXd (N=174)	36 (20.7)	0.55 (0.33, 0.89)	0.64 (0.44, 0.92)	-0.116 (-0.209, -0.023)	0.50 (0.33, 0.77)	
	T-DM1 (N=167)	54 (32.3)				0.0013	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Positive	T-DXd (N=81)	13 (16.0)	0.23 (0.11, 0.47)	0.35 (0.20, 0.61)	-0.296 (-0.425, -0.167)	0.24 (0.13, 0.45)	0.1861
	T-DM1 (N=92)	42 (45.7)				<.0001	
Negative	T-DXd (N=174)	41 (23.6)	0.43 (0.27, 0.68)	0.56 (0.41, 0.78)	-0.184 (-0.281, -0.086)	0.38 (0.25, 0.56)	
	T-DM1 (N=167)	70 (41.9)				<.0001	
Weight decreased							
Positive	T-DXd (N=81)	12 (14.8)	2.49 (0.89, 6.98)	2.27 (0.89, 5.78)	0.083 (-0.009, 0.175)	1.67 (0.62, 4.48)	0.5868
	T-DM1 (N=92)	6 (6.5)				0.3013	
Negative	T-DXd (N=174)	30 (17.2)	3.27 (1.54, 6.93)	2.88 (1.45, 5.70)	0.113 (0.046, 0.179)	2.25 (1.09, 4.62)	
	T-DM1 (N=167)	10 (6.0)				0.0235	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
Positive	T-DXd (N=81)	4 (4.9)	0.29 (0.09, 0.92)	0.32 (0.11, 0.95)	-0.103 (-0.190, -0.016)	0.22 (0.07, 0.67)	0.3414
	T-DM1 (N=92)	14 (15.2)				0.0037	
Negative	T-DXd (N=174)	13 (7.5)	0.56 (0.27, 1.16)	0.59 (0.31, 1.15)	-0.051 (-0.115, 0.013)	0.48 (0.24, 0.96)	
	T-DM1 (N=167)	21 (12.6)				0.0357	
General disorders and administration site conditions							
Any PT							
Positive	T-DXd (N=81)	50 (61.7)	2.29 (1.24, 4.22)	1.49 (1.11, 2.01)	0.204 (0.058, 0.350)	1.31 (0.86, 2.01)	0.2382
	T-DM1 (N=92)	38 (41.3)				0.2095	
Negative	T-DXd (N=174)	108 (62.1)	1.27 (0.82, 1.96)	1.10 (0.92, 1.32)	0.058 (-0.046, 0.162)	0.95 (0.72, 1.25)	
	T-DM1 (N=167)	94 (56.3)				0.7124	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Positive	T-DXd (N=81)	7 (8.6)	4.26 (0.86, 21.11)	3.98 (0.85, 18.60)	0.065 (-0.003, 0.133)	3.20 (0.66, 15.62)	0.6362
	T-DM1 (N=92)	2 (2.2)				0.1294	
Negative	T-DXd (N=174)	21 (12.1)	2.73 (1.17, 6.34)	2.52 (1.15, 5.53)	0.073 (0.015, 0.131)	2.42 (1.07, 5.46)	
	T-DM1 (N=167)	8 (4.8)				0.0287	
Pyrexia							
Positive	T-DXd (N=81)	7 (8.6)	0.78 (0.28, 2.14)	0.80 (0.32, 1.99)	-0.022 (-0.111, 0.066)	0.53 (0.20, 1.41)	0.7503
	T-DM1 (N=92)	10 (10.9)				0.1975	
Negative	T-DXd (N=174)	20 (11.5)	0.62 (0.33, 1.14)	0.66 (0.39, 1.12)	-0.059 (-0.133, 0.016)	0.42 (0.24, 0.75)	
	T-DM1 (N=167)	29 (17.4)				0.0027	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Positive	T-DXd (N=81)	47 (58.0)	4.98 (2.56, 9.66)	2.67 (1.74, 4.10)	0.363 (0.226, 0.499)	2.98 (1.76, 5.03)	0.0979
	T-DM1 (N=92)	20 (21.7)				<.0001	
Negative	T-DXd (N=174)	92 (52.9)	2.35 (1.51, 3.65)	1.64 (1.26, 2.12)	0.205 (0.103, 0.308)	1.66 (1.18, 2.34)	
	T-DM1 (N=167)	54 (32.3)				0.0031	
Alopecia							
Positive	T-DXd (N=81)	33 (40.7)	62.56 (8.30, 471.58)	37.48 (5.24, 267.94)	0.397 (0.287, 0.506)	43.64 (5.97, 319.09)	0.1694
	T-DM1 (N=92)	1 (1.1)				<.0001	
Negative	T-DXd (N=174)	62 (35.6)	12.65 (5.58, 28.66)	8.50 (4.01, 18.03)	0.314 (0.237, 0.392)	9.36 (4.28, 20.47)	
	T-DM1 (N=167)	7 (4.2)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Positive	T-DXd (N=81)	43 (53.1)	2.46 (1.32, 4.57)	1.68 (1.17, 2.42)	0.216 (0.071, 0.360)	1.71 (1.07, 2.75)	0.6434
	T-DM1 (N=92)	29 (31.5)				0.0238	
Negative	T-DXd (N=174)	78 (44.8)	1.85 (1.18, 2.88)	1.47 (1.11, 1.95)	0.143 (0.041, 0.245)	1.48 (1.04, 2.11)	
	T-DM1 (N=167)	51 (30.5)				0.0304	
Decreased appetite							
Positive	T-DXd (N=81)	29 (35.8)	2.86 (1.40, 5.86)	2.20 (1.27, 3.80)	0.195 (0.066, 0.324)	2.23 (1.19, 4.17)	0.2812
	T-DM1 (N=92)	15 (16.3)				0.0101	
Negative	T-DXd (N=174)	45 (25.9)	1.66 (0.98, 2.81)	1.49 (0.98, 2.26)	0.085 (-0.002, 0.172)	1.44 (0.90, 2.30)	
	T-DM1 (N=167)	29 (17.4)				0.1297	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
Positive	T-DXd (N=81)	36 (44.4)	1.30 (0.71, 2.39)	1.17 (0.82, 1.67)	0.064 (-0.083, 0.211)	0.86 (0.54, 1.38)	0.6263
	T-DM1 (N=92)	35 (38.0)				0.5366	
Negative	T-DXd (N=174)	80 (46.0)	1.44 (0.93, 2.22)	1.24 (0.96, 1.60)	0.089 (-0.016, 0.193)	1.00 (0.72, 1.40)	
	T-DM1 (N=167)	62 (37.1)				0.9999	
Infections and infestations							
Any PT							
Positive	T-DXd (N=81)	36 (44.4)	2.40 (1.26, 4.57)	1.78 (1.16, 2.73)	0.194 (0.055, 0.334)	1.31 (0.77, 2.22)	0.2612
	T-DM1 (N=92)	23 (25.0)				0.3194	
Negative	T-DXd (N=174)	76 (43.7)	1.35 (0.87, 2.08)	1.20 (0.92, 1.55)	0.072 (-0.032, 0.175)	0.93 (0.66, 1.30)	
	T-DM1 (N=167)	61 (36.5)				0.6629	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Positive	T-DXd (N=81)	33 (40.7)	1.35 (0.73, 2.51)	1.21 (0.82, 1.78)	0.070 (-0.074, 0.215)	0.89 (0.54, 1.45)	0.4742
	T-DM1 (N=92)	31 (33.7)				0.6319	
Negative	T-DXd (N=174)	74 (42.5)	1.83 (1.17, 2.88)	1.48 (1.10, 1.99)	0.138 (0.037, 0.238)	1.02 (0.71, 1.48)	
	T-DM1 (N=167)	48 (28.7)				0.9097	
Epistaxis							
Positive	T-DXd (N=81)	10 (12.3)	0.78 (0.33, 1.88)	0.81 (0.38, 1.73)	-0.029 (-0.131, 0.074)	0.49 (0.21, 1.11)	0.6681
	T-DM1 (N=92)	14 (15.2)				0.0797	
Negative	T-DXd (N=174)	19 (10.9)	0.61 (0.33, 1.14)	0.65 (0.38, 1.12)	-0.058 (-0.132, 0.015)	0.38 (0.21, 0.69)	
	T-DM1 (N=167)	28 (16.8)				0.0011	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Positive	T-DXd (N=81)	30 (37.0)	1.34 (0.71, 2.53)	1.22 (0.80, 1.85)	0.066 (-0.075, 0.207)	0.91 (0.54, 1.53)	0.2885
	T-DM1 (N=92)	28 (30.4)				0.7124	
Negative	T-DXd (N=174)	73 (42.0)	1.90 (1.21, 2.99)	1.52 (1.13, 2.06)	0.144 (0.044, 0.244)	1.35 (0.93, 1.95)	
	T-DM1 (N=167)	46 (27.5)				0.1082	
Anaemia							
Positive	T-DXd (N=81)	20 (24.7)	1.45 (0.70, 3.00)	1.34 (0.75, 2.37)	0.062 (-0.061, 0.185)	0.99 (0.51, 1.90)	0.0995
	T-DM1 (N=92)	17 (18.5)				0.9704	
Negative	T-DXd (N=174)	63 (36.2)	2.94 (1.76, 4.93)	2.24 (1.50, 3.33)	0.200 (0.110, 0.291)	2.05 (1.30, 3.22)	
	T-DM1 (N=167)	27 (16.2)				0.0015	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
Positive	T-DXd (N=81)	15 (18.5)	6.74 (1.87, 24.25)	5.68 (1.71, 18.91)	0.153 (0.061, 0.245)	4.39 (1.26, 15.29)	0.8907
	T-DM1 (N=92)	3 (3.3)				0.0113	
Negative	T-DXd (N=174)	26 (14.9)	7.16 (2.44, 20.99)	6.24 (2.22, 17.49)	0.125 (0.068, 0.183)	4.93 (1.72, 14.19)	
	T-DM1 (N=167)	4 (2.4)				0.0010	
Thrombocytopenia							
Positive	T-DXd (N=81)	3 (3.7)	0.28 (0.08, 1.05)	0.31 (0.09, 1.07)	-0.083 (-0.161, -0.005)	0.21 (0.06, 0.79)	0.4572
	T-DM1 (N=92)	11 (12.0)				0.0111	
Negative	T-DXd (N=174)	10 (5.7)	0.47 (0.21, 1.05)	0.51 (0.24, 1.05)	-0.056 (-0.116, 0.003)	0.38 (0.18, 0.83)	
	T-DM1 (N=167)	19 (11.4)				0.0123	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
Positive	T-DXd (N=81)	30 (37.0)	1.10 (0.59, 2.06)	1.06 (0.71, 1.59)	0.023 (-0.121, 0.166)	0.85 (0.51, 1.41)	0.9916
	T-DM1 (N=92)	32 (34.8)				0.5300	
Negative	T-DXd (N=174)	64 (36.8)	1.25 (0.80, 1.96)	1.16 (0.86, 1.56)	0.050 (-0.050, 0.151)	0.83 (0.57, 1.20)	
	T-DM1 (N=167)	53 (31.7)				0.3176	
Vascular disorders							
Any PT							
Positive	T-DXd (N=81)	11 (13.6)	1.91 (0.70, 5.18)	1.78 (0.73, 4.39)	0.060 (-0.032, 0.152)	1.47 (0.57, 3.84)	0.6138
	T-DM1 (N=92)	7 (7.6)				0.4273	
Negative	T-DXd (N=174)	34 (19.5)	2.65 (1.37, 5.15)	2.33 (1.30, 4.18)	0.112 (0.039, 0.184)	1.75 (0.93, 3.28)	
	T-DM1 (N=167)	14 (8.4)				0.0802	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
Positive	T-DXd (N=81)	11 (13.6)	1.91 (0.70, 5.18)	1.78 (0.73, 4.39)	0.060 (-0.032, 0.152)	1.16 (0.44, 3.02)	0.6128
	T-DM1 (N=92)	7 (7.6)				0.7647	
Negative	T-DXd (N=174)	30 (17.2)	1.37 (0.76, 2.49)	1.31 (0.79, 2.17)	0.041 (-0.035, 0.117)	0.87 (0.50, 1.53)	
	T-DM1 (N=167)	22 (13.2)				0.6395	
Psychiatric disorders							
Any PT							
Positive	T-DXd (N=81)	16 (19.8)	1.26 (0.58, 2.75)	1.21 (0.64, 2.29)	0.034 (-0.080, 0.149)	0.87 (0.43, 1.78)	0.9103
	T-DM1 (N=92)	15 (16.3)				0.7066	
Negative	T-DXd (N=174)	23 (13.2)	1.12 (0.59, 2.12)	1.10 (0.63, 1.93)	0.012 (-0.058, 0.083)	0.77 (0.42, 1.41)	
	T-DM1 (N=167)	20 (12.0)				0.3930	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Positive	T-DXd (N=81)	9 (11.1)	1.31 (0.48, 3.58)	1.28 (0.52, 3.16)	0.024 (-0.065, 0.114)	0.80 (0.30, 2.09)	0.8792
	T-DM1 (N=92)	8 (8.7)				0.6418	
Negative	T-DXd (N=174)	23 (13.2)	1.19 (0.62, 2.27)	1.16 (0.66, 2.05)	0.018 (-0.051, 0.088)	0.79 (0.42, 1.46)	
	T-DM1 (N=167)	19 (11.4)				0.4479	
Hepatobiliary disorders							
Any PT							
Positive	T-DXd (N=81)	8 (9.9)	0.67 (0.26, 1.70)	0.70 (0.31, 1.60)	-0.043 (-0.139, 0.054)	0.51 (0.21, 1.25)	0.9867
	T-DM1 (N=92)	13 (14.1)				0.1380	
Negative	T-DXd (N=174)	11 (6.3)	0.64 (0.29, 1.42)	0.66 (0.32, 1.38)	-0.033 (-0.090, 0.025)	0.49 (0.22, 1.07)	
	T-DM1 (N=167)	16 (9.6)				0.0694	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Yes	T-DXd (N=160)	153 (95.6)	17.13 (7.54, 38.92)	1.71 (1.48, 1.97)	0.396 (0.312, 0.480)	3.48 (2.65, 4.56)	0.0404
	T-DM1 (N=157)	88 (56.1)				<.0001	
No	T-DXd (N=97)	84 (86.6)	4.04 (2.00, 8.17)	1.41 (1.19, 1.67)	0.251 (0.135, 0.366)	2.17 (1.56, 3.01)	
	T-DM1 (N=104)	64 (61.5)				<.0001	
Nausea							
Yes	T-DXd (N=160)	130 (81.3)	9.84 (5.84, 16.59)	2.66 (2.08, 3.40)	0.507 (0.413, 0.601)	4.28 (3.06, 5.97)	0.2278
	T-DM1 (N=157)	48 (30.6)				<.0001	
No	T-DXd (N=97)	65 (67.0)	4.78 (2.63, 8.68)	2.25 (1.62, 3.12)	0.372 (0.244, 0.500)	3.00 (1.96, 4.62)	
	T-DM1 (N=104)	31 (29.8)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Yes	T-DXd (N=160)	82 (51.3)	11.64 (6.10, 22.23)	6.19 (3.60, 10.64)	0.430 (0.341, 0.518)	6.87 (3.83, 12.35)	0.2645
	T-DM1 (N=157)	13 (8.3)				<.0001	
No	T-DXd (N=97)	44 (45.4)	5.81 (2.87, 11.76)	3.63 (2.09, 6.31)	0.329 (0.211, 0.446)	4.09 (2.20, 7.60)	
	T-DM1 (N=104)	13 (12.5)				<.0001	
Constipation							
Yes	T-DXd (N=160)	65 (40.6)	2.57 (1.56, 4.23)	1.93 (1.35, 2.76)	0.196 (0.097, 0.295)	1.71 (1.12, 2.61)	0.3252
	T-DM1 (N=157)	33 (21.0)				0.0113	
No	T-DXd (N=97)	23 (23.7)	1.48 (0.74, 2.96)	1.37 (0.79, 2.38)	0.064 (-0.048, 0.176)	1.19 (0.64, 2.20)	
	T-DM1 (N=104)	18 (17.3)				0.5921	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Yes	T-DXd (N=160)	54 (33.8)	6.16 (3.14, 12.08)	4.42 (2.46, 7.93)	0.261 (0.177, 0.345)	4.61 (2.46, 8.63)	0.6902
	T-DM1 (N=157)	12 (7.6)				<.0001	
No	T-DXd (N=97)	21 (21.6)	4.51 (1.74, 11.73)	3.75 (1.58, 8.90)	0.159 (0.065, 0.252)	3.45 (1.39, 8.57)	
	T-DM1 (N=104)	6 (5.8)				0.0046	
Stomatitis							
Yes	T-DXd (N=160)	29 (18.1)	4.74 (2.01, 11.19)	4.07 (1.83, 9.01)	0.137 (0.069, 0.205)	3.44 (1.50, 7.88)	0.9729
	T-DM1 (N=157)	7 (4.5)				0.0020	
No	T-DXd (N=97)	11 (11.3)	4.31 (1.16, 15.94)	3.93 (1.13, 13.67)	0.085 (0.014, 0.155)	2.96 (0.82, 10.69)	
	T-DM1 (N=104)	3 (2.9)				0.0822	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Yes	T-DXd (N=160)	19 (11.9)	4.10 (1.49, 11.26)	3.73 (1.43, 9.74)	0.087 (0.030, 0.144)	2.98 (1.11, 8.01)	0.9858
	T-DM1 (N=157)	5 (3.2)				0.0235	
No	T-DXd (N=97)	10 (10.3)	NE (NE, NE)	NE (NE, NE)	0.103 (0.043, 0.164)	NE (NE, NE)	
	T-DM1 (N=104)	0				0.0043	
Investigations							
Any PT							
Yes	T-DXd (N=160)	88 (55.0)	0.59 (0.37, 0.93)	0.81 (0.68, 0.97)	-0.125 (-0.232, -0.019)	0.49 (0.36, 0.65)	0.0065
	T-DM1 (N=157)	106 (67.5)				<.0001	
No	T-DXd (N=97)	74 (76.3)	1.37 (0.73, 2.56)	1.09 (0.92, 1.28)	0.061 (-0.061, 0.183)	0.87 (0.63, 1.21)	
	T-DM1 (N=104)	73 (70.2)				0.5689	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
Yes	T-DXd (N=160)	40 (25.0)	4.03 (2.02, 8.02)	3.27 (1.78, 6.00)	0.174 (0.095, 0.252)	2.96 (1.55, 5.64)	0.9354
	T-DM1 (N=157)	12 (7.6)				0.0006	
No	T-DXd (N=97)	35 (36.1)	3.95 (1.94, 8.07)	2.89 (1.63, 5.12)	0.236 (0.121, 0.351)	2.85 (1.51, 5.39)	
	T-DM1 (N=104)	13 (12.5)				0.0008	
Aspartate aminotransferase increased							
Yes	T-DXd (N=160)	27 (16.9)	0.34 (0.20, 0.57)	0.45 (0.30, 0.67)	-0.207 (-0.302, -0.112)	0.29 (0.18, 0.46)	0.0052
	T-DM1 (N=157)	59 (37.6)				<.0001	
No	T-DXd (N=97)	39 (40.2)	0.85 (0.48, 1.49)	0.91 (0.66, 1.26)	-0.040 (-0.177, 0.096)	0.69 (0.45, 1.06)	
	T-DM1 (N=104)	46 (44.2)				0.1003	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
Yes	T-DXd (N=160)	21 (13.1)	5.78 (1.94, 17.25)	5.15 (1.81, 14.67)	0.106 (0.048, 0.164)	4.52 (1.55, 13.21)	0.8265
	T-DM1 (N=157)	4 (2.5)				0.0025	
No	T-DXd (N=97)	37 (38.1)	5.80 (2.68, 12.52)	3.97 (2.09, 7.53)	0.285 (0.173, 0.397)	3.67 (1.82, 7.38)	
	T-DM1 (N=104)	10 (9.6)				<.0001	
Alanine aminotransferase increased							
Yes	T-DXd (N=160)	27 (16.9)	0.46 (0.27, 0.79)	0.55 (0.36, 0.84)	-0.137 (-0.230, -0.044)	0.39 (0.24, 0.63)	0.0142
	T-DM1 (N=157)	48 (30.6)				<.0001	
No	T-DXd (N=97)	29 (29.9)	1.10 (0.60, 2.03)	1.07 (0.69, 1.65)	0.020 (-0.105, 0.146)	0.95 (0.57, 1.60)	
	T-DM1 (N=104)	29 (27.9)				0.8485	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Yes	T-DXd (N=160)	18 (11.3)	0.17 (0.10, 0.31)	0.26 (0.16, 0.42)	-0.314 (-0.406, -0.223)	0.17 (0.10, 0.30)	0.0002
	T-DM1 (N=157)	67 (42.7)				<.0001	
No	T-DXd (N=97)	36 (37.1)	0.77 (0.44, 1.36)	0.86 (0.61, 1.20)	-0.062 (-0.197, 0.074)	0.59 (0.38, 0.93)	
	T-DM1 (N=104)	45 (43.3)				0.0275	
Weight decreased							
Yes	T-DXd (N=160)	17 (10.6)	2.99 (1.15, 7.80)	2.78 (1.13, 6.87)	0.068 (0.012, 0.124)	2.30 (0.90, 5.85)	0.8603
	T-DM1 (N=157)	6 (3.8)				0.0725	
No	T-DXd (N=97)	26 (26.8)	3.44 (1.56, 7.60)	2.79 (1.42, 5.47)	0.172 (0.067, 0.277)	2.18 (1.05, 4.53)	
	T-DM1 (N=104)	10 (9.6)				0.0326	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
Yes	T-DXd (N=160)	1 (0.6)	0.08 (0.01, 0.65)	0.09 (0.01, 0.68)	-0.064 (-0.106, -0.022)	0.08 (0.01, 0.63)	0.0601
	T-DM1 (N=157)	11 (7.0)				0.0020	
No	T-DXd (N=97)	16 (16.5)	0.66 (0.33, 1.33)	0.71 (0.40, 1.26)	-0.066 (-0.175, 0.044)	0.51 (0.27, 0.96)	
	T-DM1 (N=104)	24 (23.1)				0.0359	
General disorders and administration site conditions							
Any PT							
Yes	T-DXd (N=160)	103 (64.4)	1.61 (1.03, 2.53)	1.22 (1.01, 1.47)	0.115 (0.007, 0.223)	1.08 (0.81, 1.45)	0.8814
	T-DM1 (N=157)	83 (52.9)				0.5898	
No	T-DXd (N=97)	56 (57.7)	1.48 (0.85, 2.57)	1.20 (0.92, 1.56)	0.097 (-0.041, 0.234)	0.96 (0.65, 1.41)	
	T-DM1 (N=104)	50 (48.1)				0.8401	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Yes	T-DXd (N=160)	18 (11.3)	2.36 (1.00, 5.60)	2.21 (0.99, 4.93)	0.062 (0.002, 0.121)	1.86 (0.80, 4.31)	0.2248
	T-DM1 (N=157)	8 (5.1)				0.1447	
No	T-DXd (N=97)	11 (11.3)	6.52 (1.41, 30.24)	5.90 (1.34, 25.93)	0.094 (0.026, 0.163)	5.70 (1.26, 25.74)	
	T-DM1 (N=104)	2 (1.9)				0.0106	
Pyrexia							
Yes	T-DXd (N=160)	13 (8.1)	0.73 (0.34, 1.55)	0.75 (0.38, 1.49)	-0.027 (-0.091, 0.037)	0.49 (0.23, 1.02)	0.9166
	T-DM1 (N=157)	17 (10.8)				0.0524	
No	T-DXd (N=97)	14 (14.4)	0.63 (0.30, 1.31)	0.68 (0.37, 1.26)	-0.067 (-0.172, 0.038)	0.43 (0.22, 0.86)	
	T-DM1 (N=104)	22 (21.2)				0.0135	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Yes	T-DXd (N=160)	90 (56.3)	4.03 (2.49, 6.51)	2.32 (1.71, 3.16)	0.320 (0.218, 0.422)	2.59 (1.77, 3.79)	0.0388
	T-DM1 (N=157)	38 (24.2)				<.0001	
No	T-DXd (N=97)	49 (50.5)	1.85 (1.05, 3.25)	1.42 (1.03, 1.97)	0.149 (0.014, 0.285)	1.31 (0.85, 2.02)	
	T-DM1 (N=104)	37 (35.6)				0.2209	
Alopecia							
Yes	T-DXd (N=160)	58 (36.3)	29.19 (8.91, 95.67)	18.97 (6.07, 59.28)	0.343 (0.266, 0.421)	21.25 (6.66, 67.85)	0.2608
	T-DM1 (N=157)	3 (1.9)				<.0001	
No	T-DXd (N=97)	37 (38.1)	12.21 (4.55, 32.77)	7.93 (3.25, 19.36)	0.333 (0.228, 0.438)	8.80 (3.45, 22.40)	
	T-DM1 (N=104)	5 (4.8)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Yes	T-DXd (N=160)	65 (40.6)	1.94 (1.20, 3.11)	1.56 (1.13, 2.15)	0.145 (0.043, 0.248)	1.50 (1.01, 2.22)	0.5607
	T-DM1 (N=157)	41 (26.1)				0.0433	
No	T-DXd (N=97)	57 (58.8)	2.37 (1.35, 4.19)	1.57 (1.16, 2.11)	0.213 (0.078, 0.348)	1.74 (1.15, 2.61)	
	T-DM1 (N=104)	39 (37.5)				0.0084	
Decreased appetite							
Yes	T-DXd (N=160)	41 (25.6)	1.74 (1.00, 3.01)	1.55 (1.00, 2.40)	0.091 (0.001, 0.180)	1.47 (0.90, 2.40)	0.3279
	T-DM1 (N=157)	26 (16.6)				0.1274	
No	T-DXd (N=97)	34 (35.1)	2.58 (1.34, 4.98)	2.03 (1.23, 3.34)	0.177 (0.058, 0.297)	2.06 (1.16, 3.66)	
	T-DM1 (N=104)	18 (17.3)				0.0134	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
Yes	T-DXd (N=160)	75 (46.9)	1.59 (1.01, 2.50)	1.31 (1.01, 1.72)	0.112 (0.004, 0.220)	1.05 (0.74, 1.50)	0.3150
	T-DM1 (N=157)	56 (35.7)				0.7625	
No	T-DXd (N=97)	41 (42.3)	1.08 (0.62, 1.90)	1.05 (0.75, 1.46)	0.019 (-0.117, 0.155)	0.79 (0.51, 1.22)	
	T-DM1 (N=104)	42 (40.4)				0.2854	
Infections and infestations							
Any PT							
Yes	T-DXd (N=160)	68 (42.5)	1.78 (1.12, 2.84)	1.45 (1.07, 1.96)	0.132 (0.027, 0.237)	1.15 (0.79, 1.68)	0.4171
	T-DM1 (N=157)	46 (29.3)				0.4763	
No	T-DXd (N=97)	44 (45.4)	1.38 (0.79, 2.43)	1.21 (0.87, 1.68)	0.079 (-0.057, 0.215)	0.86 (0.56, 1.33)	
	T-DM1 (N=104)	39 (37.5)				0.5008	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Yes	T-DXd (N=160)	63 (39.4)	1.52 (0.95, 2.42)	1.32 (0.97, 1.79)	0.094 (-0.010, 0.199)	0.92 (0.63, 1.35)	0.7440
	T-DM1 (N=157)	47 (29.9)				0.6745	
No	T-DXd (N=97)	44 (45.4)	1.87 (1.05, 3.33)	1.47 (1.03, 2.12)	0.146 (0.013, 0.279)	1.01 (0.64, 1.60)	
	T-DM1 (N=104)	32 (30.8)				0.9599	
Epistaxis							
Yes	T-DXd (N=160)	17 (10.6)	0.57 (0.30, 1.10)	0.62 (0.35, 1.09)	-0.066 (-0.142, 0.010)	0.35 (0.19, 0.67)	0.4189
	T-DM1 (N=157)	27 (17.2)				0.0008	
No	T-DXd (N=97)	12 (12.4)	0.84 (0.37, 1.89)	0.86 (0.42, 1.74)	-0.021 (-0.115, 0.074)	0.51 (0.23, 1.09)	
	T-DM1 (N=104)	15 (14.4)				0.0783	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Yes	T-DXd (N=160)	43 (26.9)	1.01 (0.61, 1.65)	1.00 (0.70, 1.45)	0.001 (-0.096, 0.099)	0.77 (0.50, 1.18)	0.0010
	T-DM1 (N=157)	42 (26.8)				0.2375	
No	T-DXd (N=97)	60 (61.9)	3.49 (1.95, 6.24)	1.95 (1.41, 2.69)	0.301 (0.170, 0.433)	1.99 (1.30, 3.05)	
	T-DM1 (N=104)	33 (31.7)				0.0012	
Anaemia							
Yes	T-DXd (N=160)	33 (20.6)	1.44 (0.81, 2.57)	1.35 (0.84, 2.17)	0.053 (-0.031, 0.138)	1.07 (0.63, 1.81)	0.0083
	T-DM1 (N=157)	24 (15.3)				0.8155	
No	T-DXd (N=97)	50 (51.5)	4.47 (2.38, 8.39)	2.68 (1.73, 4.16)	0.323 (0.198, 0.448)	2.70 (1.61, 4.54)	
	T-DM1 (N=104)	20 (19.2)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
Yes	T-DXd (N=160)	17 (10.6)	9.21 (2.09, 40.57)	8.34 (1.96, 35.50)	0.094 (0.043, 0.144)	6.93 (1.59, 30.14)	0.6640
	T-DM1 (N=157)	2 (1.3)				0.0028	
No	T-DXd (N=97)	24 (24.7)	6.51 (2.37, 17.87)	5.15 (2.04, 12.95)	0.199 (0.104, 0.295)	4.02 (1.53, 10.58)	
	T-DM1 (N=104)	5 (4.8)				0.0023	
Thrombocytopenia							
Yes	T-DXd (N=160)	3 (1.9)	0.15 (0.04, 0.51)	0.16 (0.05, 0.54)	-0.096 (-0.150, -0.042)	0.12 (0.04, 0.42)	0.0254
	T-DM1 (N=157)	18 (11.5)				<.0001	
No	T-DXd (N=97)	10 (10.3)	0.80 (0.34, 1.93)	0.82 (0.38, 1.79)	-0.022 (-0.110, 0.066)	0.60 (0.26, 1.40)	
	T-DM1 (N=104)	13 (12.5)				0.2322	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
Yes	T-DXd (N=160)	67 (41.9)	1.45 (0.92, 2.30)	1.26 (0.95, 1.69)	0.088 (-0.019, 0.194)	0.99 (0.69, 1.42)	0.1033
	T-DM1 (N=157)	52 (33.1)				0.9509	
No	T-DXd (N=97)	27 (27.8)	0.76 (0.42, 1.39)	0.83 (0.54, 1.26)	-0.058 (-0.185, 0.069)	0.53 (0.31, 0.88)	
	T-DM1 (N=104)	35 (33.7)				0.0133	
Vascular disorders							
Any PT							
Yes	T-DXd (N=160)	33 (20.6)	3.14 (1.56, 6.34)	2.70 (1.45, 5.03)	0.130 (0.055, 0.205)	2.06 (1.05, 4.02)	0.2501
	T-DM1 (N=157)	12 (7.6)				0.0319	
No	T-DXd (N=97)	12 (12.4)	1.49 (0.60, 3.71)	1.43 (0.63, 3.24)	0.037 (-0.048, 0.122)	1.08 (0.45, 2.59)	
	T-DM1 (N=104)	9 (8.7)				0.8558	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
Yes	T-DXd (N=160)	28 (17.5)	1.54 (0.82, 2.89)	1.45 (0.84, 2.48)	0.054 (-0.024, 0.132)	0.96 (0.53, 1.74)	0.7801
	T-DM1 (N=157)	19 (12.1)				0.8903	
No	T-DXd (N=97)	13 (13.4)	1.31 (0.56, 3.08)	1.27 (0.60, 2.69)	0.028 (-0.062, 0.118)	0.81 (0.36, 1.83)	
	T-DM1 (N=104)	11 (10.6)				0.6063	
Psychiatric disorders							
Any PT							
Yes	T-DXd (N=160)	22 (13.8)	1.40 (0.71, 2.79)	1.35 (0.74, 2.47)	0.036 (-0.036, 0.107)	0.93 (0.48, 1.78)	0.5315
	T-DM1 (N=157)	16 (10.2)				0.8197	
No	T-DXd (N=97)	17 (17.5)	0.95 (0.46, 1.96)	0.96 (0.53, 1.74)	-0.007 (-0.113, 0.099)	0.70 (0.36, 1.35)	
	T-DM1 (N=104)	19 (18.3)				0.2865	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Yes	T-DXd (N=160)	25 (15.6)	1.43 (0.75, 2.74)	1.36 (0.78, 2.40)	0.042 (-0.034, 0.117)	0.85 (0.46, 1.59)	0.4558
	T-DM1 (N=157)	18 (11.5)				0.6166	
No	T-DXd (N=97)	7 (7.2)	0.82 (0.29, 2.30)	0.83 (0.32, 2.15)	-0.014 (-0.089, 0.060)	0.55 (0.20, 1.49)	
	T-DM1 (N=104)	9 (8.7)				0.2300	
Hepatobiliary disorders							
Any PT							
Yes	T-DXd (N=160)	9 (5.6)	0.53 (0.22, 1.23)	0.55 (0.25, 1.21)	-0.046 (-0.105, 0.014)	0.40 (0.17, 0.93)	0.3281
	T-DM1 (N=157)	16 (10.2)				0.0293	
No	T-DXd (N=97)	11 (11.3)	0.90 (0.38, 2.11)	0.91 (0.43, 1.93)	-0.012 (-0.101, 0.078)	0.69 (0.31, 1.55)	
	T-DM1 (N=104)	13 (12.5)				0.3749	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
< 3 lines	T-DXd (N=186)	171 (91.9)	7.84 (4.29, 14.31)	1.55 (1.37, 1.76)	0.327 (0.247, 0.407)	2.81 (2.21, 3.59)	0.8184
	T-DM1 (N=189)	112 (59.3)				<.0001	
>= 3 lines	T-DXd (N=71)	66 (93.0)	10.56 (3.80, 29.32)	1.67 (1.35, 2.08)	0.374 (0.245, 0.503)	3.02 (2.02, 4.51)	
	T-DM1 (N=72)	40 (55.6)				<.0001	
Nausea							
< 3 lines	T-DXd (N=186)	144 (77.4)	7.74 (4.88, 12.29)	2.52 (2.01, 3.17)	0.467 (0.378, 0.556)	3.88 (2.85, 5.27)	0.7562
	T-DM1 (N=189)	58 (30.7)				<.0001	
>= 3 lines	T-DXd (N=71)	51 (71.8)	6.19 (3.00, 12.79)	2.46 (1.67, 3.63)	0.427 (0.278, 0.575)	3.42 (2.05, 5.69)	
	T-DM1 (N=72)	21 (29.2)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
< 3 lines	T-DXd (N=186)	91 (48.9)	9.69 (5.45, 17.23)	5.44 (3.38, 8.76)	0.399 (0.317, 0.482)	6.06 (3.61, 10.19)	0.4984
	T-DM1 (N=189)	17 (9.0)				<.0001	
>= 3 lines	T-DXd (N=71)	35 (49.3)	6.80 (2.94, 15.75)	3.94 (2.05, 7.59)	0.368 (0.229, 0.507)	4.39 (2.11, 9.16)	
	T-DM1 (N=72)	9 (12.5)				<.0001	
Constipation							
< 3 lines	T-DXd (N=186)	69 (37.1)	2.27 (1.43, 3.60)	1.80 (1.28, 2.52)	0.165 (0.074, 0.255)	1.58 (1.06, 2.34)	0.7785
	T-DM1 (N=189)	39 (20.6)				0.0220	
>= 3 lines	T-DXd (N=71)	19 (26.8)	1.83 (0.81, 4.12)	1.61 (0.84, 3.06)	0.101 (-0.033, 0.235)	1.35 (0.65, 2.81)	
	T-DM1 (N=72)	12 (16.7)				0.4237	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
< 3 lines	T-DXd (N=186)	60 (32.3)	7.02 (3.63, 13.60)	5.08 (2.83, 9.13)	0.259 (0.183, 0.335)	5.22 (2.81, 9.71)	0.1862
	T-DM1 (N=189)	12 (6.3)				<.0001	
>= 3 lines	T-DXd (N=71)	15 (21.1)	2.95 (1.07, 8.10)	2.54 (1.04, 6.16)	0.128 (0.014, 0.242)	2.25 (0.86, 5.84)	
	T-DM1 (N=72)	6 (8.3)				0.0888	
Stomatitis							
< 3 lines	T-DXd (N=186)	28 (15.1)	4.01 (1.78, 9.05)	3.56 (1.66, 7.60)	0.108 (0.049, 0.167)	3.06 (1.39, 6.74)	0.5698
	T-DM1 (N=189)	8 (4.2)				0.0034	
>= 3 lines	T-DXd (N=71)	12 (16.9)	7.12 (1.53, 33.09)	6.08 (1.41, 26.22)	0.141 (0.046, 0.236)	4.54 (1.01, 20.49)	
	T-DM1 (N=72)	2 (2.8)				0.0312	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
< 3 lines	T-DXd (N=186)	20 (10.8)	5.57 (1.87, 16.64)	5.08 (1.77, 14.58)	0.086 (0.037, 0.135)	3.98 (1.35, 11.69)	0.6799
	T-DM1 (N=189)	4 (2.1)				0.0068	
>= 3 lines	T-DXd (N=71)	9 (12.7)	10.30 (1.27, 83.59)	9.13 (1.19, 70.18)	0.113 (0.031, 0.195)	6.20 (0.77, 49.73)	
	T-DM1 (N=72)	1 (1.4)				0.0507	
Investigations							
Any PT							
< 3 lines	T-DXd (N=186)	108 (58.1)	0.66 (0.43, 1.01)	0.86 (0.73, 1.00)	-0.097 (-0.194, 0.001)	0.56 (0.43, 0.73)	0.1924
	T-DM1 (N=189)	128 (67.7)				<.0001	
>= 3 lines	T-DXd (N=71)	54 (76.1)	1.31 (0.62, 2.76)	1.07 (0.88, 1.31)	0.052 (-0.092, 0.197)	0.72 (0.49, 1.07)	
	T-DM1 (N=72)	51 (70.8)				0.1932	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
< 3 lines	T-DXd (N=186)	52 (28.0)	4.85 (2.58, 9.12)	3.77 (2.17, 6.57)	0.205 (0.131, 0.280)	3.52 (1.95, 6.35)	0.2206
	T-DM1 (N=189)	14 (7.4)				<.0001	
>= 3 lines	T-DXd (N=71)	23 (32.4)	2.66 (1.18, 5.98)	2.12 (1.12, 4.02)	0.171 (0.034, 0.308)	1.92 (0.93, 3.96)	
	T-DM1 (N=72)	11 (15.3)				0.0738	
Aspartate aminotransferase increased							
< 3 lines	T-DXd (N=186)	40 (21.5)	0.42 (0.26, 0.66)	0.54 (0.39, 0.75)	-0.182 (-0.273, -0.090)	0.38 (0.26, 0.56)	0.1041
	T-DM1 (N=189)	75 (39.7)				<.0001	
>= 3 lines	T-DXd (N=71)	26 (36.6)	0.81 (0.41, 1.59)	0.88 (0.58, 1.32)	-0.050 (-0.210, 0.109)	0.56 (0.32, 0.96)	
	T-DM1 (N=72)	30 (41.7)				0.0394	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
< 3 lines	T-DXd (N=186)	35 (18.8)	7.07 (2.90, 17.26)	5.93 (2.55, 13.76)	0.156 (0.095, 0.218)	5.08 (2.13, 12.09)	0.2464
	T-DM1 (N=189)	6 (3.2)				<.0001	
>= 3 lines	T-DXd (N=71)	23 (32.4)	3.83 (1.58, 9.31)	2.92 (1.40, 6.08)	0.213 (0.082, 0.344)	2.62 (1.17, 5.90)	
	T-DM1 (N=72)	8 (11.1)				0.0151	
Alanine aminotransferase increased							
< 3 lines	T-DXd (N=186)	39 (21.0)	0.57 (0.36, 0.91)	0.66 (0.47, 0.94)	-0.108 (-0.196, -0.019)	0.50 (0.34, 0.76)	0.1895
	T-DM1 (N=189)	60 (31.7)				0.0008	
>= 3 lines	T-DXd (N=71)	17 (23.9)	1.02 (0.47, 2.20)	1.01 (0.56, 1.82)	0.003 (-0.136, 0.143)	0.82 (0.41, 1.63)	
	T-DM1 (N=72)	17 (23.6)				0.5791	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
< 3 lines	T-DXd (N=186)	29 (15.6)	0.25 (0.15, 0.40)	0.36 (0.25, 0.53)	-0.273 (-0.360, -0.185)	0.23 (0.15, 0.36)	0.0077
	T-DM1 (N=189)	81 (42.9)				<.0001	
>= 3 lines	T-DXd (N=71)	25 (35.2)	0.72 (0.37, 1.41)	0.82 (0.54, 1.24)	-0.078 (-0.238, 0.081)	0.57 (0.33, 0.97)	
	T-DM1 (N=72)	31 (43.1)				0.0462	
Weight decreased							
< 3 lines	T-DXd (N=186)	26 (14.0)	3.68 (1.62, 8.35)	3.30 (1.53, 7.10)	0.097 (0.040, 0.155)	2.65 (1.20, 5.88)	0.4558
	T-DM1 (N=189)	8 (4.2)				0.0124	
>= 3 lines	T-DXd (N=71)	17 (23.9)	2.52 (1.01, 6.29)	2.15 (0.99, 4.67)	0.128 (0.005, 0.251)	1.44 (0.61, 3.41)	
	T-DM1 (N=72)	8 (11.1)				0.4002	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
< 3 lines	T-DXd (N=186)	7 (3.8)	0.30 (0.12, 0.71)	0.32 (0.14, 0.74)	-0.079 (-0.132, -0.025)	0.25 (0.11, 0.59)	0.1677
	T-DM1 (N=189)	22 (11.6)				0.0007	
>= 3 lines	T-DXd (N=71)	10 (14.1)	0.74 (0.30, 1.83)	0.78 (0.37, 1.66)	-0.040 (-0.160, 0.080)	0.55 (0.24, 1.29)	
	T-DM1 (N=72)	13 (18.1)				0.1678	
General disorders and administration site conditions							
Any PT							
< 3 lines	T-DXd (N=186)	120 (64.5)	1.69 (1.12, 2.55)	1.24 (1.05, 1.48)	0.127 (0.028, 0.226)	1.10 (0.84, 1.43)	0.4859
	T-DM1 (N=189)	98 (51.9)				0.4989	
>= 3 lines	T-DXd (N=71)	39 (54.9)	1.29 (0.67, 2.49)	1.13 (0.82, 1.55)	0.063 (-0.100, 0.227)	0.87 (0.55, 1.39)	
	T-DM1 (N=72)	35 (48.6)				0.5645	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
< 3 lines	T-DXd (N=186)	23 (12.4)	3.19 (1.39, 7.33)	2.92 (1.34, 6.36)	0.081 (0.026, 0.137)	2.57 (1.14, 5.77)	0.9636
	T-DM1 (N=189)	8 (4.2)				0.0177	
>= 3 lines	T-DXd (N=71)	6 (8.5)	3.23 (0.63, 16.58)	3.04 (0.64, 14.57)	0.057 (-0.018, 0.132)	2.99 (0.60, 14.84)	
	T-DM1 (N=72)	2 (2.8)				0.1604	
Pyrexia							
< 3 lines	T-DXd (N=186)	17 (9.1)	0.66 (0.34, 1.27)	0.69 (0.39, 1.24)	-0.041 (-0.105, 0.023)	0.45 (0.24, 0.84)	0.9134
	T-DM1 (N=189)	25 (13.2)				0.0104	
>= 3 lines	T-DXd (N=71)	10 (14.1)	0.68 (0.28, 1.65)	0.72 (0.34, 1.52)	-0.054 (-0.176, 0.068)	0.43 (0.19, 1.00)	
	T-DM1 (N=72)	14 (19.4)				0.0440	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
< 3 lines	T-DXd (N=186)	99 (53.2)	2.84 (1.86, 4.36)	1.86 (1.43, 2.42)	0.247 (0.150, 0.343)	1.93 (1.38, 2.69)	0.8950
	T-DM1 (N=189)	54 (28.6)				<.0001	
>= 3 lines	T-DXd (N=71)	40 (56.3)	3.13 (1.57, 6.26)	1.93 (1.28, 2.92)	0.272 (0.116, 0.428)	2.07 (1.22, 3.53)	
	T-DM1 (N=72)	21 (29.2)				0.0062	
Alopecia							
< 3 lines	T-DXd (N=186)	68 (36.6)	26.65 (9.47, 74.99)	17.27 (6.43, 46.39)	0.344 (0.272, 0.417)	19.21 (7.01, 52.65)	0.2250
	T-DM1 (N=189)	4 (2.1)				<.0001	
>= 3 lines	T-DXd (N=71)	27 (38.0)	10.43 (3.42, 31.86)	6.85 (2.52, 18.56)	0.325 (0.200, 0.449)	7.74 (2.71, 22.17)	
	T-DM1 (N=72)	4 (5.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
< 3 lines	T-DXd (N=186)	80 (43.0)	1.99 (1.29, 3.06)	1.56 (1.18, 2.08)	0.155 (0.059, 0.250)	1.56 (1.10, 2.22)	0.9569
	T-DM1 (N=189)	52 (27.5)				0.0120	
>= 3 lines	T-DXd (N=71)	42 (59.2)	2.28 (1.16, 4.45)	1.52 (1.07, 2.15)	0.203 (0.042, 0.363)	1.55 (0.96, 2.52)	
	T-DM1 (N=72)	28 (38.9)				0.0761	
Decreased appetite							
< 3 lines	T-DXd (N=186)	50 (26.9)	2.11 (1.26, 3.54)	1.81 (1.20, 2.75)	0.121 (0.039, 0.202)	1.79 (1.13, 2.85)	0.6591
	T-DM1 (N=189)	28 (14.8)				0.0129	
>= 3 lines	T-DXd (N=71)	25 (35.2)	1.90 (0.91, 3.98)	1.58 (0.93, 2.71)	0.130 (-0.017, 0.277)	1.47 (0.78, 2.76)	
	T-DM1 (N=72)	16 (22.2)				0.2431	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
< 3 lines	T-DXd (N=186)	80 (43.0)	1.15 (0.76, 1.73)	1.08 (0.85, 1.38)	0.033 (-0.066, 0.133)	0.85 (0.62, 1.17)	0.2076
	T-DM1 (N=189)	75 (39.7)				0.3131	
>= 3 lines	T-DXd (N=71)	36 (50.7)	2.19 (1.11, 4.32)	1.59 (1.06, 2.39)	0.188 (0.029, 0.346)	1.19 (0.70, 2.02)	
	T-DM1 (N=72)	23 (31.9)				0.5144	
Infections and infestations							
Any PT							
< 3 lines	T-DXd (N=186)	78 (41.9)	1.52 (0.99, 2.31)	1.30 (0.99, 1.70)	0.097 (-0.001, 0.194)	0.99 (0.71, 1.39)	0.9119
	T-DM1 (N=189)	61 (32.3)				0.9722	
>= 3 lines	T-DXd (N=71)	34 (47.9)	1.84 (0.93, 3.61)	1.44 (0.96, 2.16)	0.146 (-0.014, 0.305)	1.05 (0.62, 1.79)	
	T-DM1 (N=72)	24 (33.3)				0.8533	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
< 3 lines	T-DXd (N=186)	78 (41.9)	1.67 (1.09, 2.56)	1.39 (1.06, 1.83)	0.118 (0.021, 0.214)	1.02 (0.72, 1.44)	0.5564
	T-DM1 (N=189)	57 (30.2)				0.9251	
>= 3 lines	T-DXd (N=71)	29 (40.8)	1.57 (0.79, 3.13)	1.34 (0.86, 2.09)	0.103 (-0.053, 0.259)	0.80 (0.45, 1.41)	
	T-DM1 (N=72)	22 (30.6)				0.4362	
Epistaxis							
< 3 lines	T-DXd (N=186)	20 (10.8)	0.57 (0.31, 1.03)	0.62 (0.37, 1.03)	-0.067 (-0.137, 0.003)	0.38 (0.22, 0.67)	0.4248
	T-DM1 (N=189)	33 (17.5)				0.0006	
>= 3 lines	T-DXd (N=71)	9 (12.7)	1.02 (0.38, 2.73)	1.01 (0.43, 2.41)	0.002 (-0.107, 0.111)	0.45 (0.17, 1.20)	
	T-DM1 (N=72)	9 (12.5)				0.1035	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
< 3 lines	T-DXd (N=186)	57 (30.6)	1.05 (0.68, 1.63)	1.03 (0.76, 1.41)	0.010 (-0.083, 0.103)	0.78 (0.54, 1.14)	0.0003
	T-DM1 (N=189)	56 (29.6)				0.2054	
>= 3 lines	T-DXd (N=71)	46 (64.8)	5.13 (2.51, 10.50)	2.46 (1.61, 3.74)	0.384 (0.233, 0.535)	2.60 (1.52, 4.46)	
	T-DM1 (N=72)	19 (26.4)				0.0003	
Anaemia							
< 3 lines	T-DXd (N=186)	41 (22.0)	1.39 (0.83, 2.32)	1.30 (0.86, 1.97)	0.051 (-0.029, 0.131)	1.05 (0.66, 1.67)	0.0019
	T-DM1 (N=189)	32 (16.9)				0.8361	
>= 3 lines	T-DXd (N=71)	42 (59.2)	7.24 (3.32, 15.79)	3.55 (2.04, 6.16)	0.425 (0.282, 0.568)	3.55 (1.86, 6.79)	
	T-DM1 (N=72)	12 (16.7)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
< 3 lines	T-DXd (N=186)	26 (14.0)	30.53 (4.10, 227.39)	26.42 (3.62, 192.70)	0.134 (0.084, 0.185)	20.32 (2.75, 150.14)	0.0334
	T-DM1 (N=189)	1 (0.5)				<.0001	
>= 3 lines	T-DXd (N=71)	15 (21.1)	2.95 (1.07, 8.10)	2.54 (1.04, 6.16)	0.128 (0.014, 0.242)	1.84 (0.70, 4.85)	
	T-DM1 (N=72)	6 (8.3)				0.2087	
Thrombocytopenia							
< 3 lines	T-DXd (N=186)	7 (3.8)	0.35 (0.14, 0.85)	0.37 (0.16, 0.87)	-0.063 (-0.114, -0.012)	0.28 (0.12, 0.67)	0.7428
	T-DM1 (N=189)	19 (10.1)				0.0024	
>= 3 lines	T-DXd (N=71)	6 (8.5)	0.46 (0.16, 1.31)	0.51 (0.20, 1.28)	-0.082 (-0.190, 0.026)	0.34 (0.12, 0.96)	
	T-DM1 (N=72)	12 (16.7)				0.0337	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
< 3 lines	T-DXd (N=186)	68 (36.6)	1.18 (0.77, 1.81)	1.11 (0.84, 1.47)	0.038 (-0.059, 0.134)	0.83 (0.59, 1.18)	0.8202
	T-DM1 (N=189)	62 (32.8)				0.2990	
>= 3 lines	T-DXd (N=71)	26 (36.6)	1.09 (0.55, 2.15)	1.05 (0.68, 1.64)	0.019 (-0.138, 0.176)	0.74 (0.42, 1.31)	
	T-DM1 (N=72)	25 (34.7)				0.3044	
Vascular disorders							
Any PT							
< 3 lines	T-DXd (N=186)	34 (18.3)	2.59 (1.36, 4.95)	2.30 (1.30, 4.08)	0.103 (0.036, 0.171)	1.77 (0.96, 3.27)	0.6208
	T-DM1 (N=189)	15 (7.9)				0.0651	
>= 3 lines	T-DXd (N=71)	11 (15.5)	2.02 (0.70, 5.79)	1.86 (0.73, 4.76)	0.072 (-0.034, 0.177)	1.41 (0.51, 3.88)	
	T-DM1 (N=72)	6 (8.3)				0.5058	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
< 3 lines	T-DXd (N=186)	28 (15.1)	1.35 (0.74, 2.45)	1.29 (0.77, 2.18)	0.034 (-0.035, 0.103)	0.88 (0.50, 1.55)	0.7758
	T-DM1 (N=189)	22 (11.6)				0.6482	
>= 3 lines	T-DXd (N=71)	13 (18.3)	1.79 (0.69, 4.64)	1.65 (0.73, 3.73)	0.072 (-0.044, 0.188)	0.99 (0.40, 2.46)	
	T-DM1 (N=72)	8 (11.1)				0.9828	
Psychiatric disorders							
Any PT							
< 3 lines	T-DXd (N=186)	26 (14.0)	1.12 (0.62, 2.03)	1.10 (0.66, 1.85)	0.013 (-0.056, 0.082)	0.76 (0.43, 1.32)	0.9016
	T-DM1 (N=189)	24 (12.7)				0.3259	
>= 3 lines	T-DXd (N=71)	13 (18.3)	1.24 (0.52, 3.00)	1.20 (0.58, 2.49)	0.030 (-0.092, 0.153)	0.92 (0.41, 2.07)	
	T-DM1 (N=72)	11 (15.3)				0.8401	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
< 3 lines	T-DXd (N=186)	24 (12.9)	1.72 (0.87, 3.39)	1.63 (0.88, 3.00)	0.050 (-0.012, 0.111)	1.13 (0.59, 2.18)	0.0585
	T-DM1 (N=189)	15 (7.9)				0.7056	
>= 3 lines	T-DXd (N=71)	8 (11.3)	0.63 (0.24, 1.66)	0.68 (0.29, 1.55)	-0.054 (-0.167, 0.059)	0.33 (0.13, 0.83)	
	T-DM1 (N=72)	12 (16.7)				0.0151	
Hepatobiliary disorders							
Any PT							
< 3 lines	T-DXd (N=186)	15 (8.1)	0.74 (0.37, 1.50)	0.76 (0.40, 1.44)	-0.025 (-0.084, 0.034)	0.59 (0.30, 1.16)	0.5223
	T-DM1 (N=189)	20 (10.6)				0.1256	
>= 3 lines	T-DXd (N=71)	5 (7.0)	0.53 (0.17, 1.67)	0.56 (0.20, 1.60)	-0.055 (-0.151, 0.042)	0.39 (0.12, 1.22)	
	T-DM1 (N=72)	9 (12.5)				0.0971	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
< 3 lines	T-DXd (N=154)	147 (95.5)	15.87 (6.96, 36.17)	1.68 (1.45, 1.93)	0.385 (0.299, 0.471)	3.46 (2.62, 4.55)	0.7445
	T-DM1 (N=151)	86 (57.0)				<.0001	
>= 3 lines	T-DXd (N=6)	6 (100)	NE (NE, NE)	3.00 (0.97, 9.30)	0.667 (0.289, 1.000)	3.88 (0.77, 19.46)	
	T-DM1 (N=6)	2 (33.3)				0.0724	
Nausea							
< 3 lines	T-DXd (N=154)	125 (81.2)	9.54 (5.61, 16.22)	2.61 (2.03, 3.35)	0.500 (0.404, 0.597)	4.25 (3.03, 5.96)	0.7838
	T-DM1 (N=151)	47 (31.1)				<.0001	
>= 3 lines	T-DXd (N=6)	5 (83.3)	24.99 (1.20, 520.48)	5.00 (0.81, 31.00)	0.667 (0.245, 1.000)	5.22 (0.61, 44.79)	
	T-DM1 (N=6)	1 (16.7)				0.0880	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
< 3 lines	T-DXd (N=154)	79 (51.3)	11.18 (5.83, 21.43)	5.96 (3.47, 10.25)	0.427 (0.336, 0.518)	6.63 (3.68, 11.93)	0.9833
	T-DM1 (N=151)	13 (8.6)				<.0001	
>= 3 lines	T-DXd (N=6)	3 (50.0)	NE (NE, NE)	NE (NE, NE)	0.500 (0.100, 0.900)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.0947	
Constipation							
< 3 lines	T-DXd (N=154)	62 (40.3)	2.41 (1.46, 3.98)	1.84 (1.29, 2.63)	0.184 (0.082, 0.286)	1.63 (1.07, 2.50)	0.9799
	T-DM1 (N=151)	33 (21.9)				0.0224	
>= 3 lines	T-DXd (N=6)	3 (50.0)	NE (NE, NE)	NE (NE, NE)	0.500 (0.100, 0.900)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.1297	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
< 3 lines	T-DXd (N=154)	52 (33.8)	5.91 (3.00, 11.63)	4.25 (2.36, 7.64)	0.258 (0.172, 0.344)	4.45 (2.37, 8.34)	0.9854
	T-DM1 (N=151)	12 (7.9)				<.0001	
>= 3 lines	T-DXd (N=6)	2 (33.3)	NE (NE, NE)	NE (NE, NE)	0.333 (-0.044, 0.711)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.1803	
Stomatitis							
< 3 lines	T-DXd (N=154)	27 (17.5)	5.14 (2.06, 12.84)	4.41 (1.88, 10.38)	0.136 (0.068, 0.203)	3.69 (1.51, 8.99)	0.4726
	T-DM1 (N=151)	6 (4.0)				0.0021	
>= 3 lines	T-DXd (N=6)	2 (33.3)	2.50 (0.16, 38.60)	2.00 (0.24, 16.61)	0.167 (-0.314, 0.647)	1.60 (0.14, 17.84)	
	T-DM1 (N=6)	1 (16.7)				0.7002	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
< 3 lines	T-DXd (N=154)	19 (12.3)	4.11 (1.49, 11.31)	3.73 (1.43, 9.72)	0.090 (0.031, 0.150)	2.99 (1.11, 8.05)	0.9997
	T-DM1 (N=151)	5 (3.3)				0.0227	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	
Investigations							
Any PT							
< 3 lines	T-DXd (N=154)	83 (53.9)	0.53 (0.33, 0.84)	0.78 (0.65, 0.94)	-0.150 (-0.258, -0.042)	0.46 (0.35, 0.62)	0.0882
	T-DM1 (N=151)	104 (68.9)				<.0001	
>= 3 lines	T-DXd (N=6)	5 (83.3)	10.00 (0.65, 154.37)	2.50 (0.76, 8.19)	0.500 (0.019, 0.981)	0.84 (0.12, 6.14)	
	T-DM1 (N=6)	2 (33.3)				0.8626	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
< 3 lines	T-DXd (N=154)	39 (25.3)	3.93 (1.97, 7.85)	3.19 (1.74, 5.85)	0.174 (0.093, 0.255)	2.90 (1.52, 5.55)	0.9876
	T-DM1 (N=151)	12 (7.9)				0.0007	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.4142	
Aspartate aminotransferase increased							
< 3 lines	T-DXd (N=154)	25 (16.2)	0.31 (0.18, 0.53)	0.42 (0.28, 0.64)	-0.222 (-0.319, -0.125)	0.28 (0.17, 0.45)	0.2021
	T-DM1 (N=151)	58 (38.4)				<.0001	
>= 3 lines	T-DXd (N=6)	2 (33.3)	2.50 (0.16, 38.60)	2.00 (0.24, 16.61)	0.167 (-0.314, 0.647)	0.91 (0.06, 14.63)	
	T-DM1 (N=6)	1 (16.7)				0.9486	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
< 3 lines	T-DXd (N=154)	21 (13.6)	7.79 (2.27, 26.71)	6.86 (2.09, 22.53)	0.116 (0.058, 0.175)	6.13 (1.83, 20.61)	0.9875
	T-DM1 (N=151)	3 (2.0)				0.0008	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	-0.167 (-0.465, 0.132)	NE (NE, NE)	
	T-DM1 (N=6)	1 (16.7)				0.1967	
Alanine aminotransferase increased							
< 3 lines	T-DXd (N=154)	25 (16.2)	0.43 (0.25, 0.74)	0.52 (0.34, 0.80)	-0.149 (-0.243, -0.055)	0.37 (0.23, 0.61)	0.2990
	T-DM1 (N=151)	47 (31.1)				<.0001	
>= 3 lines	T-DXd (N=6)	2 (33.3)	2.50 (0.16, 38.60)	2.00 (0.24, 16.61)	0.167 (-0.314, 0.647)	0.91 (0.06, 14.63)	
	T-DM1 (N=6)	1 (16.7)				0.9486	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
< 3 lines	T-DXd (N=154)	17 (11.0)	0.16 (0.09, 0.28)	0.25 (0.15, 0.40)	-0.333 (-0.427, -0.240)	0.16 (0.09, 0.28)	0.9875
	T-DM1 (N=151)	67 (44.4)				<.0001	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.3173	
Weight decreased							
< 3 lines	T-DXd (N=154)	16 (10.4)	2.80 (1.07, 7.37)	2.61 (1.05, 6.50)	0.064 (0.007, 0.122)	2.21 (0.86, 5.67)	0.9914
	T-DM1 (N=151)	6 (4.0)				0.0896	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.5271	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
< 3 lines	T-DXd (N=154)	1 (0.6)	0.08 (0.01, 0.65)	0.09 (0.01, 0.68)	-0.066 (-0.110, -0.023)	0.08 (0.01, 0.63)	0.9995
	T-DM1 (N=151)	11 (7.3)				0.0020	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	
General disorders and administration site conditions							
Any PT							
< 3 lines	T-DXd (N=154)	99 (64.3)	1.68 (1.06, 2.67)	1.24 (1.02, 1.51)	0.126 (0.016, 0.236)	1.11 (0.83, 1.50)	0.2542
	T-DM1 (N=151)	78 (51.7)				0.4790	
>= 3 lines	T-DXd (N=6)	4 (66.7)	0.40 (0.03, 6.18)	0.80 (0.41, 1.56)	-0.167 (-0.647, 0.314)	0.67 (0.18, 2.51)	
	T-DM1 (N=6)	5 (83.3)				0.5301	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
< 3 lines	T-DXd (N=154)	17 (11.0)	2.22 (0.93, 5.31)	2.08 (0.93, 4.68)	0.057 (-0.004, 0.118)	1.74 (0.74, 4.08)	0.9900
	T-DM1 (N=151)	8 (5.3)				0.1981	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.4142	
Pyrexia							
< 3 lines	T-DXd (N=154)	12 (7.8)	0.71 (0.33, 1.56)	0.74 (0.36, 1.50)	-0.028 (-0.093, 0.037)	0.48 (0.22, 1.03)	0.9394
	T-DM1 (N=151)	16 (10.6)				0.0565	
>= 3 lines	T-DXd (N=6)	1 (16.7)	1.00 (0.05, 20.83)	1.00 (0.08, 12.56)	0.000 (-0.422, 0.422)	0.45 (0.02, 8.98)	
	T-DM1 (N=6)	1 (16.7)				0.5930	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
< 3 lines	T-DXd (N=154)	86 (55.8)	3.90 (2.39, 6.35)	2.28 (1.67, 3.12)	0.313 (0.209, 0.418)	2.57 (1.75, 3.78)	0.7331
	T-DM1 (N=151)	37 (24.5)				<.0001	
>= 3 lines	T-DXd (N=6)	4 (66.7)	10.00 (0.65, 154.37)	4.00 (0.61, 26.12)	0.500 (0.019, 0.981)	3.50 (0.39, 31.36)	
	T-DM1 (N=6)	1 (16.7)				0.2331	
Alopecia							
< 3 lines	T-DXd (N=154)	55 (35.7)	27.41 (8.34, 90.05)	17.98 (5.75, 56.22)	0.337 (0.258, 0.416)	20.45 (6.40, 65.39)	0.9889
	T-DM1 (N=151)	3 (2.0)				<.0001	
>= 3 lines	T-DXd (N=6)	3 (50.0)	NE (NE, NE)	NE (NE, NE)	0.500 (0.100, 0.900)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.1456	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
< 3 lines	T-DXd (N=154)	61 (39.6)	1.82 (1.12, 2.96)	1.50 (1.08, 2.08)	0.131 (0.027, 0.236)	1.44 (0.97, 2.16)	0.4690
	T-DM1 (N=151)	40 (26.5)				0.0715	
>= 3 lines	T-DXd (N=6)	4 (66.7)	10.00 (0.65, 154.37)	4.00 (0.61, 26.12)	0.500 (0.019, 0.981)	2.88 (0.31, 26.52)	
	T-DM1 (N=6)	1 (16.7)				0.3198	
Decreased appetite							
< 3 lines	T-DXd (N=154)	37 (24.0)	1.52 (0.87, 2.67)	1.40 (0.89, 2.19)	0.068 (-0.022, 0.159)	1.32 (0.80, 2.19)	0.9820
	T-DM1 (N=151)	26 (17.2)				0.2819	
>= 3 lines	T-DXd (N=6)	4 (66.7)	NE (NE, NE)	NE (NE, NE)	0.667 (0.289, 1.000)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.0634	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
< 3 lines	T-DXd (N=154)	71 (46.1)	1.58 (1.00, 2.51)	1.31 (1.00, 1.73)	0.110 (0.001, 0.220)	1.07 (0.75, 1.54)	0.5132
	T-DM1 (N=151)	53 (35.1)				0.7001	
>= 3 lines	T-DXd (N=6)	4 (66.7)	2.00 (0.19, 20.61)	1.33 (0.50, 3.55)	0.167 (-0.383, 0.717)	0.44 (0.08, 2.31)	
	T-DM1 (N=6)	3 (50.0)				0.3215	
Infections and infestations							
Any PT							
< 3 lines	T-DXd (N=154)	65 (42.2)	1.72 (1.07, 2.76)	1.42 (1.04, 1.92)	0.124 (0.017, 0.231)	1.12 (0.76, 1.64)	0.5755
	T-DM1 (N=151)	45 (29.8)				0.5747	
>= 3 lines	T-DXd (N=6)	3 (50.0)	5.00 (0.34, 72.76)	3.00 (0.42, 21.30)	0.333 (-0.166, 0.832)	2.55 (0.26, 24.92)	
	T-DM1 (N=6)	1 (16.7)				0.4054	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
< 3 lines	T-DXd (N=154)	60 (39.0)	1.50 (0.93, 2.42)	1.31 (0.95, 1.79)	0.092 (-0.014, 0.198)	0.93 (0.63, 1.38)	0.9685
	T-DM1 (N=151)	45 (29.8)				0.7311	
>= 3 lines	T-DXd (N=6)	3 (50.0)	2.00 (0.19, 20.61)	1.50 (0.38, 6.00)	0.167 (-0.383, 0.717)	0.82 (0.13, 5.04)	
	T-DM1 (N=6)	2 (33.3)				0.8260	
Epistaxis							
< 3 lines	T-DXd (N=154)	15 (9.7)	0.54 (0.27, 1.08)	0.59 (0.32, 1.07)	-0.068 (-0.144, 0.007)	0.34 (0.17, 0.67)	0.5925
	T-DM1 (N=151)	25 (16.6)				0.0011	
>= 3 lines	T-DXd (N=6)	2 (33.3)	1.00 (0.09, 11.03)	1.00 (0.20, 4.95)	0.000 (-0.533, 0.533)	0.46 (0.06, 3.31)	
	T-DM1 (N=6)	2 (33.3)				0.4289	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
< 3 lines	T-DXd (N=154)	39 (25.3)	1.01 (0.60, 1.69)	1.01 (0.68, 1.48)	0.002 (-0.096, 0.099)	0.77 (0.49, 1.22)	0.9435
	T-DM1 (N=151)	38 (25.2)				0.2684	
>= 3 lines	T-DXd (N=6)	4 (66.7)	1.00 (0.09, 11.03)	1.00 (0.45, 2.23)	0.000 (-0.533, 0.533)	0.70 (0.15, 3.14)	
	T-DM1 (N=6)	4 (66.7)				0.5954	
Anaemia							
< 3 lines	T-DXd (N=154)	30 (19.5)	1.50 (0.81, 2.75)	1.40 (0.84, 2.33)	0.056 (-0.028, 0.139)	1.14 (0.65, 2.01)	0.4029
	T-DM1 (N=151)	21 (13.9)				0.6373	
>= 3 lines	T-DXd (N=6)	3 (50.0)	1.00 (0.10, 9.61)	1.00 (0.32, 3.10)	0.000 (-0.566, 0.566)	0.18 (0.02, 1.80)	
	T-DM1 (N=6)	3 (50.0)				0.1036	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
< 3 lines	T-DXd (N=154)	14 (9.1)	NE (NE, NE)	NE (NE, NE)	0.091 (0.046, 0.136)	NE (NE, NE)	0.9887
	T-DM1 (N=151)	0				0.0009	
>= 3 lines	T-DXd (N=6)	3 (50.0)	2.00 (0.19, 20.61)	1.50 (0.38, 6.00)	0.167 (-0.383, 0.717)	1.27 (0.20, 7.95)	
	T-DM1 (N=6)	2 (33.3)				0.7967	
Thrombocytopenia							
< 3 lines	T-DXd (N=154)	1 (0.6)	0.06 (0.01, 0.45)	0.07 (0.01, 0.49)	-0.093 (-0.142, -0.043)	0.05 (0.01, 0.41)	0.1028
	T-DM1 (N=151)	15 (9.9)				0.0001	
>= 3 lines	T-DXd (N=6)	2 (33.3)	0.50 (0.05, 5.15)	0.67 (0.17, 2.67)	-0.167 (-0.717, 0.383)	0.21 (0.02, 2.16)	
	T-DM1 (N=6)	3 (50.0)				0.1442	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
< 3 lines	T-DXd (N=154)	63 (40.9)	1.44 (0.90, 2.30)	1.26 (0.94, 1.70)	0.085 (-0.023, 0.192)	1.02 (0.70, 1.48)	0.3377
	T-DM1 (N=151)	49 (32.5)				0.9297	
>= 3 lines	T-DXd (N=6)	4 (66.7)	2.00 (0.19, 20.61)	1.33 (0.50, 3.55)	0.167 (-0.383, 0.717)	0.26 (0.03, 2.55)	
	T-DM1 (N=6)	3 (50.0)				0.2154	
Vascular disorders							
Any PT							
< 3 lines	T-DXd (N=154)	32 (20.8)	3.70 (1.75, 7.83)	3.14 (1.60, 6.15)	0.142 (0.066, 0.217)	2.39 (1.16, 4.91)	0.1116
	T-DM1 (N=151)	10 (6.6)				0.0149	
>= 3 lines	T-DXd (N=6)	1 (16.7)	0.40 (0.03, 6.18)	0.50 (0.06, 4.15)	-0.167 (-0.647, 0.314)	0.32 (0.03, 3.61)	
	T-DM1 (N=6)	2 (33.3)				0.3352	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
< 3 lines	T-DXd (N=154)	28 (18.2)	1.64 (0.87, 3.11)	1.53 (0.88, 2.64)	0.063 (-0.017, 0.142)	1.01 (0.55, 1.86)	0.9886
	T-DM1 (N=151)	18 (11.9)				0.9620	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	-0.167 (-0.465, 0.132)	NE (NE, NE)	
	T-DM1 (N=6)	1 (16.7)				0.3173	
Psychiatric disorders							
Any PT							
< 3 lines	T-DXd (N=154)	21 (13.6)	1.33 (0.67, 2.66)	1.29 (0.70, 2.37)	0.030 (-0.043, 0.104)	0.89 (0.46, 1.72)	0.9885
	T-DM1 (N=151)	16 (10.6)				0.7274	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.4386	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
< 3 lines	T-DXd (N=154)	25 (16.2)	1.53 (0.79, 2.96)	1.44 (0.81, 2.56)	0.050 (-0.027, 0.127)	0.91 (0.49, 1.72)	0.9889
	T-DM1 (N=151)	17 (11.3)				0.7792	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	-0.167 (-0.465, 0.132)	NE (NE, NE)	
	T-DM1 (N=6)	1 (16.7)				0.3173	
Hepatobiliary disorders							
Any PT							
< 3 lines	T-DXd (N=154)	9 (5.8)	0.52 (0.22, 1.22)	0.55 (0.25, 1.21)	-0.048 (-0.109, 0.014)	0.40 (0.17, 0.94)	0.9997
	T-DM1 (N=151)	16 (10.6)				0.0296	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	122 (93.8)	11.54 (5.21, 25.56)	1.65 (1.41, 1.93)	0.369 (0.275, 0.464)	3.13 (2.33, 4.21)	0.4271
	T-DM1 (N=130)	74 (56.9)				<.0001	
Mild Impairment	T-DXd (N=92)	83 (90.2)	6.25 (2.83, 13.79)	1.51 (1.27, 1.80)	0.306 (0.194, 0.418)	2.54 (1.82, 3.55)	
	T-DM1 (N=104)	62 (59.6)				<.0001	
Moderate Impairment	T-DXd (N=30)	27 (90.0)	6.23 (1.44, 26.95)	1.52 (1.05, 2.20)	0.309 (0.077, 0.541)	2.56 (1.31, 5.00)	
	T-DM1 (N=22)	13 (59.1)				0.0043	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Nausea							
Within Normal Range	T-DXd (N=130)	103 (79.2)	6.74 (3.87, 11.73)	2.19 (1.72, 2.80)	0.431 (0.323, 0.539)	3.41 (2.41, 4.83)	0.8872
	T-DM1 (N=130)	47 (36.2)				<.0001	
Mild Impairment	T-DXd (N=92)	66 (71.7)	7.24 (3.85, 13.61)	2.76 (1.95, 3.92)	0.458 (0.333, 0.583)	3.80 (2.43, 5.96)	
	T-DM1 (N=104)	27 (26.0)				<.0001	
Moderate Impairment	T-DXd (N=30)	21 (70.0)	7.93 (2.24, 28.15)	3.08 (1.38, 6.89)	0.473 (0.233, 0.713)	4.73 (1.78, 12.61)	
	T-DM1 (N=22)	5 (22.7)				0.0006	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Within Normal Range	T-DXd (N=130)	69 (53.1)	8.67 (4.58, 16.43)	4.60 (2.78, 7.60)	0.415 (0.314, 0.517)	5.07 (2.89, 8.87)	0.9370
	T-DM1 (N=130)	15 (11.5)				<.0001	
Mild Impairment	T-DXd (N=92)	38 (41.3)	8.44 (3.67, 19.41)	5.37 (2.64, 10.91)	0.336 (0.223, 0.449)	5.61 (2.61, 12.05)	
	T-DM1 (N=104)	8 (7.7)				<.0001	
Moderate Impairment	T-DXd (N=30)	16 (53.3)	7.24 (1.76, 29.73)	3.91 (1.30, 11.79)	0.397 (0.168, 0.626)	4.69 (1.37, 16.12)	
	T-DM1 (N=22)	3 (13.6)				0.0066	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Constipation							
Within Normal Range	T-DXd (N=130)	47 (36.2)	2.38 (1.35, 4.18)	1.88 (1.24, 2.86)	0.169 (0.062, 0.276)	1.58 (0.97, 2.57)	0.9534
	T-DM1 (N=130)	25 (19.2)				0.0664	
Mild Impairment	T-DXd (N=92)	31 (33.7)	2.13 (1.11, 4.10)	1.75 (1.08, 2.85)	0.145 (0.022, 0.267)	1.65 (0.94, 2.89)	
	T-DM1 (N=104)	20 (19.2)				0.0805	
Moderate Impairment	T-DXd (N=30)	10 (33.3)	1.70 (0.49, 5.95)	1.47 (0.58, 3.69)	0.106 (-0.137, 0.349)	1.27 (0.43, 3.74)	
	T-DM1 (N=22)	5 (22.7)				0.6589	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Within Normal Range	T-DXd (N=130)	39 (30.0)	8.86 (3.60, 21.81)	6.50 (2.85, 14.82)	0.254 (0.167, 0.340)	6.41 (2.71, 15.18)	0.4202
	T-DM1 (N=130)	6 (4.6)				<.0001	
Mild Impairment	T-DXd (N=92)	26 (28.3)	4.16 (1.83, 9.44)	3.27 (1.61, 6.60)	0.196 (0.089, 0.303)	3.27 (1.53, 6.99)	
	T-DM1 (N=104)	9 (8.7)				0.0012	
Moderate Impairment	T-DXd (N=30)	7 (23.3)	3.04 (0.57, 16.36)	2.57 (0.59, 11.19)	0.142 (-0.051, 0.336)	2.66 (0.55, 12.79)	
	T-DM1 (N=22)	2 (9.1)				0.2063	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Stomatitis							
Within Normal Range	T-DXd (N=130)	15 (11.5)	4.11 (1.33, 12.74)	3.75 (1.28, 11.00)	0.085 (0.022, 0.147)	2.84 (0.93, 8.63)	0.8995
	T-DM1 (N=130)	4 (3.1)				0.0552	
Mild Impairment	T-DXd (N=92)	19 (20.7)	5.15 (1.84, 14.44)	4.30 (1.67, 11.04)	0.158 (0.066, 0.251)	3.95 (1.47, 10.60)	
	T-DM1 (N=104)	5 (4.8)				0.0033	
Moderate Impairment	T-DXd (N=30)	6 (20.0)	5.25 (0.58, 47.22)	4.40 (0.57, 33.98)	0.155 (-0.013, 0.322)	3.83 (0.46, 31.86)	
	T-DM1 (N=22)	1 (4.5)				0.1812	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Within Normal Range	T-DXd (N=130)	14 (10.8)	5.11 (1.43, 18.23)	4.67 (1.37, 15.85)	0.085 (0.025, 0.144)	3.33 (0.95, 11.74)	0.9284
	T-DM1 (N=130)	3 (2.3)				0.0474	
Mild Impairment	T-DXd (N=92)	10 (10.9)	6.22 (1.33, 29.18)	5.65 (1.27, 25.13)	0.089 (0.021, 0.158)	4.13 (0.90, 19.00)	
	T-DM1 (N=104)	2 (1.9)				0.0490	
Moderate Impairment	T-DXd (N=30)	3 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.007, 0.207)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.1903	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Within Normal Range	T-DXd (N=130)	84 (64.6)	1.03 (0.62, 1.72)	1.01 (0.84, 1.21)	0.008 (-0.109, 0.124)	0.69 (0.51, 0.94)	0.2639
	T-DM1 (N=130)	83 (63.8)				0.0404	
Mild Impairment	T-DXd (N=92)	58 (63.0)	0.69 (0.38, 1.26)	0.89 (0.73, 1.08)	-0.081 (-0.213, 0.050)	0.60 (0.43, 0.85)	
	T-DM1 (N=104)	74 (71.2)				0.0090	
Moderate Impairment	T-DXd (N=30)	18 (60.0)	0.33 (0.09, 1.23)	0.73 (0.52, 1.04)	-0.218 (-0.456, 0.020)	0.36 (0.19, 0.71)	
	T-DM1 (N=22)	18 (81.8)				0.0032	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
Within Normal Range	T-DXd (N=130)	42 (32.3)	9.86 (4.02, 24.21)	7.00 (3.08, 15.90)	0.277 (0.189, 0.365)	6.30 (2.67, 14.82)	0.0220
	T-DM1 (N=130)	6 (4.6)				<.0001	
Mild Impairment	T-DXd (N=92)	28 (30.4)	2.60 (1.28, 5.25)	2.11 (1.20, 3.70)	0.160 (0.044, 0.276)	2.11 (1.13, 3.96)	
	T-DM1 (N=104)	15 (14.4)				0.0174	
Moderate Impairment	T-DXd (N=30)	5 (16.7)	0.90 (0.21, 3.83)	0.92 (0.28, 3.03)	-0.015 (-0.224, 0.194)	0.82 (0.22, 3.08)	
	T-DM1 (N=22)	4 (18.2)				0.7741	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
Within Normal Range	T-DXd (N=130)	37 (28.5)	0.68 (0.40, 1.14)	0.77 (0.54, 1.10)	-0.085 (-0.198, 0.029)	0.56 (0.36, 0.87)	0.2764
	T-DM1 (N=130)	48 (36.9)				0.0098	
Mild Impairment	T-DXd (N=92)	18 (19.6)	0.33 (0.17, 0.63)	0.46 (0.29, 0.74)	-0.227 (-0.352, -0.103)	0.30 (0.17, 0.52)	
	T-DM1 (N=104)	44 (42.3)				<.0001	
Moderate Impairment	T-DXd (N=30)	10 (33.3)	0.60 (0.19, 1.86)	0.73 (0.37, 1.45)	-0.121 (-0.389, 0.147)	0.56 (0.23, 1.34)	
	T-DM1 (N=22)	10 (45.5)				0.1952	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
Within Normal Range	T-DXd (N=130)	35 (26.9)	9.21 (3.48, 24.40)	7.00 (2.83, 17.30)	0.231 (0.148, 0.314)	5.73 (2.23, 14.67)	0.1744
	T-DM1 (N=130)	5 (3.8)				<.0001	
Mild Impairment	T-DXd (N=92)	20 (21.7)	3.85 (1.54, 9.59)	3.23 (1.43, 7.29)	0.150 (0.053, 0.247)	3.10 (1.31, 7.35)	
	T-DM1 (N=104)	7 (6.7)				0.0067	
Moderate Impairment	T-DXd (N=30)	3 (10.0)	1.11 (0.17, 7.28)	1.10 (0.20, 6.04)	0.009 (-0.152, 0.170)	0.91 (0.15, 5.51)	
	T-DM1 (N=22)	2 (9.1)				0.9187	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
Within Normal Range	T-DXd (N=130)	34 (26.2)	1.00 (0.58, 1.74)	1.00 (0.66, 1.50)	0.000 (-0.107, 0.107)	0.80 (0.50, 1.30)	0.1079
	T-DM1 (N=130)	34 (26.2)				0.3735	
Mild Impairment	T-DXd (N=92)	15 (16.3)	0.38 (0.19, 0.76)	0.48 (0.28, 0.83)	-0.173 (-0.292, -0.055)	0.35 (0.19, 0.65)	
	T-DM1 (N=104)	35 (33.7)				0.0006	
Moderate Impairment	T-DXd (N=30)	6 (20.0)	0.44 (0.13, 1.52)	0.55 (0.22, 1.36)	-0.164 (-0.410, 0.083)	0.42 (0.15, 1.23)	
	T-DM1 (N=22)	8 (36.4)				0.1087	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Within Normal Range	T-DXd (N=130)	26 (20.0)	0.43 (0.24, 0.75)	0.54 (0.36, 0.82)	-0.169 (-0.277, -0.061)	0.34 (0.21, 0.56)	0.5114
	T-DM1 (N=130)	48 (36.9)				<.0001	
Mild Impairment	T-DXd (N=92)	23 (25.0)	0.33 (0.18, 0.61)	0.50 (0.33, 0.75)	-0.250 (-0.381, -0.119)	0.34 (0.21, 0.57)	
	T-DM1 (N=104)	52 (50.0)				<.0001	
Moderate Impairment	T-DXd (N=30)	5 (16.7)	0.17 (0.05, 0.60)	0.31 (0.13, 0.74)	-0.379 (-0.626, -0.132)	0.20 (0.07, 0.56)	
	T-DM1 (N=22)	12 (54.5)				0.0011	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
Within Normal Range	T-DXd (N=130)	23 (17.7)	3.78 (1.56, 9.15)	3.29 (1.46, 7.39)	0.123 (0.047, 0.199)	2.30 (0.98, 5.41)	0.2186
	T-DM1 (N=130)	7 (5.4)				0.0494	
Mild Impairment	T-DXd (N=92)	15 (16.3)	3.86 (1.34, 11.08)	3.39 (1.28, 8.97)	0.115 (0.029, 0.201)	2.88 (1.04, 7.94)	
	T-DM1 (N=104)	5 (4.8)				0.0327	
Moderate Impairment	T-DXd (N=30)	5 (16.7)	0.90 (0.21, 3.83)	0.92 (0.28, 3.03)	-0.015 (-0.224, 0.194)	0.66 (0.18, 2.47)	
	T-DM1 (N=22)	4 (18.2)				0.5418	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
Within Normal Range	T-DXd (N=130)	10 (7.7)	0.46 (0.21, 1.02)	0.50 (0.24, 1.03)	-0.077 (-0.154, 0.000)	0.33 (0.15, 0.72)	0.7781
	T-DM1 (N=130)	20 (15.4)				0.0040	
Mild Impairment	T-DXd (N=92)	7 (7.6)	0.63 (0.24, 1.68)	0.66 (0.27, 1.60)	-0.039 (-0.121, 0.043)	0.55 (0.22, 1.41)	
	T-DM1 (N=104)	12 (11.5)				0.2093	
Moderate Impairment	T-DXd (N=30)	0	NE (NE, NE)	NE (NE, NE)	-0.136 (-0.280, 0.007)	NE (NE, NE)	
	T-DM1 (N=22)	3 (13.6)				0.0386	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
Within Normal Range	T-DXd (N=130)	81 (62.3)	1.46 (0.89, 2.40)	1.17 (0.95, 1.45)	0.092 (-0.027, 0.212)	0.88 (0.63, 1.21)	0.2931
	T-DM1 (N=130)	69 (53.1)				0.4234	
Mild Impairment	T-DXd (N=92)	57 (62.0)	1.98 (1.12, 3.50)	1.37 (1.05, 1.79)	0.168 (0.030, 0.305)	1.35 (0.92, 1.99)	
	T-DM1 (N=104)	47 (45.2)				0.1269	
Moderate Impairment	T-DXd (N=30)	19 (63.3)	1.20 (0.39, 3.70)	1.07 (0.69, 1.67)	0.042 (-0.226, 0.311)	0.97 (0.48, 1.97)	
	T-DM1 (N=22)	13 (59.1)				0.9300	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Within Normal Range	T-DXd (N=130)	17 (13.1)	6.37 (1.82, 22.30)	5.67 (1.70, 18.87)	0.108 (0.044, 0.171)	4.35 (1.26, 15.02)	0.5414
	T-DM1 (N=130)	3 (2.3)				0.0114	
Mild Impairment	T-DXd (N=92)	11 (12.0)	2.22 (0.79, 6.26)	2.07 (0.80, 5.38)	0.062 (-0.018, 0.142)	2.12 (0.78, 5.73)	
	T-DM1 (N=104)	6 (5.8)				0.1300	
Moderate Impairment	T-DXd (N=30)	1 (3.3)	NE (NE, NE)	NE (NE, NE)	0.033 (-0.031, 0.098)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.3918	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Pyrexia							
Within Normal Range	T-DXd (N=130)	17 (13.1)	0.74 (0.37, 1.47)	0.77 (0.43, 1.39)	-0.038 (-0.125, 0.048)	0.45 (0.23, 0.87)	0.1690
	T-DM1 (N=130)	22 (16.9)				0.0150	
Mild Impairment	T-DXd (N=92)	9 (9.8)	1.02 (0.40, 2.63)	1.02 (0.43, 2.39)	0.002 (-0.081, 0.085)	0.74 (0.30, 1.85)	
	T-DM1 (N=104)	10 (9.6)				0.5215	
Moderate Impairment	T-DXd (N=30)	1 (3.3)	0.09 (0.01, 0.83)	0.12 (0.02, 0.94)	-0.239 (-0.436, -0.043)	0.07 (0.01, 0.57)	
	T-DM1 (N=22)	6 (27.3)				0.0013	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	73 (56.2)	3.62 (2.14, 6.10)	2.15 (1.55, 2.98)	0.300 (0.186, 0.414)	2.26 (1.50, 3.40)	0.0976
	T-DM1 (N=130)	34 (26.2)				<.0001	
Mild Impairment	T-DXd (N=92)	54 (58.7)	3.20 (1.78, 5.75)	1.91 (1.36, 2.67)	0.279 (0.145, 0.413)	2.20 (1.42, 3.42)	
	T-DM1 (N=104)	32 (30.8)				0.0003	
Moderate Impairment	T-DXd (N=30)	10 (33.3)	0.87 (0.28, 2.77)	0.92 (0.43, 1.94)	-0.030 (-0.293, 0.232)	0.58 (0.21, 1.57)	
	T-DM1 (N=22)	8 (36.4)				0.2779	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Alopecia							
Within Normal Range	T-DXd (N=130)	51 (39.2)	20.34 (7.07, 58.45)	12.75 (4.75, 34.25)	0.362 (0.273, 0.451)	13.94 (5.03, 38.58)	0.9964
	T-DM1 (N=130)	4 (3.1)				<.0001	
Mild Impairment	T-DXd (N=92)	39 (42.4)	18.39 (6.24, 54.22)	11.02 (4.10, 29.66)	0.385 (0.278, 0.493)	13.28 (4.74, 37.17)	
	T-DM1 (N=104)	4 (3.8)				<.0001	
Moderate Impairment	T-DXd (N=30)	5 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (0.033, 0.300)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.0517	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	69 (53.1)	2.64 (1.59, 4.39)	1.77 (1.30, 2.41)	0.231 (0.114, 0.347)	1.82 (1.22, 2.70)	0.1150
	T-DM1 (N=130)	39 (30.0)				0.0029	
Mild Impairment	T-DXd (N=92)	38 (41.3)	1.91 (1.05, 3.48)	1.53 (1.03, 2.29)	0.144 (0.012, 0.276)	1.59 (0.98, 2.60)	
	T-DM1 (N=104)	28 (26.9)				0.0622	
Moderate Impairment	T-DXd (N=30)	13 (43.3)	0.76 (0.25, 2.31)	0.87 (0.48, 1.56)	-0.067 (-0.341, 0.207)	0.62 (0.28, 1.40)	
	T-DM1 (N=22)	11 (50.0)				0.2499	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Decreased appetite							
Within Normal Range	T-DXd (N=130)	45 (34.6)	2.60 (1.45, 4.66)	2.05 (1.31, 3.20)	0.177 (0.073, 0.281)	2.03 (1.22, 3.40)	0.1523
	T-DM1 (N=130)	22 (16.9)				0.0064	
Mild Impairment	T-DXd (N=92)	24 (26.1)	2.27 (1.09, 4.71)	1.94 (1.07, 3.52)	0.126 (0.015, 0.237)	1.93 (1.00, 3.74)	
	T-DM1 (N=104)	14 (13.5)				0.0473	
Moderate Impairment	T-DXd (N=30)	6 (20.0)	0.67 (0.18, 2.44)	0.73 (0.27, 1.97)	-0.073 (-0.308, 0.162)	0.53 (0.17, 1.67)	
	T-DM1 (N=22)	6 (27.3)				0.2741	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	58 (44.6)	1.06 (0.65, 1.74)	1.04 (0.79, 1.36)	0.015 (-0.105, 0.136)	0.65 (0.44, 0.95)	0.0490
	T-DM1 (N=130)	56 (43.1)				0.0243	
Mild Impairment	T-DXd (N=92)	42 (45.7)	1.59 (0.89, 2.82)	1.32 (0.93, 1.86)	0.110 (-0.026, 0.247)	1.21 (0.77, 1.88)	
	T-DM1 (N=104)	36 (34.6)				0.4073	
Moderate Impairment	T-DXd (N=30)	13 (43.3)	2.60 (0.76, 8.91)	1.91 (0.80, 4.56)	0.206 (-0.043, 0.455)	1.73 (0.62, 4.87)	
	T-DM1 (N=22)	5 (22.7)				0.2904	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
Within Normal Range	T-DXd (N=130)	63 (48.5)	1.97 (1.19, 3.26)	1.50 (1.11, 2.04)	0.162 (0.044, 0.279)	1.10 (0.74, 1.64)	0.9003
	T-DM1 (N=130)	42 (32.3)				0.6403	
Mild Impairment	T-DXd (N=92)	36 (39.1)	1.38 (0.77, 2.49)	1.23 (0.84, 1.80)	0.074 (-0.060, 0.208)	0.98 (0.61, 1.58)	
	T-DM1 (N=104)	33 (31.7)				0.9406	
Moderate Impairment	T-DXd (N=30)	11 (36.7)	1.24 (0.39, 3.98)	1.15 (0.53, 2.49)	0.048 (-0.212, 0.309)	0.91 (0.35, 2.37)	
	T-DM1 (N=22)	7 (31.8)				0.8515	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	55 (42.3)	1.84 (1.10, 3.09)	1.49 (1.06, 2.09)	0.138 (0.023, 0.253)	1.02 (0.67, 1.56)	0.0310
	T-DM1 (N=130)	37 (28.5)				0.9186	
Mild Impairment	T-DXd (N=92)	32 (34.8)	1.01 (0.56, 1.82)	1.00 (0.68, 1.48)	0.002 (-0.132, 0.135)	0.68 (0.42, 1.11)	
	T-DM1 (N=104)	36 (34.6)				0.1249	
Moderate Impairment	T-DXd (N=30)	20 (66.7)	9.00 (2.40, 33.79)	3.67 (1.46, 9.22)	0.485 (0.252, 0.718)	2.92 (1.00, 8.57)	
	T-DM1 (N=22)	4 (18.2)				0.0410	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Epistaxis							
Within Normal Range	T-DXd (N=130)	15 (11.5)	0.76 (0.37, 1.57)	0.79 (0.42, 1.49)	-0.031 (-0.113, 0.051)	0.47 (0.23, 0.94)	0.8057
	T-DM1 (N=130)	19 (14.6)				0.0284	
Mild Impairment	T-DXd (N=92)	10 (10.9)	0.55 (0.24, 1.24)	0.59 (0.29, 1.21)	-0.074 (-0.172, 0.024)	0.35 (0.16, 0.77)	
	T-DM1 (N=104)	19 (18.3)				0.0065	
Moderate Impairment	T-DXd (N=30)	4 (13.3)	0.97 (0.19, 4.87)	0.98 (0.24, 3.93)	-0.003 (-0.191, 0.185)	0.53 (0.11, 2.43)	
	T-DM1 (N=22)	3 (13.6)				0.4040	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	57 (43.8)	1.82 (1.09, 3.04)	1.46 (1.05, 2.03)	0.138 (0.022, 0.255)	1.05 (0.69, 1.59)	0.4233
	T-DM1 (N=130)	39 (30.0)				0.8211	
Mild Impairment	T-DXd (N=92)	36 (39.1)	1.83 (1.00, 3.36)	1.51 (1.00, 2.28)	0.132 (0.001, 0.262)	1.42 (0.86, 2.35)	
	T-DM1 (N=104)	27 (26.0)				0.1649	
Moderate Impairment	T-DXd (N=30)	8 (26.7)	0.78 (0.23, 2.61)	0.84 (0.36, 1.97)	-0.052 (-0.302, 0.199)	0.75 (0.27, 2.08)	
	T-DM1 (N=22)	7 (31.8)				0.5747	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
Within Normal Range	T-DXd (N=130)	48 (36.9)	3.04 (1.69, 5.47)	2.29 (1.46, 3.59)	0.208 (0.103, 0.312)	1.73 (1.03, 2.91)	0.8563
	T-DM1 (N=130)	21 (16.2)				0.0371	
Mild Impairment	T-DXd (N=92)	26 (28.3)	1.88 (0.95, 3.72)	1.63 (0.96, 2.78)	0.110 (-0.008, 0.227)	1.53 (0.84, 2.79)	
	T-DM1 (N=104)	18 (17.3)				0.1670	
Moderate Impairment	T-DXd (N=30)	7 (23.3)	1.93 (0.44, 8.49)	1.71 (0.50, 5.89)	0.097 (-0.112, 0.305)	1.71 (0.44, 6.64)	
	T-DM1 (N=22)	3 (13.6)				0.4328	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
Within Normal Range	T-DXd (N=130)	18 (13.8)	4.02 (1.44, 11.18)	3.60 (1.38, 9.41)	0.100 (0.032, 0.168)	2.09 (0.76, 5.72)	0.2081
	T-DM1 (N=130)	5 (3.8)				0.1437	
Mild Impairment	T-DXd (N=92)	18 (19.6)	25.05 (3.27, 191.83)	20.35 (2.77, 149.46)	0.186 (0.103, 0.269)	18.74 (2.50, 140.70)	
	T-DM1 (N=104)	1 (1.0)				<.0001	
Moderate Impairment	T-DXd (N=30)	4 (13.3)	3.23 (0.34, 31.12)	2.93 (0.35, 24.47)	0.088 (-0.062, 0.237)	2.45 (0.27, 22.16)	
	T-DM1 (N=22)	1 (4.5)				0.4086	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
Within Normal Range	T-DXd (N=130)	8 (6.2)	0.38 (0.16, 0.91)	0.42 (0.19, 0.93)	-0.085 (-0.158, -0.011)	0.28 (0.12, 0.65)	0.7401
	T-DM1 (N=130)	19 (14.6)				0.0018	
Mild Impairment	T-DXd (N=92)	4 (4.3)	0.55 (0.16, 1.87)	0.57 (0.18, 1.82)	-0.033 (-0.099, 0.033)	0.48 (0.14, 1.61)	
	T-DM1 (N=104)	8 (7.7)				0.2224	
Moderate Impairment	T-DXd (N=30)	1 (3.3)	0.22 (0.02, 2.26)	0.24 (0.03, 2.20)	-0.103 (-0.260, 0.054)	0.17 (0.02, 1.74)	
	T-DM1 (N=22)	3 (13.6)				0.0975	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	52 (40.0)	1.14 (0.69, 1.88)	1.08 (0.80, 1.47)	0.031 (-0.087, 0.149)	0.76 (0.51, 1.14)	0.8281
	T-DM1 (N=130)	48 (36.9)				0.1856	
Mild Impairment	T-DXd (N=92)	29 (31.5)	1.14 (0.62, 2.09)	1.09 (0.71, 1.67)	0.027 (-0.102, 0.156)	0.78 (0.47, 1.31)	
	T-DM1 (N=104)	30 (28.8)				0.3445	
Moderate Impairment	T-DXd (N=30)	9 (30.0)	1.14 (0.34, 3.87)	1.10 (0.46, 2.64)	0.027 (-0.221, 0.275)	1.02 (0.35, 2.92)	
	T-DM1 (N=22)	6 (27.3)				0.9744	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	20 (15.4)	2.77 (1.17, 6.55)	2.50 (1.14, 5.47)	0.092 (0.018, 0.167)	1.55 (0.66, 3.62)	0.6203
	T-DM1 (N=130)	8 (6.2)				0.3076	
Mild Impairment	T-DXd (N=92)	17 (18.5)	2.13 (0.92, 4.93)	1.92 (0.93, 3.98)	0.089 (-0.009, 0.186)	1.56 (0.71, 3.42)	
	T-DM1 (N=104)	10 (9.6)				0.2614	
Moderate Impairment	T-DXd (N=30)	7 (23.3)	6.39 (0.72, 56.38)	5.13 (0.68, 38.77)	0.188 (0.013, 0.362)	5.40 (0.66, 43.90)	
	T-DM1 (N=22)	1 (4.5)				0.0769	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	24 (18.5)	1.74 (0.86, 3.49)	1.60 (0.88, 2.91)	0.069 (-0.017, 0.156)	0.96 (0.49, 1.86)	0.8580
	T-DM1 (N=130)	15 (11.5)				0.9006	
Mild Impairment	T-DXd (N=92)	12 (13.0)	1.15 (0.49, 2.70)	1.13 (0.53, 2.39)	0.015 (-0.077, 0.107)	0.81 (0.36, 1.81)	
	T-DM1 (N=104)	12 (11.5)				0.5986	
Moderate Impairment	T-DXd (N=30)	4 (13.3)	0.97 (0.19, 4.87)	0.98 (0.24, 3.93)	-0.003 (-0.191, 0.185)	0.68 (0.15, 3.05)	
	T-DM1 (N=22)	3 (13.6)				0.6090	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	24 (18.5)	1.05 (0.56, 1.98)	1.04 (0.62, 1.75)	0.008 (-0.086, 0.101)	0.66 (0.37, 1.20)	0.9891
	T-DM1 (N=130)	23 (17.7)				0.1698	
Mild Impairment	T-DXd (N=92)	10 (10.9)	0.93 (0.38, 2.28)	0.94 (0.43, 2.08)	-0.007 (-0.095, 0.082)	0.67 (0.29, 1.57)	
	T-DM1 (N=104)	12 (11.5)				0.3552	
Moderate Impairment	T-DXd (N=30)	3 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.007, 0.207)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.2190	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Within Normal Range	T-DXd (N=130)	21 (16.2)	1.73 (0.83, 3.63)	1.62 (0.85, 3.09)	0.062 (-0.020, 0.143)	1.01 (0.49, 2.06)	0.6495
	T-DM1 (N=130)	13 (10.0)				0.9857	
Mild Impairment	T-DXd (N=92)	7 (7.6)	0.87 (0.31, 2.44)	0.88 (0.34, 2.27)	-0.010 (-0.087, 0.066)	0.59 (0.22, 1.60)	
	T-DM1 (N=104)	9 (8.7)				0.2942	
Moderate Impairment	T-DXd (N=30)	4 (13.3)	0.69 (0.15, 3.14)	0.73 (0.21, 2.62)	-0.048 (-0.250, 0.153)	0.59 (0.14, 2.45)	
	T-DM1 (N=22)	4 (18.2)				0.4610	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	10 (7.7)	0.75 (0.32, 1.78)	0.77 (0.35, 1.69)	-0.023 (-0.092, 0.046)	0.63 (0.27, 1.44)	0.8534
	T-DM1 (N=130)	13 (10.0)				0.2734	
Mild Impairment	T-DXd (N=92)	8 (8.7)	0.73 (0.28, 1.87)	0.75 (0.32, 1.76)	-0.028 (-0.113, 0.056)	0.62 (0.25, 1.53)	
	T-DM1 (N=104)	12 (11.5)				0.2985	
Moderate Impairment	T-DXd (N=30)	2 (6.7)	0.45 (0.07, 2.97)	0.49 (0.09, 2.68)	-0.070 (-0.239, 0.099)	0.28 (0.04, 1.76)	
	T-DM1 (N=22)	3 (13.6)				0.1505	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	192 (92.3)	8.19 (4.59, 14.61)	1.55 (1.38, 1.75)	0.329 (0.253, 0.404)	2.78 (2.21, 3.50)	0.4407
	T-DM1 (N=212)	126 (59.4)				<.0001	
Mild Impairment	T-DXd (N=49)	45 (91.8)	9.95 (3.10, 31.95)	1.73 (1.31, 2.28)	0.388 (0.228, 0.547)	3.31 (2.02, 5.43)	
	T-DM1 (N=49)	26 (53.1)				<.0001	
Nausea							
Within Normal Range	T-DXd (N=208)	160 (76.9)	7.71 (4.98, 11.92)	2.55 (2.05, 3.17)	0.467 (0.383, 0.552)	3.80 (2.84, 5.09)	0.8278
	T-DM1 (N=212)	64 (30.2)				<.0001	
Mild Impairment	T-DXd (N=49)	35 (71.4)	5.67 (2.38, 13.50)	2.33 (1.48, 3.69)	0.408 (0.227, 0.589)	3.29 (1.79, 6.05)	
	T-DM1 (N=49)	15 (30.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Within Normal Range	T-DXd (N=208)	103 (49.5)	9.42 (5.52, 16.08)	5.25 (3.38, 8.14)	0.401 (0.322, 0.479)	5.90 (3.65, 9.53)	0.4563
	T-DM1 (N=212)	20 (9.4)				<.0001	
Mild Impairment	T-DXd (N=49)	23 (46.9)	6.34 (2.28, 17.61)	3.83 (1.71, 8.59)	0.347 (0.180, 0.514)	4.10 (1.67, 10.10)	
	T-DM1 (N=49)	6 (12.2)				0.0009	
Constipation							
Within Normal Range	T-DXd (N=208)	77 (37.0)	2.38 (1.53, 3.69)	1.87 (1.35, 2.58)	0.172 (0.087, 0.257)	1.69 (1.16, 2.47)	0.2181
	T-DM1 (N=212)	42 (19.8)				0.0057	
Mild Impairment	T-DXd (N=49)	11 (22.4)	1.29 (0.48, 3.45)	1.22 (0.56, 2.68)	0.041 (-0.119, 0.200)	0.92 (0.38, 2.24)	
	T-DM1 (N=49)	9 (18.4)				0.8530	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Within Normal Range	T-DXd (N=208)	62 (29.8)	6.50 (3.45, 12.27)	4.86 (2.76, 8.57)	0.237 (0.167, 0.307)	4.93 (2.71, 8.98)	0.2490
	T-DM1 (N=212)	13 (6.1)				<.0001	
Mild Impairment	T-DXd (N=49)	13 (26.5)	3.18 (1.04, 9.75)	2.60 (1.00, 6.74)	0.163 (0.013, 0.313)	2.34 (0.83, 6.61)	
	T-DM1 (N=49)	5 (10.2)				0.1001	
Stomatitis							
Within Normal Range	T-DXd (N=208)	33 (15.9)	4.25 (1.98, 9.13)	3.74 (1.83, 7.62)	0.116 (0.060, 0.173)	3.06 (1.46, 6.43)	0.6199
	T-DM1 (N=212)	9 (4.2)				0.0019	
Mild Impairment	T-DXd (N=49)	7 (14.3)	8.00 (0.95, 67.70)	7.00 (0.89, 54.79)	0.122 (0.017, 0.228)	6.15 (0.75, 50.19)	
	T-DM1 (N=49)	1 (2.0)				0.0528	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Within Normal Range	T-DXd (N=208)	24 (11.5)	6.78 (2.31, 19.91)	6.12 (2.16, 17.32)	0.097 (0.049, 0.144)	4.81 (1.66, 13.92)	0.8118
	T-DM1 (N=212)	4 (1.9)				0.0014	
Mild Impairment	T-DXd (N=49)	5 (10.2)	5.45 (0.61, 48.53)	5.00 (0.61, 41.25)	0.082 (-0.012, 0.175)	3.92 (0.45, 34.11)	
	T-DM1 (N=49)	1 (2.0)				0.1818	
Investigations							
Any PT							
Within Normal Range	T-DXd (N=208)	122 (58.7)	0.67 (0.45, 1.00)	0.86 (0.75, 1.00)	-0.093 (-0.185, -0.001)	0.56 (0.44, 0.72)	0.2066
	T-DM1 (N=212)	144 (67.9)				<.0001	
Mild Impairment	T-DXd (N=49)	40 (81.6)	1.78 (0.69, 4.61)	1.14 (0.92, 1.43)	0.102 (-0.065, 0.269)	0.76 (0.47, 1.22)	
	T-DM1 (N=49)	35 (71.4)				0.3159	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
Within Normal Range	T-DXd (N=208)	62 (29.8)	3.49 (2.06, 5.90)	2.75 (1.77, 4.26)	0.190 (0.115, 0.265)	2.57 (1.59, 4.16)	0.3112
	T-DM1 (N=212)	23 (10.8)				<.0001	
Mild Impairment	T-DXd (N=49)	13 (26.5)	8.49 (1.80, 40.01)	6.50 (1.55, 27.30)	0.224 (0.089, 0.360)	6.02 (1.35, 26.85)	
	T-DM1 (N=49)	2 (4.1)				0.0076	
Aspartate aminotransferase increased							
Within Normal Range	T-DXd (N=208)	47 (22.6)	0.43 (0.28, 0.65)	0.56 (0.41, 0.75)	-0.180 (-0.267, -0.093)	0.39 (0.27, 0.55)	0.1165
	T-DM1 (N=212)	86 (40.6)				<.0001	
Mild Impairment	T-DXd (N=49)	19 (38.8)	1.00 (0.44, 2.25)	1.00 (0.61, 1.64)	0.000 (-0.193, 0.193)	0.67 (0.35, 1.29)	
	T-DM1 (N=49)	19 (38.8)				0.2467	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
Within Normal Range	T-DXd (N=208)	46 (22.1)	4.35 (2.27, 8.32)	3.61 (2.01, 6.47)	0.160 (0.095, 0.225)	3.11 (1.68, 5.78)	0.2931
	T-DM1 (N=212)	13 (6.1)				0.0001	
Mild Impairment	T-DXd (N=49)	12 (24.5)	15.57 (1.94, 125.18)	12.00 (1.62, 88.77)	0.224 (0.098, 0.351)	11.36 (1.47, 87.62)	
	T-DM1 (N=49)	1 (2.0)				0.0032	
Alanine aminotransferase increased							
Within Normal Range	T-DXd (N=208)	42 (20.2)	0.57 (0.37, 0.89)	0.66 (0.47, 0.92)	-0.105 (-0.187, -0.022)	0.51 (0.34, 0.75)	0.1988
	T-DM1 (N=212)	65 (30.7)				0.0006	
Mild Impairment	T-DXd (N=49)	14 (28.6)	1.23 (0.50, 3.03)	1.17 (0.60, 2.26)	0.041 (-0.134, 0.215)	0.94 (0.43, 2.04)	
	T-DM1 (N=49)	12 (24.5)				0.8908	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Within Normal Range	T-DXd (N=208)	38 (18.3)	0.28 (0.18, 0.43)	0.41 (0.29, 0.56)	-0.265 (-0.351, -0.180)	0.27 (0.18, 0.39)	0.0121
	T-DM1 (N=212)	95 (44.8)				<.0001	
Mild Impairment	T-DXd (N=49)	16 (32.7)	0.91 (0.39, 2.11)	0.94 (0.54, 1.64)	-0.020 (-0.207, 0.167)	0.66 (0.33, 1.32)	
	T-DM1 (N=49)	17 (34.7)				0.2392	
Weight decreased							
Within Normal Range	T-DXd (N=208)	31 (14.9)	2.48 (1.28, 4.81)	2.26 (1.24, 4.12)	0.083 (0.024, 0.142)	1.74 (0.92, 3.28)	0.2821
	T-DM1 (N=212)	14 (6.6)				0.0842	
Mild Impairment	T-DXd (N=49)	12 (24.5)	7.62 (1.61, 36.19)	6.00 (1.42, 25.42)	0.204 (0.072, 0.337)	4.58 (1.02, 20.64)	
	T-DM1 (N=49)	2 (4.1)				0.0300	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
Within Normal Range	T-DXd (N=208)	7 (3.4)	0.29 (0.12, 0.68)	0.31 (0.14, 0.71)	-0.075 (-0.123, -0.026)	0.23 (0.10, 0.55)	0.1550
	T-DM1 (N=212)	23 (10.8)				0.0003	
Mild Impairment	T-DXd (N=49)	10 (20.4)	0.79 (0.31, 2.05)	0.83 (0.40, 1.75)	-0.041 (-0.206, 0.124)	0.56 (0.24, 1.33)	
	T-DM1 (N=49)	12 (24.5)				0.1894	
General disorders and administration site conditions							
Any PT							
Within Normal Range	T-DXd (N=208)	133 (63.9)	1.77 (1.20, 2.62)	1.28 (1.08, 1.51)	0.139 (0.046, 0.233)	1.15 (0.89, 1.49)	0.0640
	T-DM1 (N=212)	106 (50.0)				0.2764	
Mild Impairment	T-DXd (N=49)	26 (53.1)	0.92 (0.42, 2.04)	0.96 (0.67, 1.39)	-0.020 (-0.218, 0.177)	0.60 (0.34, 1.05)	
	T-DM1 (N=49)	27 (55.1)				0.0700	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Within Normal Range	T-DXd (N=208)	24 (11.5)	2.94 (1.33, 6.49)	2.72 (1.29, 5.71)	0.073 (0.022, 0.124)	2.42 (1.12, 5.23)	0.6032
	T-DM1 (N=212)	9 (4.2)				0.0207	
Mild Impairment	T-DXd (N=49)	5 (10.2)	5.45 (0.61, 48.53)	5.00 (0.61, 41.25)	0.082 (-0.012, 0.175)	4.42 (0.51, 37.98)	
	T-DM1 (N=49)	1 (2.0)				0.1395	
Pyrexia							
Within Normal Range	T-DXd (N=208)	19 (9.1)	0.66 (0.36, 1.22)	0.69 (0.40, 1.20)	-0.041 (-0.101, 0.019)	0.45 (0.25, 0.81)	0.8497
	T-DM1 (N=212)	28 (13.2)				0.0064	
Mild Impairment	T-DXd (N=49)	8 (16.3)	0.67 (0.25, 1.85)	0.73 (0.32, 1.65)	-0.061 (-0.217, 0.095)	0.42 (0.16, 1.07)	
	T-DM1 (N=49)	11 (22.4)				0.0634	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	109 (52.4)	2.66 (1.78, 3.98)	1.79 (1.40, 2.29)	0.232 (0.140, 0.323)	1.86 (1.36, 2.54)	0.4481
	T-DM1 (N=212)	62 (29.2)				<.0001	
Mild Impairment	T-DXd (N=49)	30 (61.2)	4.37 (1.86, 10.29)	2.31 (1.38, 3.87)	0.347 (0.163, 0.531)	2.40 (1.25, 4.61)	
	T-DM1 (N=49)	13 (26.5)				0.0067	
Alopecia							
Within Normal Range	T-DXd (N=208)	75 (36.1)	14.38 (6.72, 30.77)	9.56 (4.73, 19.31)	0.323 (0.253, 0.393)	10.71 (5.16, 22.22)	0.9846
	T-DM1 (N=212)	8 (3.8)				<.0001	
Mild Impairment	T-DXd (N=49)	20 (40.8)	NE (NE, NE)	NE (NE, NE)	0.408 (0.271, 0.546)	NE (NE, NE)	
	T-DM1 (N=49)	0				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	99 (47.6)	2.35 (1.57, 3.53)	1.71 (1.32, 2.22)	0.198 (0.107, 0.288)	1.79 (1.29, 2.47)	0.0901
	T-DM1 (N=212)	59 (27.8)				0.0004	
Mild Impairment	T-DXd (N=49)	23 (46.9)	1.18 (0.53, 2.62)	1.10 (0.71, 1.70)	0.041 (-0.156, 0.238)	0.87 (0.48, 1.60)	
	T-DM1 (N=49)	21 (42.9)				0.6578	
Decreased appetite							
Within Normal Range	T-DXd (N=208)	63 (30.3)	2.36 (1.47, 3.79)	1.95 (1.34, 2.83)	0.147 (0.068, 0.226)	2.00 (1.31, 3.05)	0.1088
	T-DM1 (N=212)	33 (15.6)				0.0011	
Mild Impairment	T-DXd (N=49)	12 (24.5)	1.12 (0.44, 2.85)	1.09 (0.53, 2.23)	0.020 (-0.147, 0.188)	0.75 (0.33, 1.74)	
	T-DM1 (N=49)	11 (22.4)				0.5025	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	97 (46.6)	1.50 (1.02, 2.22)	1.27 (1.01, 1.59)	0.098 (0.005, 0.192)	1.02 (0.76, 1.38)	0.1344
	T-DM1 (N=212)	78 (36.8)				0.8914	
Mild Impairment	T-DXd (N=49)	19 (38.8)	0.92 (0.41, 2.06)	0.95 (0.58, 1.55)	-0.020 (-0.214, 0.173)	0.61 (0.32, 1.16)	
	T-DM1 (N=49)	20 (40.8)				0.1321	
Infections and infestations							
Any PT							
Within Normal Range	T-DXd (N=208)	89 (42.8)	1.58 (1.06, 2.36)	1.33 (1.04, 1.71)	0.107 (0.015, 0.199)	1.03 (0.75, 1.42)	0.7982
	T-DM1 (N=212)	68 (32.1)				0.8586	
Mild Impairment	T-DXd (N=49)	23 (46.9)	1.67 (0.74, 3.75)	1.35 (0.83, 2.20)	0.122 (-0.071, 0.316)	0.95 (0.50, 1.80)	
	T-DM1 (N=49)	17 (34.7)				0.8734	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	85 (40.9)	1.56 (1.05, 2.34)	1.33 (1.03, 1.73)	0.102 (0.011, 0.193)	0.95 (0.68, 1.31)	0.9476
	T-DM1 (N=212)	65 (30.7)				0.7431	
Mild Impairment	T-DXd (N=49)	22 (44.9)	2.04 (0.88, 4.71)	1.57 (0.92, 2.70)	0.163 (-0.025, 0.351)	0.90 (0.45, 1.78)	
	T-DM1 (N=49)	14 (28.6)				0.7625	
Epistaxis							
Within Normal Range	T-DXd (N=208)	24 (11.5)	0.68 (0.39, 1.20)	0.72 (0.44, 1.17)	-0.045 (-0.111, 0.021)	0.42 (0.24, 0.72)	0.7061
	T-DM1 (N=212)	34 (16.0)				0.0012	
Mild Impairment	T-DXd (N=49)	5 (10.2)	0.58 (0.18, 1.93)	0.63 (0.22, 1.78)	-0.061 (-0.195, 0.073)	0.33 (0.10, 1.02)	
	T-DM1 (N=49)	8 (16.3)				0.0442	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	81 (38.9)	1.73 (1.15, 2.62)	1.45 (1.09, 1.92)	0.121 (0.031, 0.210)	1.21 (0.86, 1.70)	0.5969
	T-DM1 (N=212)	57 (26.9)				0.2666	
Mild Impairment	T-DXd (N=49)	22 (44.9)	1.40 (0.62, 3.15)	1.22 (0.76, 1.98)	0.082 (-0.112, 0.276)	1.01 (0.54, 1.89)	
	T-DM1 (N=49)	18 (36.7)				0.9888	
Anaemia							
Within Normal Range	T-DXd (N=208)	62 (29.8)	2.39 (1.48, 3.86)	1.97 (1.35, 2.89)	0.147 (0.068, 0.226)	1.72 (1.12, 2.65)	0.6650
	T-DM1 (N=212)	32 (15.1)				0.0121	
Mild Impairment	T-DXd (N=49)	21 (42.9)	2.31 (0.98, 5.48)	1.75 (0.97, 3.15)	0.184 (0.000, 0.367)	1.36 (0.66, 2.79)	
	T-DM1 (N=49)	12 (24.5)				0.3989	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
Within Normal Range	T-DXd (N=208)	33 (15.9)	7.81 (2.98, 20.43)	6.73 (2.68, 16.90)	0.135 (0.081, 0.189)	5.06 (1.96, 13.02)	0.5226
	T-DM1 (N=212)	5 (2.4)				0.0002	
Mild Impairment	T-DXd (N=49)	8 (16.3)	4.59 (0.92, 22.83)	4.00 (0.89, 17.89)	0.122 (0.005, 0.240)	3.31 (0.70, 15.75)	
	T-DM1 (N=49)	2 (4.1)				0.1115	
Thrombocytopenia							
Within Normal Range	T-DXd (N=208)	8 (3.8)	0.31 (0.14, 0.71)	0.34 (0.16, 0.74)	-0.075 (-0.125, -0.025)	0.25 (0.11, 0.56)	0.3246
	T-DM1 (N=212)	24 (11.3)				0.0003	
Mild Impairment	T-DXd (N=49)	5 (10.2)	0.68 (0.20, 2.32)	0.71 (0.24, 2.10)	-0.041 (-0.170, 0.089)	0.51 (0.16, 1.65)	
	T-DM1 (N=49)	7 (14.3)				0.2459	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	78 (37.5)	1.30 (0.87, 1.94)	1.19 (0.91, 1.55)	0.059 (-0.032, 0.150)	0.88 (0.63, 1.23)	0.0731
	T-DM1 (N=212)	67 (31.6)				0.4565	
Mild Impairment	T-DXd (N=49)	16 (32.7)	0.70 (0.31, 1.60)	0.80 (0.47, 1.35)	-0.082 (-0.272, 0.109)	0.56 (0.29, 1.11)	
	T-DM1 (N=49)	20 (40.8)				0.0934	
Vascular disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	39 (18.8)	3.03 (1.61, 5.69)	2.65 (1.51, 4.66)	0.117 (0.053, 0.180)	1.99 (1.09, 3.63)	0.1068
	T-DM1 (N=212)	15 (7.1)				0.0227	
Mild Impairment	T-DXd (N=49)	6 (12.2)	1.00 (0.30, 3.35)	1.00 (0.35, 2.89)	0.000 (-0.130, 0.130)	0.86 (0.27, 2.70)	
	T-DM1 (N=49)	6 (12.2)				0.7949	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	35 (16.8)	1.45 (0.84, 2.50)	1.37 (0.86, 2.20)	0.046 (-0.022, 0.113)	0.92 (0.55, 1.55)	0.9652
	T-DM1 (N=212)	26 (12.3)				0.7562	
Mild Impairment	T-DXd (N=49)	6 (12.2)	1.57 (0.41, 5.95)	1.50 (0.45, 4.99)	0.041 (-0.079, 0.160)	0.91 (0.25, 3.24)	
	T-DM1 (N=49)	4 (8.2)				0.8798	
Psychiatric disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	34 (16.3)	1.23 (0.72, 2.11)	1.19 (0.76, 1.89)	0.027 (-0.042, 0.095)	0.87 (0.53, 1.44)	0.4572
	T-DM1 (N=212)	29 (13.7)				0.5879	
Mild Impairment	T-DXd (N=49)	5 (10.2)	0.81 (0.23, 2.87)	0.83 (0.27, 2.55)	-0.020 (-0.145, 0.105)	0.51 (0.15, 1.69)	
	T-DM1 (N=49)	6 (12.2)				0.2632	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Within Normal Range	T-DXd (N=208)	28 (13.5)	1.28 (0.71, 2.30)	1.24 (0.74, 2.08)	0.026 (-0.036, 0.089)	0.81 (0.46, 1.42)	0.6229
	T-DM1 (N=212)	23 (10.8)				0.4666	
Mild Impairment	T-DXd (N=49)	4 (8.2)	1.00 (0.24, 4.25)	1.00 (0.26, 3.77)	0.000 (-0.108, 0.108)	0.66 (0.16, 2.73)	
	T-DM1 (N=49)	4 (8.2)				0.5713	
Hepatobiliary disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	13 (6.3)	0.68 (0.33, 1.41)	0.70 (0.35, 1.38)	-0.027 (-0.078, 0.023)	0.54 (0.26, 1.10)	0.8094
	T-DM1 (N=212)	19 (9.0)				0.0856	
Mild Impairment	T-DXd (N=49)	7 (14.3)	0.65 (0.23, 1.88)	0.70 (0.29, 1.69)	-0.061 (-0.211, 0.088)	0.44 (0.16, 1.18)	
	T-DM1 (N=49)	10 (20.4)				0.0990	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Yes	T-DXd (N=192)	176 (91.7)	7.63 (4.24, 13.75)	1.55 (1.37, 1.76)	0.326 (0.246, 0.407)	2.68 (2.10, 3.41)	0.3725
	T-DM1 (N=188)	111 (59.0)				<.0001	
No	T-DXd (N=65)	61 (93.8)	11.90 (3.91, 36.20)	1.67 (1.35, 2.07)	0.377 (0.249, 0.505)	3.42 (2.28, 5.14)	
	T-DM1 (N=73)	41 (56.2)				<.0001	
Nausea							
Yes	T-DXd (N=192)	144 (75.0)	7.44 (4.73, 11.73)	2.61 (2.05, 3.32)	0.463 (0.374, 0.552)	3.75 (2.74, 5.14)	0.9824
	T-DM1 (N=188)	54 (28.7)				<.0001	
No	T-DXd (N=65)	51 (78.5)	6.99 (3.26, 15.01)	2.29 (1.63, 3.23)	0.442 (0.294, 0.590)	3.81 (2.35, 6.18)	
	T-DM1 (N=73)	25 (34.2)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Yes	T-DXd (N=192)	100 (52.1)	9.67 (5.57, 16.80)	5.15 (3.29, 8.06)	0.420 (0.337, 0.503)	5.96 (3.65, 9.75)	0.5140
	T-DM1 (N=188)	19 (10.1)				<.0001	
No	T-DXd (N=65)	26 (40.0)	6.29 (2.50, 15.83)	4.17 (1.94, 8.96)	0.304 (0.167, 0.441)	4.15 (1.80, 9.58)	
	T-DM1 (N=73)	7 (9.6)				0.0003	
Constipation							
Yes	T-DXd (N=192)	68 (35.4)	2.78 (1.71, 4.51)	2.15 (1.48, 3.12)	0.189 (0.103, 0.275)	1.92 (1.25, 2.94)	0.0649
	T-DM1 (N=188)	31 (16.5)				0.0024	
No	T-DXd (N=65)	20 (30.8)	1.18 (0.56, 2.46)	1.12 (0.67, 1.89)	0.034 (-0.118, 0.186)	0.94 (0.50, 1.75)	
	T-DM1 (N=73)	20 (27.4)				0.8366	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Yes	T-DXd (N=192)	52 (27.1)	5.98 (3.01, 11.88)	4.63 (2.49, 8.59)	0.212 (0.141, 0.284)	4.46 (2.32, 8.56)	0.8620
	T-DM1 (N=188)	11 (5.9)				<.0001	
No	T-DXd (N=65)	23 (35.4)	5.16 (2.04, 13.09)	3.69 (1.70, 8.03)	0.258 (0.124, 0.392)	4.08 (1.75, 9.53)	
	T-DM1 (N=73)	7 (9.6)				0.0004	
Stomatitis							
Yes	T-DXd (N=192)	26 (13.5)	3.11 (1.42, 6.84)	2.83 (1.36, 5.87)	0.088 (0.030, 0.145)	2.31 (1.08, 4.96)	0.1056
	T-DM1 (N=188)	9 (4.8)				0.0270	
No	T-DXd (N=65)	14 (21.5)	19.76 (2.52, 155.11)	15.72 (2.13, 116.30)	0.202 (0.098, 0.305)	13.52 (1.77, 103.06)	
	T-DM1 (N=73)	1 (1.4)				0.0011	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Yes	T-DXd (N=192)	22 (11.5)	5.95 (2.01, 17.63)	5.39 (1.89, 15.33)	0.093 (0.044, 0.143)	4.03 (1.38, 11.79)	0.7285
	T-DM1 (N=188)	4 (2.1)				0.0060	
No	T-DXd (N=65)	7 (10.8)	8.69 (1.04, 72.64)	7.86 (0.99, 62.21)	0.094 (0.014, 0.174)	5.78 (0.71, 47.34)	
	T-DM1 (N=73)	1 (1.4)				0.0650	
Investigations							
Any PT							
Yes	T-DXd (N=192)	128 (66.7)	0.91 (0.60, 1.41)	0.97 (0.85, 1.12)	-0.020 (-0.114, 0.075)	0.68 (0.53, 0.87)	0.0876
	T-DM1 (N=188)	129 (68.6)				0.0064	
No	T-DXd (N=65)	34 (52.3)	0.50 (0.25, 1.01)	0.76 (0.58, 1.01)	-0.162 (-0.323, 0.000)	0.44 (0.28, 0.69)	
	T-DM1 (N=73)	50 (68.5)				0.0004	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
Yes	T-DXd (N=192)	59 (30.7)	4.77 (2.62, 8.66)	3.61 (2.16, 6.04)	0.222 (0.146, 0.299)	3.39 (1.95, 5.90)	0.2225
	T-DM1 (N=188)	16 (8.5)				<.0001	
No	T-DXd (N=65)	16 (24.6)	2.32 (0.95, 5.70)	2.00 (0.95, 4.21)	0.123 (-0.006, 0.252)	1.78 (0.78, 4.03)	
	T-DM1 (N=73)	9 (12.3)				0.1628	
Aspartate aminotransferase increased							
Yes	T-DXd (N=192)	53 (27.6)	0.56 (0.37, 0.86)	0.68 (0.51, 0.91)	-0.128 (-0.223, -0.034)	0.46 (0.32, 0.65)	0.4463
	T-DM1 (N=188)	76 (40.4)				<.0001	
No	T-DXd (N=65)	13 (20.0)	0.38 (0.18, 0.82)	0.50 (0.29, 0.88)	-0.197 (-0.346, -0.049)	0.38 (0.19, 0.73)	
	T-DM1 (N=73)	29 (39.7)				0.0028	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
Yes	T-DXd (N=192)	48 (25.0)	5.93 (2.90, 12.14)	4.70 (2.45, 9.01)	0.197 (0.128, 0.266)	4.12 (2.08, 8.17)	0.4353
	T-DM1 (N=188)	10 (5.3)				<.0001	
No	T-DXd (N=65)	10 (15.4)	3.14 (0.93, 10.54)	2.81 (0.93, 8.52)	0.099 (-0.003, 0.201)	2.35 (0.73, 7.54)	
	T-DM1 (N=73)	4 (5.5)				0.1380	
Alanine aminotransferase increased							
Yes	T-DXd (N=192)	43 (22.4)	0.68 (0.43, 1.08)	0.75 (0.53, 1.06)	-0.074 (-0.162, 0.014)	0.57 (0.38, 0.85)	0.8527
	T-DM1 (N=188)	56 (29.8)				0.0060	
No	T-DXd (N=65)	13 (20.0)	0.62 (0.28, 1.37)	0.70 (0.38, 1.27)	-0.088 (-0.230, 0.055)	0.56 (0.28, 1.13)	
	T-DM1 (N=73)	21 (28.8)				0.1011	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Yes	T-DXd (N=192)	42 (21.9)	0.36 (0.23, 0.57)	0.50 (0.37, 0.69)	-0.217 (-0.309, -0.126)	0.33 (0.23, 0.49)	0.5804
	T-DM1 (N=188)	82 (43.6)				<.0001	
No	T-DXd (N=65)	12 (18.5)	0.32 (0.15, 0.71)	0.45 (0.25, 0.80)	-0.226 (-0.373, -0.079)	0.30 (0.15, 0.60)	
	T-DM1 (N=73)	30 (41.1)				0.0004	
Weight decreased							
Yes	T-DXd (N=192)	36 (18.8)	4.59 (2.14, 9.83)	3.92 (1.94, 7.90)	0.140 (0.077, 0.203)	3.17 (1.52, 6.59)	0.0457
	T-DM1 (N=188)	9 (4.8)				0.0012	
No	T-DXd (N=65)	7 (10.8)	1.14 (0.38, 3.44)	1.12 (0.42, 3.03)	0.012 (-0.089, 0.113)	0.73 (0.25, 2.11)	
	T-DM1 (N=73)	7 (9.6)				0.5619	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
Yes	T-DXd (N=192)	16 (8.3)	0.62 (0.32, 1.21)	0.65 (0.36, 1.19)	-0.044 (-0.106, 0.017)	0.49 (0.26, 0.93)	0.0859
	T-DM1 (N=188)	24 (12.8)				0.0262	
No	T-DXd (N=65)	1 (1.5)	0.09 (0.01, 0.70)	0.10 (0.01, 0.77)	-0.135 (-0.223, -0.048)	0.08 (0.01, 0.65)	
	T-DM1 (N=73)	11 (15.1)				0.0026	
General disorders and administration site conditions							
Any PT							
Yes	T-DXd (N=192)	114 (59.4)	1.56 (1.04, 2.34)	1.23 (1.02, 1.48)	0.110 (0.010, 0.209)	1.01 (0.76, 1.33)	0.5785
	T-DM1 (N=188)	91 (48.4)				0.9602	
No	T-DXd (N=65)	45 (69.2)	1.66 (0.82, 3.35)	1.20 (0.93, 1.55)	0.117 (-0.043, 0.276)	1.15 (0.75, 1.75)	
	T-DM1 (N=73)	42 (57.5)				0.5283	

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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Yes	T-DXd (N=192)	21 (10.9)	3.18 (1.32, 7.66)	2.94 (1.28, 6.75)	0.072 (0.020, 0.124)	2.73 (1.16, 6.45)	0.9913
	T-DM1 (N=188)	7 (3.7)				0.0169	
No	T-DXd (N=65)	8 (12.3)	3.27 (0.83, 12.91)	2.99 (0.83, 10.82)	0.082 (-0.010, 0.174)	2.45 (0.64, 9.34)	
	T-DM1 (N=73)	3 (4.1)				0.1758	
Pyrexia							
Yes	T-DXd (N=192)	23 (12.0)	0.93 (0.50, 1.71)	0.94 (0.55, 1.60)	-0.008 (-0.074, 0.058)	0.60 (0.33, 1.08)	0.1026
	T-DM1 (N=188)	24 (12.8)				0.0886	
No	T-DXd (N=65)	4 (6.2)	0.25 (0.08, 0.81)	0.30 (0.10, 0.86)	-0.144 (-0.254, -0.034)	0.19 (0.06, 0.59)	
	T-DM1 (N=73)	15 (20.5)				0.0014	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Yes	T-DXd (N=192)	108 (56.3)	3.55 (2.31, 5.46)	2.12 (1.62, 2.77)	0.297 (0.202, 0.391)	2.32 (1.66, 3.25)	0.0502
	T-DM1 (N=188)	50 (26.6)				<.0001	
No	T-DXd (N=65)	31 (47.7)	1.75 (0.88, 3.48)	1.39 (0.93, 2.09)	0.134 (-0.029, 0.298)	1.24 (0.73, 2.11)	
	T-DM1 (N=73)	25 (34.2)				0.4169	
Alopecia							
Yes	T-DXd (N=192)	76 (39.6)	19.87 (8.38, 47.11)	12.40 (5.54, 27.78)	0.364 (0.290, 0.438)	14.26 (6.21, 32.75)	0.7603
	T-DM1 (N=188)	6 (3.2)				<.0001	
No	T-DXd (N=65)	19 (29.2)	14.66 (3.26, 65.89)	10.67 (2.58, 44.06)	0.265 (0.148, 0.382)	10.87 (2.53, 46.70)	
	T-DM1 (N=73)	2 (2.7)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Yes	T-DXd (N=192)	92 (47.9)	1.92 (1.26, 2.90)	1.48 (1.15, 1.90)	0.155 (0.057, 0.252)	1.48 (1.07, 2.05)	0.5565
	T-DM1 (N=188)	61 (32.4)				0.0187	
No	T-DXd (N=65)	30 (46.2)	2.44 (1.19, 4.98)	1.77 (1.11, 2.83)	0.201 (0.044, 0.359)	1.80 (1.01, 3.22)	
	T-DM1 (N=73)	19 (26.0)				0.0429	
Decreased appetite							
Yes	T-DXd (N=192)	57 (29.7)	2.14 (1.30, 3.51)	1.80 (1.22, 2.65)	0.132 (0.048, 0.216)	1.77 (1.14, 2.75)	0.7017
	T-DM1 (N=188)	31 (16.5)				0.0108	
No	T-DXd (N=65)	18 (27.7)	1.77 (0.79, 3.97)	1.56 (0.83, 2.92)	0.099 (-0.041, 0.239)	1.46 (0.71, 3.01)	
	T-DM1 (N=73)	13 (17.8)				0.2970	

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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
Yes	T-DXd (N=192)	86 (44.8)	1.31 (0.87, 1.97)	1.17 (0.92, 1.49)	0.065 (-0.034, 0.164)	0.88 (0.64, 1.20)	0.5114
	T-DM1 (N=188)	72 (38.3)				0.4199	
No	T-DXd (N=65)	30 (46.2)	1.55 (0.78, 3.07)	1.30 (0.86, 1.94)	0.105 (-0.058, 0.269)	1.09 (0.64, 1.85)	
	T-DM1 (N=73)	26 (35.6)				0.7473	
Infections and infestations							
Any PT							
Yes	T-DXd (N=192)	87 (45.3)	2.00 (1.31, 3.06)	1.55 (1.18, 2.03)	0.161 (0.065, 0.256)	1.20 (0.86, 1.69)	0.0733
	T-DM1 (N=188)	55 (29.3)				0.2873	
No	T-DXd (N=65)	25 (38.5)	0.90 (0.45, 1.77)	0.94 (0.62, 1.41)	-0.026 (-0.190, 0.137)	0.65 (0.38, 1.11)	
	T-DM1 (N=73)	30 (41.1)				0.1127	

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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Yes	T-DXd (N=192)	85 (44.3)	2.02 (1.32, 3.10)	1.57 (1.19, 2.07)	0.161 (0.066, 0.256)	1.12 (0.79, 1.58)	0.0901
	T-DM1 (N=188)	53 (28.2)				0.5329	
No	T-DXd (N=65)	22 (33.8)	0.92 (0.46, 1.87)	0.95 (0.60, 1.50)	-0.018 (-0.177, 0.141)	0.62 (0.35, 1.11)	
	T-DM1 (N=73)	26 (35.6)				0.1036	
Epistaxis							
Yes	T-DXd (N=192)	22 (11.5)	0.77 (0.42, 1.41)	0.80 (0.47, 1.35)	-0.029 (-0.096, 0.038)	0.51 (0.29, 0.90)	0.3968
	T-DM1 (N=188)	27 (14.4)				0.0189	
No	T-DXd (N=65)	7 (10.8)	0.47 (0.18, 1.23)	0.52 (0.23, 1.21)	-0.098 (-0.217, 0.022)	0.26 (0.10, 0.66)	
	T-DM1 (N=73)	15 (20.5)				0.0023	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Yes	T-DXd (N=192)	79 (41.1)	1.93 (1.25, 2.97)	1.55 (1.16, 2.07)	0.146 (0.052, 0.239)	1.29 (0.90, 1.84)	0.2528
	T-DM1 (N=188)	50 (26.6)				0.1568	
No	T-DXd (N=65)	24 (36.9)	1.12 (0.56, 2.26)	1.08 (0.69, 1.69)	0.027 (-0.133, 0.187)	0.90 (0.51, 1.58)	
	T-DM1 (N=73)	25 (34.2)				0.7074	
Anaemia							
Yes	T-DXd (N=192)	64 (33.3)	2.74 (1.67, 4.50)	2.16 (1.46, 3.19)	0.179 (0.095, 0.263)	1.88 (1.21, 2.92)	0.2803
	T-DM1 (N=188)	29 (15.4)				0.0045	
No	T-DXd (N=65)	19 (29.2)	1.60 (0.73, 3.48)	1.42 (0.79, 2.56)	0.087 (-0.057, 0.231)	1.15 (0.58, 2.28)	
	T-DM1 (N=73)	15 (20.5)				0.6811	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
Yes	T-DXd (N=192)	29 (15.1)	6.51 (2.46, 17.22)	5.68 (2.25, 14.36)	0.124 (0.069, 0.180)	4.28 (1.65, 11.12)	0.8009
	T-DM1 (N=188)	5 (2.7)				0.0012	
No	T-DXd (N=65)	12 (18.5)	8.04 (1.73, 37.44)	6.74 (1.57, 28.99)	0.157 (0.056, 0.259)	5.50 (1.22, 24.67)	
	T-DM1 (N=73)	2 (2.7)				0.0126	
Thrombocytopenia							
Yes	T-DXd (N=192)	9 (4.7)	0.37 (0.17, 0.83)	0.40 (0.19, 0.85)	-0.070 (-0.125, -0.015)	0.28 (0.13, 0.62)	0.7119
	T-DM1 (N=188)	22 (11.7)				0.0009	
No	T-DXd (N=65)	4 (6.2)	0.47 (0.14, 1.59)	0.50 (0.16, 1.54)	-0.062 (-0.157, 0.034)	0.40 (0.12, 1.30)	
	T-DM1 (N=73)	9 (12.3)				0.1139	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
Yes	T-DXd (N=192)	73 (38.0)	1.28 (0.84, 1.95)	1.17 (0.89, 1.54)	0.056 (-0.040, 0.152)	0.85 (0.60, 1.21)	0.4001
	T-DM1 (N=188)	61 (32.4)				0.3747	
No	T-DXd (N=65)	21 (32.3)	0.86 (0.43, 1.75)	0.91 (0.57, 1.45)	-0.033 (-0.191, 0.125)	0.64 (0.36, 1.15)	
	T-DM1 (N=73)	26 (35.6)				0.1317	
Vascular disorders							
Any PT							
Yes	T-DXd (N=192)	30 (15.6)	2.72 (1.35, 5.48)	2.45 (1.29, 4.64)	0.092 (0.030, 0.155)	1.91 (0.97, 3.77)	0.6888
	T-DM1 (N=188)	12 (6.4)				0.0573	
No	T-DXd (N=65)	15 (23.1)	2.13 (0.86, 5.28)	1.87 (0.88, 3.99)	0.107 (-0.020, 0.235)	1.41 (0.61, 3.25)	
	T-DM1 (N=73)	9 (12.3)				0.4180	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
Yes	T-DXd (N=192)	31 (16.1)	1.38 (0.77, 2.47)	1.32 (0.80, 2.18)	0.039 (-0.031, 0.109)	0.91 (0.52, 1.57)	0.6792
	T-DM1 (N=188)	23 (12.2)				0.7279	
No	T-DXd (N=65)	10 (15.4)	1.71 (0.61, 4.80)	1.60 (0.65, 3.97)	0.058 (-0.053, 0.169)	0.97 (0.36, 2.59)	
	T-DM1 (N=73)	7 (9.6)				0.9556	
Psychiatric disorders							
Any PT							
Yes	T-DXd (N=192)	28 (14.6)	1.22 (0.68, 2.21)	1.19 (0.71, 1.99)	0.023 (-0.045, 0.092)	0.85 (0.49, 1.49)	0.7643
	T-DM1 (N=188)	23 (12.2)				0.5767	
No	T-DXd (N=65)	11 (16.9)	1.04 (0.42, 2.54)	1.03 (0.49, 2.17)	0.005 (-0.120, 0.129)	0.70 (0.30, 1.60)	
	T-DM1 (N=73)	12 (16.4)				0.3939	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Yes	T-DXd (N=192)	21 (10.9)	1.09 (0.57, 2.10)	1.08 (0.60, 1.95)	0.008 (-0.053, 0.070)	0.68 (0.36, 1.28)	0.4590
	T-DM1 (N=188)	19 (10.1)				0.2314	
No	T-DXd (N=65)	11 (16.9)	1.66 (0.62, 4.41)	1.54 (0.66, 3.60)	0.060 (-0.056, 0.176)	1.05 (0.41, 2.67)	
	T-DM1 (N=73)	8 (11.0)				0.9211	
Hepatobiliary disorders							
Any PT							
Yes	T-DXd (N=192)	17 (8.9)	0.77 (0.39, 1.52)	0.79 (0.43, 1.45)	-0.023 (-0.084, 0.037)	0.61 (0.32, 1.16)	0.3593
	T-DM1 (N=188)	21 (11.2)				0.1335	
No	T-DXd (N=65)	3 (4.6)	0.39 (0.10, 1.55)	0.42 (0.12, 1.52)	-0.063 (-0.151, 0.025)	0.30 (0.08, 1.15)	
	T-DM1 (N=73)	8 (11.0)				0.0642	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Yes	T-DXd (N=41)	38 (92.7)	9.79 (2.58, 37.19)	1.64 (1.23, 2.19)	0.363 (0.188, 0.538)	2.81 (1.65, 4.79)	0.9297
	T-DM1 (N=39)	22 (56.4)				<.0001	
No	T-DXd (N=216)	199 (92.1)	8.28 (4.72, 14.54)	1.57 (1.40, 1.77)	0.336 (0.262, 0.410)	2.90 (2.31, 3.63)	
	T-DM1 (N=222)	130 (58.6)				<.0001	
Nausea							
Yes	T-DXd (N=41)	31 (75.6)	7.89 (2.91, 21.39)	2.68 (1.58, 4.55)	0.474 (0.281, 0.667)	3.84 (1.92, 7.67)	0.8573
	T-DM1 (N=39)	11 (28.2)				<.0001	
No	T-DXd (N=216)	164 (75.9)	7.14 (4.68, 10.90)	2.48 (2.01, 3.06)	0.453 (0.370, 0.536)	3.73 (2.81, 4.96)	
	T-DM1 (N=222)	68 (30.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Yes	T-DXd (N=41)	21 (51.2)	9.19 (2.76, 30.57)	4.99 (1.88, 13.24)	0.410 (0.229, 0.590)	6.22 (2.13, 18.16)	0.8562
	T-DM1 (N=39)	4 (10.3)				0.0001	
No	T-DXd (N=216)	105 (48.6)	8.60 (5.14, 14.39)	4.91 (3.22, 7.46)	0.387 (0.310, 0.464)	5.36 (3.38, 8.49)	
	T-DM1 (N=222)	22 (9.9)				<.0001	
Constipation							
Yes	T-DXd (N=41)	13 (31.7)	5.57 (1.45, 21.47)	4.12 (1.27, 13.37)	0.240 (0.075, 0.405)	3.01 (0.84, 10.84)	0.1735
	T-DM1 (N=39)	3 (7.7)				0.0782	
No	T-DXd (N=216)	75 (34.7)	1.93 (1.26, 2.95)	1.61 (1.18, 2.19)	0.131 (0.048, 0.214)	1.43 (0.99, 2.06)	
	T-DM1 (N=222)	48 (21.6)				0.0527	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Yes	T-DXd (N=41)	13 (31.7)	8.59 (1.79, 41.18)	6.18 (1.49, 25.65)	0.266 (0.107, 0.424)	5.69 (1.28, 25.42)	0.6787
	T-DM1 (N=39)	2 (5.1)				0.0103	
No	T-DXd (N=216)	62 (28.7)	5.18 (2.88, 9.33)	3.98 (2.38, 6.68)	0.215 (0.146, 0.284)	4.03 (2.32, 6.99)	
	T-DM1 (N=222)	16 (7.2)				<.0001	
Stomatitis							
Yes	T-DXd (N=41)	5 (12.2)	1.22 (0.30, 4.90)	1.19 (0.34, 4.11)	0.019 (-0.119, 0.158)	0.91 (0.24, 3.50)	0.0231
	T-DM1 (N=39)	4 (10.3)				0.8903	
No	T-DXd (N=216)	35 (16.2)	6.96 (2.86, 16.92)	6.00 (2.57, 13.96)	0.135 (0.081, 0.189)	5.05 (2.12, 12.04)	
	T-DM1 (N=222)	6 (2.7)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Yes	T-DXd (N=41)	6 (14.6)	NE (NE, NE)	NE (NE, NE)	0.146 (0.038, 0.255)	NE (NE, NE)	0.9877
	T-DM1 (N=39)	0				0.0324	
No	T-DXd (N=216)	23 (10.6)	5.17 (1.93, 13.87)	4.73 (1.83, 12.21)	0.084 (0.038, 0.129)	3.55 (1.34, 9.38)	
	T-DM1 (N=222)	5 (2.3)				0.0065	
Investigations							
Any PT							
Yes	T-DXd (N=41)	24 (58.5)	0.55 (0.22, 1.41)	0.82 (0.59, 1.13)	-0.133 (-0.339, 0.074)	0.46 (0.26, 0.80)	0.2434
	T-DM1 (N=39)	28 (71.8)				0.0073	
No	T-DXd (N=216)	138 (63.9)	0.83 (0.56, 1.24)	0.94 (0.82, 1.07)	-0.041 (-0.130, 0.047)	0.64 (0.51, 0.81)	
	T-DM1 (N=222)	151 (68.0)				0.0008	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
Yes	T-DXd (N=41)	6 (14.6)	0.94 (0.28, 3.22)	0.95 (0.34, 2.70)	-0.008 (-0.164, 0.149)	0.68 (0.22, 2.15)	0.0083
	T-DM1 (N=39)	6 (15.4)				0.5127	
No	T-DXd (N=216)	69 (31.9)	5.01 (2.89, 8.69)	3.73 (2.33, 5.98)	0.234 (0.162, 0.306)	3.62 (2.18, 6.02)	
	T-DM1 (N=222)	19 (8.6)				<.0001	
Aspartate aminotransferase increased							
Yes	T-DXd (N=41)	16 (39.0)	0.92 (0.38, 2.25)	0.95 (0.56, 1.63)	-0.020 (-0.235, 0.195)	0.62 (0.30, 1.26)	0.2056
	T-DM1 (N=39)	16 (41.0)				0.1971	
No	T-DXd (N=216)	50 (23.1)	0.45 (0.30, 0.68)	0.58 (0.43, 0.77)	-0.169 (-0.255, -0.084)	0.40 (0.28, 0.57)	
	T-DM1 (N=222)	89 (40.1)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
Yes	T-DXd (N=41)	7 (17.1)	2.47 (0.59, 10.34)	2.22 (0.62, 7.98)	0.094 (-0.049, 0.236)	1.58 (0.40, 6.27)	0.1917
	T-DM1 (N=39)	3 (7.7)				0.5069	
No	T-DXd (N=216)	51 (23.6)	5.93 (3.00, 11.73)	4.77 (2.55, 8.89)	0.187 (0.123, 0.250)	4.30 (2.24, 8.27)	
	T-DM1 (N=222)	11 (5.0)				<.0001	
Alanine aminotransferase increased							
Yes	T-DXd (N=41)	13 (31.7)	0.93 (0.36, 2.37)	0.95 (0.51, 1.79)	-0.016 (-0.222, 0.189)	0.64 (0.29, 1.44)	0.4624
	T-DM1 (N=39)	13 (33.3)				0.2889	
No	T-DXd (N=216)	43 (19.9)	0.61 (0.39, 0.96)	0.69 (0.49, 0.97)	-0.089 (-0.169, -0.009)	0.54 (0.37, 0.80)	
	T-DM1 (N=222)	64 (28.8)				0.0019	

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[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Yes	T-DXd (N=41)	12 (29.3)	0.44 (0.17, 1.09)	0.60 (0.34, 1.07)	-0.194 (-0.404, 0.015)	0.35 (0.17, 0.75)	0.6166
	T-DM1 (N=39)	19 (48.7)				0.0051	
No	T-DXd (N=216)	42 (19.4)	0.33 (0.22, 0.51)	0.46 (0.34, 0.63)	-0.224 (-0.308, -0.141)	0.31 (0.21, 0.45)	
	T-DM1 (N=222)	93 (41.9)				<.0001	
Weight decreased							
Yes	T-DXd (N=41)	8 (19.5)	4.48 (0.89, 22.64)	3.80 (0.86, 16.82)	0.144 (0.004, 0.284)	2.42 (0.50, 11.81)	0.8109
	T-DM1 (N=39)	2 (5.1)				0.2595	
No	T-DXd (N=216)	35 (16.2)	2.87 (1.50, 5.51)	2.57 (1.42, 4.64)	0.099 (0.040, 0.158)	2.04 (1.09, 3.80)	
	T-DM1 (N=222)	14 (6.3)				0.0221	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
Yes	T-DXd (N=41)	5 (12.2)	0.76 (0.21, 2.74)	0.79 (0.26, 2.39)	-0.032 (-0.183, 0.119)	0.70 (0.21, 2.30)	0.4323
	T-DM1 (N=39)	6 (15.4)				0.5614	
No	T-DXd (N=216)	12 (5.6)	0.39 (0.19, 0.79)	0.43 (0.22, 0.81)	-0.075 (-0.129, -0.021)	0.31 (0.16, 0.62)	
	T-DM1 (N=222)	29 (13.1)				0.0005	
General disorders and administration site conditions							
Any PT							
Yes	T-DXd (N=41)	24 (58.5)	2.52 (1.02, 6.21)	1.63 (1.00, 2.67)	0.226 (0.013, 0.439)	1.41 (0.72, 2.75)	0.2976
	T-DM1 (N=39)	14 (35.9)				0.3019	
No	T-DXd (N=216)	135 (62.5)	1.44 (0.99, 2.11)	1.17 (0.99, 1.37)	0.089 (-0.003, 0.181)	0.98 (0.77, 1.26)	
	T-DM1 (N=222)	119 (53.6)				0.9022	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Yes	T-DXd (N=41)	3 (7.3)	1.46 (0.23, 9.25)	1.43 (0.25, 8.09)	0.022 (-0.084, 0.127)	1.42 (0.24, 8.52)	0.3573
	T-DM1 (N=39)	2 (5.1)				0.6970	
No	T-DXd (N=216)	26 (12.0)	3.66 (1.62, 8.28)	3.34 (1.55, 7.21)	0.084 (0.034, 0.134)	2.98 (1.34, 6.61)	
	T-DM1 (N=222)	8 (3.6)				0.0048	
Pyrexia							
Yes	T-DXd (N=41)	4 (9.8)	1.30 (0.27, 6.21)	1.27 (0.30, 5.31)	0.021 (-0.103, 0.144)	0.79 (0.17, 3.73)	0.5908
	T-DM1 (N=39)	3 (7.7)				0.7695	
No	T-DXd (N=216)	23 (10.6)	0.62 (0.35, 1.08)	0.66 (0.40, 1.07)	-0.056 (-0.119, 0.008)	0.43 (0.25, 0.73)	
	T-DM1 (N=222)	36 (16.2)				0.0014	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Yes	T-DXd (N=41)	22 (53.7)	3.36 (1.30, 8.64)	2.09 (1.14, 3.83)	0.280 (0.075, 0.485)	1.91 (0.89, 4.08)	0.9354
	T-DM1 (N=39)	10 (25.6)				0.0918	
No	T-DXd (N=216)	117 (54.2)	2.85 (1.93, 4.23)	1.85 (1.46, 2.35)	0.249 (0.159, 0.338)	1.97 (1.45, 2.67)	
	T-DM1 (N=222)	65 (29.3)				<.0001	
Alopecia							
Yes	T-DXd (N=41)	12 (29.3)	4.97 (1.28, 19.28)	3.80 (1.16, 12.47)	0.216 (0.053, 0.378)	3.91 (1.09, 13.95)	0.0502
	T-DM1 (N=39)	3 (7.7)				0.0241	
No	T-DXd (N=216)	83 (38.4)	27.08 (10.71, 68.51)	17.06 (7.06, 41.25)	0.362 (0.294, 0.429)	19.36 (7.85, 47.75)	
	T-DM1 (N=222)	5 (2.3)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Yes	T-DXd (N=41)	19 (46.3)	1.24 (0.51, 3.01)	1.13 (0.69, 1.86)	0.053 (-0.164, 0.270)	1.04 (0.53, 2.05)	0.1692
	T-DM1 (N=39)	16 (41.0)				0.9253	
No	T-DXd (N=216)	103 (47.7)	2.25 (1.52, 3.34)	1.65 (1.29, 2.12)	0.189 (0.099, 0.278)	1.70 (1.24, 2.32)	
	T-DM1 (N=222)	64 (28.8)				0.0008	
Decreased appetite							
Yes	T-DXd (N=41)	11 (26.8)	1.22 (0.44, 3.38)	1.16 (0.54, 2.50)	0.038 (-0.152, 0.227)	1.03 (0.42, 2.50)	0.1981
	T-DM1 (N=39)	9 (23.1)				0.9551	
No	T-DXd (N=216)	64 (29.6)	2.25 (1.41, 3.58)	1.88 (1.30, 2.71)	0.139 (0.061, 0.216)	1.87 (1.23, 2.82)	
	T-DM1 (N=222)	35 (15.8)				0.0029	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
Yes	T-DXd (N=41)	21 (51.2)	2.10 (0.85, 5.19)	1.54 (0.90, 2.62)	0.179 (-0.034, 0.392)	1.06 (0.51, 2.17)	0.5192
	T-DM1 (N=39)	13 (33.3)				0.8772	
No	T-DXd (N=216)	95 (44.0)	1.27 (0.86, 1.85)	1.15 (0.92, 1.44)	0.057 (-0.035, 0.149)	0.90 (0.67, 1.21)	
	T-DM1 (N=222)	85 (38.3)				0.4979	
Infections and infestations							
Any PT							
Yes	T-DXd (N=41)	24 (58.5)	2.52 (1.02, 6.21)	1.63 (1.00, 2.67)	0.226 (0.013, 0.439)	1.24 (0.63, 2.46)	0.6641
	T-DM1 (N=39)	14 (35.9)				0.5295	
No	T-DXd (N=216)	88 (40.7)	1.46 (0.99, 2.16)	1.27 (0.99, 1.64)	0.088 (-0.002, 0.177)	0.96 (0.70, 1.32)	
	T-DM1 (N=222)	71 (32.0)				0.7967	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Yes	T-DXd (N=41)	17 (41.5)	2.74 (1.01, 7.42)	2.02 (0.99, 4.14)	0.210 (0.013, 0.406)	1.11 (0.47, 2.63)	0.5155
	T-DM1 (N=39)	8 (20.5)				0.8207	
No	T-DXd (N=216)	90 (41.7)	1.52 (1.03, 2.25)	1.30 (1.02, 1.67)	0.097 (0.007, 0.187)	0.95 (0.69, 1.30)	
	T-DM1 (N=222)	71 (32.0)				0.7276	
Epistaxis							
Yes	T-DXd (N=41)	5 (12.2)	2.57 (0.47, 14.10)	2.38 (0.49, 11.55)	0.071 (-0.051, 0.192)	1.34 (0.25, 7.17)	0.1557
	T-DM1 (N=39)	2 (5.1)				0.7323	
No	T-DXd (N=216)	24 (11.1)	0.57 (0.33, 0.98)	0.62 (0.39, 0.99)	-0.069 (-0.135, -0.003)	0.37 (0.22, 0.62)	
	T-DM1 (N=222)	40 (18.0)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Yes	T-DXd (N=41)	20 (48.8)	2.76 (1.07, 7.10)	1.90 (1.02, 3.54)	0.231 (0.026, 0.437)	1.59 (0.74, 3.42)	0.4332
	T-DM1 (N=39)	10 (25.6)				0.2207	
No	T-DXd (N=216)	83 (38.4)	1.51 (1.01, 2.25)	1.31 (1.01, 1.71)	0.091 (0.003, 0.180)	1.09 (0.79, 1.51)	
	T-DM1 (N=222)	65 (29.3)				0.5937	
Anaemia							
Yes	T-DXd (N=41)	18 (43.9)	3.03 (1.12, 8.18)	2.14 (1.05, 4.34)	0.234 (0.036, 0.432)	1.85 (0.80, 4.28)	0.8909
	T-DM1 (N=39)	8 (20.5)				0.1418	
No	T-DXd (N=216)	65 (30.1)	2.22 (1.40, 3.52)	1.86 (1.29, 2.66)	0.139 (0.061, 0.217)	1.58 (1.05, 2.38)	
	T-DM1 (N=222)	36 (16.2)				0.0274	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
Yes	T-DXd (N=41)	7 (17.1)	NE (NE, NE)	NE (NE, NE)	0.171 (0.056, 0.286)	NE (NE, NE)	0.9855
	T-DM1 (N=39)	0				0.0289	
No	T-DXd (N=216)	34 (15.7)	5.74 (2.48, 13.25)	4.99 (2.26, 11.02)	0.126 (0.072, 0.180)	3.91 (1.72, 8.85)	
	T-DM1 (N=222)	7 (3.2)				0.0004	
Thrombocytopenia							
Yes	T-DXd (N=41)	1 (2.4)	0.46 (0.04, 5.32)	0.48 (0.04, 5.04)	-0.027 (-0.111, 0.057)	0.30 (0.02, 3.65)	0.9887
	T-DM1 (N=39)	2 (5.1)				0.3253	
No	T-DXd (N=216)	12 (5.6)	0.39 (0.19, 0.79)	0.43 (0.22, 0.81)	-0.075 (-0.129, -0.021)	0.32 (0.16, 0.63)	
	T-DM1 (N=222)	29 (13.1)				0.0006	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
Yes	T-DXd (N=41)	18 (43.9)	3.58 (1.28, 9.96)	2.45 (1.15, 5.20)	0.260 (0.066, 0.453)	1.92 (0.78, 4.70)	0.0434
	T-DM1 (N=39)	7 (17.9)				0.1472	
No	T-DXd (N=216)	76 (35.2)	0.96 (0.65, 1.42)	0.98 (0.76, 1.26)	-0.009 (-0.098, 0.081)	0.70 (0.51, 0.96)	
	T-DM1 (N=222)	80 (36.0)				0.0280	
Vascular disorders							
Any PT							
Yes	T-DXd (N=41)	5 (12.2)	1.67 (0.37, 7.50)	1.59 (0.41, 6.19)	0.045 (-0.085, 0.176)	0.59 (0.12, 2.94)	0.4120
	T-DM1 (N=39)	3 (7.7)				0.5146	
No	T-DXd (N=216)	40 (18.5)	2.58 (1.43, 4.65)	2.28 (1.35, 3.86)	0.104 (0.041, 0.167)	1.85 (1.05, 3.24)	
	T-DM1 (N=222)	18 (8.1)				0.0297	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
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[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
Yes	T-DXd (N=41)	8 (19.5)	2.91 (0.71, 11.90)	2.54 (0.73, 8.87)	0.118 (-0.029, 0.266)	1.52 (0.39, 5.87)	0.4659
	T-DM1 (N=39)	3 (7.7)				0.5377	
No	T-DXd (N=216)	33 (15.3)	1.30 (0.75, 2.25)	1.26 (0.78, 2.02)	0.031 (-0.033, 0.096)	0.85 (0.51, 1.42)	
	T-DM1 (N=222)	27 (12.2)				0.5279	
Psychiatric disorders							
Any PT							
Yes	T-DXd (N=41)	6 (14.6)	1.17 (0.33, 4.18)	1.14 (0.38, 3.44)	0.018 (-0.133, 0.169)	0.66 (0.19, 2.26)	0.7954
	T-DM1 (N=39)	5 (12.8)				0.5075	
No	T-DXd (N=216)	33 (15.3)	1.15 (0.68, 1.97)	1.13 (0.72, 1.79)	0.018 (-0.048, 0.083)	0.82 (0.50, 1.36)	
	T-DM1 (N=222)	30 (13.5)				0.4451	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Yes	T-DXd (N=41)	5 (12.2)	0.94 (0.25, 3.55)	0.95 (0.30, 3.03)	-0.006 (-0.151, 0.139)	0.51 (0.14, 1.87)	0.4328
	T-DM1 (N=39)	5 (12.8)				0.2985	
No	T-DXd (N=216)	27 (12.5)	1.30 (0.71, 2.36)	1.26 (0.74, 2.14)	0.026 (-0.033, 0.085)	0.85 (0.48, 1.51)	
	T-DM1 (N=222)	22 (9.9)				0.5889	
Hepatobiliary disorders							
Any PT							
Yes	T-DXd (N=41)	5 (12.2)	0.54 (0.16, 1.82)	0.59 (0.21, 1.66)	-0.083 (-0.245, 0.078)	0.40 (0.13, 1.25)	0.6083
	T-DM1 (N=39)	8 (20.5)				0.1063	
No	T-DXd (N=216)	15 (6.9)	0.71 (0.36, 1.43)	0.73 (0.39, 1.39)	-0.025 (-0.076, 0.026)	0.55 (0.28, 1.09)	
	T-DM1 (N=222)	21 (9.5)				0.0833	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Yes	T-DXd (N=60)	55 (91.7)	8.72 (3.00, 25.35)	1.64 (1.28, 2.12)	0.359 (0.207, 0.511)	2.68 (1.70, 4.22)	0.8471
	T-DM1 (N=52)	29 (55.8)				<.0001	
No	T-DXd (N=197)	182 (92.4)	8.48 (4.68, 15.37)	1.57 (1.39, 1.77)	0.335 (0.259, 0.412)	2.92 (2.31, 3.69)	
	T-DM1 (N=209)	123 (58.9)				<.0001	
Nausea							
Yes	T-DXd (N=60)	44 (73.3)	6.19 (2.72, 14.06)	2.38 (1.54, 3.68)	0.426 (0.258, 0.594)	3.35 (1.89, 5.96)	0.7600
	T-DM1 (N=52)	16 (30.8)				<.0001	
No	T-DXd (N=197)	151 (76.6)	7.61 (4.88, 11.85)	2.54 (2.04, 3.17)	0.465 (0.379, 0.551)	3.87 (2.88, 5.20)	
	T-DM1 (N=209)	63 (30.1)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Yes	T-DXd (N=60)	29 (48.3)	6.01 (2.34, 15.45)	3.59 (1.72, 7.50)	0.349 (0.192, 0.506)	3.94 (1.72, 9.02)	0.4047
	T-DM1 (N=52)	7 (13.5)				0.0005	
No	T-DXd (N=197)	97 (49.2)	9.70 (5.61, 16.78)	5.42 (3.45, 8.51)	0.401 (0.322, 0.481)	6.01 (3.67, 9.84)	
	T-DM1 (N=209)	19 (9.1)				<.0001	
Constipation							
Yes	T-DXd (N=60)	18 (30.0)	3.29 (1.19, 9.06)	2.60 (1.12, 6.06)	0.185 (0.040, 0.329)	2.08 (0.81, 5.32)	0.3751
	T-DM1 (N=52)	6 (11.5)				0.1208	
No	T-DXd (N=197)	70 (35.5)	2.01 (1.29, 3.12)	1.65 (1.20, 2.27)	0.140 (0.053, 0.227)	1.46 (1.00, 2.13)	
	T-DM1 (N=209)	45 (21.5)				0.0476	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Yes	T-DXd (N=60)	17 (28.3)	4.74 (1.48, 15.20)	3.68 (1.32, 10.25)	0.206 (0.071, 0.341)	3.61 (1.21, 10.76)	0.7153
	T-DM1 (N=52)	4 (7.7)				0.0141	
No	T-DXd (N=197)	58 (29.4)	5.81 (3.12, 10.83)	4.40 (2.54, 7.62)	0.227 (0.155, 0.300)	4.41 (2.46, 7.92)	
	T-DM1 (N=209)	14 (6.7)				<.0001	
Stomatitis							
Yes	T-DXd (N=60)	7 (11.7)	1.58 (0.44, 5.75)	1.52 (0.47, 4.89)	0.040 (-0.069, 0.149)	1.22 (0.35, 4.25)	0.0561
	T-DM1 (N=52)	4 (7.7)				0.7510	
No	T-DXd (N=197)	33 (16.8)	6.81 (2.78, 16.64)	5.84 (2.50, 13.62)	0.139 (0.082, 0.196)	4.89 (2.04, 11.69)	
	T-DM1 (N=209)	6 (2.9)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Yes	T-DXd (N=60)	7 (11.7)	NE (NE, NE)	NE (NE, NE)	0.117 (0.035, 0.198)	NE (NE, NE)	0.9857
	T-DM1 (N=52)	0				0.0272	
No	T-DXd (N=197)	22 (11.2)	5.13 (1.90, 13.83)	4.67 (1.80, 12.09)	0.088 (0.039, 0.136)	3.49 (1.31, 9.26)	
	T-DM1 (N=209)	5 (2.4)				0.0077	
Investigations							
Any PT							
Yes	T-DXd (N=60)	33 (55.0)	0.54 (0.25, 1.18)	0.79 (0.59, 1.06)	-0.142 (-0.320, 0.035)	0.48 (0.30, 0.78)	0.2634
	T-DM1 (N=52)	36 (69.2)				0.0031	
No	T-DXd (N=197)	129 (65.5)	0.88 (0.58, 1.32)	0.96 (0.83, 1.10)	-0.029 (-0.121, 0.062)	0.65 (0.51, 0.83)	
	T-DM1 (N=209)	143 (68.4)				0.0021	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
Yes	T-DXd (N=60)	8 (13.3)	0.99 (0.33, 2.94)	0.99 (0.39, 2.55)	-0.001 (-0.128, 0.125)	0.84 (0.30, 2.32)	0.0063
	T-DM1 (N=52)	7 (13.5)				0.7287	
No	T-DXd (N=197)	67 (34.0)	5.47 (3.10, 9.63)	3.95 (2.44, 6.40)	0.254 (0.178, 0.330)	3.82 (2.27, 6.43)	
	T-DM1 (N=209)	18 (8.6)				<.0001	
Aspartate aminotransferase increased							
Yes	T-DXd (N=60)	17 (28.3)	0.63 (0.29, 1.40)	0.74 (0.43, 1.25)	-0.101 (-0.276, 0.073)	0.48 (0.24, 0.93)	0.6579
	T-DM1 (N=52)	20 (38.5)				0.0306	
No	T-DXd (N=197)	49 (24.9)	0.48 (0.32, 0.74)	0.61 (0.46, 0.82)	-0.158 (-0.248, -0.068)	0.43 (0.30, 0.61)	
	T-DM1 (N=209)	85 (40.7)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
Yes	T-DXd (N=60)	8 (13.3)	1.45 (0.44, 4.73)	1.39 (0.48, 3.98)	0.037 (-0.080, 0.155)	1.21 (0.40, 3.72)	0.0183
	T-DM1 (N=52)	5 (9.6)				0.7330	
No	T-DXd (N=197)	50 (25.4)	7.56 (3.60, 15.86)	5.89 (2.98, 11.66)	0.211 (0.144, 0.277)	5.23 (2.57, 10.64)	
	T-DM1 (N=209)	9 (4.3)				<.0001	
Alanine aminotransferase increased							
Yes	T-DXd (N=60)	13 (21.7)	0.52 (0.23, 1.21)	0.63 (0.34, 1.15)	-0.129 (-0.296, 0.037)	0.41 (0.20, 0.87)	0.5455
	T-DM1 (N=52)	18 (34.6)				0.0176	
No	T-DXd (N=197)	43 (21.8)	0.71 (0.45, 1.12)	0.77 (0.55, 1.09)	-0.064 (-0.148, 0.020)	0.61 (0.41, 0.91)	
	T-DM1 (N=209)	59 (28.2)				0.0153	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Yes	T-DXd (N=60)	15 (25.0)	0.42 (0.19, 0.94)	0.57 (0.33, 0.96)	-0.192 (-0.366, -0.018)	0.37 (0.19, 0.72)	0.4908
	T-DM1 (N=52)	23 (44.2)				0.0025	
No	T-DXd (N=197)	39 (19.8)	0.33 (0.21, 0.52)	0.46 (0.34, 0.64)	-0.228 (-0.315, -0.141)	0.31 (0.21, 0.45)	
	T-DM1 (N=209)	89 (42.6)				<.0001	
Weight decreased							
Yes	T-DXd (N=60)	12 (20.0)	4.08 (1.08, 15.37)	3.47 (1.03, 11.62)	0.142 (0.023, 0.262)	2.44 (0.68, 8.79)	0.7322
	T-DM1 (N=52)	3 (5.8)				0.1594	
No	T-DXd (N=197)	31 (15.7)	2.82 (1.43, 5.56)	2.53 (1.36, 4.69)	0.095 (0.035, 0.156)	1.98 (1.03, 3.79)	
	T-DM1 (N=209)	13 (6.2)				0.0366	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
Yes	T-DXd (N=60)	4 (6.7)	0.39 (0.11, 1.39)	0.43 (0.14, 1.36)	-0.087 (-0.204, 0.029)	0.39 (0.12, 1.31)	0.7698
	T-DM1 (N=52)	8 (15.4)				0.1154	
No	T-DXd (N=197)	13 (6.6)	0.48 (0.24, 0.95)	0.51 (0.27, 0.96)	-0.063 (-0.120, -0.006)	0.37 (0.19, 0.73)	
	T-DM1 (N=209)	27 (12.9)				0.0029	
General disorders and administration site conditions							
Any PT							
Yes	T-DXd (N=60)	37 (61.7)	1.61 (0.76, 3.41)	1.23 (0.88, 1.73)	0.117 (-0.067, 0.300)	1.02 (0.61, 1.70)	0.9321
	T-DM1 (N=52)	26 (50.0)				0.9368	
No	T-DXd (N=197)	122 (61.9)	1.55 (1.04, 2.30)	1.21 (1.02, 1.44)	0.107 (0.011, 0.203)	1.03 (0.79, 1.34)	
	T-DM1 (N=209)	107 (51.2)				0.8143	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Yes	T-DXd (N=60)	6 (10.0)	2.78 (0.54, 14.40)	2.60 (0.55, 12.33)	0.062 (-0.031, 0.154)	2.67 (0.54, 13.21)	0.8555
	T-DM1 (N=52)	2 (3.8)				0.2118	
No	T-DXd (N=197)	23 (11.7)	3.32 (1.45, 7.61)	3.05 (1.40, 6.66)	0.078 (0.027, 0.130)	2.66 (1.19, 5.98)	
	T-DM1 (N=209)	8 (3.8)				0.0137	
Pyrexia							
Yes	T-DXd (N=60)	7 (11.7)	1.58 (0.44, 5.75)	1.52 (0.47, 4.89)	0.040 (-0.069, 0.149)	0.95 (0.27, 3.35)	0.2373
	T-DM1 (N=52)	4 (7.7)				0.9412	
No	T-DXd (N=197)	20 (10.2)	0.56 (0.31, 1.01)	0.61 (0.36, 1.01)	-0.066 (-0.132, 0.000)	0.39 (0.22, 0.69)	
	T-DM1 (N=209)	35 (16.7)				0.0007	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Yes	T-DXd (N=60)	26 (43.3)	2.29 (1.02, 5.15)	1.73 (1.00, 3.01)	0.183 (0.011, 0.355)	1.60 (0.81, 3.14)	0.5780
	T-DM1 (N=52)	13 (25.0)				0.1702	
No	T-DXd (N=197)	113 (57.4)	3.19 (2.12, 4.80)	1.93 (1.52, 2.46)	0.277 (0.184, 0.370)	2.09 (1.53, 2.85)	
	T-DM1 (N=209)	62 (29.7)				<.0001	
Alopecia							
Yes	T-DXd (N=60)	15 (25.0)	5.44 (1.48, 20.06)	4.33 (1.33, 14.14)	0.192 (0.066, 0.319)	4.19 (1.21, 14.58)	0.0642
	T-DM1 (N=52)	3 (5.8)				0.0145	
No	T-DXd (N=197)	80 (40.6)	27.90 (10.99, 70.82)	16.97 (7.02, 41.02)	0.382 (0.311, 0.454)	19.61 (7.95, 48.40)	
	T-DM1 (N=209)	5 (2.4)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Yes	T-DXd (N=60)	29 (48.3)	1.62 (0.76, 3.47)	1.32 (0.85, 2.06)	0.118 (-0.064, 0.300)	1.26 (0.70, 2.27)	0.4494
	T-DM1 (N=52)	19 (36.5)				0.4488	
No	T-DXd (N=197)	93 (47.2)	2.17 (1.44, 3.27)	1.62 (1.25, 2.09)	0.180 (0.087, 0.273)	1.65 (1.20, 2.28)	
	T-DM1 (N=209)	61 (29.2)				0.0022	
Decreased appetite							
Yes	T-DXd (N=60)	16 (26.7)	1.36 (0.56, 3.26)	1.26 (0.64, 2.47)	0.055 (-0.102, 0.213)	1.13 (0.52, 2.46)	0.2631
	T-DM1 (N=52)	11 (21.2)				0.7553	
No	T-DXd (N=197)	59 (29.9)	2.28 (1.41, 3.69)	1.90 (1.30, 2.77)	0.142 (0.061, 0.222)	1.88 (1.23, 2.89)	
	T-DM1 (N=209)	33 (15.8)				0.0034	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
Yes	T-DXd (N=60)	31 (51.7)	1.71 (0.80, 3.64)	1.34 (0.88, 2.05)	0.132 (-0.051, 0.315)	0.92 (0.51, 1.64)	0.7503
	T-DM1 (N=52)	20 (38.5)				0.7752	
No	T-DXd (N=197)	85 (43.1)	1.27 (0.86, 1.90)	1.16 (0.91, 1.47)	0.058 (-0.037, 0.154)	0.91 (0.67, 1.25)	
	T-DM1 (N=209)	78 (37.3)				0.5749	
Infections and infestations							
Any PT							
Yes	T-DXd (N=60)	32 (53.3)	2.35 (1.09, 5.08)	1.63 (1.03, 2.57)	0.206 (0.027, 0.386)	1.21 (0.66, 2.23)	0.4066
	T-DM1 (N=52)	17 (32.7)				0.5295	
No	T-DXd (N=197)	80 (40.6)	1.42 (0.94, 2.13)	1.25 (0.96, 1.62)	0.081 (-0.013, 0.174)	0.93 (0.67, 1.29)	
	T-DM1 (N=209)	68 (32.5)				0.6841	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Yes	T-DXd (N=60)	24 (40.0)	2.48 (1.07, 5.77)	1.89 (1.03, 3.48)	0.188 (0.022, 0.355)	1.10 (0.53, 2.31)	0.4146
	T-DM1 (N=52)	11 (21.2)				0.7958	
No	T-DXd (N=197)	83 (42.1)	1.51 (1.01, 2.26)	1.29 (1.00, 1.67)	0.096 (0.002, 0.190)	0.93 (0.68, 1.29)	
	T-DM1 (N=209)	68 (32.5)				0.6825	
Epistaxis							
Yes	T-DXd (N=60)	6 (10.0)	1.33 (0.35, 5.01)	1.30 (0.39, 4.36)	0.023 (-0.082, 0.128)	0.73 (0.20, 2.69)	0.3225
	T-DM1 (N=52)	4 (7.7)				0.6394	
No	T-DXd (N=197)	23 (11.7)	0.59 (0.34, 1.04)	0.64 (0.40, 1.04)	-0.065 (-0.134, 0.004)	0.38 (0.23, 0.65)	
	T-DM1 (N=209)	38 (18.2)				0.0002	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Yes	T-DXd (N=60)	27 (45.0)	1.84 (0.85, 4.01)	1.46 (0.89, 2.40)	0.142 (-0.035, 0.320)	1.19 (0.64, 2.22)	0.9248
	T-DM1 (N=52)	16 (30.8)				0.5723	
No	T-DXd (N=197)	76 (38.6)	1.60 (1.05, 2.42)	1.37 (1.03, 1.81)	0.103 (0.012, 0.195)	1.14 (0.81, 1.61)	
	T-DM1 (N=209)	59 (28.2)				0.4483	
Anaemia							
Yes	T-DXd (N=60)	23 (38.3)	1.86 (0.83, 4.21)	1.53 (0.87, 2.71)	0.133 (-0.037, 0.304)	1.19 (0.59, 2.37)	0.3269
	T-DM1 (N=52)	13 (25.0)				0.6232	
No	T-DXd (N=197)	60 (30.5)	2.51 (1.54, 4.09)	2.05 (1.39, 3.02)	0.156 (0.076, 0.237)	1.78 (1.15, 2.76)	
	T-DM1 (N=209)	31 (14.8)				0.0084	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
Yes	T-DXd (N=60)	10 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (0.072, 0.261)	NE (NE, NE)	0.9829
	T-DM1 (N=52)	0				0.0063	
No	T-DXd (N=197)	31 (15.7)	5.39 (2.31, 12.55)	4.70 (2.12, 10.42)	0.124 (0.067, 0.180)	3.54 (1.55, 8.09)	
	T-DM1 (N=209)	7 (3.3)				0.0014	
Thrombocytopenia							
Yes	T-DXd (N=60)	3 (5.0)	0.86 (0.17, 4.45)	0.87 (0.18, 4.11)	-0.008 (-0.092, 0.076)	0.53 (0.10, 2.93)	0.3858
	T-DM1 (N=52)	3 (5.8)				0.4659	
No	T-DXd (N=197)	10 (5.1)	0.35 (0.16, 0.73)	0.38 (0.19, 0.76)	-0.083 (-0.139, -0.028)	0.29 (0.14, 0.59)	
	T-DM1 (N=209)	28 (13.4)				0.0003	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
Yes	T-DXd (N=60)	24 (40.0)	2.00 (0.89, 4.51)	1.60 (0.91, 2.81)	0.150 (-0.021, 0.321)	1.10 (0.55, 2.21)	0.2478
	T-DM1 (N=52)	13 (25.0)				0.7915	
No	T-DXd (N=197)	70 (35.5)	1.01 (0.67, 1.51)	1.00 (0.77, 1.30)	0.001 (-0.092, 0.094)	0.73 (0.52, 1.02)	
	T-DM1 (N=209)	74 (35.4)				0.0616	
Vascular disorders							
Any PT							
Yes	T-DXd (N=60)	11 (18.3)	2.11 (0.68, 6.53)	1.91 (0.71, 5.13)	0.087 (-0.039, 0.214)	1.25 (0.41, 3.79)	0.6330
	T-DM1 (N=52)	5 (9.6)				0.6910	
No	T-DXd (N=197)	34 (17.3)	2.52 (1.34, 4.72)	2.25 (1.29, 3.95)	0.096 (0.032, 0.160)	1.75 (0.96, 3.19)	
	T-DM1 (N=209)	16 (7.7)				0.0642	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
Yes	T-DXd (N=60)	9 (15.0)	1.66 (0.52, 5.31)	1.56 (0.56, 4.36)	0.054 (-0.067, 0.175)	1.08 (0.36, 3.28)	0.9304
	T-DM1 (N=52)	5 (9.6)				0.8870	
No	T-DXd (N=197)	32 (16.2)	1.43 (0.81, 2.51)	1.36 (0.84, 2.21)	0.043 (-0.025, 0.111)	0.90 (0.53, 1.53)	
	T-DM1 (N=209)	25 (12.0)				0.6910	
Psychiatric disorders							
Any PT							
Yes	T-DXd (N=60)	9 (15.0)	1.13 (0.39, 3.29)	1.11 (0.45, 2.78)	0.015 (-0.114, 0.145)	0.76 (0.28, 2.10)	0.8825
	T-DM1 (N=52)	7 (13.5)				0.5988	
No	T-DXd (N=197)	30 (15.2)	1.16 (0.67, 2.03)	1.14 (0.71, 1.83)	0.018 (-0.050, 0.087)	0.81 (0.48, 1.37)	
	T-DM1 (N=209)	28 (13.4)				0.4336	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 33 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 10% in at least one arm by pre-specified subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Yes	T-DXd (N=60)	7 (11.7)	0.85 (0.28, 2.60)	0.87 (0.33, 2.31)	-0.018 (-0.141, 0.105)	0.47 (0.15, 1.42)	0.3152
	T-DM1 (N=52)	7 (13.5)				0.1710	
No	T-DXd (N=197)	25 (12.7)	1.37 (0.74, 2.56)	1.33 (0.76, 2.31)	0.031 (-0.030, 0.092)	0.90 (0.50, 1.63)	
	T-DM1 (N=209)	20 (9.6)				0.7314	
Hepatobiliary disorders							
Any PT							
Yes	T-DXd (N=60)	4 (6.7)	0.34 (0.10, 1.18)	0.39 (0.13, 1.18)	-0.106 (-0.227, 0.014)	0.29 (0.09, 0.94)	0.2062
	T-DM1 (N=52)	9 (17.3)				0.0282	
No	T-DXd (N=197)	16 (8.1)	0.84 (0.42, 1.66)	0.85 (0.45, 1.59)	-0.014 (-0.070, 0.041)	0.64 (0.33, 1.25)	
	T-DM1 (N=209)	20 (9.6)				0.1941	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
<65	T-DXd (N=209)	198 (94.7)	14.21 (7.29, 27.69)	1.70 (1.49, 1.92)	0.389 (0.314, 0.463)	3.11 (2.46, 3.94)	0.0649
	T-DM1 (N=204)	114 (55.9)				<.0001	
>=65	T-DXd (N=48)	39 (81.3)	2.17 (0.87, 5.38)	1.22 (0.97, 1.53)	0.146 (-0.019, 0.311)	2.02 (1.28, 3.17)	
	T-DM1 (N=57)	38 (66.7)				0.0024	
Nausea							
<65	T-DXd (N=209)	164 (78.5)	7.79 (5.01, 12.13)	2.46 (1.99, 3.05)	0.466 (0.381, 0.551)	3.68 (2.76, 4.91)	0.9953
	T-DM1 (N=204)	65 (31.9)				<.0001	
>=65	T-DXd (N=48)	31 (64.6)	5.60 (2.41, 13.04)	2.63 (1.59, 4.34)	0.400 (0.225, 0.576)	3.80 (2.02, 7.16)	
	T-DM1 (N=57)	14 (24.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
<65	T-DXd (N=209)	105 (50.2)	9.83 (5.70, 16.95)	5.39 (3.44, 8.45)	0.409 (0.331, 0.488)	5.90 (3.62, 9.63)	0.4712
	T-DM1 (N=204)	19 (9.3)				<.0001	
>=65	T-DXd (N=48)	21 (43.8)	5.55 (2.10, 14.73)	3.56 (1.66, 7.65)	0.315 (0.151, 0.479)	4.19 (1.78, 9.88)	
	T-DM1 (N=57)	7 (12.3)				0.0004	
Constipation							
<65	T-DXd (N=209)	74 (35.4)	2.56 (1.62, 4.04)	2.01 (1.42, 2.84)	0.178 (0.094, 0.261)	1.74 (1.16, 2.59)	0.2862
	T-DM1 (N=204)	36 (17.6)				0.0063	
>=65	T-DXd (N=48)	14 (29.2)	1.15 (0.49, 2.72)	1.11 (0.60, 2.06)	0.029 (-0.144, 0.201)	1.04 (0.50, 2.16)	
	T-DM1 (N=57)	15 (26.3)				0.9132	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
<65	T-DXd (N=209)	62 (29.7)	6.20 (3.28, 11.70)	4.66 (2.64, 8.20)	0.233 (0.163, 0.303)	4.55 (2.50, 8.29)	0.5841
	T-DM1 (N=204)	13 (6.4)				<.0001	
>=65	T-DXd (N=48)	13 (27.1)	3.86 (1.26, 11.80)	3.09 (1.19, 8.04)	0.183 (0.038, 0.329)	3.30 (1.17, 9.26)	
	T-DM1 (N=57)	5 (8.8)				0.0161	
Stomatitis							
<65	T-DXd (N=209)	28 (13.4)	7.73 (2.66, 22.48)	6.83 (2.44, 19.13)	0.114 (0.064, 0.164)	5.54 (1.94, 15.86)	0.2427
	T-DM1 (N=204)	4 (2.0)				0.0003	
>=65	T-DXd (N=48)	12 (25.0)	2.83 (0.97, 8.25)	2.38 (0.96, 5.85)	0.145 (-0.001, 0.291)	2.30 (0.86, 6.14)	
	T-DM1 (N=57)	6 (10.5)				0.0869	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
<65	T-DXd (N=209)	24 (11.5)	8.69 (2.57, 29.34)	7.81 (2.39, 25.53)	0.100 (0.054, 0.146)	5.62 (1.68, 18.78)	0.4454
	T-DM1 (N=204)	3 (1.5)				0.0017	
>=65	T-DXd (N=48)	5 (10.4)	3.20 (0.59, 17.29)	2.97 (0.60, 14.62)	0.069 (-0.030, 0.168)	2.54 (0.49, 13.18)	
	T-DM1 (N=57)	2 (3.5)				0.2487	
Dry mouth							
<65	T-DXd (N=209)	7 (3.3)	0.36 (0.15, 0.88)	0.38 (0.16, 0.89)	-0.055 (-0.101, -0.009)	0.29 (0.12, 0.70)	0.5344
	T-DM1 (N=204)	18 (8.8)				0.0035	
>=65	T-DXd (N=48)	1 (2.1)	0.15 (0.02, 1.28)	0.17 (0.02, 1.33)	-0.102 (-0.196, -0.008)	0.14 (0.02, 1.11)	
	T-DM1 (N=57)	7 (12.3)				0.0299	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
<65	T-DXd (N=209)	127 (60.8)	0.68 (0.45, 1.02)	0.87 (0.76, 1.01)	-0.088 (-0.180, 0.003)	0.55 (0.43, 0.70)	0.0642
	T-DM1 (N=204)	142 (69.6)				<.0001	
>=65	T-DXd (N=48)	35 (72.9)	1.46 (0.63, 3.36)	1.12 (0.87, 1.45)	0.080 (-0.096, 0.257)	0.92 (0.58, 1.46)	
	T-DM1 (N=57)	37 (64.9)				0.8216	
Neutrophil count decreased							
<65	T-DXd (N=209)	55 (26.3)	4.20 (2.31, 7.61)	3.36 (1.99, 5.66)	0.185 (0.115, 0.255)	3.02 (1.73, 5.27)	0.9902
	T-DM1 (N=204)	16 (7.8)				<.0001	
>=65	T-DXd (N=48)	20 (41.7)	3.81 (1.53, 9.51)	2.64 (1.33, 5.24)	0.259 (0.090, 0.427)	2.96 (1.35, 6.50)	
	T-DM1 (N=57)	9 (15.8)				0.0047	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
<65	T-DXd (N=209)	58 (27.8)	0.57 (0.38, 0.86)	0.69 (0.52, 0.91)	-0.124 (-0.215, -0.034)	0.47 (0.33, 0.66)	0.3376
	T-DM1 (N=204)	82 (40.2)				<.0001	
>=65	T-DXd (N=48)	8 (16.7)	0.30 (0.12, 0.75)	0.41 (0.20, 0.84)	-0.237 (-0.402, -0.072)	0.31 (0.14, 0.69)	
	T-DM1 (N=57)	23 (40.4)				0.0026	
White blood cell count decreased							
<65	T-DXd (N=209)	45 (21.5)	4.81 (2.41, 9.61)	3.99 (2.13, 7.50)	0.161 (0.098, 0.225)	3.38 (1.74, 6.55)	0.5378
	T-DM1 (N=204)	11 (5.4)				0.0001	
>=65	T-DXd (N=48)	13 (27.1)	6.69 (1.78, 25.16)	5.15 (1.56, 17.00)	0.218 (0.080, 0.357)	5.07 (1.44, 17.81)	
	T-DM1 (N=57)	3 (5.3)				0.0049	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
<65	T-DXd (N=209)	50 (23.9)	0.74 (0.48, 1.14)	0.80 (0.58, 1.10)	-0.060 (-0.145, 0.026)	0.61 (0.42, 0.89)	0.2862
	T-DM1 (N=204)	61 (29.9)				0.0106	
>=65	T-DXd (N=48)	6 (12.5)	0.37 (0.13, 1.03)	0.45 (0.19, 1.05)	-0.156 (-0.305, -0.006)	0.36 (0.14, 0.93)	
	T-DM1 (N=57)	16 (28.1)				0.0284	
Platelet count decreased							
<65	T-DXd (N=209)	40 (19.1)	0.32 (0.21, 0.51)	0.45 (0.33, 0.63)	-0.230 (-0.316, -0.144)	0.29 (0.20, 0.43)	0.2391
	T-DM1 (N=204)	86 (42.2)				<.0001	
>=65	T-DXd (N=48)	14 (29.2)	0.49 (0.22, 1.11)	0.64 (0.38, 1.08)	-0.164 (-0.347, 0.018)	0.47 (0.25, 0.91)	
	T-DM1 (N=57)	26 (45.6)				0.0249	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
<65	T-DXd (N=209)	36 (17.2)	4.04 (1.95, 8.37)	3.51 (1.79, 6.89)	0.123 (0.064, 0.182)	2.64 (1.30, 5.34)	0.2293
	T-DM1 (N=204)	10 (4.9)				0.0051	
>=65	T-DXd (N=48)	7 (14.6)	1.45 (0.45, 4.65)	1.39 (0.50, 3.84)	0.041 (-0.087, 0.168)	1.17 (0.39, 3.49)	
	T-DM1 (N=57)	6 (10.5)				0.7788	
Blood lactate dehydrogenase increased							
<65	T-DXd (N=209)	13 (6.2)	0.40 (0.20, 0.79)	0.44 (0.23, 0.82)	-0.080 (-0.138, -0.022)	0.32 (0.17, 0.63)	0.3341
	T-DM1 (N=204)	29 (14.2)				0.0005	
>=65	T-DXd (N=48)	4 (8.3)	0.77 (0.20, 2.92)	0.79 (0.24, 2.64)	-0.022 (-0.134, 0.090)	0.69 (0.19, 2.45)	
	T-DM1 (N=57)	6 (10.5)				0.5598	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
<65	T-DXd (N=209)	9 (4.3)	4.54 (0.97, 21.30)	4.39 (0.96, 20.08)	0.033 (0.003, 0.064)	3.15 (0.67, 14.78)	0.7147
	T-DM1 (N=204)	2 (1.0)				0.1260	
>=65	T-DXd (N=48)	5 (10.4)	6.51 (0.73, 57.80)	5.94 (0.72, 49.09)	0.087 (-0.006, 0.180)	4.76 (0.55, 40.79)	
	T-DM1 (N=57)	1 (1.8)				0.1163	
General disorders and administration site conditions							
Any PT							
<65	T-DXd (N=209)	132 (63.2)	1.78 (1.20, 2.64)	1.29 (1.08, 1.53)	0.141 (0.047, 0.236)	1.12 (0.86, 1.46)	0.3130
	T-DM1 (N=204)	100 (49.0)				0.3866	
>=65	T-DXd (N=48)	27 (56.3)	0.94 (0.43, 2.03)	0.97 (0.70, 1.36)	-0.016 (-0.207, 0.174)	0.76 (0.45, 1.26)	
	T-DM1 (N=57)	33 (57.9)				0.2905	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
<65	T-DXd (N=209)	26 (12.4)	3.48 (1.54, 7.88)	3.17 (1.47, 6.84)	0.085 (0.033, 0.137)	2.78 (1.25, 6.18)	0.5953
	T-DM1 (N=204)	8 (3.9)				0.0088	
>=65	T-DXd (N=48)	3 (6.3)	1.83 (0.29, 11.45)	1.78 (0.31, 10.22)	0.027 (-0.056, 0.111)	1.75 (0.29, 10.50)	
	T-DM1 (N=57)	2 (3.5)				0.5328	
Pyrexia							
<65	T-DXd (N=209)	22 (10.5)	0.81 (0.44, 1.47)	0.83 (0.48, 1.41)	-0.022 (-0.084, 0.040)	0.55 (0.31, 0.99)	0.5175
	T-DM1 (N=204)	26 (12.7)				0.0426	
>=65	T-DXd (N=48)	5 (10.4)	0.39 (0.13, 1.20)	0.46 (0.18, 1.19)	-0.124 (-0.263, 0.015)	0.30 (0.11, 0.84)	
	T-DM1 (N=57)	13 (22.8)				0.0158	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
<65	T-DXd (N=209)	111 (53.1)	3.07 (2.03, 4.63)	1.97 (1.52, 2.55)	0.261 (0.170, 0.353)	2.03 (1.47, 2.82)	0.7828
	T-DM1 (N=204)	55 (27.0)				<.0001	
>=65	T-DXd (N=48)	28 (58.3)	2.59 (1.17, 5.71)	1.66 (1.09, 2.55)	0.232 (0.046, 0.419)	1.83 (1.03, 3.26)	
	T-DM1 (N=57)	20 (35.1)				0.0369	
Alopecia							
<65	T-DXd (N=209)	79 (37.8)	24.19 (9.54, 61.33)	15.42 (6.38, 37.29)	0.353 (0.284, 0.423)	17.14 (6.94, 42.33)	0.2640
	T-DM1 (N=204)	5 (2.5)				<.0001	
>=65	T-DXd (N=48)	16 (33.3)	9.00 (2.43, 33.30)	6.33 (1.96, 20.44)	0.281 (0.135, 0.426)	7.05 (2.05, 24.21)	
	T-DM1 (N=57)	3 (5.3)				0.0003	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
<65	T-DXd (N=209)	13 (6.2)	0.78 (0.36, 1.66)	0.79 (0.39, 1.61)	-0.016 (-0.066, 0.033)	0.52 (0.25, 1.10)	0.5544
	T-DM1 (N=204)	16 (7.8)				0.0814	
>=65	T-DXd (N=48)	3 (6.3)	0.41 (0.10, 1.63)	0.45 (0.13, 1.59)	-0.078 (-0.191, 0.035)	0.38 (0.10, 1.43)	
	T-DM1 (N=57)	8 (14.0)				0.1367	
Skin hyperpigmentation							
<65	T-DXd (N=209)	8 (3.8)	NE (NE, NE)	NE (NE, NE)	0.038 (0.012, 0.064)	NE (NE, NE)	0.9999
	T-DM1 (N=204)	0				0.0118	
>=65	T-DXd (N=48)	3 (6.3)	NE (NE, NE)	NE (NE, NE)	0.063 (-0.006, 0.131)	NE (NE, NE)	
	T-DM1 (N=57)	0				0.1049	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
<65	T-DXd (N=209)	101 (48.3)	2.35 (1.57, 3.54)	1.70 (1.31, 2.20)	0.199 (0.107, 0.291)	1.73 (1.25, 2.40)	0.2074
	T-DM1 (N=204)	58 (28.4)				0.0008	
>=65	T-DXd (N=48)	21 (43.8)	1.24 (0.57, 2.70)	1.13 (0.72, 1.79)	0.052 (-0.137, 0.240)	1.08 (0.59, 1.97)	
	T-DM1 (N=57)	22 (38.6)				0.8058	
Decreased appetite							
<65	T-DXd (N=209)	62 (29.7)	2.55 (1.56, 4.16)	2.09 (1.40, 3.10)	0.154 (0.076, 0.233)	2.06 (1.33, 3.21)	0.0902
	T-DM1 (N=204)	29 (14.2)				0.0011	
>=65	T-DXd (N=48)	13 (27.1)	1.04 (0.44, 2.48)	1.03 (0.54, 1.94)	0.008 (-0.162, 0.178)	0.94 (0.44, 1.97)	
	T-DM1 (N=57)	15 (26.3)				0.8593	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
<65	T-DXd (N=209)	9 (4.3)	NE (NE, NE)	NE (NE, NE)	0.043 (0.016, 0.071)	NE (NE, NE)	1.0000
	T-DM1 (N=204)	0				0.0034	
>=65	T-DXd (N=48)	2 (4.2)	NE (NE, NE)	NE (NE, NE)	0.042 (-0.015, 0.098)	NE (NE, NE)	
	T-DM1 (N=57)	0				0.1213	
Nervous system disorders							
Any PT							
<65	T-DXd (N=209)	93 (44.5)	1.17 (0.79, 1.73)	1.09 (0.87, 1.37)	0.038 (-0.057, 0.133)	0.78 (0.58, 1.05)	0.0185
	T-DM1 (N=204)	83 (40.7)				0.1077	
>=65	T-DXd (N=48)	23 (47.9)	2.58 (1.14, 5.83)	1.82 (1.08, 3.08)	0.216 (0.034, 0.398)	1.87 (0.98, 3.59)	
	T-DM1 (N=57)	15 (26.3)				0.0544	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
<65	T-DXd (N=209)	15 (7.2)	0.67 (0.34, 1.35)	0.70 (0.37, 1.31)	-0.031 (-0.086, 0.023)	0.44 (0.23, 0.87)	0.3196
	T-DM1 (N=204)	21 (10.3)				0.0160	
>=65	T-DXd (N=48)	4 (8.3)	1.20 (0.28, 5.10)	1.19 (0.31, 4.50)	0.013 (-0.089, 0.116)	1.06 (0.26, 4.29)	
	T-DM1 (N=57)	4 (7.0)				0.9279	
Infections and infestations							
Any PT							
<65	T-DXd (N=209)	88 (42.1)	1.56 (1.04, 2.33)	1.32 (1.02, 1.71)	0.102 (0.010, 0.195)	0.98 (0.71, 1.36)	0.4664
	T-DM1 (N=204)	65 (31.9)				0.9209	
>=65	T-DXd (N=48)	24 (50.0)	1.85 (0.84, 4.06)	1.43 (0.91, 2.24)	0.149 (-0.039, 0.337)	1.16 (0.64, 2.11)	
	T-DM1 (N=57)	20 (35.1)				0.6325	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
<65	T-DXd (N=209)	81 (38.8)	1.56 (1.03, 2.35)	1.34 (1.02, 1.76)	0.098 (0.008, 0.189)	0.91 (0.65, 1.28)	0.3641
	T-DM1 (N=204)	59 (28.9)				0.5866	
>=65	T-DXd (N=48)	26 (54.2)	2.19 (1.00, 4.80)	1.54 (1.00, 2.39)	0.191 (0.003, 0.378)	1.19 (0.66, 2.15)	
	T-DM1 (N=57)	20 (35.1)				0.5581	
Epistaxis							
<65	T-DXd (N=209)	22 (10.5)	0.66 (0.37, 1.18)	0.69 (0.42, 1.15)	-0.047 (-0.111, 0.018)	0.40 (0.23, 0.70)	0.7178
	T-DM1 (N=204)	31 (15.2)				0.0009	
>=65	T-DXd (N=48)	7 (14.6)	0.71 (0.25, 2.01)	0.76 (0.32, 1.80)	-0.047 (-0.190, 0.096)	0.45 (0.17, 1.21)	
	T-DM1 (N=57)	11 (19.3)				0.1072	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
<65	T-DXd (N=209)	12 (5.7)	NE (NE, NE)	NE (NE, NE)	0.057 (0.026, 0.089)	NE (NE, NE)	0.9891
	T-DM1 (N=204)	0				0.0084	
>=65	T-DXd (N=48)	6 (12.5)	8.00 (0.93, 68.98)	7.13 (0.89, 57.14)	0.107 (0.008, 0.207)	5.37 (0.65, 44.65)	
	T-DM1 (N=57)	1 (1.8)				0.0815	
Blood and lymphatic system disorders							
Any PT							
<65	T-DXd (N=209)	83 (39.7)	1.78 (1.18, 2.70)	1.47 (1.11, 1.95)	0.128 (0.037, 0.218)	1.19 (0.85, 1.68)	0.7974
	T-DM1 (N=204)	55 (27.0)				0.3107	
>=65	T-DXd (N=48)	20 (41.7)	1.32 (0.60, 2.91)	1.19 (0.73, 1.93)	0.066 (-0.121, 0.252)	1.11 (0.59, 2.06)	
	T-DM1 (N=57)	20 (35.1)				0.7399	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
<65	T-DXd (N=209)	66 (31.6)	2.39 (1.49, 3.84)	1.95 (1.35, 2.83)	0.154 (0.073, 0.235)	1.61 (1.05, 2.45)	0.7776
	T-DM1 (N=204)	33 (16.2)				0.0263	
>=65	T-DXd (N=48)	17 (35.4)	2.29 (0.95, 5.55)	1.84 (0.95, 3.53)	0.161 (-0.009, 0.331)	1.84 (0.86, 3.94)	
	T-DM1 (N=57)	11 (19.3)				0.1114	
Neutropenia							
<65	T-DXd (N=209)	37 (17.7)	7.10 (2.93, 17.23)	6.02 (2.60, 13.95)	0.148 (0.091, 0.204)	4.38 (1.84, 10.45)	0.9427
	T-DM1 (N=204)	6 (2.9)				0.0003	
>=65	T-DXd (N=48)	4 (8.3)	5.09 (0.55, 47.18)	4.75 (0.55, 41.08)	0.066 (-0.020, 0.151)	4.61 (0.51, 41.29)	
	T-DM1 (N=57)	1 (1.8)				0.1333	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
<65	T-DXd (N=209)	12 (5.7)	0.48 (0.23, 0.99)	0.51 (0.26, 1.00)	-0.055 (-0.109, -0.002)	0.35 (0.17, 0.72)	0.2962
	T-DM1 (N=204)	23 (11.3)				0.0029	
>=65	T-DXd (N=48)	1 (2.1)	0.13 (0.02, 1.08)	0.15 (0.02, 1.15)	-0.120 (-0.218, -0.021)	0.13 (0.02, 1.07)	
	T-DM1 (N=57)	8 (14.0)				0.0249	
Musculoskeletal and connective tissue disorders							
Any PT							
<65	T-DXd (N=209)	78 (37.3)	1.09 (0.73, 1.63)	1.06 (0.82, 1.37)	0.020 (-0.072, 0.113)	0.73 (0.53, 1.01)	0.2818
	T-DM1 (N=204)	72 (35.3)				0.0597	
>=65	T-DXd (N=48)	16 (33.3)	1.40 (0.60, 3.25)	1.27 (0.70, 2.29)	0.070 (-0.105, 0.246)	1.12 (0.55, 2.28)	
	T-DM1 (N=57)	15 (26.3)				0.7474	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
<65	T-DXd (N=209)	32 (15.3)	2.66 (1.35, 5.22)	2.40 (1.30, 4.44)	0.089 (0.030, 0.149)	1.80 (0.94, 3.47)	0.9721
	T-DM1 (N=204)	13 (6.4)				0.0738	
>=65	T-DXd (N=48)	13 (27.1)	2.27 (0.85, 6.07)	1.93 (0.87, 4.26)	0.130 (-0.024, 0.285)	1.68 (0.69, 4.06)	
	T-DM1 (N=57)	8 (14.0)				0.2484	
Eye disorders							
Any PT							
<65	T-DXd (N=209)	32 (15.3)	1.36 (0.77, 2.39)	1.30 (0.80, 2.13)	0.035 (-0.030, 0.101)	0.79 (0.46, 1.36)	0.3237
	T-DM1 (N=204)	24 (11.8)				0.3928	
>=65	T-DXd (N=48)	9 (18.8)	1.96 (0.64, 5.98)	1.78 (0.68, 4.65)	0.082 (-0.054, 0.218)	1.51 (0.54, 4.26)	
	T-DM1 (N=57)	6 (10.5)				0.4301	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
<65	T-DXd (N=209)	34 (16.3)	1.17 (0.68, 2.01)	1.14 (0.73, 1.81)	0.021 (-0.049, 0.090)	0.77 (0.47, 1.28)	0.9633
	T-DM1 (N=204)	29 (14.2)				0.3099	
>=65	T-DXd (N=48)	5 (10.4)	0.99 (0.28, 3.46)	0.99 (0.32, 3.04)	-0.001 (-0.119, 0.116)	0.81 (0.25, 2.67)	
	T-DM1 (N=57)	6 (10.5)				0.7302	
Insomnia							
<65	T-DXd (N=209)	13 (6.2)	0.55 (0.27, 1.12)	0.58 (0.30, 1.11)	-0.046 (-0.099, 0.008)	0.38 (0.19, 0.77)	0.3770
	T-DM1 (N=204)	22 (10.8)				0.0055	
>=65	T-DXd (N=48)	2 (4.2)	1.20 (0.16, 8.82)	1.19 (0.17, 8.12)	0.007 (-0.067, 0.081)	1.09 (0.15, 7.72)	
	T-DM1 (N=57)	2 (3.5)				0.9347	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
<65	T-DXd (N=209)	28 (13.4)	1.70 (0.90, 3.22)	1.61 (0.91, 2.85)	0.051 (-0.009, 0.110)	1.03 (0.56, 1.90)	0.1061
	T-DM1 (N=204)	17 (8.3)				0.9245	
>=65	T-DXd (N=48)	4 (8.3)	0.43 (0.12, 1.46)	0.48 (0.16, 1.42)	-0.092 (-0.218, 0.034)	0.36 (0.11, 1.16)	
	T-DM1 (N=57)	10 (17.5)				0.0743	
Cardiac disorders							
Any PT							
<65	T-DXd (N=209)	19 (9.1)	1.94 (0.88, 4.28)	1.85 (0.88, 3.89)	0.042 (-0.007, 0.091)	1.26 (0.58, 2.75)	0.7347
	T-DM1 (N=204)	10 (4.9)				0.5548	
>=65	T-DXd (N=48)	2 (4.2)	2.43 (0.21, 27.71)	2.38 (0.22, 25.39)	0.024 (-0.042, 0.090)	1.49 (0.14, 16.53)	
	T-DM1 (N=57)	1 (1.8)				0.7413	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
<65	T-DXd (N=209)	17 (8.1)	3.52 (1.27, 9.74)	3.32 (1.25, 8.83)	0.057 (0.014, 0.100)	2.23 (0.81, 6.13)	0.3380
	T-DM1 (N=204)	5 (2.5)				0.1102	
>=65	T-DXd (N=48)	4 (8.3)	1.20 (0.28, 5.10)	1.19 (0.31, 4.50)	0.013 (-0.089, 0.116)	0.97 (0.24, 3.90)	
	T-DM1 (N=57)	4 (7.0)				0.9700	
Reproductive system and breast disorders							
Any PT							
<65	T-DXd (N=209)	20 (9.6)	1.33 (0.66, 2.68)	1.30 (0.69, 2.47)	0.022 (-0.031, 0.076)	0.84 (0.43, 1.67)	0.6843
	T-DM1 (N=204)	15 (7.4)				0.6229	
>=65	T-DXd (N=48)	1 (2.1)	0.59 (0.05, 6.66)	0.59 (0.06, 6.35)	-0.014 (-0.077, 0.048)	0.45 (0.04, 5.05)	
	T-DM1 (N=57)	2 (3.5)				0.5092	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
<65	T-DXd (N=209)	14 (6.7)	0.54 (0.27, 1.07)	0.57 (0.30, 1.07)	-0.051 (-0.106, 0.005)	0.44 (0.22, 0.85)	0.1149
	T-DM1 (N=204)	24 (11.8)				0.0132	
>=65	T-DXd (N=48)	6 (12.5)	1.49 (0.42, 5.21)	1.43 (0.46, 4.38)	0.037 (-0.082, 0.156)	1.12 (0.34, 3.71)	
	T-DM1 (N=57)	5 (8.8)				0.8475	
Renal and urinary disorders							
Any PT							
<65	T-DXd (N=209)	12 (5.7)	2.42 (0.84, 7.01)	2.34 (0.84, 6.53)	0.033 (-0.005, 0.071)	1.59 (0.55, 4.58)	0.1663
	T-DM1 (N=204)	5 (2.5)				0.3850	
>=65	T-DXd (N=48)	3 (6.3)	0.57 (0.13, 2.40)	0.59 (0.16, 2.25)	-0.043 (-0.148, 0.062)	0.50 (0.13, 2.01)	
	T-DM1 (N=57)	6 (10.5)				0.3216	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
<75	T-DXd (N=250)	230 (92.0)	8.29 (4.93, 13.96)	1.58 (1.42, 1.77)	0.339 (0.269, 0.408)	2.86 (2.31, 3.53)	0.9235
	T-DM1 (N=253)	147 (58.1)				<.0001	
>=75	T-DXd (N=7)	7 (100)	NE (NE, NE)	1.60 (0.94, 2.74)	0.375 (0.040, 0.710)	2.57 (0.78, 8.40)	
	T-DM1 (N=8)	5 (62.5)				0.0944	
Nausea							
<75	T-DXd (N=250)	189 (75.6)	7.22 (4.86, 10.70)	2.52 (2.06, 3.08)	0.456 (0.378, 0.533)	3.74 (2.86, 4.89)	0.8785
	T-DM1 (N=253)	76 (30.0)				<.0001	
>=75	T-DXd (N=7)	6 (85.7)	10.00 (0.78, 128.77)	2.29 (0.89, 5.88)	0.482 (0.058, 0.906)	3.50 (0.86, 14.23)	
	T-DM1 (N=8)	3 (37.5)				0.0541	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
<75	T-DXd (N=250)	123 (49.2)	8.46 (5.26, 13.60)	4.79 (3.26, 7.04)	0.389 (0.317, 0.462)	5.30 (3.47, 8.10)	0.9795
	T-DM1 (N=253)	26 (10.3)				<.0001	
>=75	T-DXd (N=7)	3 (42.9)	NE (NE, NE)	NE (NE, NE)	0.429 (0.062, 0.795)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.0442	
Constipation							
<75	T-DXd (N=250)	85 (34.0)	2.14 (1.43, 3.22)	1.76 (1.29, 2.38)	0.146 (0.070, 0.223)	1.53 (1.07, 2.18)	0.8712
	T-DM1 (N=253)	49 (19.4)				0.0178	
>=75	T-DXd (N=7)	3 (42.9)	2.25 (0.25, 20.13)	1.71 (0.39, 7.48)	0.179 (-0.295, 0.652)	1.78 (0.30, 10.71)	
	T-DM1 (N=8)	2 (25.0)				0.5205	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
<75	T-DXd (N=250)	73 (29.2)	5.73 (3.26, 10.05)	4.35 (2.64, 7.15)	0.225 (0.161, 0.289)	4.34 (2.56, 7.36)	0.5777
	T-DM1 (N=253)	17 (6.7)				<.0001	
>=75	T-DXd (N=7)	2 (28.6)	2.80 (0.20, 40.06)	2.29 (0.26, 20.13)	0.161 (-0.245, 0.566)	2.20 (0.20, 24.32)	
	T-DM1 (N=8)	1 (12.5)				0.5084	
Stomatitis							
<75	T-DXd (N=250)	39 (15.6)	4.49 (2.19, 9.22)	3.95 (2.01, 7.73)	0.116 (0.065, 0.167)	3.31 (1.65, 6.65)	0.9885
	T-DM1 (N=253)	10 (4.0)				0.0004	
>=75	T-DXd (N=7)	1 (14.3)	NE (NE, NE)	NE (NE, NE)	0.143 (-0.116, 0.402)	NE (NE, NE)	
	T-DM1 (N=8)	0				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
<75	T-DXd (N=250)	28 (11.2)	6.26 (2.37, 16.48)	5.67 (2.22, 14.44)	0.092 (0.050, 0.135)	4.30 (1.65, 11.18)	0.9909
	T-DM1 (N=253)	5 (2.0)				0.0012	
>=75	T-DXd (N=7)	1 (14.3)	NE (NE, NE)	NE (NE, NE)	0.143 (-0.116, 0.402)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.3711	
Dry mouth							
<75	T-DXd (N=250)	8 (3.2)	0.30 (0.13, 0.68)	0.32 (0.15, 0.70)	-0.067 (-0.110, -0.024)	0.25 (0.11, 0.55)	0.9993
	T-DM1 (N=253)	25 (9.9)				0.0002	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
<75	T-DXd (N=250)	159 (63.6)	0.81 (0.56, 1.17)	0.93 (0.82, 1.05)	-0.048 (-0.131, 0.035)	0.62 (0.50, 0.77)	0.4170
	T-DM1 (N=253)	173 (68.4)				<.0001	
>=75	T-DXd (N=7)	3 (42.9)	0.25 (0.03, 2.24)	0.57 (0.22, 1.47)	-0.321 (-0.795, 0.152)	0.34 (0.08, 1.36)	
	T-DM1 (N=8)	6 (75.0)				0.1197	
Neutrophil count decreased							
<75	T-DXd (N=250)	73 (29.2)	3.93 (2.38, 6.50)	3.08 (2.01, 4.72)	0.197 (0.130, 0.264)	2.85 (1.80, 4.53)	0.8808
	T-DM1 (N=253)	24 (9.5)				<.0001	
>=75	T-DXd (N=7)	2 (28.6)	2.80 (0.20, 40.06)	2.29 (0.26, 20.13)	0.161 (-0.245, 0.566)	2.50 (0.22, 27.90)	
	T-DM1 (N=8)	1 (12.5)				0.4420	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
<75	T-DXd (N=250)	66 (26.4)	0.55 (0.38, 0.80)	0.67 (0.52, 0.86)	-0.131 (-0.213, -0.050)	0.47 (0.34, 0.64)	0.9734
	T-DM1 (N=253)	100 (39.5)				<.0001	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	-0.625 (-0.960, -0.290)	NE (NE, NE)	
	T-DM1 (N=8)	5 (62.5)				0.0047	
White blood cell count decreased							
<75	T-DXd (N=250)	58 (23.2)	5.16 (2.79, 9.53)	4.19 (2.40, 7.32)	0.177 (0.117, 0.236)	3.67 (2.04, 6.58)	0.9994
	T-DM1 (N=253)	14 (5.5)				<.0001	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
<75	T-DXd (N=250)	56 (22.4)	0.71 (0.48, 1.06)	0.78 (0.57, 1.05)	-0.065 (-0.141, 0.012)	0.60 (0.42, 0.86)	0.9765
	T-DM1 (N=253)	73 (28.9)				0.0049	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	-0.500 (-0.846, -0.154)	NE (NE, NE)	
	T-DM1 (N=8)	4 (50.0)				0.0292	
Platelet count decreased							
<75	T-DXd (N=250)	54 (21.6)	0.36 (0.25, 0.54)	0.50 (0.38, 0.66)	-0.215 (-0.294, -0.135)	0.33 (0.24, 0.46)	0.9772
	T-DM1 (N=253)	109 (43.1)				<.0001	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	-0.375 (-0.710, -0.040)	NE (NE, NE)	
	T-DM1 (N=8)	3 (37.5)				0.0801	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
<75	T-DXd (N=250)	43 (17.2)	3.30 (1.78, 6.11)	2.90 (1.66, 5.08)	0.113 (0.058, 0.168)	2.24 (1.24, 4.04)	0.9837
	T-DM1 (N=253)	15 (5.9)				0.0062	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	-0.125 (-0.354, 0.104)	NE (NE, NE)	
	T-DM1 (N=8)	1 (12.5)				0.3173	
Blood lactate dehydrogenase increased							
<75	T-DXd (N=250)	17 (6.8)	0.45 (0.25, 0.83)	0.49 (0.28, 0.85)	-0.070 (-0.123, -0.018)	0.37 (0.21, 0.67)	0.9996
	T-DM1 (N=253)	35 (13.8)				0.0007	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
<75	T-DXd (N=250)	14 (5.6)	4.94 (1.40, 17.42)	4.72 (1.37, 16.23)	0.044 (0.013, 0.076)	3.48 (0.99, 12.20)	0.9997
	T-DM1 (N=253)	3 (1.2)				0.0379	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	
General disorders and administration site conditions							
Any PT							
<75	T-DXd (N=250)	154 (61.6)	1.54 (1.08, 2.20)	1.21 (1.03, 1.41)	0.106 (0.020, 0.192)	1.02 (0.81, 1.29)	0.5492
	T-DM1 (N=253)	129 (51.0)				0.8534	
>=75	T-DXd (N=7)	5 (71.4)	2.50 (0.29, 21.39)	1.43 (0.62, 3.30)	0.214 (-0.267, 0.696)	1.53 (0.41, 5.73)	
	T-DM1 (N=8)	4 (50.0)				0.5221	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
<75	T-DXd (N=250)	29 (11.6)	3.19 (1.52, 6.69)	2.93 (1.46, 5.89)	0.076 (0.030, 0.123)	2.64 (1.28, 5.43)	0.9996
	T-DM1 (N=253)	10 (4.0)				0.0064	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	
Pyrexia							
<75	T-DXd (N=250)	26 (10.4)	0.66 (0.39, 1.12)	0.69 (0.43, 1.10)	-0.046 (-0.104, 0.012)	0.44 (0.26, 0.72)	0.6566
	T-DM1 (N=253)	38 (15.0)				0.0011	
>=75	T-DXd (N=7)	1 (14.3)	1.17 (0.06, 22.94)	1.14 (0.09, 15.08)	0.018 (-0.328, 0.364)	0.99 (0.06, 15.94)	
	T-DM1 (N=8)	1 (12.5)				0.9942	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
<75	T-DXd (N=250)	137 (54.8)	2.99 (2.07, 4.32)	1.90 (1.52, 2.38)	0.259 (0.176, 0.343)	1.98 (1.49, 2.64)	0.5660
	T-DM1 (N=253)	73 (28.9)				<.0001	
>=75	T-DXd (N=7)	2 (28.6)	1.20 (0.12, 11.87)	1.14 (0.21, 6.11)	0.036 (-0.414, 0.485)	1.37 (0.19, 9.79)	
	T-DM1 (N=8)	2 (25.0)				0.7507	
Alopecia							
<75	T-DXd (N=250)	93 (37.2)	18.14 (8.57, 38.38)	11.76 (5.84, 23.71)	0.340 (0.277, 0.404)	13.15 (6.38, 27.08)	0.9854
	T-DM1 (N=253)	8 (3.2)				<.0001	
>=75	T-DXd (N=7)	2 (28.6)	NE (NE, NE)	NE (NE, NE)	0.286 (-0.049, 0.620)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.1159	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
<75	T-DXd (N=250)	16 (6.4)	0.68 (0.35, 1.33)	0.70 (0.38, 1.30)	-0.027 (-0.074, 0.020)	0.49 (0.26, 0.95)	0.9876
	T-DM1 (N=253)	23 (9.1)				0.0299	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	-0.125 (-0.354, 0.104)	NE (NE, NE)	
	T-DM1 (N=8)	1 (12.5)				0.3613	
Skin hyperpigmentation							
<75	T-DXd (N=250)	11 (4.4)	NE (NE, NE)	NE (NE, NE)	0.044 (0.019, 0.069)	NE (NE, NE)	0.9990
	T-DM1 (N=253)	0				0.0031	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
<75	T-DXd (N=250)	120 (48.0)	2.15 (1.49, 3.10)	1.60 (1.27, 2.01)	0.180 (0.096, 0.263)	1.61 (1.21, 2.15)	0.2084
	T-DM1 (N=253)	76 (30.0)				0.0011	
>=75	T-DXd (N=7)	2 (28.6)	0.40 (0.05, 3.42)	0.57 (0.15, 2.23)	-0.214 (-0.696, 0.267)	0.57 (0.10, 3.12)	
	T-DM1 (N=8)	4 (50.0)				0.5123	
Decreased appetite							
<75	T-DXd (N=250)	74 (29.6)	2.17 (1.41, 3.34)	1.83 (1.30, 2.56)	0.134 (0.061, 0.206)	1.79 (1.22, 2.62)	0.1633
	T-DM1 (N=253)	41 (16.2)				0.0028	
>=75	T-DXd (N=7)	1 (14.3)	0.28 (0.02, 3.58)	0.38 (0.05, 2.88)	-0.232 (-0.656, 0.192)	0.38 (0.04, 3.70)	
	T-DM1 (N=8)	3 (37.5)				0.3897	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
<75	T-DXd (N=250)	10 (4.0)	NE (NE, NE)	NE (NE, NE)	0.040 (0.016, 0.064)	NE (NE, NE)	0.9999
	T-DM1 (N=253)	0				0.0016	
>=75	T-DXd (N=7)	1 (14.3)	NE (NE, NE)	NE (NE, NE)	0.143 (-0.116, 0.402)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.2850	
Nervous system disorders							
Any PT							
<75	T-DXd (N=250)	114 (45.6)	1.37 (0.96, 1.96)	1.20 (0.98, 1.48)	0.077 (-0.009, 0.163)	0.94 (0.71, 1.23)	0.9372
	T-DM1 (N=253)	96 (37.9)				0.6392	
>=75	T-DXd (N=7)	2 (28.6)	1.20 (0.12, 11.87)	1.14 (0.21, 6.11)	0.036 (-0.414, 0.485)	0.98 (0.14, 6.97)	
	T-DM1 (N=8)	2 (25.0)				0.9822	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
<75	T-DXd (N=250)	19 (7.6)	0.75 (0.40, 1.40)	0.77 (0.43, 1.36)	-0.023 (-0.072, 0.026)	0.54 (0.30, 0.99)	0.9998
	T-DM1 (N=253)	25 (9.9)				0.0435	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	
Infections and infestations							
Any PT							
<75	T-DXd (N=250)	110 (44.0)	1.58 (1.10, 2.27)	1.33 (1.06, 1.66)	0.108 (0.023, 0.193)	1.00 (0.75, 1.33)	0.6977
	T-DM1 (N=253)	84 (33.2)				0.9954	
>=75	T-DXd (N=7)	2 (28.6)	2.80 (0.20, 40.06)	2.29 (0.26, 20.13)	0.161 (-0.245, 0.566)	2.58 (0.23, 28.48)	
	T-DM1 (N=8)	1 (12.5)				0.4228	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
<75	T-DXd (N=250)	105 (42.0)	1.62 (1.13, 2.34)	1.36 (1.08, 1.72)	0.112 (0.028, 0.195)	0.95 (0.70, 1.27)	0.5657
	T-DM1 (N=253)	78 (30.8)				0.7204	
>=75	T-DXd (N=7)	2 (28.6)	2.80 (0.20, 40.06)	2.29 (0.26, 20.13)	0.161 (-0.245, 0.566)	1.91 (0.17, 21.23)	
	T-DM1 (N=8)	1 (12.5)				0.5922	
Epistaxis							
<75	T-DXd (N=250)	29 (11.6)	0.66 (0.40, 1.10)	0.70 (0.45, 1.08)	-0.050 (-0.111, 0.011)	0.41 (0.25, 0.67)	0.9996
	T-DM1 (N=253)	42 (16.6)				0.0002	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
<75	T-DXd (N=250)	18 (7.2)	19.55 (2.59, 147.60)	18.22 (2.45, 135.42)	0.068 (0.035, 0.101)	11.00 (1.46, 82.59)	0.9991
	T-DM1 (N=253)	1 (0.4)				0.0035	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	
Blood and lymphatic system disorders							
Any PT							
<75	T-DXd (N=250)	102 (40.8)	1.70 (1.17, 2.46)	1.41 (1.11, 1.81)	0.119 (0.037, 0.202)	1.19 (0.88, 1.60)	0.3788
	T-DM1 (N=253)	73 (28.9)				0.2642	
>=75	T-DXd (N=7)	1 (14.3)	0.50 (0.04, 7.10)	0.57 (0.06, 5.03)	-0.107 (-0.504, 0.289)	0.44 (0.04, 4.91)	
	T-DM1 (N=8)	2 (25.0)				0.4896	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
<75	T-DXd (N=250)	82 (32.8)	2.38 (1.56, 3.63)	1.93 (1.39, 2.67)	0.158 (0.084, 0.232)	1.66 (1.14, 2.41)	0.6320
	T-DM1 (N=253)	43 (17.0)				0.0069	
>=75	T-DXd (N=7)	1 (14.3)	1.17 (0.06, 22.94)	1.14 (0.09, 15.08)	0.018 (-0.328, 0.364)	0.96 (0.06, 15.46)	
	T-DM1 (N=8)	1 (12.5)				0.9748	
Neutropenia							
<75	T-DXd (N=250)	41 (16.4)	6.89 (3.03, 15.69)	5.93 (2.71, 12.96)	0.136 (0.086, 0.186)	4.58 (2.05, 10.26)	0.9994
	T-DM1 (N=253)	7 (2.8)				<.0001	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
<75	T-DXd (N=250)	13 (5.2)	0.39 (0.20, 0.77)	0.42 (0.23, 0.79)	-0.071 (-0.119, -0.022)	0.31 (0.16, 0.60)	0.9996
	T-DM1 (N=253)	31 (12.3)				0.0002	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	
Musculoskeletal and connective tissue disorders							
Any PT							
<75	T-DXd (N=250)	92 (36.8)	1.11 (0.77, 1.60)	1.07 (0.85, 1.35)	0.024 (-0.060, 0.108)	0.77 (0.57, 1.03)	0.9730
	T-DM1 (N=253)	87 (34.4)				0.0816	
>=75	T-DXd (N=7)	2 (28.6)	NE (NE, NE)	NE (NE, NE)	0.286 (-0.049, 0.620)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.1286	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
<75	T-DXd (N=250)	42 (16.8)	2.23 (1.28, 3.89)	2.02 (1.24, 3.32)	0.085 (0.028, 0.142)	1.52 (0.89, 2.58)	0.9841
	T-DM1 (N=253)	21 (8.3)				0.1215	
>=75	T-DXd (N=7)	3 (42.9)	NE (NE, NE)	NE (NE, NE)	0.429 (0.062, 0.795)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.0537	
Eye disorders							
Any PT							
<75	T-DXd (N=250)	40 (16.0)	1.47 (0.88, 2.46)	1.40 (0.89, 2.18)	0.045 (-0.015, 0.105)	0.91 (0.56, 1.49)	0.9708
	T-DM1 (N=253)	29 (11.5)				0.7172	
>=75	T-DXd (N=7)	1 (14.3)	1.17 (0.06, 22.94)	1.14 (0.09, 15.08)	0.018 (-0.328, 0.364)	1.15 (0.07, 18.46)	
	T-DM1 (N=8)	1 (12.5)				0.9189	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
<75	T-DXd (N=250)	39 (15.6)	1.19 (0.72, 1.96)	1.16 (0.76, 1.78)	0.022 (-0.040, 0.083)	0.82 (0.52, 1.31)	0.9827
	T-DM1 (N=253)	34 (13.4)				0.4147	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	-0.125 (-0.354, 0.104)	NE (NE, NE)	
	T-DM1 (N=8)	1 (12.5)				0.1967	
Insomnia							
<75	T-DXd (N=250)	15 (6.0)	0.61 (0.31, 1.19)	0.63 (0.34, 1.18)	-0.035 (-0.081, 0.012)	0.45 (0.24, 0.87)	0.9997
	T-DM1 (N=253)	24 (9.5)				0.0150	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
<75	T-DXd (N=250)	31 (12.4)	1.29 (0.74, 2.26)	1.25 (0.76, 2.06)	0.025 (-0.030, 0.080)	0.82 (0.48, 1.41)	0.4398
	T-DM1 (N=253)	25 (9.9)				0.4789	
>=75	T-DXd (N=7)	1 (14.3)	0.50 (0.04, 7.10)	0.57 (0.06, 5.03)	-0.107 (-0.504, 0.289)	0.37 (0.03, 4.38)	
	T-DM1 (N=8)	2 (25.0)				0.4167	
Cardiac disorders							
Any PT							
<75	T-DXd (N=250)	21 (8.4)	2.02 (0.95, 4.28)	1.93 (0.95, 3.92)	0.041 (-0.002, 0.083)	1.33 (0.64, 2.79)	0.9999
	T-DM1 (N=253)	11 (4.3)				0.4476	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
<75	T-DXd (N=250)	20 (8.0)	2.36 (1.05, 5.28)	2.25 (1.04, 4.84)	0.044 (0.004, 0.085)	1.56 (0.70, 3.45)	0.9901
	T-DM1 (N=253)	9 (3.6)				0.2722	
>=75	T-DXd (N=7)	1 (14.3)	NE (NE, NE)	NE (NE, NE)	0.143 (-0.116, 0.402)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.3173	
Reproductive system and breast disorders							
Any PT							
<75	T-DXd (N=250)	21 (8.4)	1.27 (0.65, 2.47)	1.25 (0.68, 2.31)	0.017 (-0.029, 0.063)	0.85 (0.45, 1.63)	0.9999
	T-DM1 (N=253)	17 (6.7)				0.6290	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
<75	T-DXd (N=250)	20 (8.0)	0.67 (0.37, 1.22)	0.70 (0.41, 1.20)	-0.035 (-0.086, 0.017)	0.52 (0.29, 0.94)	0.9997
	T-DM1 (N=253)	29 (11.5)				0.0273	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	
Renal and urinary disorders							
Any PT							
<75	T-DXd (N=250)	14 (5.6)	1.31 (0.58, 2.93)	1.29 (0.60, 2.78)	0.013 (-0.025, 0.051)	0.91 (0.41, 2.03)	0.9902
	T-DM1 (N=253)	11 (4.3)				0.8247	
>=75	T-DXd (N=7)	1 (14.3)	NE (NE, NE)	NE (NE, NE)	0.143 (-0.116, 0.402)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.2850	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Asia	T-DXd (N=147)	128 (87.1)	6.01 (3.39, 10.67)	1.65 (1.41, 1.93)	0.342 (0.248, 0.437)	2.74 (2.07, 3.62)	0.3160
	T-DM1 (N=159)	84 (52.8)				<.0001	
North America	T-DXd (N=17)	17 (100)	NE (NE, NE)	1.42 (1.04, 1.93)	0.294 (0.078, 0.511)	1.48 (0.70, 3.12)	
	T-DM1 (N=17)	12 (70.6)				0.2603	
Europe	T-DXd (N=52)	52 (100)	NE (NE, NE)	1.69 (1.34, 2.13)	0.408 (0.271, 0.546)	3.95 (2.44, 6.40)	
	T-DM1 (N=49)	29 (59.2)				<.0001	
Rest of World	T-DXd (N=41)	40 (97.6)	13.33 (1.60, 111.32)	1.30 (1.07, 1.58)	0.226 (0.076, 0.375)	3.46 (2.03, 5.90)	
	T-DM1 (N=36)	27 (75.0)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Nausea							
Asia	T-DXd (N=147)	100 (68.0)	6.12 (3.73, 10.06)	2.64 (1.98, 3.51)	0.422 (0.321, 0.524)	3.72 (2.58, 5.36)	0.1529
	T-DM1 (N=159)	41 (25.8)				<.0001	
North America	T-DXd (N=17)	15 (88.2)	5.25 (0.90, 30.61)	1.50 (0.97, 2.31)	0.294 (0.014, 0.574)	1.56 (0.70, 3.48)	
	T-DM1 (N=17)	10 (58.8)				0.2251	
Europe	T-DXd (N=52)	45 (86.5)	16.07 (5.86, 44.09)	3.03 (1.92, 4.78)	0.580 (0.423, 0.737)	5.12 (2.79, 9.40)	
	T-DM1 (N=49)	14 (28.6)				<.0001	
Rest of World	T-DXd (N=41)	35 (85.4)	9.17 (3.07, 27.39)	2.20 (1.43, 3.37)	0.465 (0.272, 0.657)	3.48 (1.86, 6.49)	
	T-DM1 (N=36)	14 (38.9)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Asia	T-DXd (N=147)	70 (47.6)	8.73 (4.68, 16.26)	5.05 (3.03, 8.41)	0.382 (0.289, 0.474)	5.49 (3.14, 9.60)	0.4459
	T-DM1 (N=159)	15 (9.4)				<.0001	
North America	T-DXd (N=17)	11 (64.7)	8.56 (1.74, 42.17)	3.67 (1.24, 10.85)	0.471 (0.180, 0.761)	3.59 (1.00, 12.87)	
	T-DM1 (N=17)	3 (17.6)				0.0339	
Europe	T-DXd (N=52)	25 (48.1)	21.76 (4.78, 99.10)	11.78 (2.94, 47.12)	0.440 (0.293, 0.587)	13.43 (3.18, 56.80)	
	T-DM1 (N=49)	2 (4.1)				<.0001	
Rest of World	T-DXd (N=41)	20 (48.8)	4.76 (1.63, 13.87)	2.93 (1.32, 6.48)	0.321 (0.126, 0.517)	3.50 (1.40, 8.73)	
	T-DM1 (N=36)	6 (16.7)				0.0043	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Constipation							
Asia	T-DXd (N=147)	50 (34.0)	2.22 (1.31, 3.74)	1.80 (1.22, 2.67)	0.151 (0.054, 0.249)	1.68 (1.06, 2.64)	0.1517
	T-DM1 (N=159)	30 (18.9)				0.0253	
North America	T-DXd (N=17)	7 (41.2)	0.79 (0.20, 3.06)	0.88 (0.41, 1.87)	-0.059 (-0.392, 0.274)	0.63 (0.22, 1.78)	
	T-DM1 (N=17)	8 (47.1)				0.3730	
Europe	T-DXd (N=52)	22 (42.3)	3.76 (1.47, 9.58)	2.59 (1.28, 5.26)	0.260 (0.090, 0.429)	2.35 (1.05, 5.28)	
	T-DM1 (N=49)	8 (16.3)				0.0331	
Rest of World	T-DXd (N=41)	9 (22.0)	1.74 (0.53, 5.79)	1.58 (0.58, 4.28)	0.081 (-0.089, 0.250)	1.19 (0.40, 3.57)	
	T-DM1 (N=36)	5 (13.9)				0.7590	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Asia	T-DXd (N=147)	35 (23.8)	7.97 (3.24, 19.59)	6.31 (2.73, 14.56)	0.200 (0.125, 0.275)	6.04 (2.54, 14.40)	0.2679
	T-DM1 (N=159)	6 (3.8)				<.0001	
North America	T-DXd (N=17)	4 (23.5)	4.92 (0.49, 49.61)	4.00 (0.50, 32.20)	0.176 (-0.054, 0.407)	4.02 (0.45, 35.99)	
	T-DM1 (N=17)	1 (5.9)				0.1789	
Europe	T-DXd (N=52)	24 (46.2)	7.54 (2.58, 22.07)	4.52 (1.87, 10.92)	0.359 (0.200, 0.519)	5.44 (2.07, 14.27)	
	T-DM1 (N=49)	5 (10.2)				0.0001	
Rest of World	T-DXd (N=41)	12 (29.3)	2.07 (0.69, 6.25)	1.76 (0.73, 4.20)	0.126 (-0.059, 0.311)	1.66 (0.62, 4.44)	
	T-DM1 (N=36)	6 (16.7)				0.3102	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Stomatitis							
Asia	T-DXd (N=147)	24 (16.3)	3.68 (1.60, 8.49)	3.24 (1.51, 6.99)	0.113 (0.044, 0.182)	2.54 (1.13, 5.69)	0.9998
	T-DM1 (N=159)	8 (5.0)				0.0190	
North America	T-DXd (N=17)	3 (17.6)	NE (NE, NE)	NE (NE, NE)	0.176 (-0.005, 0.358)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.1191	
Europe	T-DXd (N=52)	6 (11.5)	3.06 (0.59, 15.98)	2.83 (0.60, 13.35)	0.075 (-0.028, 0.178)	2.57 (0.52, 12.80)	
	T-DM1 (N=49)	2 (4.1)				0.2286	
Rest of World	T-DXd (N=41)	7 (17.1)	NE (NE, NE)	NE (NE, NE)	0.171 (0.056, 0.286)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.0187	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Asia	T-DXd (N=147)	9 (6.1)	10.30 (1.29, 82.28)	9.73 (1.25, 75.90)	0.055 (0.014, 0.096)	7.72 (0.97, 61.38)	0.5581
	T-DM1 (N=159)	1 (0.6)				0.0230	
North America	T-DXd (N=17)	4 (23.5)	2.31 (0.36, 14.72)	2.00 (0.42, 9.50)	0.118 (-0.136, 0.371)	1.32 (0.24, 7.41)	
	T-DM1 (N=17)	2 (11.8)				0.7507	
Europe	T-DXd (N=52)	8 (15.4)	8.73 (1.05, 72.60)	7.54 (0.98, 58.09)	0.133 (0.028, 0.239)	6.34 (0.79, 50.97)	
	T-DM1 (N=49)	1 (2.0)				0.0465	
Rest of World	T-DXd (N=41)	8 (19.5)	8.48 (1.01, 71.57)	7.02 (0.92, 53.49)	0.167 (0.035, 0.300)	5.14 (0.64, 41.49)	
	T-DM1 (N=36)	1 (2.8)				0.0880	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Dry mouth							
Asia	T-DXd (N=147)	5 (3.4)	0.34 (0.12, 0.95)	0.36 (0.13, 0.97)	-0.060 (-0.114, -0.006)	0.26 (0.09, 0.72)	0.8333
	T-DM1 (N=159)	15 (9.4)				0.0057	
North America	T-DXd (N=17)	1 (5.9)	0.29 (0.03, 3.13)	0.33 (0.04, 2.89)	-0.118 (-0.331, 0.095)	0.27 (0.03, 2.61)	
	T-DM1 (N=17)	3 (17.6)				0.2242	
Europe	T-DXd (N=52)	0	NE (NE, NE)	NE (NE, NE)	-0.102 (-0.187, -0.017)	NE (NE, NE)	
	T-DM1 (N=49)	5 (10.2)				0.0122	
Rest of World	T-DXd (N=41)	2 (4.9)	0.87 (0.12, 6.53)	0.88 (0.13, 5.92)	-0.007 (-0.107, 0.093)	0.68 (0.09, 5.01)	
	T-DM1 (N=36)	2 (5.6)				0.7058	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Asia	T-DXd (N=147)	100 (68.0)	0.62 (0.37, 1.03)	0.88 (0.77, 1.01)	-0.093 (-0.193, 0.006)	0.52 (0.39, 0.67)	0.0530
	T-DM1 (N=159)	123 (77.4)				<.0001	
North America	T-DXd (N=17)	11 (64.7)	4.40 (1.04, 18.60)	2.20 (0.97, 4.97)	0.353 (0.039, 0.667)	2.32 (0.80, 6.69)	
	T-DM1 (N=17)	5 (29.4)				0.1050	
Europe	T-DXd (N=52)	26 (50.0)	0.69 (0.31, 1.52)	0.84 (0.59, 1.21)	-0.092 (-0.285, 0.102)	0.59 (0.35, 1.01)	
	T-DM1 (N=49)	29 (59.2)				0.0569	
Rest of World	T-DXd (N=41)	25 (61.0)	0.99 (0.40, 2.49)	1.00 (0.70, 1.43)	-0.001 (-0.220, 0.217)	0.71 (0.40, 1.28)	
	T-DM1 (N=36)	22 (61.1)				0.2680	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
Asia	T-DXd (N=147)	62 (42.2)	4.31 (2.49, 7.47)	2.92 (1.91, 4.45)	0.277 (0.180, 0.374)	2.84 (1.76, 4.59)	0.9233
	T-DM1 (N=159)	23 (14.5)				<.0001	
North America	T-DXd (N=17)	1 (5.9)	NE (NE, NE)	NE (NE, NE)	0.059 (-0.053, 0.171)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.4008	
Europe	T-DXd (N=52)	6 (11.5)	6.26 (0.73, 54.03)	5.65 (0.71, 45.29)	0.095 (0.000, 0.190)	5.02 (0.60, 41.77)	
	T-DM1 (N=49)	1 (2.0)				0.0969	
Rest of World	T-DXd (N=41)	6 (14.6)	6.00 (0.69, 52.46)	5.27 (0.67, 41.71)	0.119 (-0.002, 0.239)	4.30 (0.52, 35.84)	
	T-DM1 (N=36)	1 (2.8)				0.1417	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
Asia	T-DXd (N=147)	38 (25.9)	0.50 (0.31, 0.82)	0.63 (0.45, 0.88)	-0.150 (-0.254, -0.046)	0.43 (0.29, 0.65)	0.9439
	T-DM1 (N=159)	65 (40.9)				<.0001	
North America	T-DXd (N=17)	1 (5.9)	0.47 (0.04, 5.72)	0.50 (0.05, 5.01)	-0.059 (-0.248, 0.131)	0.47 (0.04, 5.18)	
	T-DM1 (N=17)	2 (11.8)				0.5352	
Europe	T-DXd (N=52)	14 (26.9)	0.58 (0.25, 1.35)	0.69 (0.39, 1.23)	-0.119 (-0.301, 0.064)	0.53 (0.26, 1.06)	
	T-DM1 (N=49)	19 (38.8)				0.0706	
Rest of World	T-DXd (N=41)	13 (31.7)	0.42 (0.16, 1.05)	0.60 (0.35, 1.04)	-0.211 (-0.427, 0.006)	0.34 (0.16, 0.72)	
	T-DM1 (N=36)	19 (52.8)				0.0035	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
Asia	T-DXd (N=147)	52 (35.4)	6.15 (3.18, 11.90)	4.33 (2.46, 7.61)	0.272 (0.184, 0.360)	3.91 (2.12, 7.20)	0.7436
	T-DM1 (N=159)	13 (8.2)				<.0001	
North America	T-DXd (N=17)	1 (5.9)	1.00 (0.06, 17.41)	1.00 (0.07, 14.72)	0.000 (-0.158, 0.158)	0.83 (0.05, 13.46)	
	T-DM1 (N=17)	1 (5.9)				0.8969	
Europe	T-DXd (N=52)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=49)	0				NE	
Rest of World	T-DXd (N=41)	5 (12.2)	NE (NE, NE)	NE (NE, NE)	0.122 (0.022, 0.222)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.0572	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
Asia	T-DXd (N=147)	30 (20.4)	0.53 (0.31, 0.89)	0.62 (0.42, 0.92)	-0.123 (-0.221, -0.025)	0.46 (0.29, 0.73)	0.6852
	T-DM1 (N=159)	52 (32.7)				0.0007	
North America	T-DXd (N=17)	1 (5.9)	NE (NE, NE)	NE (NE, NE)	0.059 (-0.053, 0.171)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.3173	
Europe	T-DXd (N=52)	13 (25.0)	0.83 (0.34, 2.01)	0.88 (0.46, 1.67)	-0.036 (-0.208, 0.137)	0.71 (0.33, 1.51)	
	T-DM1 (N=49)	14 (28.6)				0.3776	
Rest of World	T-DXd (N=41)	12 (29.3)	0.94 (0.35, 2.50)	0.96 (0.48, 1.90)	-0.013 (-0.218, 0.192)	0.76 (0.33, 1.73)	
	T-DM1 (N=36)	11 (30.6)				0.5198	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Asia	T-DXd (N=147)	46 (31.3)	0.31 (0.19, 0.49)	0.52 (0.40, 0.69)	-0.285 (-0.391, -0.178)	0.30 (0.21, 0.43)	0.3951
	T-DM1 (N=159)	95 (59.7)				<.0001	
North America	T-DXd (N=17)	2 (11.8)	1.00 (0.12, 8.06)	1.00 (0.16, 6.30)	0.000 (-0.217, 0.217)	0.73 (0.10, 5.20)	
	T-DM1 (N=17)	2 (11.8)				0.7491	
Europe	T-DXd (N=52)	2 (3.8)	0.16 (0.03, 0.75)	0.19 (0.04, 0.82)	-0.166 (-0.290, -0.041)	0.16 (0.04, 0.74)	
	T-DM1 (N=49)	10 (20.4)				0.0076	
Rest of World	T-DXd (N=41)	4 (9.8)	0.67 (0.17, 2.71)	0.70 (0.20, 2.42)	-0.041 (-0.186, 0.104)	0.49 (0.13, 1.85)	
	T-DM1 (N=36)	5 (13.9)				0.2856	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
Asia	T-DXd (N=147)	30 (20.4)	3.14 (1.54, 6.40)	2.70 (1.44, 5.08)	0.129 (0.052, 0.206)	1.94 (0.99, 3.81)	0.7814
	T-DM1 (N=159)	12 (7.5)				0.0496	
North America	T-DXd (N=17)	5 (29.4)	NE (NE, NE)	NE (NE, NE)	0.294 (0.078, 0.511)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.0265	
Europe	T-DXd (N=52)	4 (7.7)	4.00 (0.43, 37.11)	3.77 (0.44, 32.56)	0.057 (-0.026, 0.139)	3.39 (0.38, 30.34)	
	T-DM1 (N=49)	1 (2.0)				0.2461	
Rest of World	T-DXd (N=41)	4 (9.8)	1.19 (0.25, 5.71)	1.17 (0.28, 4.88)	0.014 (-0.114, 0.142)	0.85 (0.19, 3.85)	
	T-DM1 (N=36)	3 (8.3)				0.8294	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
Asia	T-DXd (N=147)	11 (7.5)	0.50 (0.24, 1.08)	0.54 (0.27, 1.08)	-0.064 (-0.132, 0.005)	0.42 (0.20, 0.88)	0.9950
	T-DM1 (N=159)	22 (13.8)				0.0189	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	-0.059 (-0.171, 0.053)	NE (NE, NE)	
	T-DM1 (N=17)	1 (5.9)				0.2705	
Europe	T-DXd (N=52)	0	NE (NE, NE)	NE (NE, NE)	-0.061 (-0.128, 0.006)	NE (NE, NE)	
	T-DM1 (N=49)	3 (6.1)				0.0693	
Rest of World	T-DXd (N=41)	6 (14.6)	0.51 (0.16, 1.62)	0.59 (0.23, 1.49)	-0.104 (-0.282, 0.074)	0.40 (0.14, 1.16)	
	T-DM1 (N=36)	9 (25.0)				0.0813	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
Asia	T-DXd (N=147)	3 (2.0)	1.64 (0.27, 9.93)	1.62 (0.27, 9.57)	0.008 (-0.021, 0.037)	1.07 (0.17, 6.56)	0.9566
	T-DM1 (N=159)	2 (1.3)				0.9442	
North America	T-DXd (N=17)	3 (17.6)	3.43 (0.32, 36.82)	3.00 (0.35, 26.04)	0.118 (-0.095, 0.331)	2.63 (0.27, 25.40)	
	T-DM1 (N=17)	1 (5.9)				0.3866	
Europe	T-DXd (N=52)	3 (5.8)	NE (NE, NE)	NE (NE, NE)	0.058 (-0.006, 0.121)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.1429	
Rest of World	T-DXd (N=41)	5 (12.2)	NE (NE, NE)	NE (NE, NE)	0.122 (0.022, 0.222)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.0590	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
Asia	T-DXd (N=147)	87 (59.2)	1.58 (1.01, 2.49)	1.24 (1.00, 1.53)	0.114 (0.003, 0.225)	1.03 (0.75, 1.40)	0.8282
	T-DM1 (N=159)	76 (47.8)				0.8487	
North America	T-DXd (N=17)	13 (76.5)	2.89 (0.66, 12.57)	1.44 (0.86, 2.43)	0.235 (-0.076, 0.547)	1.48 (0.63, 3.48)	
	T-DM1 (N=17)	9 (52.9)				0.3646	
Europe	T-DXd (N=52)	38 (73.1)	1.58 (0.68, 3.67)	1.16 (0.88, 1.51)	0.098 (-0.083, 0.279)	1.09 (0.68, 1.75)	
	T-DM1 (N=49)	31 (63.3)				0.7275	
Rest of World	T-DXd (N=41)	21 (51.2)	1.17 (0.48, 2.88)	1.08 (0.69, 1.71)	0.040 (-0.184, 0.264)	0.89 (0.46, 1.69)	
	T-DM1 (N=36)	17 (47.2)				0.7141	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Asia	T-DXd (N=147)	27 (18.4)	3.75 (1.70, 8.28)	3.24 (1.58, 6.67)	0.127 (0.055, 0.199)	3.03 (1.42, 6.46)	0.8487
	T-DM1 (N=159)	9 (5.7)				0.0026	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	1 (1.9)	0.94 (0.06, 15.47)	0.94 (0.06, 14.65)	-0.001 (-0.056, 0.053)	0.54 (0.03, 9.65)	
	T-DM1 (N=49)	1 (2.0)				0.6734	
Rest of World	T-DXd (N=41)	1 (2.4)	NE (NE, NE)	NE (NE, NE)	0.024 (-0.023, 0.072)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.3930	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Pyrexia							
Asia	T-DXd (N=147)	20 (13.6)	0.84 (0.45, 1.59)	0.87 (0.50, 1.49)	-0.021 (-0.100, 0.058)	0.59 (0.32, 1.07)	0.7495
	T-DM1 (N=159)	25 (15.7)				0.0780	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	4 (7.7)	0.43 (0.12, 1.52)	0.47 (0.15, 1.47)	-0.086 (-0.213, 0.040)	0.27 (0.08, 0.91)	
	T-DM1 (N=49)	8 (16.3)				0.0244	
Rest of World	T-DXd (N=41)	3 (7.3)	0.39 (0.09, 1.71)	0.44 (0.12, 1.63)	-0.093 (-0.239, 0.052)	0.30 (0.07, 1.22)	
	T-DM1 (N=36)	6 (16.7)				0.0762	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Asia	T-DXd (N=147)	84 (57.1)	3.60 (2.23, 5.81)	2.11 (1.58, 2.83)	0.301 (0.195, 0.407)	2.25 (1.55, 3.26)	0.6157
	T-DM1 (N=159)	43 (27.0)				<.0001	
North America	T-DXd (N=17)	4 (23.5)	1.44 (0.27, 7.68)	1.33 (0.35, 5.08)	0.059 (-0.212, 0.330)	1.27 (0.28, 5.69)	
	T-DM1 (N=17)	3 (17.6)				0.7550	
Europe	T-DXd (N=52)	27 (51.9)	2.23 (0.99, 5.00)	1.59 (0.98, 2.57)	0.193 (0.004, 0.382)	1.54 (0.83, 2.87)	
	T-DM1 (N=49)	16 (32.7)				0.1682	
Rest of World	T-DXd (N=41)	24 (58.5)	2.50 (0.99, 6.27)	1.62 (0.98, 2.69)	0.224 (0.007, 0.442)	1.86 (0.94, 3.66)	
	T-DM1 (N=36)	13 (36.1)				0.0695	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Alopecia							
Asia	T-DXd (N=147)	56 (38.1)	15.69 (6.50, 37.85)	10.10 (4.48, 22.73)	0.343 (0.259, 0.427)	11.24 (4.84, 26.10)	0.9986
	T-DM1 (N=159)	6 (3.8)				<.0001	
North America	T-DXd (N=17)	3 (17.6)	NE (NE, NE)	NE (NE, NE)	0.176 (-0.005, 0.358)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.0739	
Europe	T-DXd (N=52)	17 (32.7)	NE (NE, NE)	NE (NE, NE)	0.327 (0.199, 0.454)	NE (NE, NE)	
	T-DM1 (N=49)	0				<.0001	
Rest of World	T-DXd (N=41)	19 (46.3)	14.68 (3.11, 69.34)	8.34 (2.08, 33.37)	0.408 (0.238, 0.578)	9.69 (2.25, 41.62)	
	T-DM1 (N=36)	2 (5.6)				0.0002	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
Asia	T-DXd (N=147)	9 (6.1)	0.54 (0.23, 1.26)	0.57 (0.26, 1.24)	-0.046 (-0.107, 0.016)	0.35 (0.15, 0.79)	0.7682
	T-DM1 (N=159)	17 (10.7)				0.0091	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	3 (5.8)	0.69 (0.15, 3.25)	0.71 (0.17, 3.00)	-0.024 (-0.123, 0.076)	0.58 (0.13, 2.63)	
	T-DM1 (N=49)	4 (8.2)				0.4746	
Rest of World	T-DXd (N=41)	4 (9.8)	1.19 (0.25, 5.71)	1.17 (0.28, 4.88)	0.014 (-0.114, 0.142)	0.98 (0.22, 4.45)	
	T-DM1 (N=36)	3 (8.3)				0.9899	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Skin hyperpigmentation							
Asia	T-DXd (N=147)	8 (5.4)	NE (NE, NE)	NE (NE, NE)	0.054 (0.018, 0.091)	NE (NE, NE)	1.0000
	T-DM1 (N=159)	0				0.0106	
North America	T-DXd (N=17)	1 (5.9)	NE (NE, NE)	NE (NE, NE)	0.059 (-0.053, 0.171)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.4008	
Europe	T-DXd (N=52)	1 (1.9)	NE (NE, NE)	NE (NE, NE)	0.019 (-0.018, 0.057)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.3833	
Rest of World	T-DXd (N=41)	1 (2.4)	NE (NE, NE)	NE (NE, NE)	0.024 (-0.023, 0.072)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.3945	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Asia	T-DXd (N=147)	72 (49.0)	1.87 (1.18, 2.96)	1.44 (1.10, 1.89)	0.150 (0.041, 0.259)	1.50 (1.05, 2.13)	0.9320
	T-DM1 (N=159)	54 (34.0)				0.0268	
North America	T-DXd (N=17)	10 (58.8)	3.43 (0.83, 14.21)	2.00 (0.87, 4.62)	0.294 (-0.025, 0.613)	1.98 (0.68, 5.81)	
	T-DM1 (N=17)	5 (29.4)				0.2014	
Europe	T-DXd (N=52)	21 (40.4)	2.34 (0.98, 5.59)	1.80 (0.97, 3.33)	0.179 (0.002, 0.357)	1.82 (0.88, 3.78)	
	T-DM1 (N=49)	11 (22.4)				0.1037	
Rest of World	T-DXd (N=41)	19 (46.3)	2.25 (0.87, 5.82)	1.67 (0.90, 3.11)	0.186 (-0.026, 0.397)	1.50 (0.69, 3.26)	
	T-DM1 (N=36)	10 (27.8)				0.3036	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Decreased appetite							
Asia	T-DXd (N=147)	48 (32.7)	2.17 (1.28, 3.69)	1.79 (1.20, 2.68)	0.144 (0.047, 0.241)	1.75 (1.10, 2.78)	0.9119
	T-DM1 (N=159)	29 (18.2)				0.0180	
North America	T-DXd (N=17)	3 (17.6)	1.61 (0.23, 11.09)	1.50 (0.29, 7.87)	0.059 (-0.178, 0.296)	1.41 (0.23, 8.48)	
	T-DM1 (N=17)	2 (11.8)				0.7051	
Europe	T-DXd (N=52)	12 (23.1)	1.54 (0.57, 4.16)	1.41 (0.63, 3.16)	0.068 (-0.087, 0.222)	1.38 (0.56, 3.37)	
	T-DM1 (N=49)	8 (16.3)				0.4830	
Rest of World	T-DXd (N=41)	12 (29.3)	2.57 (0.80, 8.18)	2.11 (0.82, 5.41)	0.154 (-0.026, 0.333)	2.12 (0.74, 6.02)	
	T-DM1 (N=36)	5 (13.9)				0.1536	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
Asia	T-DXd (N=147)	3 (2.0)	NE (NE, NE)	NE (NE, NE)	0.020 (-0.002, 0.043)	NE (NE, NE)	1.0000
	T-DM1 (N=159)	0				0.0737	
North America	T-DXd (N=17)	5 (29.4)	NE (NE, NE)	NE (NE, NE)	0.294 (0.078, 0.511)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.0228	
Europe	T-DXd (N=52)	1 (1.9)	NE (NE, NE)	NE (NE, NE)	0.019 (-0.018, 0.057)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.3317	
Rest of World	T-DXd (N=41)	2 (4.9)	NE (NE, NE)	NE (NE, NE)	0.049 (-0.017, 0.115)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.1824	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
Asia	T-DXd (N=147)	51 (34.7)	1.16 (0.72, 1.87)	1.10 (0.80, 1.52)	0.032 (-0.073, 0.138)	0.83 (0.56, 1.24)	0.8881
	T-DM1 (N=159)	50 (31.4)				0.3639	
North America	T-DXd (N=17)	10 (58.8)	2.62 (0.65, 10.48)	1.67 (0.78, 3.55)	0.235 (-0.091, 0.561)	1.25 (0.45, 3.47)	
	T-DM1 (N=17)	6 (35.3)				0.6688	
Europe	T-DXd (N=52)	27 (51.9)	1.33 (0.61, 2.90)	1.16 (0.77, 1.74)	0.070 (-0.124, 0.265)	0.85 (0.49, 1.50)	
	T-DM1 (N=49)	22 (44.9)				0.5932	
Rest of World	T-DXd (N=41)	28 (68.3)	1.72 (0.68, 4.37)	1.23 (0.86, 1.76)	0.127 (-0.089, 0.343)	0.94 (0.52, 1.68)	
	T-DM1 (N=36)	20 (55.6)				0.8540	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
Asia	T-DXd (N=147)	15 (10.2)	0.84 (0.41, 1.72)	0.85 (0.45, 1.62)	-0.017 (-0.088, 0.053)	0.56 (0.28, 1.11)	0.9995
	T-DM1 (N=159)	19 (11.9)				0.0914	
North America	T-DXd (N=17)	1 (5.9)	NE (NE, NE)	NE (NE, NE)	0.059 (-0.053, 0.171)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.4008	
Europe	T-DXd (N=52)	0	NE (NE, NE)	NE (NE, NE)	-0.061 (-0.128, 0.006)	NE (NE, NE)	
	T-DM1 (N=49)	3 (6.1)				0.0492	
Rest of World	T-DXd (N=41)	3 (7.3)	0.87 (0.16, 4.60)	0.88 (0.19, 4.08)	-0.010 (-0.131, 0.110)	0.71 (0.14, 3.55)	
	T-DM1 (N=36)	3 (8.3)				0.6711	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
Asia	T-DXd (N=147)	61 (41.5)	1.69 (1.05, 2.71)	1.40 (1.03, 1.91)	0.119 (0.013, 0.226)	1.02 (0.69, 1.50)	0.2707
	T-DM1 (N=159)	47 (29.6)				0.9282	
North America	T-DXd (N=17)	8 (47.1)	6.66 (1.15, 38.58)	4.00 (0.99, 16.16)	0.353 (0.071, 0.635)	4.24 (0.90, 20.01)	
	T-DM1 (N=17)	2 (11.8)				0.0468	
Europe	T-DXd (N=52)	21 (40.4)	1.17 (0.52, 2.60)	1.10 (0.67, 1.80)	0.036 (-0.153, 0.226)	0.83 (0.44, 1.58)	
	T-DM1 (N=49)	18 (36.7)				0.5718	
Rest of World	T-DXd (N=41)	22 (53.7)	1.16 (0.47, 2.84)	1.07 (0.70, 1.65)	0.037 (-0.187, 0.260)	0.81 (0.43, 1.53)	
	T-DM1 (N=36)	18 (50.0)				0.5238	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Asia	T-DXd (N=147)	60 (40.8)	1.98 (1.22, 3.22)	1.58 (1.14, 2.20)	0.150 (0.046, 0.255)	1.07 (0.72, 1.61)	0.3182
	T-DM1 (N=159)	41 (25.8)				0.7260	
North America	T-DXd (N=17)	10 (58.8)	1.27 (0.33, 4.93)	1.11 (0.61, 2.02)	0.059 (-0.274, 0.392)	0.75 (0.30, 1.86)	
	T-DM1 (N=17)	9 (52.9)				0.5342	
Europe	T-DXd (N=52)	17 (32.7)	0.84 (0.37, 1.90)	0.89 (0.52, 1.52)	-0.040 (-0.226, 0.145)	0.64 (0.32, 1.25)	
	T-DM1 (N=49)	18 (36.7)				0.1859	
Rest of World	T-DXd (N=41)	20 (48.8)	2.16 (0.85, 5.52)	1.60 (0.89, 2.86)	0.182 (-0.032, 0.397)	1.23 (0.59, 2.57)	
	T-DM1 (N=36)	11 (30.6)				0.5857	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Epistaxis							
Asia	T-DXd (N=147)	14 (9.5)	0.82 (0.39, 1.72)	0.84 (0.43, 1.63)	-0.018 (-0.086, 0.050)	0.47 (0.23, 0.96)	0.5680
	T-DM1 (N=159)	18 (11.3)				0.0355	
North America	T-DXd (N=17)	3 (17.6)	0.70 (0.13, 3.72)	0.75 (0.20, 2.86)	-0.059 (-0.330, 0.212)	0.52 (0.11, 2.39)	
	T-DM1 (N=17)	4 (23.5)				0.3947	
Europe	T-DXd (N=52)	6 (11.5)	0.33 (0.11, 0.93)	0.40 (0.17, 0.97)	-0.170 (-0.324, -0.017)	0.23 (0.08, 0.63)	
	T-DM1 (N=49)	14 (28.6)				0.0021	
Rest of World	T-DXd (N=41)	6 (14.6)	0.86 (0.25, 2.94)	0.88 (0.31, 2.48)	-0.020 (-0.183, 0.143)	0.54 (0.17, 1.71)	
	T-DM1 (N=36)	6 (16.7)				0.2921	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
Asia	T-DXd (N=147)	10 (6.8)	11.53 (1.46, 91.24)	10.82 (1.40, 83.46)	0.062 (0.019, 0.104)	5.27 (0.67, 41.40)	1.0000
	T-DM1 (N=159)	1 (0.6)				0.0774	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	2 (3.8)	NE (NE, NE)	NE (NE, NE)	0.038 (-0.014, 0.091)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.2615	
Rest of World	T-DXd (N=41)	6 (14.6)	NE (NE, NE)	NE (NE, NE)	0.146 (0.038, 0.255)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.0331	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Asia	T-DXd (N=147)	57 (38.8)	2.09 (1.27, 3.43)	1.67 (1.18, 2.36)	0.155 (0.052, 0.258)	1.43 (0.94, 2.16)	0.2209
	T-DM1 (N=159)	37 (23.3)				0.0926	
North America	T-DXd (N=17)	6 (35.3)	2.55 (0.52, 12.55)	2.00 (0.60, 6.72)	0.176 (-0.114, 0.467)	1.18 (0.27, 5.05)	
	T-DM1 (N=17)	3 (17.6)				0.8266	
Europe	T-DXd (N=52)	13 (25.0)	0.69 (0.29, 1.63)	0.77 (0.41, 1.42)	-0.077 (-0.253, 0.100)	0.58 (0.28, 1.22)	
	T-DM1 (N=49)	16 (32.7)				0.1479	
Rest of World	T-DXd (N=41)	27 (65.9)	1.73 (0.69, 4.33)	1.25 (0.85, 1.82)	0.131 (-0.088, 0.349)	1.17 (0.65, 2.11)	
	T-DM1 (N=36)	19 (52.8)				0.5924	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
Asia	T-DXd (N=147)	51 (34.7)	2.60 (1.52, 4.44)	2.04 (1.36, 3.08)	0.177 (0.081, 0.274)	1.80 (1.13, 2.89)	0.6934
	T-DM1 (N=159)	27 (17.0)				0.0123	
North America	T-DXd (N=17)	4 (23.5)	2.31 (0.36, 14.72)	2.00 (0.42, 9.50)	0.118 (-0.136, 0.371)	0.94 (0.15, 5.74)	
	T-DM1 (N=17)	2 (11.8)				0.9471	
Europe	T-DXd (N=52)	9 (17.3)	1.26 (0.43, 3.68)	1.21 (0.49, 3.00)	0.030 (-0.112, 0.172)	0.96 (0.35, 2.60)	
	T-DM1 (N=49)	7 (14.3)				0.9377	
Rest of World	T-DXd (N=41)	19 (46.3)	3.02 (1.12, 8.19)	2.09 (1.04, 4.18)	0.241 (0.037, 0.445)	2.00 (0.87, 4.58)	
	T-DM1 (N=36)	8 (22.2)				0.0950	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
Asia	T-DXd (N=147)	11 (7.5)	6.35 (1.38, 29.15)	5.95 (1.34, 26.39)	0.062 (0.016, 0.108)	4.28 (0.94, 19.58)	0.9024
	T-DM1 (N=159)	2 (1.3)				0.0419	
North America	T-DXd (N=17)	2 (11.8)	2.13 (0.17, 26.03)	2.00 (0.20, 20.04)	0.059 (-0.131, 0.248)	1.83 (0.16, 20.38)	
	T-DM1 (N=17)	1 (5.9)				0.6164	
Europe	T-DXd (N=52)	9 (17.3)	NE (NE, NE)	NE (NE, NE)	0.173 (0.070, 0.276)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.0050	
Rest of World	T-DXd (N=41)	19 (46.3)	6.91 (2.07, 23.10)	4.17 (1.56, 11.12)	0.352 (0.168, 0.536)	3.87 (1.31, 11.40)	
	T-DM1 (N=36)	4 (11.1)				0.0082	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
Asia	T-DXd (N=147)	3 (2.0)	0.28 (0.08, 1.03)	0.29 (0.08, 1.04)	-0.049 (-0.094, -0.003)	0.25 (0.07, 0.90)	0.2774
	T-DM1 (N=159)	11 (6.9)				0.0225	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	-0.118 (-0.271, 0.036)	NE (NE, NE)	
	T-DM1 (N=17)	2 (11.8)				0.0797	
Europe	T-DXd (N=52)	1 (1.9)	0.10 (0.01, 0.84)	0.12 (0.02, 0.91)	-0.144 (-0.254, -0.034)	0.09 (0.01, 0.71)	
	T-DM1 (N=49)	8 (16.3)				0.0042	
Rest of World	T-DXd (N=41)	9 (22.0)	0.73 (0.26, 2.07)	0.79 (0.36, 1.73)	-0.058 (-0.252, 0.135)	0.60 (0.24, 1.49)	
	T-DM1 (N=36)	10 (27.8)				0.2593	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
Asia	T-DXd (N=147)	39 (26.5)	1.07 (0.64, 1.79)	1.05 (0.72, 1.54)	0.014 (-0.084, 0.112)	0.73 (0.47, 1.15)	0.7231
	T-DM1 (N=159)	40 (25.2)				0.1712	
North America	T-DXd (N=17)	11 (64.7)	2.62 (0.65, 10.48)	1.57 (0.81, 3.06)	0.235 (-0.091, 0.561)	1.23 (0.47, 3.21)	
	T-DM1 (N=17)	7 (41.2)				0.6758	
Europe	T-DXd (N=52)	23 (44.2)	1.06 (0.48, 2.32)	1.03 (0.66, 1.61)	0.014 (-0.180, 0.207)	0.72 (0.40, 1.32)	
	T-DM1 (N=49)	21 (42.9)				0.2943	
Rest of World	T-DXd (N=41)	21 (51.2)	0.94 (0.38, 2.30)	0.97 (0.63, 1.49)	-0.016 (-0.239, 0.208)	0.72 (0.39, 1.36)	
	T-DM1 (N=36)	19 (52.8)				0.3139	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
Asia	T-DXd (N=147)	20 (13.6)	4.01 (1.56, 10.30)	3.61 (1.49, 8.73)	0.098 (0.035, 0.161)	2.63 (1.05, 6.60)	0.2830
	T-DM1 (N=159)	6 (3.8)				0.0333	
North America	T-DXd (N=17)	6 (35.3)	4.09 (0.69, 24.24)	3.00 (0.70, 12.82)	0.235 (-0.039, 0.509)	3.05 (0.61, 15.17)	
	T-DM1 (N=17)	2 (11.8)				0.1539	
Europe	T-DXd (N=52)	13 (25.0)	2.00 (0.72, 5.53)	1.75 (0.76, 4.02)	0.107 (-0.046, 0.260)	1.30 (0.51, 3.32)	
	T-DM1 (N=49)	7 (14.3)				0.5817	
Rest of World	T-DXd (N=41)	6 (14.6)	0.86 (0.25, 2.94)	0.88 (0.31, 2.48)	-0.020 (-0.183, 0.143)	0.71 (0.23, 2.22)	
	T-DM1 (N=36)	6 (16.7)				0.5620	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
Asia	T-DXd (N=147)	20 (13.6)	1.32 (0.66, 2.62)	1.27 (0.69, 2.33)	0.029 (-0.044, 0.102)	0.73 (0.38, 1.42)	0.6778
	T-DM1 (N=159)	17 (10.7)				0.3558	
North America	T-DXd (N=17)	4 (23.5)	4.92 (0.49, 49.61)	4.00 (0.50, 32.20)	0.176 (-0.054, 0.407)	3.26 (0.36, 29.29)	
	T-DM1 (N=17)	1 (5.9)				0.2644	
Europe	T-DXd (N=52)	9 (17.3)	1.07 (0.38, 3.05)	1.06 (0.44, 2.53)	0.010 (-0.136, 0.156)	0.87 (0.33, 2.25)	
	T-DM1 (N=49)	8 (16.3)				0.7665	
Rest of World	T-DXd (N=41)	8 (19.5)	1.94 (0.53, 7.08)	1.76 (0.58, 5.35)	0.084 (-0.075, 0.243)	1.16 (0.34, 3.90)	
	T-DM1 (N=36)	4 (11.1)				0.8122	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
Asia	T-DXd (N=147)	19 (12.9)	0.83 (0.44, 1.60)	0.86 (0.49, 1.50)	-0.022 (-0.099, 0.056)	0.57 (0.31, 1.06)	0.2186
	T-DM1 (N=159)	24 (15.1)				0.0720	
North America	T-DXd (N=17)	1 (5.9)	1.00 (0.06, 17.41)	1.00 (0.07, 14.72)	0.000 (-0.158, 0.158)	0.69 (0.04, 11.09)	
	T-DM1 (N=17)	1 (5.9)				0.7932	
Europe	T-DXd (N=52)	10 (19.2)	3.65 (0.94, 14.17)	3.14 (0.92, 10.74)	0.131 (0.005, 0.257)	2.41 (0.66, 8.85)	
	T-DM1 (N=49)	3 (6.1)				0.1702	
Rest of World	T-DXd (N=41)	9 (22.0)	1.17 (0.38, 3.53)	1.13 (0.47, 2.72)	0.025 (-0.156, 0.206)	0.89 (0.33, 2.41)	
	T-DM1 (N=36)	7 (19.4)				0.8202	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Insomnia							
Asia	T-DXd (N=147)	10 (6.8)	0.61 (0.27, 1.38)	0.64 (0.30, 1.34)	-0.039 (-0.102, 0.024)	0.42 (0.19, 0.92)	0.9606
	T-DM1 (N=159)	17 (10.7)				0.0265	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	-0.059 (-0.171, 0.053)	NE (NE, NE)	
	T-DM1 (N=17)	1 (5.9)				0.2059	
Europe	T-DXd (N=52)	2 (3.8)	0.94 (0.13, 6.95)	0.94 (0.14, 6.43)	-0.002 (-0.079, 0.074)	0.77 (0.11, 5.54)	
	T-DM1 (N=49)	2 (4.1)				0.7926	
Rest of World	T-DXd (N=41)	3 (7.3)	0.63 (0.13, 3.03)	0.66 (0.16, 2.75)	-0.038 (-0.168, 0.092)	0.56 (0.13, 2.51)	
	T-DM1 (N=36)	4 (11.1)				0.4422	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Asia	T-DXd (N=147)	16 (10.9)	1.26 (0.59, 2.69)	1.24 (0.63, 2.44)	0.021 (-0.046, 0.088)	0.76 (0.37, 1.59)	0.7228
	T-DM1 (N=159)	14 (8.8)				0.4722	
North America	T-DXd (N=17)	4 (23.5)	4.92 (0.49, 49.61)	4.00 (0.50, 32.20)	0.176 (-0.054, 0.407)	2.51 (0.27, 22.89)	
	T-DM1 (N=17)	1 (5.9)				0.4000	
Europe	T-DXd (N=52)	8 (15.4)	0.93 (0.32, 2.71)	0.94 (0.38, 2.32)	-0.009 (-0.152, 0.133)	0.62 (0.22, 1.74)	
	T-DM1 (N=49)	8 (16.3)				0.3588	
Rest of World	T-DXd (N=41)	4 (9.8)	0.86 (0.20, 3.74)	0.88 (0.24, 3.26)	-0.014 (-0.151, 0.124)	0.63 (0.16, 2.56)	
	T-DM1 (N=36)	4 (11.1)				0.5176	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Cardiac disorders							
Any PT							
Asia	T-DXd (N=147)	15 (10.2)	4.40 (1.43, 13.59)	4.06 (1.38, 11.94)	0.077 (0.022, 0.132)	2.61 (0.85, 7.96)	0.2166
	T-DM1 (N=159)	4 (2.5)				0.0809	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	2 (3.8)	0.45 (0.08, 2.58)	0.47 (0.09, 2.46)	-0.043 (-0.136, 0.050)	0.32 (0.06, 1.75)	
	T-DM1 (N=49)	4 (8.2)				0.1646	
Rest of World	T-DXd (N=41)	4 (9.8)	1.19 (0.25, 5.71)	1.17 (0.28, 4.88)	0.014 (-0.114, 0.142)	1.02 (0.23, 4.59)	
	T-DM1 (N=36)	3 (8.3)				0.9799	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
Asia	T-DXd (N=147)	10 (6.8)	2.25 (0.75, 6.74)	2.16 (0.76, 6.18)	0.037 (-0.012, 0.085)	1.23 (0.41, 3.68)	0.8045
	T-DM1 (N=159)	5 (3.1)				0.7127	
North America	T-DXd (N=17)	3 (17.6)	3.43 (0.32, 36.82)	3.00 (0.35, 26.04)	0.118 (-0.095, 0.331)	2.43 (0.25, 23.49)	
	T-DM1 (N=17)	1 (5.9)				0.4272	
Europe	T-DXd (N=52)	5 (9.6)	5.11 (0.57, 45.37)	4.71 (0.57, 38.91)	0.076 (-0.014, 0.165)	3.85 (0.45, 33.36)	
	T-DM1 (N=49)	1 (2.0)				0.1885	
Rest of World	T-DXd (N=41)	3 (7.3)	1.34 (0.21, 8.52)	1.32 (0.23, 7.45)	0.018 (-0.092, 0.127)	1.12 (0.19, 6.70)	
	T-DM1 (N=36)	2 (5.6)				0.9029	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Reproductive system and breast disorders							
Any PT							
Asia	T-DXd (N=147)	8 (5.4)	1.25 (0.44, 3.54)	1.24 (0.46, 3.32)	0.010 (-0.038, 0.059)	0.68 (0.24, 1.91)	0.9814
	T-DM1 (N=159)	7 (4.4)				0.4595	
North America	T-DXd (N=17)	2 (11.8)	2.13 (0.17, 26.03)	2.00 (0.20, 20.04)	0.059 (-0.131, 0.248)	0.80 (0.05, 13.07)	
	T-DM1 (N=17)	1 (5.9)				0.8782	
Europe	T-DXd (N=52)	5 (9.6)	1.20 (0.30, 4.74)	1.18 (0.34, 4.13)	0.015 (-0.096, 0.125)	0.93 (0.25, 3.51)	
	T-DM1 (N=49)	4 (8.2)				0.9168	
Rest of World	T-DXd (N=41)	6 (14.6)	1.06 (0.30, 3.83)	1.05 (0.35, 3.16)	0.007 (-0.149, 0.164)	0.93 (0.28, 3.04)	
	T-DM1 (N=36)	5 (13.9)				0.9002	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
Asia	T-DXd (N=147)	16 (10.9)	0.80 (0.40, 1.60)	0.82 (0.45, 1.52)	-0.023 (-0.096, 0.050)	0.66 (0.34, 1.27)	0.6311
	T-DM1 (N=159)	21 (13.2)				0.2182	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	-0.059 (-0.171, 0.053)	NE (NE, NE)	
	T-DM1 (N=17)	1 (5.9)				0.3173	
Europe	T-DXd (N=52)	2 (3.8)	0.29 (0.05, 1.49)	0.31 (0.07, 1.48)	-0.084 (-0.190, 0.022)	0.20 (0.04, 1.01)	
	T-DM1 (N=49)	6 (12.2)				0.0317	
Rest of World	T-DXd (N=41)	2 (4.9)	1.79 (0.16, 20.66)	1.76 (0.17, 18.57)	0.021 (-0.064, 0.106)	0.94 (0.08, 10.89)	
	T-DM1 (N=36)	1 (2.8)				0.9627	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Renal and urinary disorders							
Any PT							
Asia	T-DXd (N=147)	4 (2.7)	0.61 (0.17, 2.12)	0.62 (0.18, 2.07)	-0.017 (-0.058, 0.025)	0.47 (0.14, 1.63)	0.2942
	T-DM1 (N=159)	7 (4.4)				0.2262	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	5 (9.6)	1.63 (0.37, 7.22)	1.57 (0.40, 6.22)	0.035 (-0.070, 0.139)	1.09 (0.26, 4.60)	
	T-DM1 (N=49)	3 (6.1)				0.9070	
Rest of World	T-DXd (N=41)	6 (14.6)	6.00 (0.69, 52.46)	5.27 (0.67, 41.71)	0.119 (-0.002, 0.239)	4.35 (0.52, 36.26)	
	T-DM1 (N=36)	1 (2.8)				0.1380	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
White	T-DXd (N=71)	71 (100)	NE (NE, NE)	1.51 (1.28, 1.78)	0.338 (0.228, 0.448)	3.42 (2.31, 5.05)	0.7249
	T-DM1 (N=71)	47 (66.2)				<.0001	
Black or African American	T-DXd (N=10)	10 (100)	NE (NE, NE)	1.80 (1.00, 3.23)	0.444 (0.120, 0.769)	4.23 (1.27, 14.10)	
	T-DM1 (N=9)	5 (55.6)				0.0111	
Asian	T-DXd (N=149)	130 (87.2)	5.97 (3.37, 10.57)	1.63 (1.40, 1.91)	0.338 (0.244, 0.432)	2.71 (2.06, 3.57)	
	T-DM1 (N=161)	86 (53.4)				<.0001	
Other	T-DXd (N=27)	26 (96.3)	11.14 (1.22, 102.02)	1.38 (1.02, 1.85)	0.263 (0.050, 0.476)	2.37 (1.22, 4.63)	
	T-DM1 (N=20)	14 (70.0)				0.0104	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Nausea							
White	T-DXd (N=71)	62 (87.3)	12.68 (5.41, 29.72)	2.48 (1.79, 3.44)	0.521 (0.386, 0.657)	3.85 (2.41, 6.16)	0.9797
	T-DM1 (N=71)	25 (35.2)				<.0001	
Black or African American	T-DXd (N=10)	10 (100)	NE (NE, NE)	2.25 (1.08, 4.67)	0.556 (0.231, 0.880)	4.53 (1.37, 14.99)	
	T-DM1 (N=9)	4 (44.4)				0.0061	
Asian	T-DXd (N=149)	102 (68.5)	5.96 (3.64, 9.73)	2.56 (1.94, 3.39)	0.417 (0.316, 0.519)	3.61 (2.52, 5.16)	
	T-DM1 (N=161)	43 (26.7)				<.0001	
Other	T-DXd (N=27)	21 (77.8)	6.50 (1.79, 23.64)	2.22 (1.18, 4.17)	0.428 (0.166, 0.689)	3.32 (1.40, 7.84)	
	T-DM1 (N=20)	7 (35.0)				0.0039	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
White	T-DXd (N=71)	38 (53.5)	7.93 (3.42, 18.38)	4.22 (2.21, 8.07)	0.408 (0.269, 0.548)	4.65 (2.25, 9.64)	0.9394
	T-DM1 (N=71)	9 (12.7)				<.0001	
Black or African American	T-DXd (N=10)	5 (50.0)	8.00 (0.71, 90.00)	4.50 (0.64, 31.60)	0.389 (0.017, 0.761)	4.99 (0.58, 42.80)	
	T-DM1 (N=9)	1 (11.1)				0.1005	
Asian	T-DXd (N=149)	72 (48.3)	9.10 (4.89, 16.94)	5.19 (3.12, 8.63)	0.390 (0.298, 0.482)	5.72 (3.28, 9.99)	
	T-DM1 (N=161)	15 (9.3)				<.0001	
Other	T-DXd (N=27)	11 (40.7)	13.06 (1.52, 112.38)	8.15 (1.14, 58.06)	0.357 (0.149, 0.566)	9.47 (1.22, 73.59)	
	T-DM1 (N=20)	1 (5.0)				0.0087	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Constipation							
White	T-DXd (N=71)	25 (35.2)	2.03 (0.96, 4.29)	1.67 (0.96, 2.89)	0.141 (-0.005, 0.287)	1.38 (0.72, 2.62)	0.9666
	T-DM1 (N=71)	15 (21.1)				0.3258	
Black or African American	T-DXd (N=10)	3 (30.0)	3.43 (0.29, 40.94)	2.70 (0.34, 21.53)	0.189 (-0.162, 0.539)	2.35 (0.24, 22.83)	
	T-DM1 (N=9)	1 (11.1)				0.4476	
Asian	T-DXd (N=149)	50 (33.6)	2.21 (1.31, 3.72)	1.80 (1.21, 2.67)	0.149 (0.052, 0.246)	1.68 (1.06, 2.65)	
	T-DM1 (N=161)	30 (18.6)				0.0248	
Other	T-DXd (N=27)	10 (37.0)	1.76 (0.49, 6.34)	1.48 (0.60, 3.66)	0.120 (-0.143, 0.383)	1.25 (0.43, 3.69)	
	T-DM1 (N=20)	5 (25.0)				0.6806	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
White	T-DXd (N=71)	27 (38.0)	4.23 (1.81, 9.87)	3.00 (1.52, 5.92)	0.254 (0.117, 0.390)	3.27 (1.54, 6.97)	0.7647
	T-DM1 (N=71)	9 (12.7)				0.0011	
Black or African American	T-DXd (N=10)	1 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.086, 0.286)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.3865	
Asian	T-DXd (N=149)	35 (23.5)	7.93 (3.23, 19.49)	6.30 (2.73, 14.55)	0.198 (0.124, 0.272)	6.04 (2.54, 14.40)	
	T-DM1 (N=161)	6 (3.7)				<.0001	
Other	T-DXd (N=27)	12 (44.4)	4.53 (1.07, 19.19)	2.96 (0.96, 9.13)	0.294 (0.050, 0.539)	3.29 (0.93, 11.69)	
	T-DM1 (N=20)	3 (15.0)				0.0512	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Stomatitis							
White	T-DXd (N=71)	10 (14.1)	11.48 (1.43, 92.23)	10.00 (1.31, 76.08)	0.127 (0.041, 0.212)	9.08 (1.16, 71.06)	0.7987
	T-DM1 (N=71)	1 (1.4)				0.0107	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	26 (17.4)	4.04 (1.77, 9.24)	3.51 (1.64, 7.51)	0.125 (0.055, 0.194)	2.78 (1.25, 6.17)	
	T-DM1 (N=161)	8 (5.0)				0.0089	
Other	T-DXd (N=27)	4 (14.8)	3.30 (0.34, 32.10)	2.96 (0.36, 24.53)	0.098 (-0.066, 0.263)	2.53 (0.28, 23.01)	
	T-DM1 (N=20)	1 (5.0)				0.3936	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
White	T-DXd (N=71)	16 (22.5)	10.04 (2.21, 45.52)	8.00 (1.91, 33.52)	0.197 (0.093, 0.302)	6.15 (1.41, 26.80)	0.8850
	T-DM1 (N=71)	2 (2.8)				0.0058	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	9 (6.0)	5.11 (1.09, 24.05)	4.86 (1.07, 22.14)	0.048 (0.006, 0.090)	3.90 (0.84, 18.24)	
	T-DM1 (N=161)	2 (1.2)				0.0625	
Other	T-DXd (N=27)	4 (14.8)	3.30 (0.34, 32.10)	2.96 (0.36, 24.53)	0.098 (-0.066, 0.263)	2.71 (0.30, 24.50)	
	T-DM1 (N=20)	1 (5.0)				0.3565	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Dry mouth							
White	T-DXd (N=71)	3 (4.2)	0.40 (0.10, 1.63)	0.43 (0.12, 1.59)	-0.056 (-0.140, 0.027)	0.36 (0.09, 1.42)	0.9968
	T-DM1 (N=71)	7 (9.9)				0.1307	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	5 (3.4)	0.34 (0.12, 0.95)	0.36 (0.13, 0.97)	-0.060 (-0.113, -0.006)	0.26 (0.09, 0.72)	
	T-DM1 (N=161)	15 (9.3)				0.0058	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	-0.150 (-0.306, 0.006)	NE (NE, NE)	
	T-DM1 (N=20)	3 (15.0)				0.0223	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
White	T-DXd (N=71)	39 (54.9)	1.18 (0.61, 2.29)	1.08 (0.79, 1.48)	0.042 (-0.122, 0.206)	0.82 (0.52, 1.30)	0.2213
	T-DM1 (N=71)	36 (50.7)				0.4176	
Black or African American	T-DXd (N=10)	8 (80.0)	2.00 (0.25, 15.99)	1.20 (0.69, 2.09)	0.133 (-0.262, 0.529)	0.86 (0.30, 2.51)	
	T-DM1 (N=9)	6 (66.7)				0.8253	
Asian	T-DXd (N=149)	101 (67.8)	0.61 (0.37, 1.00)	0.87 (0.76, 1.00)	-0.099 (-0.197, 0.000)	0.51 (0.39, 0.67)	
	T-DM1 (N=161)	125 (77.6)				<.0001	
Other	T-DXd (N=27)	14 (51.9)	0.72 (0.22, 2.31)	0.86 (0.52, 1.44)	-0.081 (-0.367, 0.204)	0.61 (0.28, 1.33)	
	T-DM1 (N=20)	12 (60.0)				0.2154	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
White	T-DXd (N=71)	7 (9.9)	3.77 (0.76, 18.83)	3.50 (0.75, 16.27)	0.070 (-0.009, 0.150)	2.66 (0.55, 12.87)	1.0000
	T-DM1 (N=71)	2 (2.8)				0.2055	
Black or African American	T-DXd (N=10)	2 (20.0)	NE (NE, NE)	NE (NE, NE)	0.200 (-0.048, 0.448)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.2117	
Asian	T-DXd (N=149)	63 (42.3)	4.40 (2.54, 7.60)	2.96 (1.94, 4.52)	0.280 (0.184, 0.376)	2.91 (1.80, 4.69)	
	T-DM1 (N=161)	23 (14.3)				<.0001	
Other	T-DXd (N=27)	3 (11.1)	NE (NE, NE)	NE (NE, NE)	0.111 (-0.007, 0.230)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.1540	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
White	T-DXd (N=71)	16 (22.5)	0.54 (0.26, 1.12)	0.64 (0.38, 1.09)	-0.127 (-0.274, 0.021)	0.47 (0.25, 0.89)	0.5682
	T-DM1 (N=71)	25 (35.2)				0.0195	
Black or African American	T-DXd (N=10)	3 (30.0)	0.21 (0.03, 1.49)	0.45 (0.16, 1.29)	-0.367 (-0.786, 0.052)	0.16 (0.03, 0.82)	
	T-DM1 (N=9)	6 (66.7)				0.0146	
Asian	T-DXd (N=149)	38 (25.5)	0.49 (0.30, 0.80)	0.62 (0.45, 0.87)	-0.155 (-0.258, -0.052)	0.42 (0.28, 0.64)	
	T-DM1 (N=161)	66 (41.0)				<.0001	
Other	T-DXd (N=27)	9 (33.3)	0.75 (0.23, 2.49)	0.83 (0.39, 1.78)	-0.067 (-0.345, 0.212)	0.61 (0.23, 1.60)	
	T-DM1 (N=20)	8 (40.0)				0.3217	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
White	T-DXd (N=71)	4 (5.6)	4.18 (0.46, 38.35)	4.00 (0.46, 34.91)	0.042 (-0.018, 0.102)	3.09 (0.34, 27.89)	0.9990
	T-DM1 (N=71)	1 (1.4)				0.2901	
Black or African American	T-DXd (N=10)	2 (20.0)	NE (NE, NE)	NE (NE, NE)	0.200 (-0.048, 0.448)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.2262	
Asian	T-DXd (N=149)	52 (34.9)	6.10 (3.16, 11.80)	4.32 (2.46, 7.61)	0.268 (0.181, 0.356)	3.92 (2.13, 7.21)	
	T-DM1 (N=161)	13 (8.1)				<.0001	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=20)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
White	T-DXd (N=71)	17 (23.9)	1.08 (0.50, 2.36)	1.06 (0.58, 1.93)	0.014 (-0.125, 0.153)	0.93 (0.47, 1.85)	0.3618
	T-DM1 (N=71)	16 (22.5)				0.8445	
Black or African American	T-DXd (N=10)	3 (30.0)	1.50 (0.19, 11.93)	1.35 (0.29, 6.34)	0.078 (-0.315, 0.471)	0.99 (0.16, 6.01)	
	T-DM1 (N=9)	2 (22.2)				0.9950	
Asian	T-DXd (N=149)	30 (20.1)	0.51 (0.31, 0.86)	0.61 (0.41, 0.90)	-0.128 (-0.225, -0.031)	0.45 (0.29, 0.71)	
	T-DM1 (N=161)	53 (32.9)				0.0005	
Other	T-DXd (N=27)	6 (22.2)	0.67 (0.18, 2.49)	0.74 (0.28, 1.96)	-0.078 (-0.333, 0.177)	0.54 (0.17, 1.69)	
	T-DM1 (N=20)	6 (30.0)				0.2945	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
White	T-DXd (N=71)	4 (5.6)	0.29 (0.09, 0.96)	0.33 (0.11, 0.98)	-0.113 (-0.215, -0.010)	0.24 (0.08, 0.77)	0.9794
	T-DM1 (N=71)	12 (16.9)				0.0101	
Black or African American	T-DXd (N=10)	2 (20.0)	NE (NE, NE)	NE (NE, NE)	0.200 (-0.048, 0.448)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.2183	
Asian	T-DXd (N=149)	47 (31.5)	0.30 (0.19, 0.49)	0.52 (0.40, 0.68)	-0.287 (-0.393, -0.181)	0.30 (0.21, 0.42)	
	T-DM1 (N=161)	97 (60.2)				<.0001	
Other	T-DXd (N=27)	1 (3.7)	0.22 (0.02, 2.27)	0.25 (0.03, 2.20)	-0.113 (-0.285, 0.059)	0.17 (0.02, 1.70)	
	T-DM1 (N=20)	3 (15.0)				0.0910	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
White	T-DXd (N=71)	9 (12.7)	5.01 (1.04, 24.07)	4.50 (1.01, 20.10)	0.099 (0.012, 0.185)	3.72 (0.80, 17.29)	0.8318
	T-DM1 (N=71)	2 (2.8)				0.0729	
Black or African American	T-DXd (N=10)	2 (20.0)	2.00 (0.15, 26.73)	1.80 (0.19, 16.66)	0.089 (-0.233, 0.411)	1.66 (0.15, 18.39)	
	T-DM1 (N=9)	1 (11.1)				0.6751	
Asian	T-DXd (N=149)	30 (20.1)	3.13 (1.54, 6.38)	2.70 (1.44, 5.08)	0.127 (0.051, 0.203)	1.96 (1.00, 3.84)	
	T-DM1 (N=161)	12 (7.5)				0.0471	
Other	T-DXd (N=27)	2 (7.4)	1.52 (0.13, 18.03)	1.48 (0.14, 15.22)	0.024 (-0.113, 0.161)	1.30 (0.12, 14.47)	
	T-DM1 (N=20)	1 (5.0)				0.8299	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
White	T-DXd (N=71)	4 (5.6)	0.55 (0.15, 1.95)	0.57 (0.17, 1.87)	-0.042 (-0.130, 0.045)	0.47 (0.14, 1.61)	0.9382
	T-DM1 (N=71)	7 (9.9)				0.2199	
Black or African American	T-DXd (N=10)	2 (20.0)	0.20 (0.03, 1.53)	0.36 (0.09, 1.42)	-0.356 (-0.764, 0.053)	0.19 (0.03, 1.00)	
	T-DM1 (N=9)	5 (55.6)				0.0306	
Asian	T-DXd (N=149)	11 (7.4)	0.50 (0.24, 1.08)	0.54 (0.27, 1.08)	-0.063 (-0.130, 0.005)	0.42 (0.20, 0.88)	
	T-DM1 (N=161)	22 (13.7)				0.0192	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	-0.050 (-0.146, 0.046)	NE (NE, NE)	
	T-DM1 (N=20)	1 (5.0)				0.2332	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
White	T-DXd (N=71)	6 (8.5)	6.46 (0.76, 55.12)	6.00 (0.74, 48.57)	0.070 (0.000, 0.141)	4.64 (0.55, 38.91)	0.8736
	T-DM1 (N=71)	1 (1.4)				0.1199	
Black or African American	T-DXd (N=10)	2 (20.0)	NE (NE, NE)	NE (NE, NE)	0.200 (-0.048, 0.448)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.2262	
Asian	T-DXd (N=149)	4 (2.7)	2.19 (0.40, 12.15)	2.16 (0.40, 11.63)	0.014 (-0.017, 0.046)	1.46 (0.26, 8.13)	
	T-DM1 (N=161)	2 (1.2)				0.6627	
Other	T-DXd (N=27)	2 (7.4)	NE (NE, NE)	NE (NE, NE)	0.074 (-0.025, 0.173)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.3078	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
White	T-DXd (N=71)	46 (64.8)	1.79 (0.91, 3.51)	1.28 (0.96, 1.70)	0.141 (-0.020, 0.302)	1.12 (0.72, 1.74)	0.8044
	T-DM1 (N=71)	36 (50.7)				0.6114	
Black or African American	T-DXd (N=10)	7 (70.0)	1.87 (0.28, 12.31)	1.26 (0.62, 2.57)	0.144 (-0.287, 0.576)	1.03 (0.32, 3.27)	
	T-DM1 (N=9)	5 (55.6)				0.9829	
Asian	T-DXd (N=149)	88 (59.1)	1.54 (0.98, 2.41)	1.22 (0.99, 1.50)	0.106 (-0.004, 0.217)	1.01 (0.74, 1.38)	
	T-DM1 (N=161)	78 (48.4)				0.9269	
Other	T-DXd (N=27)	18 (66.7)	0.86 (0.25, 2.98)	0.95 (0.64, 1.41)	-0.033 (-0.302, 0.235)	0.81 (0.39, 1.65)	
	T-DM1 (N=20)	14 (70.0)				0.5341	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
White	T-DXd (N=71)	2 (2.8)	2.03 (0.18, 22.89)	2.00 (0.19, 21.56)	0.014 (-0.033, 0.061)	1.26 (0.11, 14.80)	0.9802
	T-DM1 (N=71)	1 (1.4)				0.8539	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	27 (18.1)	3.74 (1.69, 8.24)	3.24 (1.58, 6.66)	0.125 (0.054, 0.197)	3.03 (1.42, 6.46)	
	T-DM1 (N=161)	9 (5.6)				0.0027	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=20)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Pyrexia							
White	T-DXd (N=71)	3 (4.2)	0.35 (0.09, 1.37)	0.38 (0.10, 1.36)	-0.070 (-0.158, 0.017)	0.25 (0.06, 0.95)	0.6483
	T-DM1 (N=71)	8 (11.3)				0.0281	
Black or African American	T-DXd (N=10)	1 (10.0)	0.89 (0.05, 16.66)	0.90 (0.07, 12.38)	-0.011 (-0.288, 0.266)	0.67 (0.04, 11.05)	
	T-DM1 (N=9)	1 (11.1)				0.7787	
Asian	T-DXd (N=149)	20 (13.4)	0.84 (0.45, 1.59)	0.86 (0.50, 1.49)	-0.021 (-0.099, 0.057)	0.59 (0.32, 1.07)	
	T-DM1 (N=161)	25 (15.5)				0.0810	
Other	T-DXd (N=27)	3 (11.1)	0.38 (0.08, 1.80)	0.44 (0.12, 1.65)	-0.139 (-0.363, 0.085)	0.24 (0.06, 1.03)	
	T-DM1 (N=20)	5 (25.0)				0.0384	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
White	T-DXd (N=71)	29 (40.8)	1.64 (0.82, 3.30)	1.38 (0.88, 2.18)	0.113 (-0.043, 0.269)	1.41 (0.80, 2.47)	0.5467
	T-DM1 (N=71)	21 (29.6)				0.2374	
Black or African American	T-DXd (N=10)	6 (60.0)	3.00 (0.46, 19.59)	1.80 (0.63, 5.16)	0.267 (-0.166, 0.699)	1.94 (0.48, 7.77)	
	T-DM1 (N=9)	3 (33.3)				0.3403	
Asian	T-DXd (N=149)	84 (56.4)	3.44 (2.14, 5.52)	2.06 (1.55, 2.75)	0.290 (0.185, 0.396)	2.19 (1.52, 3.17)	
	T-DM1 (N=161)	44 (27.3)				<.0001	
Other	T-DXd (N=27)	20 (74.1)	5.31 (1.51, 18.69)	2.12 (1.12, 4.00)	0.391 (0.124, 0.657)	2.18 (0.92, 5.17)	
	T-DM1 (N=20)	7 (35.0)				0.0697	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Alopecia							
White	T-DXd (N=71)	24 (33.8)	NE (NE, NE)	NE (NE, NE)	0.338 (0.228, 0.448)	NE (NE, NE)	0.7872
	T-DM1 (N=71)	0				<.0001	
Black or African American	T-DXd (N=10)	3 (30.0)	3.43 (0.29, 40.94)	2.70 (0.34, 21.53)	0.189 (-0.162, 0.539)	2.93 (0.30, 28.21)	
	T-DM1 (N=9)	1 (11.1)				0.3228	
Asian	T-DXd (N=149)	56 (37.6)	13.25 (5.79, 30.28)	8.64 (4.07, 18.36)	0.332 (0.248, 0.416)	9.59 (4.37, 21.06)	
	T-DM1 (N=161)	7 (4.3)				<.0001	
Other	T-DXd (N=27)	12 (44.4)	NE (NE, NE)	NE (NE, NE)	0.444 (0.257, 0.632)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.0011	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
White	T-DXd (N=71)	5 (7.0)	1.00 (0.28, 3.62)	1.00 (0.30, 3.30)	0.000 (-0.084, 0.084)	0.93 (0.27, 3.23)	0.7870
	T-DM1 (N=71)	5 (7.0)				0.9146	
Black or African American	T-DXd (N=10)	1 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.086, 0.286)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.4292	
Asian	T-DXd (N=149)	9 (6.0)	0.54 (0.23, 1.26)	0.57 (0.26, 1.24)	-0.045 (-0.106, 0.016)	0.35 (0.15, 0.80)	
	T-DM1 (N=161)	17 (10.6)				0.0096	
Other	T-DXd (N=27)	1 (3.7)	0.35 (0.03, 4.11)	0.37 (0.04, 3.81)	-0.063 (-0.212, 0.087)	0.25 (0.02, 2.75)	
	T-DM1 (N=20)	2 (10.0)				0.2184	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Skin hyperpigmentation							
White	T-DXd (N=71)	1 (1.4)	NE (NE, NE)	NE (NE, NE)	0.014 (-0.013, 0.041)	NE (NE, NE)	1.0000
	T-DM1 (N=71)	0				0.3674	
Black or African American	T-DXd (N=10)	2 (20.0)	NE (NE, NE)	NE (NE, NE)	0.200 (-0.048, 0.448)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.2605	
Asian	T-DXd (N=149)	8 (5.4)	NE (NE, NE)	NE (NE, NE)	0.054 (0.017, 0.090)	NE (NE, NE)	
	T-DM1 (N=161)	0				0.0103	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=20)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
White	T-DXd (N=71)	31 (43.7)	2.28 (1.12, 4.65)	1.72 (1.07, 2.78)	0.183 (0.030, 0.337)	1.74 (0.97, 3.11)	0.8510
	T-DM1 (N=71)	18 (25.4)				0.0611	
Black or African American	T-DXd (N=10)	7 (70.0)	8.17 (1.03, 64.94)	3.15 (0.87, 11.42)	0.478 (0.085, 0.871)	2.26 (0.47, 10.99)	
	T-DM1 (N=9)	2 (22.2)				0.2990	
Asian	T-DXd (N=149)	72 (48.3)	1.85 (1.17, 2.93)	1.44 (1.10, 1.89)	0.148 (0.039, 0.256)	1.49 (1.05, 2.13)	
	T-DM1 (N=161)	54 (33.5)				0.0275	
Other	T-DXd (N=27)	12 (44.4)	1.87 (0.55, 6.33)	1.48 (0.67, 3.27)	0.144 (-0.130, 0.419)	1.43 (0.54, 3.83)	
	T-DM1 (N=20)	6 (30.0)				0.4740	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Decreased appetite							
White	T-DXd (N=71)	16 (22.5)	1.59 (0.68, 3.71)	1.45 (0.73, 2.91)	0.070 (-0.058, 0.199)	1.42 (0.66, 3.07)	0.8800
	T-DM1 (N=71)	11 (15.5)				0.3714	
Black or African American	T-DXd (N=10)	4 (40.0)	5.33 (0.47, 60.77)	3.60 (0.49, 26.54)	0.289 (-0.078, 0.655)	3.57 (0.40, 32.22)	
	T-DM1 (N=9)	1 (11.1)				0.2256	
Asian	T-DXd (N=149)	48 (32.2)	2.16 (1.27, 3.67)	1.79 (1.19, 2.68)	0.142 (0.046, 0.238)	1.75 (1.10, 2.78)	
	T-DM1 (N=161)	29 (18.0)				0.0182	
Other	T-DXd (N=27)	7 (25.9)	1.98 (0.44, 8.88)	1.73 (0.51, 5.87)	0.109 (-0.118, 0.337)	1.85 (0.48, 7.16)	
	T-DM1 (N=20)	3 (15.0)				0.3663	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
White	T-DXd (N=71)	7 (9.9)	NE (NE, NE)	NE (NE, NE)	0.099 (0.029, 0.168)	NE (NE, NE)	1.0000
	T-DM1 (N=71)	0				0.0073	
Black or African American	T-DXd (N=10)	1 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.086, 0.286)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.4386	
Asian	T-DXd (N=149)	3 (2.0)	NE (NE, NE)	NE (NE, NE)	0.020 (-0.002, 0.043)	NE (NE, NE)	
	T-DM1 (N=161)	0				0.0739	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=20)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
White	T-DXd (N=71)	42 (59.2)	1.58 (0.81, 3.06)	1.24 (0.91, 1.68)	0.113 (-0.050, 0.276)	1.00 (0.63, 1.57)	0.9850
	T-DM1 (N=71)	34 (47.9)				0.9950	
Black or African American	T-DXd (N=10)	7 (70.0)	1.87 (0.28, 12.31)	1.26 (0.62, 2.57)	0.144 (-0.287, 0.576)	0.85 (0.27, 2.69)	
	T-DM1 (N=9)	5 (55.6)				0.7945	
Asian	T-DXd (N=149)	53 (35.6)	1.23 (0.76, 1.97)	1.15 (0.84, 1.57)	0.045 (-0.060, 0.150)	0.88 (0.59, 1.30)	
	T-DM1 (N=161)	50 (31.1)				0.5145	
Other	T-DXd (N=27)	14 (51.9)	1.32 (0.41, 4.20)	1.15 (0.63, 2.11)	0.069 (-0.220, 0.357)	0.72 (0.31, 1.70)	
	T-DM1 (N=20)	9 (45.0)				0.4534	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
White	T-DXd (N=71)	3 (4.2)	0.74 (0.16, 3.43)	0.75 (0.17, 3.23)	-0.014 (-0.085, 0.057)	0.59 (0.13, 2.69)	1.0000
	T-DM1 (N=71)	4 (5.6)				0.4862	
Black or African American	T-DXd (N=10)	1 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.086, 0.286)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.4386	
Asian	T-DXd (N=149)	15 (10.1)	0.84 (0.41, 1.71)	0.85 (0.45, 1.62)	-0.017 (-0.087, 0.052)	0.56 (0.28, 1.11)	
	T-DM1 (N=161)	19 (11.8)				0.0933	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	-0.100 (-0.231, 0.031)	NE (NE, NE)	
	T-DM1 (N=20)	2 (10.0)				0.0619	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
White	T-DXd (N=71)	33 (46.5)	1.42 (0.73, 2.76)	1.22 (0.83, 1.80)	0.085 (-0.077, 0.246)	0.92 (0.55, 1.55)	0.8854
	T-DM1 (N=71)	27 (38.0)				0.7639	
Black or African American	T-DXd (N=10)	6 (60.0)	1.87 (0.30, 11.63)	1.35 (0.56, 3.28)	0.156 (-0.289, 0.600)	1.22 (0.34, 4.35)	
	T-DM1 (N=9)	4 (44.4)				0.7564	
Asian	T-DXd (N=149)	62 (41.6)	1.73 (1.08, 2.77)	1.43 (1.05, 1.94)	0.124 (0.018, 0.230)	1.05 (0.72, 1.55)	
	T-DM1 (N=161)	47 (29.2)				0.7911	
Other	T-DXd (N=27)	11 (40.7)	1.28 (0.39, 4.23)	1.16 (0.55, 2.47)	0.057 (-0.222, 0.337)	0.86 (0.33, 2.23)	
	T-DM1 (N=20)	7 (35.0)				0.7598	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
White	T-DXd (N=71)	30 (42.3)	1.43 (0.73, 2.83)	1.25 (0.82, 1.91)	0.085 (-0.075, 0.244)	1.00 (0.58, 1.72)	0.6134
	T-DM1 (N=71)	24 (33.8)				0.9889	
Black or African American	T-DXd (N=10)	5 (50.0)	1.25 (0.21, 7.62)	1.13 (0.43, 2.93)	0.056 (-0.393, 0.504)	0.60 (0.16, 2.29)	
	T-DM1 (N=9)	4 (44.4)				0.4480	
Asian	T-DXd (N=149)	61 (40.9)	1.90 (1.18, 3.07)	1.53 (1.11, 2.11)	0.142 (0.038, 0.247)	1.04 (0.70, 1.55)	
	T-DM1 (N=161)	43 (26.7)				0.8294	
Other	T-DXd (N=27)	11 (40.7)	1.03 (0.32, 3.35)	1.02 (0.50, 2.06)	0.007 (-0.276, 0.291)	0.58 (0.22, 1.49)	
	T-DM1 (N=20)	8 (40.0)				0.2469	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Epistaxis							
White	T-DXd (N=71)	10 (14.1)	0.67 (0.27, 1.62)	0.71 (0.34, 1.50)	-0.056 (-0.179, 0.067)	0.49 (0.22, 1.12)	0.5821
	T-DM1 (N=71)	14 (19.7)				0.0833	
Black or African American	T-DXd (N=10)	1 (10.0)	0.39 (0.03, 5.21)	0.45 (0.05, 4.16)	-0.122 (-0.451, 0.207)	0.26 (0.02, 2.97)	
	T-DM1 (N=9)	2 (22.2)				0.2454	
Asian	T-DXd (N=149)	15 (10.1)	0.79 (0.39, 1.61)	0.81 (0.43, 1.52)	-0.024 (-0.094, 0.047)	0.45 (0.23, 0.90)	
	T-DM1 (N=161)	20 (12.4)				0.0216	
Other	T-DXd (N=27)	3 (11.1)	0.29 (0.06, 1.35)	0.37 (0.11, 1.31)	-0.189 (-0.422, 0.044)	0.14 (0.03, 0.70)	
	T-DM1 (N=20)	6 (30.0)				0.0057	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
White	T-DXd (N=71)	5 (7.0)	NE (NE, NE)	NE (NE, NE)	0.070 (0.011, 0.130)	NE (NE, NE)	1.0000
	T-DM1 (N=71)	0				0.0587	
Black or African American	T-DXd (N=10)	1 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.086, 0.286)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.4386	
Asian	T-DXd (N=149)	10 (6.7)	11.51 (1.46, 91.05)	10.81 (1.40, 83.39)	0.061 (0.019, 0.103)	5.32 (0.68, 41.78)	
	T-DM1 (N=161)	1 (0.6)				0.0756	
Other	T-DXd (N=27)	2 (7.4)	NE (NE, NE)	NE (NE, NE)	0.074 (-0.025, 0.173)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.2717	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
White	T-DXd (N=71)	29 (40.8)	1.44 (0.73, 2.86)	1.26 (0.81, 1.95)	0.085 (-0.073, 0.242)	1.07 (0.62, 1.86)	0.3835
	T-DM1 (N=71)	23 (32.4)				0.7903	
Black or African American	T-DXd (N=10)	7 (70.0)	1.17 (0.17, 8.09)	1.05 (0.57, 1.94)	0.033 (-0.386, 0.452)	0.65 (0.21, 2.06)	
	T-DM1 (N=9)	6 (66.7)				0.4575	
Asian	T-DXd (N=149)	58 (38.9)	2.06 (1.26, 3.37)	1.65 (1.17, 2.32)	0.153 (0.051, 0.255)	1.41 (0.94, 2.13)	
	T-DM1 (N=161)	38 (23.6)				0.0964	
Other	T-DXd (N=27)	9 (33.3)	0.75 (0.23, 2.49)	0.83 (0.39, 1.78)	-0.067 (-0.345, 0.212)	0.63 (0.24, 1.66)	
	T-DM1 (N=20)	8 (40.0)				0.3489	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
White	T-DXd (N=71)	17 (23.9)	1.92 (0.81, 4.55)	1.70 (0.84, 3.45)	0.099 (-0.029, 0.227)	1.42 (0.65, 3.13)	0.8340
	T-DM1 (N=71)	10 (14.1)				0.3733	
Black or African American	T-DXd (N=10)	7 (70.0)	4.67 (0.67, 32.36)	2.10 (0.77, 5.76)	0.367 (-0.052, 0.786)	1.74 (0.43, 6.99)	
	T-DM1 (N=9)	3 (33.3)				0.4228	
Asian	T-DXd (N=149)	52 (34.9)	2.66 (1.56, 4.54)	2.08 (1.38, 3.13)	0.181 (0.085, 0.277)	1.86 (1.16, 2.96)	
	T-DM1 (N=161)	27 (16.8)				0.0084	
Other	T-DXd (N=27)	7 (25.9)	1.40 (0.35, 5.64)	1.30 (0.44, 3.83)	0.059 (-0.182, 0.300)	0.88 (0.25, 3.10)	
	T-DM1 (N=20)	4 (20.0)				0.8394	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
White	T-DXd (N=71)	22 (31.0)	10.18 (2.88, 35.91)	7.33 (2.30, 23.41)	0.268 (0.150, 0.385)	6.77 (2.02, 22.66)	0.4499
	T-DM1 (N=71)	3 (4.2)				0.0003	
Black or African American	T-DXd (N=10)	3 (30.0)	1.50 (0.19, 11.93)	1.35 (0.29, 6.34)	0.078 (-0.315, 0.471)	1.11 (0.18, 6.72)	
	T-DM1 (N=9)	2 (22.2)				0.9063	
Asian	T-DXd (N=149)	11 (7.4)	6.34 (1.38, 29.08)	5.94 (1.34, 26.37)	0.061 (0.016, 0.107)	4.31 (0.94, 19.68)	
	T-DM1 (N=161)	2 (1.2)				0.0409	
Other	T-DXd (N=27)	5 (18.5)	NE (NE, NE)	NE (NE, NE)	0.185 (0.039, 0.332)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.0536	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
White	T-DXd (N=71)	8 (11.3)	0.62 (0.24, 1.63)	0.67 (0.29, 1.53)	-0.056 (-0.170, 0.058)	0.53 (0.22, 1.31)	0.4659
	T-DM1 (N=71)	12 (16.9)				0.1628	
Black or African American	T-DXd (N=10)	1 (10.0)	0.14 (0.01, 1.61)	0.23 (0.03, 1.66)	-0.344 (-0.719, 0.030)	0.09 (0.01, 0.90)	
	T-DM1 (N=9)	4 (44.4)				0.0139	
Asian	T-DXd (N=149)	3 (2.0)	0.26 (0.07, 0.92)	0.27 (0.08, 0.94)	-0.054 (-0.101, -0.008)	0.23 (0.06, 0.82)	
	T-DM1 (N=161)	12 (7.5)				0.0138	
Other	T-DXd (N=27)	1 (3.7)	0.22 (0.02, 2.27)	0.25 (0.03, 2.20)	-0.113 (-0.285, 0.059)	0.18 (0.02, 1.79)	
	T-DM1 (N=20)	3 (15.0)				0.1030	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
White	T-DXd (N=71)	37 (52.1)	1.33 (0.69, 2.57)	1.16 (0.82, 1.62)	0.070 (-0.094, 0.234)	0.90 (0.56, 1.44)	0.1526
	T-DM1 (N=71)	32 (45.1)				0.6550	
Black or African American	T-DXd (N=10)	6 (60.0)	3.00 (0.46, 19.59)	1.80 (0.63, 5.16)	0.267 (-0.166, 0.699)	1.59 (0.40, 6.39)	
	T-DM1 (N=9)	3 (33.3)				0.5032	
Asian	T-DXd (N=149)	40 (26.8)	1.11 (0.67, 1.85)	1.08 (0.74, 1.58)	0.020 (-0.078, 0.118)	0.76 (0.49, 1.19)	
	T-DM1 (N=161)	40 (24.8)				0.2317	
Other	T-DXd (N=27)	11 (40.7)	0.46 (0.14, 1.49)	0.68 (0.38, 1.21)	-0.193 (-0.476, 0.091)	0.28 (0.11, 0.72)	
	T-DM1 (N=20)	12 (60.0)				0.0053	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
White	T-DXd (N=71)	14 (19.7)	1.69 (0.68, 4.21)	1.56 (0.72, 3.36)	0.070 (-0.050, 0.191)	1.31 (0.56, 3.04)	0.5385
	T-DM1 (N=71)	9 (12.7)				0.5372	
Black or African American	T-DXd (N=10)	1 (10.0)	0.89 (0.05, 16.66)	0.90 (0.07, 12.38)	-0.011 (-0.288, 0.266)	0.90 (0.06, 14.40)	
	T-DM1 (N=9)	1 (11.1)				0.9389	
Asian	T-DXd (N=149)	22 (14.8)	3.81 (1.58, 9.21)	3.40 (1.49, 7.72)	0.104 (0.039, 0.169)	2.54 (1.07, 5.98)	
	T-DM1 (N=161)	7 (4.3)				0.0281	
Other	T-DXd (N=27)	8 (29.6)	1.68 (0.43, 6.64)	1.48 (0.52, 4.24)	0.096 (-0.149, 0.342)	1.02 (0.30, 3.50)	
	T-DM1 (N=20)	4 (20.0)				0.9716	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
White	T-DXd (N=71)	14 (19.7)	1.50 (0.62, 3.64)	1.40 (0.67, 2.94)	0.056 (-0.067, 0.179)	1.05 (0.46, 2.38)	0.9252
	T-DM1 (N=71)	10 (14.1)				0.9085	
Black or African American	T-DXd (N=10)	3 (30.0)	NE (NE, NE)	NE (NE, NE)	0.300 (0.016, 0.584)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.1639	
Asian	T-DXd (N=149)	21 (14.1)	1.39 (0.70, 2.75)	1.33 (0.73, 2.43)	0.035 (-0.038, 0.109)	0.79 (0.41, 1.52)	
	T-DM1 (N=161)	17 (10.6)				0.4760	
Other	T-DXd (N=27)	3 (11.1)	0.71 (0.13, 3.94)	0.74 (0.17, 3.29)	-0.039 (-0.235, 0.157)	0.59 (0.12, 2.94)	
	T-DM1 (N=20)	3 (15.0)				0.5168	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
White	T-DXd (N=71)	13 (18.3)	2.05 (0.77, 5.49)	1.86 (0.79, 4.38)	0.085 (-0.029, 0.198)	1.43 (0.57, 3.61)	0.4392
	T-DM1 (N=71)	7 (9.9)				0.4450	
Black or African American	T-DXd (N=10)	1 (10.0)	0.89 (0.05, 16.66)	0.90 (0.07, 12.38)	-0.011 (-0.288, 0.266)	0.58 (0.03, 9.93)	
	T-DM1 (N=9)	1 (11.1)				0.7047	
Asian	T-DXd (N=149)	20 (13.4)	0.89 (0.47, 1.68)	0.90 (0.52, 1.56)	-0.015 (-0.092, 0.063)	0.61 (0.33, 1.11)	
	T-DM1 (N=161)	24 (14.9)				0.1041	
Other	T-DXd (N=27)	5 (18.5)	1.29 (0.27, 6.16)	1.23 (0.33, 4.57)	0.035 (-0.179, 0.250)	0.93 (0.22, 3.93)	
	T-DM1 (N=20)	3 (15.0)				0.9159	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Insomnia							
White	T-DXd (N=71)	3 (4.2)	0.58 (0.13, 2.54)	0.60 (0.15, 2.42)	-0.028 (-0.104, 0.048)	0.52 (0.12, 2.17)	0.9937
	T-DM1 (N=71)	5 (7.0)				0.3602	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	10 (6.7)	0.61 (0.27, 1.38)	0.64 (0.30, 1.34)	-0.038 (-0.101, 0.024)	0.42 (0.19, 0.93)	
	T-DM1 (N=161)	17 (10.6)				0.0271	
Other	T-DXd (N=27)	2 (7.4)	0.72 (0.09, 5.60)	0.74 (0.11, 4.82)	-0.026 (-0.190, 0.139)	0.54 (0.08, 3.87)	
	T-DM1 (N=20)	2 (10.0)				0.5334	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
White	T-DXd (N=71)	11 (15.5)	1.12 (0.44, 2.83)	1.10 (0.50, 2.43)	0.014 (-0.103, 0.131)	0.77 (0.32, 1.82)	0.9990
	T-DM1 (N=71)	10 (14.1)				0.5456	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	-0.111 (-0.316, 0.094)	NE (NE, NE)	
	T-DM1 (N=9)	1 (11.1)				0.2059	
Asian	T-DXd (N=149)	17 (11.4)	1.35 (0.64, 2.85)	1.31 (0.67, 2.57)	0.027 (-0.040, 0.094)	0.80 (0.39, 1.66)	
	T-DM1 (N=161)	14 (8.7)				0.5558	
Other	T-DXd (N=27)	4 (14.8)	1.56 (0.26, 9.52)	1.48 (0.30, 7.31)	0.048 (-0.140, 0.236)	0.96 (0.16, 5.80)	
	T-DM1 (N=20)	2 (10.0)				0.9672	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Cardiac disorders							
Any PT							
White	T-DXd (N=71)	4 (5.6)	0.55 (0.15, 1.95)	0.57 (0.17, 1.87)	-0.042 (-0.130, 0.045)	0.41 (0.12, 1.43)	0.1647
	T-DM1 (N=71)	7 (9.9)				0.1510	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	15 (10.1)	4.39 (1.42, 13.56)	4.05 (1.38, 11.93)	0.076 (0.022, 0.130)	2.62 (0.86, 8.01)	
	T-DM1 (N=161)	4 (2.5)				0.0789	
Other	T-DXd (N=27)	2 (7.4)	NE (NE, NE)	NE (NE, NE)	0.074 (-0.025, 0.173)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.2650	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
White	T-DXd (N=71)	7 (9.9)	2.48 (0.61, 10.00)	2.33 (0.63, 8.66)	0.056 (-0.027, 0.140)	1.76 (0.45, 6.85)	0.9957
	T-DM1 (N=71)	3 (4.2)				0.4077	
Black or African American	T-DXd (N=10)	1 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.086, 0.286)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.4561	
Asian	T-DXd (N=149)	10 (6.7)	2.24 (0.75, 6.73)	2.16 (0.76, 6.18)	0.036 (-0.012, 0.084)	1.24 (0.41, 3.70)	
	T-DM1 (N=161)	5 (3.1)				0.7037	
Other	T-DXd (N=27)	3 (11.1)	2.37 (0.23, 24.70)	2.22 (0.25, 19.82)	0.061 (-0.091, 0.213)	2.33 (0.24, 22.36)	
	T-DM1 (N=20)	1 (5.0)				0.4545	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Reproductive system and breast disorders							
Any PT							
White	T-DXd (N=71)	6 (8.5)	1.00 (0.31, 3.26)	1.00 (0.34, 2.95)	0.000 (-0.091, 0.091)	0.81 (0.26, 2.54)	0.9720
	T-DM1 (N=71)	6 (8.5)				0.7229	
Black or African American	T-DXd (N=10)	2 (20.0)	0.87 (0.10, 7.95)	0.90 (0.16, 5.13)	-0.022 (-0.390, 0.346)	0.69 (0.10, 4.96)	
	T-DM1 (N=9)	2 (22.2)				0.7140	
Asian	T-DXd (N=149)	9 (6.0)	1.41 (0.51, 3.90)	1.39 (0.53, 3.64)	0.017 (-0.033, 0.066)	0.76 (0.28, 2.07)	
	T-DM1 (N=161)	7 (4.3)				0.5886	
Other	T-DXd (N=27)	4 (14.8)	1.56 (0.26, 9.52)	1.48 (0.30, 7.31)	0.048 (-0.140, 0.236)	1.29 (0.23, 7.08)	
	T-DM1 (N=20)	2 (10.0)				0.7741	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
White	T-DXd (N=71)	3 (4.2)	1.00 (0.19, 5.13)	1.00 (0.21, 4.79)	0.000 (-0.066, 0.066)	0.61 (0.12, 3.14)	0.4370
	T-DM1 (N=71)	3 (4.2)				0.5538	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	16 (10.7)	0.80 (0.40, 1.60)	0.82 (0.45, 1.52)	-0.023 (-0.095, 0.049)	0.66 (0.34, 1.27)	
	T-DM1 (N=161)	21 (13.0)				0.2196	
Other	T-DXd (N=27)	1 (3.7)	0.12 (0.01, 1.08)	0.15 (0.02, 1.17)	-0.213 (-0.416, -0.010)	0.08 (0.01, 0.76)	
	T-DM1 (N=20)	5 (25.0)				0.0066	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Renal and urinary disorders							
Any PT							
White	T-DXd (N=71)	8 (11.3)	2.88 (0.73, 11.33)	2.67 (0.74, 9.64)	0.070 (-0.017, 0.158)	2.16 (0.57, 8.17)	0.3890
	T-DM1 (N=71)	3 (4.2)				0.2461	
Black or African American	T-DXd (N=10)	1 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.086, 0.286)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.4386	
Asian	T-DXd (N=149)	4 (2.7)	0.61 (0.17, 2.12)	0.62 (0.18, 2.07)	-0.017 (-0.057, 0.024)	0.48 (0.14, 1.64)	
	T-DM1 (N=161)	7 (4.3)				0.2306	
Other	T-DXd (N=27)	2 (7.4)	1.52 (0.13, 18.03)	1.48 (0.14, 15.22)	0.024 (-0.113, 0.161)	0.67 (0.06, 7.47)	
	T-DM1 (N=20)	1 (5.0)				0.7413	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
0	T-DXd (N=152)	144 (94.7)	11.83 (5.45, 25.65)	1.57 (1.38, 1.78)	0.344 (0.263, 0.425)	2.90 (2.25, 3.76)	0.8441
	T-DM1 (N=174)	105 (60.3)				<.0001	
1	T-DXd (N=105)	93 (88.6)	6.59 (3.16, 13.74)	1.64 (1.33, 2.01)	0.345 (0.224, 0.467)	2.88 (2.02, 4.11)	
	T-DM1 (N=87)	47 (54.0)				<.0001	
Nausea							
0	T-DXd (N=152)	114 (75.0)	7.24 (4.43, 11.83)	2.56 (2.00, 3.28)	0.457 (0.360, 0.553)	3.75 (2.69, 5.23)	0.9714
	T-DM1 (N=174)	51 (29.3)				<.0001	
1	T-DXd (N=105)	81 (77.1)	7.11 (3.75, 13.49)	2.40 (1.74, 3.31)	0.450 (0.323, 0.576)	3.63 (2.36, 5.60)	
	T-DM1 (N=87)	28 (32.2)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
0	T-DXd (N=152)	78 (51.3)	9.14 (5.10, 16.36)	4.96 (3.12, 7.89)	0.410 (0.318, 0.501)	5.46 (3.27, 9.13)	0.9931
	T-DM1 (N=174)	18 (10.3)				<.0001	
1	T-DXd (N=105)	48 (45.7)	8.32 (3.65, 18.93)	4.97 (2.49, 9.94)	0.365 (0.252, 0.478)	5.54 (2.62, 11.72)	
	T-DM1 (N=87)	8 (9.2)				<.0001	
Constipation							
0	T-DXd (N=152)	59 (38.8)	2.43 (1.49, 3.97)	1.88 (1.32, 2.67)	0.181 (0.083, 0.279)	1.68 (1.11, 2.56)	0.6651
	T-DM1 (N=174)	36 (20.7)				0.0132	
1	T-DXd (N=105)	29 (27.6)	1.83 (0.91, 3.69)	1.60 (0.92, 2.79)	0.104 (-0.013, 0.220)	1.34 (0.71, 2.52)	
	T-DM1 (N=87)	15 (17.2)				0.3601	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
0	T-DXd (N=152)	46 (30.3)	5.37 (2.77, 10.43)	4.05 (2.28, 7.20)	0.228 (0.145, 0.311)	3.96 (2.14, 7.35)	0.7195
	T-DM1 (N=174)	13 (7.5)				<.0001	
1	T-DXd (N=105)	29 (27.6)	6.26 (2.30, 16.99)	4.81 (1.94, 11.89)	0.219 (0.120, 0.317)	4.94 (1.91, 12.79)	
	T-DM1 (N=87)	5 (5.7)				0.0003	
Stomatitis							
0	T-DXd (N=152)	22 (14.5)	4.74 (1.87, 12.02)	4.20 (1.75, 10.08)	0.110 (0.048, 0.172)	3.64 (1.47, 9.02)	0.8860
	T-DM1 (N=174)	6 (3.4)				0.0028	
1	T-DXd (N=105)	18 (17.1)	4.29 (1.39, 13.22)	3.73 (1.31, 10.61)	0.125 (0.041, 0.210)	2.88 (0.97, 8.58)	
	T-DM1 (N=87)	4 (4.6)				0.0465	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
0	T-DXd (N=152)	17 (11.2)	7.18 (2.06, 25.00)	6.49 (1.94, 21.71)	0.095 (0.041, 0.148)	4.77 (1.39, 16.40)	0.8247
	T-DM1 (N=174)	3 (1.7)				0.0064	
1	T-DXd (N=105)	12 (11.4)	5.48 (1.19, 25.21)	4.97 (1.14, 21.62)	0.091 (0.023, 0.160)	3.88 (0.86, 17.44)	
	T-DM1 (N=87)	2 (2.3)				0.0571	
Dry mouth							
0	T-DXd (N=152)	5 (3.3)	0.29 (0.11, 0.81)	0.32 (0.12, 0.84)	-0.071 (-0.124, -0.017)	0.26 (0.09, 0.70)	0.8490
	T-DM1 (N=174)	18 (10.3)				0.0042	
1	T-DXd (N=105)	3 (2.9)	0.34 (0.08, 1.34)	0.36 (0.09, 1.33)	-0.052 (-0.117, 0.014)	0.23 (0.06, 0.93)	
	T-DM1 (N=87)	7 (8.0)				0.0255	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
0	T-DXd (N=152)	95 (62.5)	0.71 (0.45, 1.13)	0.89 (0.76, 1.04)	-0.076 (-0.179, 0.027)	0.55 (0.42, 0.72)	0.3089
	T-DM1 (N=174)	122 (70.1)				<.0001	
1	T-DXd (N=105)	67 (63.8)	0.93 (0.51, 1.68)	0.97 (0.79, 1.20)	-0.017 (-0.153, 0.119)	0.71 (0.50, 1.01)	
	T-DM1 (N=87)	57 (65.5)				0.1050	
Neutrophil count decreased							
0	T-DXd (N=152)	42 (27.6)	3.77 (2.02, 7.04)	3.00 (1.76, 5.12)	0.184 (0.101, 0.267)	2.68 (1.50, 4.77)	0.8290
	T-DM1 (N=174)	16 (9.2)				0.0005	
1	T-DXd (N=105)	33 (31.4)	3.97 (1.78, 8.87)	3.04 (1.54, 6.00)	0.211 (0.101, 0.320)	2.95 (1.41, 6.18)	
	T-DM1 (N=87)	9 (10.3)				0.0026	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
0	T-DXd (N=152)	36 (23.7)	0.46 (0.28, 0.75)	0.59 (0.42, 0.83)	-0.165 (-0.265, -0.066)	0.40 (0.26, 0.60)	0.3963
	T-DM1 (N=174)	70 (40.2)				<.0001	
1	T-DXd (N=105)	30 (28.6)	0.59 (0.33, 1.09)	0.71 (0.48, 1.06)	-0.117 (-0.251, 0.018)	0.51 (0.31, 0.83)	
	T-DM1 (N=87)	35 (40.2)				0.0069	
White blood cell count decreased							
0	T-DXd (N=152)	26 (17.1)	4.28 (1.87, 9.77)	3.72 (1.74, 7.97)	0.125 (0.058, 0.193)	2.97 (1.34, 6.58)	0.6011
	T-DM1 (N=174)	8 (4.6)				0.0050	
1	T-DXd (N=105)	32 (30.5)	5.92 (2.34, 14.96)	4.42 (1.94, 10.08)	0.236 (0.133, 0.339)	4.24 (1.77, 10.15)	
	T-DM1 (N=87)	6 (6.9)				0.0004	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
0	T-DXd (N=152)	35 (23.0)	0.66 (0.40, 1.09)	0.74 (0.51, 1.07)	-0.080 (-0.176, 0.016)	0.56 (0.36, 0.86)	0.7686
	T-DM1 (N=174)	54 (31.0)				0.0080	
1	T-DXd (N=105)	21 (20.0)	0.70 (0.35, 1.37)	0.76 (0.45, 1.27)	-0.064 (-0.185, 0.056)	0.61 (0.34, 1.11)	
	T-DM1 (N=87)	23 (26.4)				0.1009	
Platelet count decreased							
0	T-DXd (N=152)	22 (14.5)	0.19 (0.11, 0.33)	0.31 (0.20, 0.47)	-0.327 (-0.419, -0.234)	0.20 (0.12, 0.32)	0.0002
	T-DM1 (N=174)	82 (47.1)				<.0001	
1	T-DXd (N=105)	32 (30.5)	0.83 (0.45, 1.53)	0.88 (0.59, 1.33)	-0.040 (-0.173, 0.093)	0.64 (0.38, 1.06)	
	T-DM1 (N=87)	30 (34.5)				0.0980	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
0	T-DXd (N=152)	23 (15.1)	3.27 (1.46, 7.31)	2.93 (1.40, 6.13)	0.100 (0.034, 0.165)	2.19 (1.01, 4.76)	0.8085
	T-DM1 (N=174)	9 (5.2)				0.0423	
1	T-DXd (N=105)	20 (19.0)	2.69 (1.08, 6.70)	2.37 (1.05, 5.33)	0.110 (0.016, 0.204)	1.88 (0.79, 4.47)	
	T-DM1 (N=87)	7 (8.0)				0.1480	
Blood lactate dehydrogenase increased							
0	T-DXd (N=152)	6 (3.9)	0.41 (0.15, 1.07)	0.43 (0.17, 1.07)	-0.052 (-0.105, 0.000)	0.27 (0.10, 0.71)	0.8155
	T-DM1 (N=174)	16 (9.2)				0.0050	
1	T-DXd (N=105)	11 (10.5)	0.42 (0.19, 0.94)	0.48 (0.24, 0.95)	-0.114 (-0.218, -0.009)	0.40 (0.19, 0.84)	
	T-DM1 (N=87)	19 (21.8)				0.0121	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
0	T-DXd (N=152)	4 (2.6)	4.68 (0.52, 42.29)	4.58 (0.52, 40.53)	0.021 (-0.007, 0.048)	2.78 (0.31, 25.11)	0.9874
	T-DM1 (N=174)	1 (0.6)				0.3433	
1	T-DXd (N=105)	10 (9.5)	4.47 (0.95, 21.00)	4.14 (0.93, 18.41)	0.072 (0.008, 0.137)	3.39 (0.74, 15.56)	
	T-DM1 (N=87)	2 (2.3)				0.0950	
General disorders and administration site conditions							
Any PT							
0	T-DXd (N=152)	95 (62.5)	1.67 (1.07, 2.60)	1.25 (1.03, 1.52)	0.125 (0.018, 0.232)	1.12 (0.84, 1.50)	0.4408
	T-DM1 (N=174)	87 (50.0)				0.4574	
1	T-DXd (N=105)	64 (61.0)	1.39 (0.78, 2.47)	1.15 (0.90, 1.48)	0.081 (-0.060, 0.221)	0.90 (0.61, 1.31)	
	T-DM1 (N=87)	46 (52.9)				0.5825	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
0	T-DXd (N=152)	20 (13.2)	2.48 (1.12, 5.49)	2.29 (1.11, 4.74)	0.074 (0.010, 0.138)	2.07 (0.96, 4.44)	0.9854
	T-DM1 (N=174)	10 (5.7)				0.0570	
1	T-DXd (N=105)	9 (8.6)	NE (NE, NE)	NE (NE, NE)	0.086 (0.032, 0.139)	NE (NE, NE)	
	T-DM1 (N=87)	0				0.0109	
Pyrexia							
0	T-DXd (N=152)	13 (8.6)	0.53 (0.26, 1.08)	0.57 (0.31, 1.07)	-0.064 (-0.133, 0.005)	0.35 (0.18, 0.69)	0.2761
	T-DM1 (N=174)	26 (14.9)				0.0018	
1	T-DXd (N=105)	14 (13.3)	0.88 (0.39, 1.98)	0.89 (0.44, 1.80)	-0.016 (-0.115, 0.083)	0.59 (0.27, 1.27)	
	T-DM1 (N=87)	13 (14.9)				0.1740	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
0	T-DXd (N=152)	86 (56.6)	3.23 (2.04, 5.11)	1.97 (1.50, 2.59)	0.278 (0.175, 0.382)	2.09 (1.47, 2.98)	0.5665
	T-DM1 (N=174)	50 (28.7)				<.0001	
1	T-DXd (N=105)	53 (50.5)	2.53 (1.38, 4.61)	1.76 (1.20, 2.57)	0.217 (0.083, 0.352)	1.74 (1.08, 2.81)	
	T-DM1 (N=87)	25 (28.7)				0.0217	
Alopecia							
0	T-DXd (N=152)	60 (39.5)	22.04 (8.55, 56.83)	13.74 (5.66, 33.32)	0.366 (0.284, 0.448)	15.32 (6.15, 38.18)	0.6524
	T-DM1 (N=174)	5 (2.9)				<.0001	
1	T-DXd (N=105)	35 (33.3)	13.99 (4.13, 47.43)	9.67 (3.08, 30.36)	0.299 (0.201, 0.397)	10.82 (3.33, 35.18)	
	T-DM1 (N=87)	3 (3.4)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
0	T-DXd (N=152)	9 (5.9)	0.46 (0.20, 1.03)	0.49 (0.23, 1.04)	-0.061 (-0.123, 0.000)	0.32 (0.14, 0.70)	0.0658
	T-DM1 (N=174)	21 (12.1)				0.0030	
1	T-DXd (N=105)	7 (6.7)	2.00 (0.50, 7.98)	1.93 (0.52, 7.25)	0.032 (-0.029, 0.093)	1.50 (0.38, 5.82)	
	T-DM1 (N=87)	3 (3.4)				0.5586	
Skin hyperpigmentation							
0	T-DXd (N=152)	8 (5.3)	NE (NE, NE)	NE (NE, NE)	0.053 (0.017, 0.088)	NE (NE, NE)	0.9999
	T-DM1 (N=174)	0				0.0064	
1	T-DXd (N=105)	3 (2.9)	NE (NE, NE)	NE (NE, NE)	0.029 (-0.003, 0.060)	NE (NE, NE)	
	T-DM1 (N=87)	0				0.1922	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
0	T-DXd (N=152)	67 (44.1)	2.26 (1.42, 3.60)	1.70 (1.25, 2.32)	0.182 (0.080, 0.284)	1.66 (1.14, 2.43)	0.4063
	T-DM1 (N=174)	45 (25.9)				0.0083	
1	T-DXd (N=105)	55 (52.4)	1.63 (0.92, 2.90)	1.30 (0.95, 1.78)	0.122 (-0.019, 0.262)	1.34 (0.88, 2.06)	
	T-DM1 (N=87)	35 (40.2)				0.1757	
Decreased appetite							
0	T-DXd (N=152)	48 (31.6)	2.75 (1.60, 4.74)	2.20 (1.43, 3.38)	0.172 (0.082, 0.263)	2.13 (1.31, 3.46)	0.0856
	T-DM1 (N=174)	25 (14.4)				0.0019	
1	T-DXd (N=105)	27 (25.7)	1.24 (0.63, 2.42)	1.18 (0.70, 1.97)	0.039 (-0.082, 0.159)	1.16 (0.64, 2.08)	
	T-DM1 (N=87)	19 (21.8)				0.6391	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
0	T-DXd (N=152)	6 (3.9)	NE (NE, NE)	NE (NE, NE)	0.039 (0.009, 0.070)	NE (NE, NE)	1.0000
	T-DM1 (N=174)	0				0.0100	
1	T-DXd (N=105)	5 (4.8)	NE (NE, NE)	NE (NE, NE)	0.048 (0.007, 0.088)	NE (NE, NE)	
	T-DM1 (N=87)	0				0.0401	
Nervous system disorders							
Any PT							
0	T-DXd (N=152)	66 (43.4)	1.35 (0.87, 2.11)	1.20 (0.92, 1.57)	0.072 (-0.034, 0.178)	0.90 (0.64, 1.28)	0.8262
	T-DM1 (N=174)	63 (36.2)				0.5649	
1	T-DXd (N=105)	50 (47.6)	1.35 (0.76, 2.40)	1.18 (0.85, 1.64)	0.074 (-0.067, 0.214)	0.94 (0.61, 1.46)	
	T-DM1 (N=87)	35 (40.2)				0.7943	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
0	T-DXd (N=152)	12 (7.9)	0.85 (0.39, 1.85)	0.86 (0.42, 1.76)	-0.013 (-0.074, 0.048)	0.62 (0.29, 1.31)	0.6163
	T-DM1 (N=174)	16 (9.2)				0.2057	
1	T-DXd (N=105)	7 (6.7)	0.62 (0.22, 1.74)	0.64 (0.25, 1.66)	-0.037 (-0.117, 0.043)	0.42 (0.15, 1.15)	
	T-DM1 (N=87)	9 (10.3)				0.0823	
Infections and infestations							
Any PT							
0	T-DXd (N=152)	66 (43.4)	2.01 (1.27, 3.20)	1.57 (1.16, 2.13)	0.158 (0.055, 0.261)	1.17 (0.80, 1.71)	0.1306
	T-DM1 (N=174)	48 (27.6)				0.4104	
1	T-DXd (N=105)	46 (43.8)	1.05 (0.59, 1.87)	1.03 (0.74, 1.43)	0.013 (-0.128, 0.154)	0.78 (0.50, 1.20)	
	T-DM1 (N=87)	37 (42.5)				0.2534	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
0	T-DXd (N=152)	68 (44.7)	1.85 (1.17, 2.91)	1.47 (1.10, 1.95)	0.143 (0.038, 0.247)	0.96 (0.67, 1.39)	0.8353
	T-DM1 (N=174)	53 (30.5)				0.8417	
1	T-DXd (N=105)	39 (37.1)	1.39 (0.76, 2.54)	1.24 (0.83, 1.87)	0.073 (-0.061, 0.206)	0.95 (0.58, 1.56)	
	T-DM1 (N=87)	26 (29.9)				0.8334	
Epistaxis							
0	T-DXd (N=152)	20 (13.2)	0.73 (0.39, 1.34)	0.76 (0.45, 1.29)	-0.041 (-0.119, 0.037)	0.43 (0.24, 0.76)	0.8522
	T-DM1 (N=174)	30 (17.2)				0.0032	
1	T-DXd (N=105)	9 (8.6)	0.59 (0.23, 1.46)	0.62 (0.27, 1.41)	-0.052 (-0.142, 0.038)	0.41 (0.17, 0.97)	
	T-DM1 (N=87)	12 (13.8)				0.0372	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
0	T-DXd (N=152)	11 (7.2)	13.50 (1.72, 105.80)	12.59 (1.64, 96.41)	0.067 (0.024, 0.109)	7.05 (0.90, 54.92)	0.9920
	T-DM1 (N=174)	1 (0.6)				0.0303	
1	T-DXd (N=105)	7 (6.7)	NE (NE, NE)	NE (NE, NE)	0.067 (0.019, 0.114)	NE (NE, NE)	
	T-DM1 (N=87)	0				0.0483	
Blood and lymphatic system disorders							
Any PT							
0	T-DXd (N=152)	55 (36.2)	1.68 (1.04, 2.70)	1.43 (1.03, 1.99)	0.109 (0.009, 0.209)	1.13 (0.75, 1.68)	0.9303
	T-DM1 (N=174)	44 (25.3)				0.5584	
1	T-DXd (N=105)	48 (45.7)	1.52 (0.85, 2.73)	1.28 (0.90, 1.82)	0.101 (-0.038, 0.239)	1.12 (0.71, 1.76)	
	T-DM1 (N=87)	31 (35.6)				0.6234	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
0	T-DXd (N=152)	39 (25.7)	2.16 (1.23, 3.79)	1.86 (1.17, 2.95)	0.119 (0.032, 0.205)	1.44 (0.86, 2.41)	0.7214
	T-DM1 (N=174)	24 (13.8)				0.1599	
1	T-DXd (N=105)	44 (41.9)	2.42 (1.28, 4.55)	1.82 (1.17, 2.85)	0.189 (0.060, 0.318)	1.73 (1.02, 2.94)	
	T-DM1 (N=87)	20 (23.0)				0.0405	
Neutropenia							
0	T-DXd (N=152)	26 (17.1)	8.77 (2.99, 25.76)	7.44 (2.66, 20.84)	0.148 (0.084, 0.212)	5.72 (1.98, 16.47)	0.4867
	T-DM1 (N=174)	4 (2.3)				0.0003	
1	T-DXd (N=105)	15 (14.3)	4.67 (1.30, 16.70)	4.14 (1.24, 13.85)	0.108 (0.031, 0.186)	3.17 (0.91, 11.08)	
	T-DM1 (N=87)	3 (3.4)				0.0564	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
0	T-DXd (N=152)	10 (6.6)	0.57 (0.26, 1.28)	0.60 (0.29, 1.26)	-0.043 (-0.104, 0.017)	0.42 (0.19, 0.93)	0.1647
	T-DM1 (N=174)	19 (10.9)				0.0267	
1	T-DXd (N=105)	3 (2.9)	0.18 (0.05, 0.67)	0.21 (0.06, 0.71)	-0.109 (-0.189, -0.030)	0.16 (0.05, 0.59)	
	T-DM1 (N=87)	12 (13.8)				0.0017	
Musculoskeletal and connective tissue disorders							
Any PT							
0	T-DXd (N=152)	61 (40.1)	1.38 (0.87, 2.16)	1.23 (0.92, 1.63)	0.074 (-0.031, 0.178)	0.87 (0.61, 1.26)	0.2889
	T-DM1 (N=174)	57 (32.8)				0.4716	
1	T-DXd (N=105)	33 (31.4)	0.87 (0.48, 1.59)	0.91 (0.61, 1.37)	-0.031 (-0.164, 0.103)	0.68 (0.41, 1.13)	
	T-DM1 (N=87)	30 (34.5)				0.1336	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
0	T-DXd (N=152)	26 (17.1)	2.79 (1.35, 5.74)	2.48 (1.30, 4.74)	0.102 (0.031, 0.173)	1.79 (0.89, 3.58)	0.5526
	T-DM1 (N=174)	12 (6.9)				0.0972	
1	T-DXd (N=105)	19 (18.1)	1.91 (0.82, 4.48)	1.75 (0.83, 3.67)	0.078 (-0.020, 0.175)	1.43 (0.64, 3.18)	
	T-DM1 (N=87)	9 (10.3)				0.3787	
Eye disorders							
Any PT							
0	T-DXd (N=152)	24 (15.8)	1.73 (0.89, 3.36)	1.62 (0.90, 2.89)	0.060 (-0.013, 0.133)	1.10 (0.58, 2.06)	0.3624
	T-DM1 (N=174)	17 (9.8)				0.7726	
1	T-DXd (N=105)	17 (16.2)	1.10 (0.50, 2.41)	1.08 (0.56, 2.10)	0.012 (-0.090, 0.115)	0.66 (0.31, 1.38)	
	T-DM1 (N=87)	13 (14.9)				0.2674	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
0	T-DXd (N=152)	28 (18.4)	1.65 (0.89, 3.04)	1.53 (0.91, 2.57)	0.064 (-0.015, 0.142)	1.06 (0.60, 1.88)	0.0705
	T-DM1 (N=174)	21 (12.1)				0.8376	
1	T-DXd (N=105)	11 (10.5)	0.61 (0.26, 1.42)	0.65 (0.31, 1.36)	-0.056 (-0.153, 0.041)	0.47 (0.21, 1.03)	
	T-DM1 (N=87)	14 (16.1)				0.0543	
Insomnia							
0	T-DXd (N=152)	11 (7.2)	0.77 (0.35, 1.72)	0.79 (0.38, 1.64)	-0.020 (-0.079, 0.040)	0.56 (0.26, 1.23)	0.3592
	T-DM1 (N=174)	16 (9.2)				0.1431	
1	T-DXd (N=105)	4 (3.8)	0.39 (0.11, 1.35)	0.41 (0.13, 1.33)	-0.054 (-0.125, 0.017)	0.30 (0.09, 1.01)	
	T-DM1 (N=87)	8 (9.2)				0.0405	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
0	T-DXd (N=152)	18 (11.8)	1.99 (0.91, 4.36)	1.87 (0.91, 3.84)	0.055 (-0.008, 0.118)	1.30 (0.61, 2.79)	0.0737
	T-DM1 (N=174)	11 (6.3)				0.4913	
1	T-DXd (N=105)	14 (13.3)	0.68 (0.31, 1.49)	0.73 (0.38, 1.40)	-0.051 (-0.155, 0.054)	0.42 (0.20, 0.88)	
	T-DM1 (N=87)	16 (18.4)				0.0180	
Cardiac disorders							
Any PT							
0	T-DXd (N=152)	9 (5.9)	2.13 (0.70, 6.49)	2.06 (0.71, 6.02)	0.030 (-0.015, 0.075)	1.27 (0.42, 3.88)	0.8655
	T-DM1 (N=174)	5 (2.9)				0.6730	
1	T-DXd (N=105)	12 (11.4)	1.74 (0.63, 4.85)	1.66 (0.65, 4.23)	0.045 (-0.036, 0.126)	1.26 (0.47, 3.38)	
	T-DM1 (N=87)	6 (6.9)				0.6423	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
0	T-DXd (N=152)	14 (9.2)	2.84 (1.06, 7.59)	2.67 (1.05, 6.78)	0.058 (0.004, 0.111)	1.84 (0.70, 4.85)	0.7371
	T-DM1 (N=174)	6 (3.4)				0.2109	
1	T-DXd (N=105)	7 (6.7)	2.00 (0.50, 7.98)	1.93 (0.52, 7.25)	0.032 (-0.029, 0.093)	1.37 (0.35, 5.31)	
	T-DM1 (N=87)	3 (3.4)				0.6516	
Reproductive system and breast disorders							
Any PT							
0	T-DXd (N=152)	12 (7.9)	1.41 (0.59, 3.35)	1.37 (0.61, 3.09)	0.021 (-0.034, 0.077)	0.80 (0.34, 1.87)	0.7922
	T-DM1 (N=174)	10 (5.7)				0.5993	
1	T-DXd (N=105)	9 (8.6)	1.07 (0.38, 3.01)	1.07 (0.41, 2.74)	0.005 (-0.073, 0.084)	0.87 (0.32, 2.36)	
	T-DM1 (N=87)	7 (8.0)				0.7774	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
0	T-DXd (N=152)	9 (5.9)	0.55 (0.24, 1.25)	0.57 (0.27, 1.24)	-0.044 (-0.103, 0.015)	0.42 (0.19, 0.96)	0.5195
	T-DM1 (N=174)	18 (10.3)				0.0340	
1	T-DXd (N=105)	11 (10.5)	0.81 (0.33, 1.97)	0.83 (0.38, 1.82)	-0.022 (-0.113, 0.069)	0.63 (0.27, 1.46)	
	T-DM1 (N=87)	11 (12.6)				0.2832	
Renal and urinary disorders							
Any PT							
0	T-DXd (N=152)	10 (6.6)	1.68 (0.62, 4.53)	1.64 (0.64, 4.19)	0.026 (-0.023, 0.075)	1.18 (0.44, 3.12)	0.6072
	T-DM1 (N=174)	7 (4.0)				0.7460	
1	T-DXd (N=105)	5 (4.8)	1.04 (0.27, 3.99)	1.04 (0.29, 3.74)	0.002 (-0.058, 0.062)	0.75 (0.20, 2.82)	
	T-DM1 (N=87)	4 (4.6)				0.6642	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Positive	T-DXd (N=133)	122 (91.7)	8.42 (4.17, 17.00)	1.61 (1.38, 1.88)	0.349 (0.254, 0.444)	2.89 (2.16, 3.85)	0.6544
	T-DM1 (N=139)	79 (56.8)				<.0001	
Negative	T-DXd (N=123)	114 (92.7)	8.33 (3.86, 17.99)	1.54 (1.32, 1.79)	0.324 (0.225, 0.422)	2.75 (2.04, 3.71)	
	T-DM1 (N=121)	73 (60.3)				<.0001	
Nausea							
Positive	T-DXd (N=133)	105 (78.9)	10.34 (5.90, 18.12)	2.97 (2.22, 3.96)	0.523 (0.422, 0.624)	4.62 (3.17, 6.75)	0.0885
	T-DM1 (N=139)	37 (26.6)				<.0001	
Negative	T-DXd (N=123)	89 (72.4)	4.92 (2.86, 8.49)	2.08 (1.60, 2.72)	0.376 (0.261, 0.492)	2.95 (2.04, 4.26)	
	T-DM1 (N=121)	42 (34.7)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Positive	T-DXd (N=133)	63 (47.4)	8.72 (4.49, 16.96)	5.06 (2.93, 8.76)	0.380 (0.282, 0.478)	5.61 (3.08, 10.20)	0.8514
	T-DM1 (N=139)	13 (9.4)				<.0001	
Negative	T-DXd (N=123)	62 (50.4)	8.44 (4.30, 16.59)	4.69 (2.73, 8.07)	0.397 (0.292, 0.501)	5.12 (2.81, 9.34)	
	T-DM1 (N=121)	13 (10.7)				<.0001	
Constipation							
Positive	T-DXd (N=133)	50 (37.6)	2.62 (1.51, 4.55)	2.01 (1.33, 3.03)	0.189 (0.084, 0.294)	1.73 (1.07, 2.78)	0.4208
	T-DM1 (N=139)	26 (18.7)				0.0222	
Negative	T-DXd (N=123)	38 (30.9)	1.72 (0.96, 3.08)	1.50 (0.97, 2.32)	0.102 (-0.007, 0.211)	1.36 (0.82, 2.26)	
	T-DM1 (N=121)	25 (20.7)				0.2342	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Positive	T-DXd (N=133)	42 (31.6)	5.95 (2.84, 12.48)	4.39 (2.30, 8.39)	0.244 (0.154, 0.334)	4.45 (2.23, 8.89)	0.8166
	T-DM1 (N=139)	10 (7.2)				<.0001	
Negative	T-DXd (N=123)	32 (26.0)	4.97 (2.18, 11.31)	3.93 (1.89, 8.19)	0.194 (0.105, 0.283)	3.81 (1.75, 8.29)	
	T-DM1 (N=121)	8 (6.6)				0.0003	
Stomatitis							
Positive	T-DXd (N=133)	21 (15.8)	5.02 (1.84, 13.76)	4.39 (1.70, 11.30)	0.122 (0.053, 0.191)	3.69 (1.39, 9.82)	0.8280
	T-DM1 (N=139)	5 (3.6)				0.0051	
Negative	T-DXd (N=123)	19 (15.4)	4.24 (1.53, 11.75)	3.74 (1.44, 9.69)	0.113 (0.040, 0.186)	3.04 (1.13, 8.20)	
	T-DM1 (N=121)	5 (4.1)				0.0208	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Positive	T-DXd (N=133)	17 (12.8)	20.22 (2.65, 154.26)	17.77 (2.40, 131.64)	0.121 (0.062, 0.179)	14.25 (1.89, 107.37)	0.1203
	T-DM1 (N=139)	1 (0.7)				0.0007	
Negative	T-DXd (N=123)	12 (9.8)	3.16 (0.99, 10.10)	2.95 (0.98, 8.90)	0.065 (0.003, 0.126)	2.07 (0.66, 6.48)	
	T-DM1 (N=121)	4 (3.3)				0.2047	
Dry mouth							
Positive	T-DXd (N=133)	6 (4.5)	0.39 (0.15, 1.04)	0.42 (0.17, 1.05)	-0.063 (-0.125, 0.000)	0.33 (0.13, 0.85)	0.3998
	T-DM1 (N=139)	15 (10.8)				0.0163	
Negative	T-DXd (N=123)	2 (1.6)	0.18 (0.04, 0.86)	0.20 (0.04, 0.88)	-0.066 (-0.120, -0.012)	0.14 (0.03, 0.65)	
	T-DM1 (N=121)	10 (8.3)				0.0040	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Positive	T-DXd (N=133)	85 (63.9)	0.69 (0.41, 1.15)	0.89 (0.75, 1.05)	-0.080 (-0.191, 0.030)	0.55 (0.41, 0.73)	0.3061
	T-DM1 (N=139)	100 (71.9)				0.0002	
Negative	T-DXd (N=123)	77 (62.6)	0.89 (0.53, 1.50)	0.96 (0.79, 1.16)	-0.027 (-0.147, 0.094)	0.69 (0.51, 0.95)	
	T-DM1 (N=121)	79 (65.3)				0.0427	
Neutrophil count decreased							
Positive	T-DXd (N=133)	40 (30.1)	5.00 (2.44, 10.27)	3.80 (2.04, 7.09)	0.222 (0.132, 0.312)	3.60 (1.84, 7.02)	0.3233
	T-DM1 (N=139)	11 (7.9)				<.0001	
Negative	T-DXd (N=123)	35 (28.5)	3.04 (1.54, 6.01)	2.46 (1.40, 4.33)	0.169 (0.071, 0.267)	2.25 (1.21, 4.19)	
	T-DM1 (N=121)	14 (11.6)				0.0087	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
Positive	T-DXd (N=133)	32 (24.1)	0.38 (0.23, 0.64)	0.53 (0.37, 0.76)	-0.213 (-0.323, -0.103)	0.34 (0.22, 0.53)	0.0852
	T-DM1 (N=139)	63 (45.3)				<.0001	
Negative	T-DXd (N=123)	34 (27.6)	0.72 (0.42, 1.24)	0.80 (0.55, 1.16)	-0.071 (-0.187, 0.045)	0.60 (0.38, 0.95)	
	T-DM1 (N=121)	42 (34.7)				0.0335	
White blood cell count decreased							
Positive	T-DXd (N=133)	27 (20.3)	4.17 (1.82, 9.56)	3.53 (1.66, 7.48)	0.145 (0.067, 0.224)	2.89 (1.31, 6.39)	0.4404
	T-DM1 (N=139)	8 (5.8)				0.0060	
Negative	T-DXd (N=123)	31 (25.2)	6.46 (2.58, 16.14)	5.08 (2.20, 11.74)	0.202 (0.117, 0.288)	4.78 (1.99, 11.46)	
	T-DM1 (N=121)	6 (5.0)				0.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
Positive	T-DXd (N=133)	27 (20.3)	0.55 (0.32, 0.96)	0.64 (0.42, 0.97)	-0.114 (-0.217, -0.010)	0.48 (0.30, 0.79)	0.2627
	T-DM1 (N=139)	44 (31.7)				0.0029	
Negative	T-DXd (N=123)	29 (23.6)	0.82 (0.46, 1.47)	0.86 (0.56, 1.33)	-0.037 (-0.146, 0.072)	0.70 (0.42, 1.15)	
	T-DM1 (N=121)	33 (27.3)				0.1670	
Platelet count decreased							
Positive	T-DXd (N=133)	26 (19.5)	0.32 (0.19, 0.55)	0.45 (0.31, 0.67)	-0.236 (-0.343, -0.130)	0.30 (0.19, 0.48)	0.4743
	T-DM1 (N=139)	60 (43.2)				<.0001	
Negative	T-DXd (N=123)	28 (22.8)	0.39 (0.22, 0.68)	0.53 (0.36, 0.78)	-0.202 (-0.317, -0.087)	0.36 (0.23, 0.58)	
	T-DM1 (N=121)	52 (43.0)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
Positive	T-DXd (N=133)	19 (14.3)	3.69 (1.43, 9.56)	3.31 (1.36, 8.03)	0.100 (0.031, 0.168)	2.68 (1.07, 6.73)	0.6130
	T-DM1 (N=139)	6 (4.3)				0.0292	
Negative	T-DXd (N=123)	24 (19.5)	2.69 (1.23, 5.90)	2.36 (1.18, 4.72)	0.112 (0.027, 0.198)	1.78 (0.84, 3.73)	
	T-DM1 (N=121)	10 (8.3)				0.1253	
Blood lactate dehydrogenase increased							
Positive	T-DXd (N=133)	8 (6.0)	0.34 (0.15, 0.79)	0.38 (0.18, 0.82)	-0.098 (-0.171, -0.025)	0.28 (0.12, 0.64)	0.2983
	T-DM1 (N=139)	22 (15.8)				0.0013	
Negative	T-DXd (N=123)	9 (7.3)	0.66 (0.27, 1.60)	0.68 (0.30, 1.53)	-0.034 (-0.106, 0.038)	0.53 (0.22, 1.25)	
	T-DM1 (N=121)	13 (10.7)				0.1432	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
Positive	T-DXd (N=133)	9 (6.8)	NE (NE, NE)	NE (NE, NE)	0.068 (0.025, 0.110)	NE (NE, NE)	0.9922
	T-DM1 (N=139)	0				0.0088	
Negative	T-DXd (N=123)	5 (4.1)	1.67 (0.39, 7.13)	1.64 (0.40, 6.71)	0.016 (-0.029, 0.060)	1.22 (0.29, 5.16)	
	T-DM1 (N=121)	3 (2.5)				0.7893	
General disorders and administration site conditions							
Any PT							
Positive	T-DXd (N=133)	82 (61.7)	1.88 (1.16, 3.05)	1.34 (1.07, 1.68)	0.156 (0.039, 0.273)	1.16 (0.84, 1.62)	0.3397
	T-DM1 (N=139)	64 (46.0)				0.3712	
Negative	T-DXd (N=123)	76 (61.8)	1.22 (0.73, 2.03)	1.08 (0.88, 1.33)	0.048 (-0.075, 0.171)	0.92 (0.66, 1.27)	
	T-DM1 (N=121)	69 (57.0)				0.6118	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Positive	T-DXd (N=133)	13 (9.8)	3.66 (1.16, 11.51)	3.40 (1.14, 10.15)	0.069 (0.011, 0.127)	3.00 (0.97, 9.25)	0.6949
	T-DM1 (N=139)	4 (2.9)				0.0452	
Negative	T-DXd (N=123)	15 (12.2)	2.66 (1.00, 7.11)	2.46 (0.99, 6.13)	0.072 (0.003, 0.142)	2.34 (0.90, 6.04)	
	T-DM1 (N=121)	6 (5.0)				0.0712	
Pyrexia							
Positive	T-DXd (N=133)	13 (9.8)	0.68 (0.32, 1.45)	0.72 (0.37, 1.39)	-0.039 (-0.115, 0.037)	0.46 (0.23, 0.95)	0.9514
	T-DM1 (N=139)	19 (13.7)				0.0316	
Negative	T-DXd (N=123)	14 (11.4)	0.65 (0.31, 1.35)	0.69 (0.36, 1.30)	-0.051 (-0.138, 0.035)	0.43 (0.21, 0.86)	
	T-DM1 (N=121)	20 (16.5)				0.0152	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Positive	T-DXd (N=133)	78 (58.6)	4.06 (2.43, 6.78)	2.26 (1.65, 3.10)	0.327 (0.217, 0.438)	2.45 (1.65, 3.65)	0.1108
	T-DM1 (N=139)	36 (25.9)				<.0001	
Negative	T-DXd (N=123)	61 (49.6)	2.07 (1.23, 3.48)	1.54 (1.12, 2.11)	0.174 (0.052, 0.295)	1.55 (1.04, 2.33)	
	T-DM1 (N=121)	39 (32.2)				0.0318	
Alopecia							
Positive	T-DXd (N=133)	54 (40.6)	30.99 (9.38, 102.38)	18.81 (6.03, 58.70)	0.384 (0.298, 0.471)	21.25 (6.64, 67.99)	0.2531
	T-DM1 (N=139)	3 (2.2)				<.0001	
Negative	T-DXd (N=123)	41 (33.3)	11.60 (4.39, 30.61)	8.07 (3.30, 19.72)	0.292 (0.201, 0.383)	8.96 (3.54, 22.68)	
	T-DM1 (N=121)	5 (4.1)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
Positive	T-DXd (N=133)	9 (6.8)	0.77 (0.31, 1.89)	0.78 (0.34, 1.80)	-0.019 (-0.082, 0.045)	0.51 (0.21, 1.24)	0.6318
	T-DM1 (N=139)	12 (8.6)				0.1324	
Negative	T-DXd (N=123)	7 (5.7)	0.55 (0.21, 1.44)	0.57 (0.23, 1.41)	-0.042 (-0.109, 0.025)	0.44 (0.17, 1.13)	
	T-DM1 (N=121)	12 (9.9)				0.0810	
Skin hyperpigmentation							
Positive	T-DXd (N=133)	6 (4.5)	NE (NE, NE)	NE (NE, NE)	0.045 (0.010, 0.080)	NE (NE, NE)	1.0000
	T-DM1 (N=139)	0				0.0240	
Negative	T-DXd (N=123)	5 (4.1)	NE (NE, NE)	NE (NE, NE)	0.041 (0.006, 0.076)	NE (NE, NE)	
	T-DM1 (N=121)	0				0.0511	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Positive	T-DXd (N=133)	62 (46.6)	2.09 (1.27, 3.44)	1.58 (1.15, 2.17)	0.171 (0.057, 0.285)	1.64 (1.10, 2.43)	0.8093
	T-DM1 (N=139)	41 (29.5)				0.0140	
Negative	T-DXd (N=123)	59 (48.0)	1.94 (1.15, 3.26)	1.49 (1.08, 2.04)	0.157 (0.036, 0.279)	1.47 (0.98, 2.21)	
	T-DM1 (N=121)	39 (32.2)				0.0626	
Decreased appetite							
Positive	T-DXd (N=133)	42 (31.6)	2.59 (1.44, 4.68)	2.09 (1.31, 3.33)	0.165 (0.066, 0.264)	2.13 (1.26, 3.61)	0.2045
	T-DM1 (N=139)	21 (15.1)				0.0040	
Negative	T-DXd (N=123)	32 (26.0)	1.50 (0.82, 2.75)	1.37 (0.85, 2.20)	0.070 (-0.034, 0.174)	1.29 (0.75, 2.21)	
	T-DM1 (N=121)	23 (19.0)				0.3638	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
Positive	T-DXd (N=133)	5 (3.8)	NE (NE, NE)	NE (NE, NE)	0.038 (0.005, 0.070)	NE (NE, NE)	0.9999
	T-DM1 (N=139)	0				0.0240	
Negative	T-DXd (N=123)	6 (4.9)	NE (NE, NE)	NE (NE, NE)	0.049 (0.011, 0.087)	NE (NE, NE)	
	T-DM1 (N=121)	0				0.0154	
Nervous system disorders							
Any PT							
Positive	T-DXd (N=133)	59 (44.4)	1.26 (0.77, 2.03)	1.14 (0.86, 1.51)	0.055 (-0.062, 0.172)	0.85 (0.59, 1.24)	0.4637
	T-DM1 (N=139)	54 (38.8)				0.4097	
Negative	T-DXd (N=123)	57 (46.3)	1.51 (0.91, 2.52)	1.27 (0.94, 1.73)	0.100 (-0.023, 0.223)	1.05 (0.71, 1.56)	
	T-DM1 (N=121)	44 (36.4)				0.8043	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
Positive	T-DXd (N=133)	9 (6.8)	0.94 (0.37, 2.38)	0.94 (0.39, 2.24)	-0.004 (-0.065, 0.056)	0.68 (0.27, 1.70)	0.5896
	T-DM1 (N=139)	10 (7.2)				0.4079	
Negative	T-DXd (N=123)	10 (8.1)	0.63 (0.27, 1.45)	0.66 (0.31, 1.40)	-0.043 (-0.119, 0.033)	0.45 (0.20, 1.01)	
	T-DM1 (N=121)	15 (12.4)				0.0485	
Infections and infestations							
Any PT							
Positive	T-DXd (N=133)	63 (47.4)	2.39 (1.44, 3.96)	1.73 (1.25, 2.40)	0.200 (0.088, 0.313)	1.32 (0.88, 1.98)	0.0543
	T-DM1 (N=139)	38 (27.3)				0.1825	
Negative	T-DXd (N=123)	49 (39.8)	1.04 (0.62, 1.74)	1.03 (0.75, 1.40)	0.010 (-0.113, 0.133)	0.77 (0.51, 1.16)	
	T-DM1 (N=121)	47 (38.8)				0.2170	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Positive	T-DXd (N=133)	55 (41.4)	1.52 (0.93, 2.50)	1.31 (0.95, 1.79)	0.097 (-0.017, 0.211)	0.97 (0.65, 1.44)	0.7685
	T-DM1 (N=139)	44 (31.7)				0.8637	
Negative	T-DXd (N=123)	52 (42.3)	1.80 (1.06, 3.06)	1.46 (1.03, 2.07)	0.134 (0.015, 0.252)	0.96 (0.62, 1.49)	
	T-DM1 (N=121)	35 (28.9)				0.8593	
Epistaxis							
Positive	T-DXd (N=133)	15 (11.3)	0.68 (0.33, 1.37)	0.71 (0.39, 1.31)	-0.045 (-0.127, 0.036)	0.44 (0.23, 0.85)	0.9286
	T-DM1 (N=139)	22 (15.8)				0.0129	
Negative	T-DXd (N=123)	14 (11.4)	0.65 (0.31, 1.35)	0.69 (0.36, 1.30)	-0.051 (-0.138, 0.035)	0.39 (0.19, 0.79)	
	T-DM1 (N=121)	20 (16.5)				0.0068	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
Positive	T-DXd (N=133)	9 (6.8)	NE (NE, NE)	NE (NE, NE)	0.068 (0.025, 0.110)	NE (NE, NE)	0.9892
	T-DM1 (N=139)	0				0.0153	
Negative	T-DXd (N=123)	9 (7.3)	9.47 (1.18, 75.92)	8.85 (1.14, 68.82)	0.065 (0.016, 0.114)	4.99 (0.62, 39.90)	
	T-DM1 (N=121)	1 (0.8)				0.0938	
Blood and lymphatic system disorders							
Any PT							
Positive	T-DXd (N=133)	53 (39.8)	1.58 (0.96, 2.62)	1.35 (0.97, 1.88)	0.104 (-0.009, 0.216)	1.09 (0.72, 1.64)	0.6094
	T-DM1 (N=139)	41 (29.5)				0.6749	
Negative	T-DXd (N=123)	50 (40.7)	1.83 (1.07, 3.13)	1.49 (1.04, 2.14)	0.134 (0.016, 0.251)	1.31 (0.84, 2.03)	
	T-DM1 (N=121)	33 (27.3)				0.2275	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
Positive	T-DXd (N=133)	40 (30.1)	2.06 (1.16, 3.66)	1.74 (1.11, 2.72)	0.128 (0.028, 0.228)	1.41 (0.84, 2.34)	0.4899
	T-DM1 (N=139)	24 (17.3)				0.1893	
Negative	T-DXd (N=123)	43 (35.0)	2.71 (1.48, 4.98)	2.12 (1.33, 3.38)	0.184 (0.077, 0.291)	1.94 (1.14, 3.30)	
	T-DM1 (N=121)	20 (16.5)				0.0129	
Neutropenia							
Positive	T-DXd (N=133)	24 (18.0)	7.43 (2.50, 22.06)	6.27 (2.24, 17.59)	0.152 (0.081, 0.223)	4.95 (1.71, 14.36)	0.8839
	T-DM1 (N=139)	4 (2.9)				0.0011	
Negative	T-DXd (N=123)	17 (13.8)	6.31 (1.80, 22.13)	5.57 (1.68, 18.53)	0.113 (0.046, 0.180)	4.18 (1.22, 14.39)	
	T-DM1 (N=121)	3 (2.5)				0.0139	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
Positive	T-DXd (N=133)	8 (6.0)	0.46 (0.19, 1.10)	0.49 (0.22, 1.10)	-0.062 (-0.130, 0.006)	0.34 (0.15, 0.80)	0.7485
	T-DM1 (N=139)	17 (12.2)				0.0099	
Negative	T-DXd (N=123)	5 (4.1)	0.35 (0.12, 1.02)	0.38 (0.14, 1.03)	-0.067 (-0.132, -0.002)	0.29 (0.10, 0.83)	
	T-DM1 (N=121)	13 (10.7)				0.0146	
Musculoskeletal and connective tissue disorders							
Any PT							
Positive	T-DXd (N=133)	50 (37.6)	1.01 (0.62, 1.65)	1.00 (0.74, 1.37)	0.002 (-0.113, 0.117)	0.74 (0.50, 1.10)	0.4060
	T-DM1 (N=139)	52 (37.4)				0.1376	
Negative	T-DXd (N=123)	44 (35.8)	1.43 (0.83, 2.45)	1.27 (0.88, 1.84)	0.077 (-0.040, 0.193)	0.91 (0.58, 1.44)	
	T-DM1 (N=121)	34 (28.1)				0.6906	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
Positive	T-DXd (N=133)	20 (15.0)	1.87 (0.88, 4.00)	1.74 (0.89, 3.42)	0.064 (-0.013, 0.141)	1.37 (0.66, 2.82)	0.3551
	T-DM1 (N=139)	12 (8.6)				0.4002	
Negative	T-DXd (N=123)	25 (20.3)	3.17 (1.41, 7.13)	2.73 (1.33, 5.61)	0.129 (0.044, 0.214)	2.03 (0.94, 4.40)	
	T-DM1 (N=121)	9 (7.4)				0.0666	
Eye disorders							
Any PT							
Positive	T-DXd (N=133)	21 (15.8)	1.67 (0.81, 3.45)	1.57 (0.83, 2.95)	0.057 (-0.022, 0.137)	1.10 (0.55, 2.17)	0.5629
	T-DM1 (N=139)	14 (10.1)				0.7934	
Negative	T-DXd (N=123)	20 (16.3)	1.27 (0.63, 2.60)	1.23 (0.67, 2.26)	0.030 (-0.058, 0.119)	0.78 (0.40, 1.52)	
	T-DM1 (N=121)	16 (13.2)				0.4634	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
Positive	T-DXd (N=133)	19 (14.3)	0.84 (0.43, 1.63)	0.86 (0.49, 1.51)	-0.023 (-0.108, 0.063)	0.61 (0.33, 1.13)	0.1404
	T-DM1 (N=139)	23 (16.5)				0.1159	
Negative	T-DXd (N=123)	20 (16.3)	1.76 (0.82, 3.79)	1.64 (0.84, 3.20)	0.063 (-0.021, 0.148)	1.15 (0.56, 2.38)	
	T-DM1 (N=121)	12 (9.9)				0.6993	
Insomnia							
Positive	T-DXd (N=133)	7 (5.3)	0.40 (0.16, 1.00)	0.43 (0.18, 1.00)	-0.070 (-0.136, -0.003)	0.32 (0.13, 0.78)	0.1352
	T-DM1 (N=139)	17 (12.2)				0.0085	
Negative	T-DXd (N=123)	8 (6.5)	1.13 (0.40, 3.23)	1.12 (0.42, 3.00)	0.007 (-0.053, 0.067)	0.77 (0.28, 2.15)	
	T-DM1 (N=121)	7 (5.8)				0.6199	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Positive	T-DXd (N=133)	14 (10.5)	1.05 (0.48, 2.30)	1.05 (0.52, 2.11)	0.005 (-0.068, 0.077)	0.67 (0.32, 1.43)	0.5819
	T-DM1 (N=139)	14 (10.1)				0.3018	
Negative	T-DXd (N=123)	18 (14.6)	1.42 (0.66, 3.05)	1.36 (0.70, 2.66)	0.039 (-0.044, 0.122)	0.90 (0.43, 1.87)	
	T-DM1 (N=121)	13 (10.7)				0.7769	
Cardiac disorders							
Any PT							
Positive	T-DXd (N=133)	11 (8.3)	2.42 (0.82, 7.15)	2.30 (0.82, 6.44)	0.047 (-0.009, 0.103)	1.51 (0.52, 4.40)	0.6675
	T-DM1 (N=139)	5 (3.6)				0.4503	
Negative	T-DXd (N=123)	10 (8.1)	1.70 (0.60, 4.82)	1.64 (0.62, 4.37)	0.032 (-0.030, 0.094)	1.22 (0.44, 3.38)	
	T-DM1 (N=121)	6 (5.0)				0.7080	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
Positive	T-DXd (N=133)	12 (9.0)	2.20 (0.80, 6.04)	2.09 (0.81, 5.41)	0.047 (-0.012, 0.106)	1.41 (0.52, 3.81)	0.6496
	T-DM1 (N=139)	6 (4.3)				0.4920	
Negative	T-DXd (N=123)	9 (7.3)	3.10 (0.82, 11.76)	2.95 (0.82, 10.64)	0.048 (-0.005, 0.102)	2.16 (0.58, 8.05)	
	T-DM1 (N=121)	3 (2.5)				0.2414	
Reproductive system and breast disorders							
Any PT							
Positive	T-DXd (N=133)	12 (9.0)	1.43 (0.58, 3.52)	1.39 (0.61, 3.20)	0.025 (-0.038, 0.089)	1.01 (0.42, 2.42)	0.7045
	T-DM1 (N=139)	9 (6.5)				0.9848	
Negative	T-DXd (N=123)	9 (7.3)	1.12 (0.42, 2.99)	1.11 (0.44, 2.77)	0.007 (-0.057, 0.071)	0.70 (0.26, 1.85)	
	T-DM1 (N=121)	8 (6.6)				0.4653	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
Positive	T-DXd (N=133)	15 (11.3)	0.71 (0.35, 1.45)	0.75 (0.40, 1.39)	-0.038 (-0.119, 0.042)	0.55 (0.28, 1.07)	0.5922
	T-DM1 (N=139)	21 (15.1)				0.0762	
Negative	T-DXd (N=123)	4 (3.3)	0.47 (0.14, 1.62)	0.49 (0.15, 1.59)	-0.034 (-0.088, 0.021)	0.37 (0.11, 1.27)	
	T-DM1 (N=121)	8 (6.6)				0.1029	
Renal and urinary disorders							
Any PT							
Positive	T-DXd (N=133)	10 (7.5)	1.80 (0.64, 5.11)	1.74 (0.65, 4.66)	0.032 (-0.024, 0.088)	1.14 (0.41, 3.17)	0.5036
	T-DM1 (N=139)	6 (4.3)				0.8045	
Negative	T-DXd (N=123)	5 (4.1)	0.98 (0.28, 3.49)	0.98 (0.29, 3.31)	-0.001 (-0.050, 0.049)	0.83 (0.24, 2.87)	
	T-DM1 (N=121)	5 (4.1)				0.7636	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Positive	T-DXd (N=129)	118 (91.5)	8.67 (4.28, 17.58)	1.65 (1.41, 1.95)	0.362 (0.264, 0.459)	2.98 (2.21, 4.01)	0.4712
	T-DM1 (N=132)	73 (55.3)				<.0001	
Negative	T-DXd (N=127)	118 (92.9)	8.24 (3.83, 17.72)	1.51 (1.31, 1.75)	0.315 (0.219, 0.411)	2.69 (2.01, 3.60)	
	T-DM1 (N=127)	78 (61.4)				<.0001	
Nausea							
Positive	T-DXd (N=129)	101 (78.3)	10.00 (5.66, 17.67)	2.95 (2.19, 3.98)	0.518 (0.414, 0.621)	4.58 (3.11, 6.75)	0.1053
	T-DM1 (N=132)	35 (26.5)				<.0001	
Negative	T-DXd (N=127)	93 (73.2)	5.16 (3.02, 8.82)	2.11 (1.63, 2.74)	0.386 (0.273, 0.499)	3.00 (2.09, 4.30)	
	T-DM1 (N=127)	44 (34.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Positive	T-DXd (N=129)	61 (47.3)	8.97 (4.51, 17.83)	5.20 (2.94, 9.19)	0.382 (0.283, 0.481)	5.77 (3.10, 10.72)	0.7589
	T-DM1 (N=132)	12 (9.1)				<.0001	
Negative	T-DXd (N=127)	64 (50.4)	8.20 (4.26, 15.79)	4.57 (2.71, 7.72)	0.394 (0.291, 0.496)	4.99 (2.79, 8.91)	
	T-DM1 (N=127)	14 (11.0)				<.0001	
Constipation							
Positive	T-DXd (N=129)	48 (37.2)	2.96 (1.66, 5.29)	2.23 (1.43, 3.48)	0.205 (0.101, 0.310)	1.96 (1.18, 3.26)	0.1938
	T-DM1 (N=132)	22 (16.7)				0.0078	
Negative	T-DXd (N=127)	40 (31.5)	1.63 (0.93, 2.85)	1.43 (0.94, 2.16)	0.094 (-0.014, 0.203)	1.26 (0.78, 2.06)	
	T-DM1 (N=127)	28 (22.0)				0.3454	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Positive	T-DXd (N=129)	40 (31.0)	5.48 (2.60, 11.55)	4.09 (2.14, 7.83)	0.234 (0.143, 0.326)	4.15 (2.07, 8.30)	0.9597
	T-DM1 (N=132)	10 (7.6)				<.0001	
Negative	T-DXd (N=127)	34 (26.8)	5.44 (2.40, 12.30)	4.25 (2.05, 8.82)	0.205 (0.117, 0.293)	4.13 (1.90, 8.94)	
	T-DM1 (N=127)	8 (6.3)				<.0001	
Stomatitis							
Positive	T-DXd (N=129)	21 (16.3)	4.94 (1.80, 13.54)	4.30 (1.67, 11.05)	0.125 (0.053, 0.196)	3.63 (1.36, 9.66)	0.8572
	T-DM1 (N=132)	5 (3.8)				0.0058	
Negative	T-DXd (N=127)	19 (15.0)	4.29 (1.55, 11.89)	3.80 (1.46, 9.86)	0.110 (0.040, 0.181)	3.08 (1.14, 8.30)	
	T-DM1 (N=127)	5 (3.9)				0.0194	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Positive	T-DXd (N=129)	17 (13.2)	NE (NE, NE)	NE (NE, NE)	0.132 (0.073, 0.190)	NE (NE, NE)	0.9893
	T-DM1 (N=132)	0				0.0002	
Negative	T-DXd (N=127)	12 (9.4)	2.55 (0.87, 7.45)	2.40 (0.87, 6.61)	0.055 (-0.006, 0.116)	1.69 (0.59, 4.86)	
	T-DM1 (N=127)	5 (3.9)				0.3240	
Dry mouth							
Positive	T-DXd (N=129)	5 (3.9)	0.34 (0.12, 0.97)	0.37 (0.14, 0.99)	-0.067 (-0.129, -0.005)	0.29 (0.10, 0.80)	0.7123
	T-DM1 (N=132)	14 (10.6)				0.0110	
Negative	T-DXd (N=127)	3 (2.4)	0.26 (0.07, 0.94)	0.27 (0.08, 0.95)	-0.063 (-0.119, -0.007)	0.20 (0.05, 0.73)	
	T-DM1 (N=127)	11 (8.7)				0.0074	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Positive	T-DXd (N=129)	82 (63.6)	0.68 (0.40, 1.15)	0.88 (0.75, 1.05)	-0.084 (-0.197, 0.029)	0.55 (0.41, 0.74)	0.3705
	T-DM1 (N=132)	95 (72.0)				0.0002	
Negative	T-DXd (N=127)	80 (63.0)	0.87 (0.52, 1.46)	0.95 (0.79, 1.14)	-0.031 (-0.149, 0.086)	0.67 (0.49, 0.91)	
	T-DM1 (N=127)	84 (66.1)				0.0239	
Neutrophil count decreased							
Positive	T-DXd (N=129)	39 (30.2)	4.77 (2.31, 9.82)	3.63 (1.94, 6.77)	0.219 (0.127, 0.311)	3.46 (1.77, 6.76)	0.4112
	T-DM1 (N=132)	11 (8.3)				0.0001	
Negative	T-DXd (N=127)	36 (28.3)	3.19 (1.62, 6.28)	2.57 (1.46, 4.53)	0.173 (0.078, 0.269)	2.33 (1.25, 4.32)	
	T-DM1 (N=127)	14 (11.0)				0.0059	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
Positive	T-DXd (N=129)	30 (23.3)	0.37 (0.22, 0.64)	0.52 (0.36, 0.75)	-0.214 (-0.326, -0.103)	0.34 (0.22, 0.53)	0.0988
	T-DM1 (N=132)	59 (44.7)				<.0001	
Negative	T-DXd (N=127)	36 (28.3)	0.70 (0.41, 1.18)	0.78 (0.55, 1.12)	-0.079 (-0.193, 0.036)	0.58 (0.37, 0.89)	
	T-DM1 (N=127)	46 (36.2)				0.0168	
White blood cell count decreased							
Positive	T-DXd (N=129)	26 (20.2)	4.51 (1.88, 10.81)	3.80 (1.71, 8.45)	0.149 (0.069, 0.228)	3.12 (1.35, 7.22)	0.6632
	T-DM1 (N=132)	7 (5.3)				0.0051	
Negative	T-DXd (N=127)	32 (25.2)	5.77 (2.44, 13.66)	4.57 (2.10, 9.97)	0.197 (0.112, 0.282)	4.22 (1.86, 9.58)	
	T-DM1 (N=127)	7 (5.5)				0.0002	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
Positive	T-DXd (N=129)	26 (20.2)	0.54 (0.31, 0.95)	0.63 (0.41, 0.97)	-0.117 (-0.222, -0.011)	0.48 (0.29, 0.78)	0.2591
	T-DM1 (N=132)	42 (31.8)				0.0027	
Negative	T-DXd (N=127)	30 (23.6)	0.81 (0.46, 1.43)	0.86 (0.56, 1.31)	-0.039 (-0.147, 0.068)	0.69 (0.42, 1.13)	
	T-DM1 (N=127)	35 (27.6)				0.1453	
Platelet count decreased							
Positive	T-DXd (N=129)	25 (19.4)	0.33 (0.19, 0.57)	0.46 (0.30, 0.68)	-0.230 (-0.339, -0.122)	0.30 (0.18, 0.48)	0.5416
	T-DM1 (N=132)	56 (42.4)				<.0001	
Negative	T-DXd (N=127)	29 (22.8)	0.38 (0.22, 0.65)	0.52 (0.36, 0.75)	-0.213 (-0.326, -0.100)	0.35 (0.22, 0.56)	
	T-DM1 (N=127)	56 (44.1)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
Positive	T-DXd (N=129)	18 (14.0)	4.12 (1.48, 11.46)	3.68 (1.41, 9.63)	0.102 (0.034, 0.170)	3.03 (1.12, 8.18)	0.4506
	T-DM1 (N=132)	5 (3.8)				0.0217	
Negative	T-DXd (N=127)	25 (19.7)	2.58 (1.21, 5.51)	2.27 (1.17, 4.42)	0.110 (0.026, 0.195)	1.68 (0.82, 3.44)	
	T-DM1 (N=127)	11 (8.7)				0.1485	
Blood lactate dehydrogenase increased							
Positive	T-DXd (N=129)	8 (6.2)	0.37 (0.16, 0.87)	0.41 (0.19, 0.90)	-0.089 (-0.163, -0.016)	0.31 (0.13, 0.71)	0.4823
	T-DM1 (N=132)	20 (15.2)				0.0035	
Negative	T-DXd (N=127)	9 (7.1)	0.57 (0.24, 1.35)	0.60 (0.27, 1.32)	-0.047 (-0.119, 0.024)	0.46 (0.20, 1.06)	
	T-DM1 (N=127)	15 (11.8)				0.0614	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
Positive	T-DXd (N=129)	9 (7.0)	NE (NE, NE)	NE (NE, NE)	0.070 (0.026, 0.114)	NE (NE, NE)	0.9881
	T-DM1 (N=132)	0				0.0095	
Negative	T-DXd (N=127)	5 (3.9)	1.69 (0.40, 7.24)	1.67 (0.41, 6.83)	0.016 (-0.027, 0.059)	1.22 (0.29, 5.18)	
	T-DM1 (N=127)	3 (2.4)				0.7862	
General disorders and administration site conditions							
Any PT							
Positive	T-DXd (N=129)	79 (61.2)	1.78 (1.09, 2.92)	1.30 (1.04, 1.64)	0.143 (0.023, 0.262)	1.12 (0.80, 1.57)	0.6203
	T-DM1 (N=132)	62 (47.0)				0.5047	
Negative	T-DXd (N=127)	79 (62.2)	1.34 (0.81, 2.21)	1.13 (0.92, 1.39)	0.071 (-0.050, 0.192)	0.97 (0.70, 1.35)	
	T-DM1 (N=127)	70 (55.1)				0.8799	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Positive	T-DXd (N=129)	12 (9.3)	3.28 (1.03, 10.46)	3.07 (1.02, 9.27)	0.063 (0.005, 0.121)	2.67 (0.85, 8.33)	0.8883
	T-DM1 (N=132)	4 (3.0)				0.0795	
Negative	T-DXd (N=127)	16 (12.6)	2.91 (1.10, 7.69)	2.67 (1.08, 6.59)	0.079 (0.010, 0.147)	2.55 (0.99, 6.53)	
	T-DM1 (N=127)	6 (4.7)				0.0436	
Pyrexia							
Positive	T-DXd (N=129)	13 (10.1)	0.67 (0.31, 1.41)	0.70 (0.36, 1.36)	-0.043 (-0.122, 0.036)	0.45 (0.22, 0.92)	0.9829
	T-DM1 (N=132)	19 (14.4)				0.0259	
Negative	T-DXd (N=127)	14 (11.0)	0.66 (0.32, 1.38)	0.70 (0.37, 1.32)	-0.047 (-0.131, 0.036)	0.44 (0.22, 0.88)	
	T-DM1 (N=127)	20 (15.7)				0.0170	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Positive	T-DXd (N=129)	76 (58.9)	3.82 (2.27, 6.43)	2.16 (1.58, 2.96)	0.316 (0.202, 0.430)	2.32 (1.56, 3.46)	0.2158
	T-DM1 (N=132)	36 (27.3)				<.0001	
Negative	T-DXd (N=127)	63 (49.6)	2.22 (1.33, 3.71)	1.62 (1.18, 2.21)	0.189 (0.071, 0.307)	1.64 (1.09, 2.45)	
	T-DM1 (N=127)	39 (30.7)				0.0153	
Alopecia							
Positive	T-DXd (N=129)	53 (41.1)	29.99 (9.06, 99.28)	18.08 (5.80, 56.39)	0.388 (0.300, 0.477)	20.47 (6.39, 65.53)	0.2955
	T-DM1 (N=132)	3 (2.3)				<.0001	
Negative	T-DXd (N=127)	42 (33.1)	12.05 (4.58, 31.73)	8.40 (3.44, 20.54)	0.291 (0.203, 0.380)	9.31 (3.68, 23.54)	
	T-DM1 (N=127)	5 (3.9)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
Positive	T-DXd (N=129)	9 (7.0)	0.75 (0.30, 1.85)	0.77 (0.33, 1.76)	-0.021 (-0.087, 0.045)	0.50 (0.21, 1.21)	0.6652
	T-DM1 (N=132)	12 (9.1)				0.1191	
Negative	T-DXd (N=127)	7 (5.5)	0.56 (0.21, 1.47)	0.58 (0.24, 1.43)	-0.039 (-0.104, 0.025)	0.44 (0.17, 1.14)	
	T-DM1 (N=127)	12 (9.4)				0.0839	
Skin hyperpigmentation							
Positive	T-DXd (N=129)	6 (4.7)	NE (NE, NE)	NE (NE, NE)	0.047 (0.010, 0.083)	NE (NE, NE)	1.0000
	T-DM1 (N=132)	0				0.0248	
Negative	T-DXd (N=127)	5 (3.9)	NE (NE, NE)	NE (NE, NE)	0.039 (0.006, 0.073)	NE (NE, NE)	
	T-DM1 (N=127)	0				0.0516	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Positive	T-DXd (N=129)	59 (45.7)	2.16 (1.29, 3.62)	1.63 (1.17, 2.27)	0.177 (0.062, 0.292)	1.71 (1.13, 2.58)	0.5993
	T-DM1 (N=132)	37 (28.0)				0.0100	
Negative	T-DXd (N=127)	62 (48.8)	1.86 (1.12, 3.09)	1.44 (1.07, 1.95)	0.150 (0.030, 0.269)	1.41 (0.95, 2.09)	
	T-DM1 (N=127)	43 (33.9)				0.0865	
Decreased appetite							
Positive	T-DXd (N=129)	41 (31.8)	2.77 (1.50, 5.11)	2.21 (1.36, 3.59)	0.174 (0.074, 0.274)	2.26 (1.31, 3.91)	0.1229
	T-DM1 (N=132)	19 (14.4)				0.0026	
Negative	T-DXd (N=127)	33 (26.0)	1.43 (0.79, 2.58)	1.32 (0.84, 2.09)	0.063 (-0.040, 0.166)	1.24 (0.74, 2.09)	
	T-DM1 (N=127)	25 (19.7)				0.4339	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
Positive	T-DXd (N=129)	5 (3.9)	NE (NE, NE)	NE (NE, NE)	0.039 (0.005, 0.072)	NE (NE, NE)	0.9999
	T-DM1 (N=132)	0				0.0254	
Negative	T-DXd (N=127)	6 (4.7)	NE (NE, NE)	NE (NE, NE)	0.047 (0.010, 0.084)	NE (NE, NE)	
	T-DM1 (N=127)	0				0.0145	
Nervous system disorders							
Any PT							
Positive	T-DXd (N=129)	58 (45.0)	1.30 (0.79, 2.12)	1.16 (0.87, 1.55)	0.063 (-0.056, 0.183)	0.88 (0.60, 1.29)	0.5843
	T-DM1 (N=132)	51 (38.6)				0.5221	
Negative	T-DXd (N=127)	58 (45.7)	1.48 (0.90, 2.45)	1.26 (0.94, 1.70)	0.094 (-0.026, 0.215)	1.02 (0.69, 1.51)	
	T-DM1 (N=127)	46 (36.2)				0.9107	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
Positive	T-DXd (N=129)	9 (7.0)	1.03 (0.39, 2.67)	1.02 (0.42, 2.50)	0.002 (-0.060, 0.063)	0.74 (0.29, 1.89)	0.4143
	T-DM1 (N=132)	9 (6.8)				0.5295	
Negative	T-DXd (N=127)	10 (7.9)	0.59 (0.26, 1.36)	0.63 (0.29, 1.32)	-0.047 (-0.122, 0.027)	0.42 (0.19, 0.94)	
	T-DM1 (N=127)	16 (12.6)				0.0302	
Infections and infestations							
Any PT							
Positive	T-DXd (N=129)	61 (47.3)	2.30 (1.38, 3.85)	1.69 (1.21, 2.34)	0.193 (0.077, 0.308)	1.28 (0.84, 1.93)	0.0863
	T-DM1 (N=132)	37 (28.0)				0.2464	
Negative	T-DXd (N=127)	51 (40.2)	1.10 (0.67, 1.83)	1.06 (0.78, 1.45)	0.024 (-0.096, 0.144)	0.80 (0.53, 1.19)	
	T-DM1 (N=127)	48 (37.8)				0.2726	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Positive	T-DXd (N=129)	54 (41.9)	1.60 (0.96, 2.66)	1.35 (0.97, 1.87)	0.108 (-0.008, 0.224)	1.00 (0.67, 1.51)	0.9350
	T-DM1 (N=132)	41 (31.1)				0.9925	
Negative	T-DXd (N=127)	53 (41.7)	1.74 (1.04, 2.93)	1.43 (1.02, 2.01)	0.126 (0.009, 0.243)	0.95 (0.62, 1.46)	
	T-DM1 (N=127)	37 (29.1)				0.8127	
Epistaxis							
Positive	T-DXd (N=129)	15 (11.6)	0.70 (0.34, 1.42)	0.73 (0.39, 1.35)	-0.043 (-0.126, 0.041)	0.45 (0.23, 0.88)	0.8889
	T-DM1 (N=132)	21 (15.9)				0.0176	
Negative	T-DXd (N=127)	14 (11.0)	0.66 (0.32, 1.38)	0.70 (0.37, 1.32)	-0.047 (-0.131, 0.036)	0.39 (0.19, 0.80)	
	T-DM1 (N=127)	20 (15.7)				0.0076	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
Positive	T-DXd (N=129)	9 (7.0)	NE (NE, NE)	NE (NE, NE)	0.070 (0.026, 0.114)	NE (NE, NE)	0.9894
	T-DM1 (N=132)	0				0.0158	
Negative	T-DXd (N=127)	9 (7.1)	9.61 (1.20, 76.96)	9.00 (1.16, 70.00)	0.063 (0.016, 0.110)	4.97 (0.62, 39.79)	
	T-DM1 (N=127)	1 (0.8)				0.0945	
Blood and lymphatic system disorders							
Any PT							
Positive	T-DXd (N=129)	51 (39.5)	1.62 (0.97, 2.71)	1.37 (0.97, 1.93)	0.107 (-0.007, 0.222)	1.12 (0.73, 1.71)	0.7402
	T-DM1 (N=132)	38 (28.8)				0.5918	
Negative	T-DXd (N=127)	52 (40.9)	1.75 (1.04, 2.96)	1.44 (1.02, 2.04)	0.126 (0.010, 0.242)	1.25 (0.81, 1.92)	
	T-DM1 (N=127)	36 (28.3)				0.2996	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
Positive	T-DXd (N=129)	38 (29.5)	2.21 (1.21, 4.02)	1.85 (1.15, 2.98)	0.135 (0.035, 0.236)	1.52 (0.89, 2.61)	0.7857
	T-DM1 (N=132)	21 (15.9)				0.1234	
Negative	T-DXd (N=127)	45 (35.4)	2.48 (1.39, 4.43)	1.96 (1.26, 3.03)	0.173 (0.066, 0.280)	1.75 (1.06, 2.90)	
	T-DM1 (N=127)	23 (18.1)				0.0272	
Neutropenia							
Positive	T-DXd (N=129)	23 (17.8)	6.94 (2.33, 20.70)	5.88 (2.09, 16.54)	0.148 (0.076, 0.220)	4.63 (1.59, 13.45)	0.9955
	T-DM1 (N=132)	4 (3.0)				0.0020	
Negative	T-DXd (N=127)	18 (14.2)	6.83 (1.96, 23.80)	6.00 (1.81, 19.87)	0.118 (0.052, 0.184)	4.52 (1.32, 15.46)	
	T-DM1 (N=127)	3 (2.4)				0.0086	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
Positive	T-DXd (N=129)	8 (6.2)	0.45 (0.19, 1.08)	0.48 (0.22, 1.08)	-0.067 (-0.137, 0.004)	0.33 (0.14, 0.78)	0.7930
	T-DM1 (N=132)	17 (12.9)				0.0083	
Negative	T-DXd (N=127)	5 (3.9)	0.36 (0.12, 1.04)	0.38 (0.14, 1.05)	-0.063 (-0.126, 0.000)	0.29 (0.10, 0.84)	
	T-DM1 (N=127)	13 (10.2)				0.0161	
Musculoskeletal and connective tissue disorders							
Any PT							
Positive	T-DXd (N=129)	50 (38.8)	1.07 (0.65, 1.77)	1.04 (0.77, 1.42)	0.016 (-0.101, 0.134)	0.79 (0.53, 1.17)	0.6349
	T-DM1 (N=132)	49 (37.1)				0.2368	
Negative	T-DXd (N=127)	44 (34.6)	1.34 (0.79, 2.28)	1.22 (0.85, 1.76)	0.063 (-0.051, 0.177)	0.86 (0.55, 1.35)	
	T-DM1 (N=127)	36 (28.3)				0.5177	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
Positive	T-DXd (N=129)	20 (15.5)	1.83 (0.86, 3.93)	1.71 (0.87, 3.34)	0.064 (-0.015, 0.144)	1.33 (0.64, 2.75)	0.3223
	T-DM1 (N=132)	12 (9.1)				0.4419	
Negative	T-DXd (N=127)	25 (19.7)	3.21 (1.43, 7.20)	2.78 (1.35, 5.71)	0.126 (0.044, 0.208)	2.05 (0.95, 4.43)	
	T-DM1 (N=127)	9 (7.1)				0.0635	
Eye disorders							
Any PT							
Positive	T-DXd (N=129)	21 (16.3)	1.64 (0.79, 3.38)	1.53 (0.82, 2.89)	0.057 (-0.026, 0.139)	1.07 (0.54, 2.13)	0.6015
	T-DM1 (N=132)	14 (10.6)				0.8390	
Negative	T-DXd (N=127)	20 (15.7)	1.30 (0.64, 2.63)	1.25 (0.68, 2.30)	0.031 (-0.054, 0.117)	0.78 (0.40, 1.53)	
	T-DM1 (N=127)	16 (12.6)				0.4748	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
Positive	T-DXd (N=129)	17 (13.2)	0.76 (0.38, 1.51)	0.79 (0.44, 1.42)	-0.035 (-0.121, 0.051)	0.57 (0.30, 1.09)	0.0827
	T-DM1 (N=132)	22 (16.7)				0.0862	
Negative	T-DXd (N=127)	22 (17.3)	1.84 (0.88, 3.83)	1.69 (0.89, 3.21)	0.071 (-0.013, 0.155)	1.15 (0.58, 2.30)	
	T-DM1 (N=127)	13 (10.2)				0.6919	
Insomnia							
Positive	T-DXd (N=129)	6 (4.7)	0.33 (0.13, 0.87)	0.36 (0.15, 0.89)	-0.082 (-0.150, -0.015)	0.28 (0.11, 0.71)	0.0553
	T-DM1 (N=132)	17 (12.9)				0.0042	
Negative	T-DXd (N=127)	9 (7.1)	1.31 (0.47, 3.63)	1.29 (0.49, 3.35)	0.016 (-0.044, 0.075)	0.84 (0.31, 2.29)	
	T-DM1 (N=127)	7 (5.5)				0.7338	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Positive	T-DXd (N=129)	14 (10.9)	1.22 (0.54, 2.74)	1.19 (0.57, 2.48)	0.018 (-0.055, 0.090)	0.75 (0.34, 1.63)	0.9776
	T-DM1 (N=132)	12 (9.1)				0.4643	
Negative	T-DXd (N=127)	18 (14.2)	1.23 (0.59, 2.57)	1.20 (0.63, 2.27)	0.024 (-0.059, 0.106)	0.80 (0.40, 1.61)	
	T-DM1 (N=127)	15 (11.8)				0.5266	
Cardiac disorders							
Any PT							
Positive	T-DXd (N=129)	11 (8.5)	2.37 (0.80, 7.02)	2.25 (0.80, 6.30)	0.047 (-0.011, 0.106)	1.48 (0.51, 4.33)	0.6887
	T-DM1 (N=132)	5 (3.8)				0.4690	
Negative	T-DXd (N=127)	10 (7.9)	1.72 (0.61, 4.89)	1.67 (0.62, 4.45)	0.031 (-0.028, 0.091)	1.22 (0.44, 3.39)	
	T-DM1 (N=127)	6 (4.7)				0.7023	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
Positive	T-DXd (N=129)	12 (9.3)	2.15 (0.78, 5.92)	2.05 (0.79, 5.29)	0.048 (-0.014, 0.109)	1.38 (0.51, 3.72)	0.6268
	T-DM1 (N=132)	6 (4.5)				0.5213	
Negative	T-DXd (N=127)	9 (7.1)	3.15 (0.83, 11.93)	3.00 (0.83, 10.83)	0.047 (-0.005, 0.099)	2.17 (0.58, 8.08)	
	T-DM1 (N=127)	3 (2.4)				0.2392	
Reproductive system and breast disorders							
Any PT							
Positive	T-DXd (N=129)	11 (8.5)	1.44 (0.56, 3.72)	1.41 (0.58, 3.38)	0.025 (-0.038, 0.088)	0.99 (0.39, 2.48)	0.6804
	T-DM1 (N=132)	8 (6.1)				0.9810	
Negative	T-DXd (N=127)	10 (7.9)	1.12 (0.44, 2.86)	1.11 (0.47, 2.64)	0.008 (-0.057, 0.073)	0.73 (0.29, 1.83)	
	T-DM1 (N=127)	9 (7.1)				0.4963	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
Positive	T-DXd (N=129)	15 (11.6)	0.70 (0.34, 1.42)	0.73 (0.39, 1.35)	-0.043 (-0.126, 0.041)	0.53 (0.27, 1.05)	0.6278
	T-DM1 (N=132)	21 (15.9)				0.0660	
Negative	T-DXd (N=127)	4 (3.1)	0.48 (0.14, 1.65)	0.50 (0.15, 1.62)	-0.031 (-0.084, 0.021)	0.38 (0.11, 1.29)	
	T-DM1 (N=127)	8 (6.3)				0.1083	
Renal and urinary disorders							
Any PT							
Positive	T-DXd (N=129)	10 (7.8)	1.76 (0.62, 5.01)	1.71 (0.64, 4.56)	0.032 (-0.026, 0.090)	1.11 (0.40, 3.11)	0.5231
	T-DM1 (N=132)	6 (4.5)				0.8356	
Negative	T-DXd (N=127)	5 (3.9)	1.00 (0.28, 3.54)	1.00 (0.30, 3.37)	0.000 (-0.048, 0.048)	0.83 (0.24, 2.89)	
	T-DM1 (N=127)	5 (3.9)				0.7710	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Positive	T-DXd (N=81)	76 (93.8)	10.70 (3.95, 28.94)	1.60 (1.33, 1.91)	0.351 (0.238, 0.465)	2.86 (2.00, 4.08)	0.9627
	T-DM1 (N=92)	54 (58.7)				<.0001	
Negative	T-DXd (N=174)	159 (91.4)	7.65 (4.15, 14.11)	1.57 (1.37, 1.80)	0.333 (0.247, 0.419)	2.85 (2.20, 3.68)	
	T-DM1 (N=167)	97 (58.1)				<.0001	
Nausea							
Positive	T-DXd (N=81)	69 (85.2)	16.29 (7.55, 35.17)	3.27 (2.29, 4.66)	0.591 (0.473, 0.709)	5.46 (3.41, 8.75)	0.0784
	T-DM1 (N=92)	24 (26.1)				<.0001	
Negative	T-DXd (N=174)	124 (71.3)	5.19 (3.27, 8.23)	2.20 (1.74, 2.80)	0.389 (0.292, 0.487)	3.14 (2.28, 4.33)	
	T-DM1 (N=167)	54 (32.3)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Positive	T-DXd (N=81)	40 (49.4)	8.00 (3.64, 17.59)	4.54 (2.43, 8.49)	0.385 (0.259, 0.511)	5.01 (2.50, 10.04)	0.8130
	T-DM1 (N=92)	10 (10.9)				<.0001	
Negative	T-DXd (N=174)	85 (48.9)	9.01 (4.97, 16.34)	5.10 (3.12, 8.32)	0.393 (0.306, 0.479)	5.65 (3.31, 9.65)	
	T-DM1 (N=167)	16 (9.6)				<.0001	
Constipation							
Positive	T-DXd (N=81)	33 (40.7)	2.32 (1.20, 4.49)	1.78 (1.13, 2.82)	0.179 (0.042, 0.316)	1.42 (0.82, 2.45)	0.7725
	T-DM1 (N=92)	21 (22.8)				0.2103	
Negative	T-DXd (N=174)	55 (31.6)	2.11 (1.27, 3.51)	1.76 (1.19, 2.60)	0.136 (0.046, 0.227)	1.63 (1.04, 2.55)	
	T-DM1 (N=167)	30 (18.0)				0.0320	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Positive	T-DXd (N=81)	29 (35.8)	6.77 (2.77, 16.57)	4.71 (2.18, 10.16)	0.282 (0.164, 0.400)	4.74 (2.07, 10.83)	0.6642
	T-DM1 (N=92)	7 (7.6)				<.0001	
Negative	T-DXd (N=174)	45 (25.9)	4.95 (2.46, 9.96)	3.93 (2.10, 7.33)	0.193 (0.118, 0.268)	3.88 (2.01, 7.52)	
	T-DM1 (N=167)	11 (6.6)				<.0001	
Stomatitis							
Positive	T-DXd (N=81)	14 (17.3)	3.64 (1.25, 10.59)	3.18 (1.20, 8.44)	0.118 (0.024, 0.213)	2.82 (1.01, 7.86)	0.5021
	T-DM1 (N=92)	5 (5.4)				0.0382	
Negative	T-DXd (N=174)	26 (14.9)	5.69 (2.13, 15.21)	4.99 (1.96, 12.69)	0.119 (0.061, 0.178)	3.98 (1.52, 10.42)	
	T-DM1 (N=167)	5 (3.0)				0.0024	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Positive	T-DXd (N=81)	14 (17.3)	19.01 (2.44, 148.17)	15.90 (2.14, 118.28)	0.162 (0.077, 0.247)	13.30 (1.74, 101.46)	0.1966
	T-DM1 (N=92)	1 (1.1)				0.0012	
Negative	T-DXd (N=174)	15 (8.6)	3.84 (1.25, 11.83)	3.60 (1.22, 10.62)	0.062 (0.015, 0.110)	2.49 (0.82, 7.58)	
	T-DM1 (N=167)	4 (2.4)				0.0978	
Dry mouth							
Positive	T-DXd (N=81)	5 (6.2)	0.44 (0.15, 1.30)	0.47 (0.17, 1.29)	-0.069 (-0.155, 0.018)	0.36 (0.13, 1.03)	0.3791
	T-DM1 (N=92)	12 (13.0)				0.0476	
Negative	T-DXd (N=174)	3 (1.7)	0.21 (0.06, 0.74)	0.22 (0.06, 0.76)	-0.061 (-0.106, -0.016)	0.16 (0.05, 0.59)	
	T-DM1 (N=167)	13 (7.8)				0.0017	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Positive	T-DXd (N=81)	53 (65.4)	0.75 (0.39, 1.42)	0.91 (0.74, 1.12)	-0.063 (-0.202, 0.075)	0.56 (0.39, 0.81)	0.8217
	T-DM1 (N=92)	66 (71.7)				0.0048	
Negative	T-DXd (N=174)	108 (62.1)	0.78 (0.50, 1.22)	0.92 (0.78, 1.07)	-0.056 (-0.157, 0.045)	0.63 (0.48, 0.82)	
	T-DM1 (N=167)	113 (67.7)				0.0016	
Neutrophil count decreased							
Positive	T-DXd (N=81)	22 (27.2)	3.91 (1.63, 9.39)	3.12 (1.47, 6.63)	0.185 (0.072, 0.297)	2.78 (1.24, 6.27)	0.9961
	T-DM1 (N=92)	8 (8.7)				0.0101	
Negative	T-DXd (N=174)	53 (30.5)	3.86 (2.13, 7.02)	2.99 (1.81, 4.95)	0.203 (0.120, 0.285)	2.83 (1.64, 4.90)	
	T-DM1 (N=167)	17 (10.2)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
Positive	T-DXd (N=81)	22 (27.2)	0.53 (0.28, 1.01)	0.66 (0.43, 1.01)	-0.141 (-0.281, -0.002)	0.41 (0.24, 0.70)	0.9881
	T-DM1 (N=92)	38 (41.3)				0.0010	
Negative	T-DXd (N=174)	44 (25.3)	0.51 (0.32, 0.80)	0.63 (0.46, 0.86)	-0.148 (-0.247, -0.050)	0.46 (0.31, 0.67)	
	T-DM1 (N=167)	67 (40.1)				<.0001	
White blood cell count decreased							
Positive	T-DXd (N=81)	11 (13.6)	2.25 (0.79, 6.40)	2.08 (0.81, 5.38)	0.071 (-0.019, 0.161)	1.77 (0.65, 4.83)	0.0700
	T-DM1 (N=92)	6 (6.5)				0.2556	
Negative	T-DXd (N=174)	47 (27.0)	7.36 (3.35, 16.13)	5.64 (2.75, 11.57)	0.222 (0.149, 0.296)	5.14 (2.43, 10.89)	
	T-DM1 (N=167)	8 (4.8)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
Positive	T-DXd (N=81)	20 (24.7)	0.98 (0.49, 1.96)	0.99 (0.59, 1.66)	-0.003 (-0.132, 0.126)	0.76 (0.42, 1.40)	0.2112
	T-DM1 (N=92)	23 (25.0)				0.3748	
Negative	T-DXd (N=174)	36 (20.7)	0.55 (0.33, 0.89)	0.64 (0.44, 0.92)	-0.116 (-0.209, -0.023)	0.50 (0.33, 0.77)	
	T-DM1 (N=167)	54 (32.3)				0.0013	
Platelet count decreased							
Positive	T-DXd (N=81)	13 (16.0)	0.23 (0.11, 0.47)	0.35 (0.20, 0.61)	-0.296 (-0.425, -0.167)	0.24 (0.13, 0.45)	0.1861
	T-DM1 (N=92)	42 (45.7)				<.0001	
Negative	T-DXd (N=174)	41 (23.6)	0.43 (0.27, 0.68)	0.56 (0.41, 0.78)	-0.184 (-0.281, -0.086)	0.38 (0.25, 0.56)	
	T-DM1 (N=167)	70 (41.9)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
Positive	T-DXd (N=81)	12 (14.8)	2.49 (0.89, 6.98)	2.27 (0.89, 5.78)	0.083 (-0.009, 0.175)	1.67 (0.62, 4.48)	0.5868
	T-DM1 (N=92)	6 (6.5)				0.3013	
Negative	T-DXd (N=174)	30 (17.2)	3.27 (1.54, 6.93)	2.88 (1.45, 5.70)	0.113 (0.046, 0.179)	2.25 (1.09, 4.62)	
	T-DM1 (N=167)	10 (6.0)				0.0235	
Blood lactate dehydrogenase increased							
Positive	T-DXd (N=81)	4 (4.9)	0.29 (0.09, 0.92)	0.32 (0.11, 0.95)	-0.103 (-0.190, -0.016)	0.22 (0.07, 0.67)	0.3414
	T-DM1 (N=92)	14 (15.2)				0.0037	
Negative	T-DXd (N=174)	13 (7.5)	0.56 (0.27, 1.16)	0.59 (0.31, 1.15)	-0.051 (-0.115, 0.013)	0.48 (0.24, 0.96)	
	T-DM1 (N=167)	21 (12.6)				0.0357	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
Positive	T-DXd (N=81)	5 (6.2)	NE (NE, NE)	NE (NE, NE)	0.062 (0.009, 0.114)	NE (NE, NE)	0.9906
	T-DM1 (N=92)	0				0.0419	
Negative	T-DXd (N=174)	9 (5.2)	2.98 (0.79, 11.21)	2.88 (0.79, 10.45)	0.034 (-0.005, 0.072)	2.13 (0.57, 7.93)	
	T-DM1 (N=167)	3 (1.8)				0.2510	
General disorders and administration site conditions							
Any PT							
Positive	T-DXd (N=81)	50 (61.7)	2.29 (1.24, 4.22)	1.49 (1.11, 2.01)	0.204 (0.058, 0.350)	1.31 (0.86, 2.01)	0.2382
	T-DM1 (N=92)	38 (41.3)				0.2095	
Negative	T-DXd (N=174)	108 (62.1)	1.27 (0.82, 1.96)	1.10 (0.92, 1.32)	0.058 (-0.046, 0.162)	0.95 (0.72, 1.25)	
	T-DM1 (N=167)	94 (56.3)				0.7124	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Positive	T-DXd (N=81)	7 (8.6)	4.26 (0.86, 21.11)	3.98 (0.85, 18.60)	0.065 (-0.003, 0.133)	3.20 (0.66, 15.62)	0.6362
	T-DM1 (N=92)	2 (2.2)				0.1294	
Negative	T-DXd (N=174)	21 (12.1)	2.73 (1.17, 6.34)	2.52 (1.15, 5.53)	0.073 (0.015, 0.131)	2.42 (1.07, 5.46)	
	T-DM1 (N=167)	8 (4.8)				0.0287	
Pyrexia							
Positive	T-DXd (N=81)	7 (8.6)	0.78 (0.28, 2.14)	0.80 (0.32, 1.99)	-0.022 (-0.111, 0.066)	0.53 (0.20, 1.41)	0.7503
	T-DM1 (N=92)	10 (10.9)				0.1975	
Negative	T-DXd (N=174)	20 (11.5)	0.62 (0.33, 1.14)	0.66 (0.39, 1.12)	-0.059 (-0.133, 0.016)	0.42 (0.24, 0.75)	
	T-DM1 (N=167)	29 (17.4)				0.0027	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Positive	T-DXd (N=81)	47 (58.0)	4.98 (2.56, 9.66)	2.67 (1.74, 4.10)	0.363 (0.226, 0.499)	2.98 (1.76, 5.03)	0.0979
	T-DM1 (N=92)	20 (21.7)				<.0001	
Negative	T-DXd (N=174)	92 (52.9)	2.35 (1.51, 3.65)	1.64 (1.26, 2.12)	0.205 (0.103, 0.308)	1.66 (1.18, 2.34)	
	T-DM1 (N=167)	54 (32.3)				0.0031	
Alopecia							
Positive	T-DXd (N=81)	33 (40.7)	62.56 (8.30, 471.58)	37.48 (5.24, 267.94)	0.397 (0.287, 0.506)	43.64 (5.97, 319.09)	0.1694
	T-DM1 (N=92)	1 (1.1)				<.0001	
Negative	T-DXd (N=174)	62 (35.6)	12.65 (5.58, 28.66)	8.50 (4.01, 18.03)	0.314 (0.237, 0.392)	9.36 (4.28, 20.47)	
	T-DM1 (N=167)	7 (4.2)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
Positive	T-DXd (N=81)	3 (3.7)	0.55 (0.13, 2.28)	0.57 (0.15, 2.20)	-0.028 (-0.093, 0.037)	0.36 (0.09, 1.46)	0.7155
	T-DM1 (N=92)	6 (6.5)				0.1355	
Negative	T-DXd (N=174)	13 (7.5)	0.71 (0.33, 1.52)	0.73 (0.37, 1.46)	-0.027 (-0.087, 0.033)	0.54 (0.26, 1.12)	
	T-DM1 (N=167)	17 (10.2)				0.0920	
Skin hyperpigmentation							
Positive	T-DXd (N=81)	3 (3.7)	NE (NE, NE)	NE (NE, NE)	0.037 (-0.004, 0.078)	NE (NE, NE)	1.0000
	T-DM1 (N=92)	0				0.0930	
Negative	T-DXd (N=174)	8 (4.6)	NE (NE, NE)	NE (NE, NE)	0.046 (0.015, 0.077)	NE (NE, NE)	
	T-DM1 (N=167)	0				0.0141	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Positive	T-DXd (N=81)	43 (53.1)	2.46 (1.32, 4.57)	1.68 (1.17, 2.42)	0.216 (0.071, 0.360)	1.71 (1.07, 2.75)	0.6434
	T-DM1 (N=92)	29 (31.5)				0.0238	
Negative	T-DXd (N=174)	78 (44.8)	1.85 (1.18, 2.88)	1.47 (1.11, 1.95)	0.143 (0.041, 0.245)	1.48 (1.04, 2.11)	
	T-DM1 (N=167)	51 (30.5)				0.0304	
Decreased appetite							
Positive	T-DXd (N=81)	29 (35.8)	2.86 (1.40, 5.86)	2.20 (1.27, 3.80)	0.195 (0.066, 0.324)	2.23 (1.19, 4.17)	0.2812
	T-DM1 (N=92)	15 (16.3)				0.0101	
Negative	T-DXd (N=174)	45 (25.9)	1.66 (0.98, 2.81)	1.49 (0.98, 2.26)	0.085 (-0.002, 0.172)	1.44 (0.90, 2.30)	
	T-DM1 (N=167)	29 (17.4)				0.1297	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
Positive	T-DXd (N=81)	5 (6.2)	NE (NE, NE)	NE (NE, NE)	0.062 (0.009, 0.114)	NE (NE, NE)	0.9999
	T-DM1 (N=92)	0				0.0187	
Negative	T-DXd (N=174)	6 (3.4)	NE (NE, NE)	NE (NE, NE)	0.034 (0.007, 0.062)	NE (NE, NE)	
	T-DM1 (N=167)	0				0.0166	
Nervous system disorders							
Any PT							
Positive	T-DXd (N=81)	36 (44.4)	1.30 (0.71, 2.39)	1.17 (0.82, 1.67)	0.064 (-0.083, 0.211)	0.86 (0.54, 1.38)	0.6263
	T-DM1 (N=92)	35 (38.0)				0.5366	
Negative	T-DXd (N=174)	80 (46.0)	1.44 (0.93, 2.22)	1.24 (0.96, 1.60)	0.089 (-0.016, 0.193)	1.00 (0.72, 1.40)	
	T-DM1 (N=167)	62 (37.1)				0.9999	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
Positive	T-DXd (N=81)	6 (7.4)	1.76 (0.48, 6.47)	1.70 (0.50, 5.83)	0.031 (-0.040, 0.101)	1.23 (0.34, 4.43)	0.1628
	T-DM1 (N=92)	4 (4.3)				0.7532	
Negative	T-DXd (N=174)	13 (7.5)	0.56 (0.27, 1.16)	0.59 (0.31, 1.15)	-0.051 (-0.115, 0.013)	0.42 (0.21, 0.84)	
	T-DM1 (N=167)	21 (12.6)				0.0119	
Infections and infestations							
Any PT							
Positive	T-DXd (N=81)	36 (44.4)	2.40 (1.26, 4.57)	1.78 (1.16, 2.73)	0.194 (0.055, 0.334)	1.31 (0.77, 2.22)	0.2612
	T-DM1 (N=92)	23 (25.0)				0.3194	
Negative	T-DXd (N=174)	76 (43.7)	1.35 (0.87, 2.08)	1.20 (0.92, 1.55)	0.072 (-0.032, 0.175)	0.93 (0.66, 1.30)	
	T-DM1 (N=167)	61 (36.5)				0.6629	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Positive	T-DXd (N=81)	33 (40.7)	1.35 (0.73, 2.51)	1.21 (0.82, 1.78)	0.070 (-0.074, 0.215)	0.89 (0.54, 1.45)	0.4742
	T-DM1 (N=92)	31 (33.7)				0.6319	
Negative	T-DXd (N=174)	74 (42.5)	1.83 (1.17, 2.88)	1.48 (1.10, 1.99)	0.138 (0.037, 0.238)	1.02 (0.71, 1.48)	
	T-DM1 (N=167)	48 (28.7)				0.9097	
Epistaxis							
Positive	T-DXd (N=81)	10 (12.3)	0.78 (0.33, 1.88)	0.81 (0.38, 1.73)	-0.029 (-0.131, 0.074)	0.49 (0.21, 1.11)	0.6681
	T-DM1 (N=92)	14 (15.2)				0.0797	
Negative	T-DXd (N=174)	19 (10.9)	0.61 (0.33, 1.14)	0.65 (0.38, 1.12)	-0.058 (-0.132, 0.015)	0.38 (0.21, 0.69)	
	T-DM1 (N=167)	28 (16.8)				0.0011	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
Positive	T-DXd (N=81)	5 (6.2)	NE (NE, NE)	NE (NE, NE)	0.062 (0.009, 0.114)	NE (NE, NE)	0.9919
	T-DM1 (N=92)	0				0.0812	
Negative	T-DXd (N=174)	13 (7.5)	13.40 (1.73, 103.65)	12.48 (1.65, 94.32)	0.069 (0.028, 0.110)	7.88 (1.03, 60.58)	
	T-DM1 (N=167)	1 (0.6)				0.0189	
Blood and lymphatic system disorders							
Any PT							
Positive	T-DXd (N=81)	30 (37.0)	1.34 (0.71, 2.53)	1.22 (0.80, 1.85)	0.066 (-0.075, 0.207)	0.91 (0.54, 1.53)	0.2885
	T-DM1 (N=92)	28 (30.4)				0.7124	
Negative	T-DXd (N=174)	73 (42.0)	1.90 (1.21, 2.99)	1.52 (1.13, 2.06)	0.144 (0.044, 0.244)	1.35 (0.93, 1.95)	
	T-DM1 (N=167)	46 (27.5)				0.1082	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
Positive	T-DXd (N=81)	20 (24.7)	1.45 (0.70, 3.00)	1.34 (0.75, 2.37)	0.062 (-0.061, 0.185)	0.99 (0.51, 1.90)	0.0995
	T-DM1 (N=92)	17 (18.5)				0.9704	
Negative	T-DXd (N=174)	63 (36.2)	2.94 (1.76, 4.93)	2.24 (1.50, 3.33)	0.200 (0.110, 0.291)	2.05 (1.30, 3.22)	
	T-DM1 (N=167)	27 (16.2)				0.0015	
Neutropenia							
Positive	T-DXd (N=81)	15 (18.5)	6.74 (1.87, 24.25)	5.68 (1.71, 18.91)	0.153 (0.061, 0.245)	4.39 (1.26, 15.29)	0.8907
	T-DM1 (N=92)	3 (3.3)				0.0113	
Negative	T-DXd (N=174)	26 (14.9)	7.16 (2.44, 20.99)	6.24 (2.22, 17.49)	0.125 (0.068, 0.183)	4.93 (1.72, 14.19)	
	T-DM1 (N=167)	4 (2.4)				0.0010	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
Positive	T-DXd (N=81)	3 (3.7)	0.28 (0.08, 1.05)	0.31 (0.09, 1.07)	-0.083 (-0.161, -0.005)	0.21 (0.06, 0.79)	0.4572
	T-DM1 (N=92)	11 (12.0)				0.0111	
Negative	T-DXd (N=174)	10 (5.7)	0.47 (0.21, 1.05)	0.51 (0.24, 1.05)	-0.056 (-0.116, 0.003)	0.38 (0.18, 0.83)	
	T-DM1 (N=167)	19 (11.4)				0.0123	
Musculoskeletal and connective tissue disorders							
Any PT							
Positive	T-DXd (N=81)	30 (37.0)	1.10 (0.59, 2.06)	1.06 (0.71, 1.59)	0.023 (-0.121, 0.166)	0.85 (0.51, 1.41)	0.9916
	T-DM1 (N=92)	32 (34.8)				0.5300	
Negative	T-DXd (N=174)	64 (36.8)	1.25 (0.80, 1.96)	1.16 (0.86, 1.56)	0.050 (-0.050, 0.151)	0.83 (0.57, 1.20)	
	T-DM1 (N=167)	53 (31.7)				0.3176	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
Positive	T-DXd (N=81)	11 (13.6)	1.91 (0.70, 5.18)	1.78 (0.73, 4.39)	0.060 (-0.032, 0.152)	1.47 (0.57, 3.84)	0.6138
	T-DM1 (N=92)	7 (7.6)				0.4273	
Negative	T-DXd (N=174)	34 (19.5)	2.65 (1.37, 5.15)	2.33 (1.30, 4.18)	0.112 (0.039, 0.184)	1.75 (0.93, 3.28)	
	T-DM1 (N=167)	14 (8.4)				0.0802	
Eye disorders							
Any PT							
Positive	T-DXd (N=81)	11 (13.6)	1.91 (0.70, 5.18)	1.78 (0.73, 4.39)	0.060 (-0.032, 0.152)	1.16 (0.44, 3.02)	0.6128
	T-DM1 (N=92)	7 (7.6)				0.7647	
Negative	T-DXd (N=174)	30 (17.2)	1.37 (0.76, 2.49)	1.31 (0.79, 2.17)	0.041 (-0.035, 0.117)	0.87 (0.50, 1.53)	
	T-DM1 (N=167)	22 (13.2)				0.6395	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
Positive	T-DXd (N=81)	16 (19.8)	1.26 (0.58, 2.75)	1.21 (0.64, 2.29)	0.034 (-0.080, 0.149)	0.87 (0.43, 1.78)	0.9103
	T-DM1 (N=92)	15 (16.3)				0.7066	
Negative	T-DXd (N=174)	23 (13.2)	1.12 (0.59, 2.12)	1.10 (0.63, 1.93)	0.012 (-0.058, 0.083)	0.77 (0.42, 1.41)	
	T-DM1 (N=167)	20 (12.0)				0.3930	
Insomnia							
Positive	T-DXd (N=81)	6 (7.4)	0.53 (0.19, 1.49)	0.57 (0.22, 1.44)	-0.056 (-0.146, 0.033)	0.42 (0.16, 1.13)	0.6686
	T-DM1 (N=92)	12 (13.0)				0.0768	
Negative	T-DXd (N=174)	9 (5.2)	0.70 (0.29, 1.72)	0.72 (0.31, 1.66)	-0.020 (-0.071, 0.031)	0.50 (0.21, 1.21)	
	T-DM1 (N=167)	12 (7.2)				0.1170	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Positive	T-DXd (N=81)	9 (11.1)	1.31 (0.48, 3.58)	1.28 (0.52, 3.16)	0.024 (-0.065, 0.114)	0.80 (0.30, 2.09)	0.8792
	T-DM1 (N=92)	8 (8.7)				0.6418	
Negative	T-DXd (N=174)	23 (13.2)	1.19 (0.62, 2.27)	1.16 (0.66, 2.05)	0.018 (-0.051, 0.088)	0.79 (0.42, 1.46)	
	T-DM1 (N=167)	19 (11.4)				0.4479	
Cardiac disorders							
Any PT							
Positive	T-DXd (N=81)	6 (7.4)	1.76 (0.48, 6.47)	1.70 (0.50, 5.83)	0.031 (-0.040, 0.101)	1.02 (0.28, 3.69)	0.7390
	T-DM1 (N=92)	4 (4.3)				0.9748	
Negative	T-DXd (N=174)	15 (8.6)	2.16 (0.86, 5.43)	2.06 (0.86, 4.92)	0.044 (-0.007, 0.096)	1.50 (0.60, 3.72)	
	T-DM1 (N=167)	7 (4.2)				0.3798	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
Positive	T-DXd (N=81)	8 (9.9)	2.41 (0.70, 8.33)	2.27 (0.71, 7.26)	0.055 (-0.022, 0.132)	1.50 (0.44, 5.06)	0.8461
	T-DM1 (N=92)	4 (4.3)				0.5137	
Negative	T-DXd (N=174)	13 (7.5)	2.62 (0.91, 7.51)	2.50 (0.91, 6.85)	0.045 (-0.002, 0.092)	1.82 (0.64, 5.14)	
	T-DM1 (N=167)	5 (3.0)				0.2527	
Reproductive system and breast disorders							
Any PT							
Positive	T-DXd (N=81)	10 (12.3)	1.30 (0.50, 3.37)	1.26 (0.54, 2.95)	0.026 (-0.068, 0.120)	0.88 (0.35, 2.19)	0.9058
	T-DM1 (N=92)	9 (9.8)				0.7852	
Negative	T-DXd (N=174)	11 (6.3)	1.34 (0.53, 3.42)	1.32 (0.54, 3.20)	0.015 (-0.033, 0.064)	0.89 (0.35, 2.25)	
	T-DM1 (N=167)	8 (4.8)				0.8065	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
Positive	T-DXd (N=81)	8 (9.9)	0.67 (0.26, 1.70)	0.70 (0.31, 1.60)	-0.043 (-0.139, 0.054)	0.51 (0.21, 1.25)	0.9867
	T-DM1 (N=92)	13 (14.1)				0.1380	
Negative	T-DXd (N=174)	11 (6.3)	0.64 (0.29, 1.42)	0.66 (0.32, 1.38)	-0.033 (-0.090, 0.025)	0.49 (0.22, 1.07)	
	T-DM1 (N=167)	16 (9.6)				0.0694	
Renal and urinary disorders							
Any PT							
Positive	T-DXd (N=81)	6 (7.4)	7.28 (0.86, 61.81)	6.81 (0.84, 55.42)	0.063 (0.002, 0.124)	4.19 (0.49, 35.54)	0.0866
	T-DM1 (N=92)	1 (1.1)				0.1548	
Negative	T-DXd (N=174)	9 (5.2)	0.86 (0.34, 2.16)	0.86 (0.36, 2.07)	-0.008 (-0.057, 0.041)	0.69 (0.28, 1.71)	
	T-DM1 (N=167)	10 (6.0)				0.4241	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Yes	T-DXd (N=160)	153 (95.6)	17.13 (7.54, 38.92)	1.71 (1.48, 1.97)	0.396 (0.312, 0.480)	3.48 (2.65, 4.56)	0.0404
	T-DM1 (N=157)	88 (56.1)				<.0001	
No	T-DXd (N=97)	84 (86.6)	4.04 (2.00, 8.17)	1.41 (1.19, 1.67)	0.251 (0.135, 0.366)	2.17 (1.56, 3.01)	
	T-DM1 (N=104)	64 (61.5)				<.0001	
Nausea							
Yes	T-DXd (N=160)	130 (81.3)	9.84 (5.84, 16.59)	2.66 (2.08, 3.40)	0.507 (0.413, 0.601)	4.28 (3.06, 5.97)	0.2278
	T-DM1 (N=157)	48 (30.6)				<.0001	
No	T-DXd (N=97)	65 (67.0)	4.78 (2.63, 8.68)	2.25 (1.62, 3.12)	0.372 (0.244, 0.500)	3.00 (1.96, 4.62)	
	T-DM1 (N=104)	31 (29.8)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Yes	T-DXd (N=160)	82 (51.3)	11.64 (6.10, 22.23)	6.19 (3.60, 10.64)	0.430 (0.341, 0.518)	6.87 (3.83, 12.35)	0.2645
	T-DM1 (N=157)	13 (8.3)				<.0001	
No	T-DXd (N=97)	44 (45.4)	5.81 (2.87, 11.76)	3.63 (2.09, 6.31)	0.329 (0.211, 0.446)	4.09 (2.20, 7.60)	
	T-DM1 (N=104)	13 (12.5)				<.0001	
Constipation							
Yes	T-DXd (N=160)	65 (40.6)	2.57 (1.56, 4.23)	1.93 (1.35, 2.76)	0.196 (0.097, 0.295)	1.71 (1.12, 2.61)	0.3252
	T-DM1 (N=157)	33 (21.0)				0.0113	
No	T-DXd (N=97)	23 (23.7)	1.48 (0.74, 2.96)	1.37 (0.79, 2.38)	0.064 (-0.048, 0.176)	1.19 (0.64, 2.20)	
	T-DM1 (N=104)	18 (17.3)				0.5921	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Yes	T-DXd (N=160)	54 (33.8)	6.16 (3.14, 12.08)	4.42 (2.46, 7.93)	0.261 (0.177, 0.345)	4.61 (2.46, 8.63)	0.6902
	T-DM1 (N=157)	12 (7.6)				<.0001	
No	T-DXd (N=97)	21 (21.6)	4.51 (1.74, 11.73)	3.75 (1.58, 8.90)	0.159 (0.065, 0.252)	3.45 (1.39, 8.57)	
	T-DM1 (N=104)	6 (5.8)				0.0046	
Stomatitis							
Yes	T-DXd (N=160)	29 (18.1)	4.74 (2.01, 11.19)	4.07 (1.83, 9.01)	0.137 (0.069, 0.205)	3.44 (1.50, 7.88)	0.9729
	T-DM1 (N=157)	7 (4.5)				0.0020	
No	T-DXd (N=97)	11 (11.3)	4.31 (1.16, 15.94)	3.93 (1.13, 13.67)	0.085 (0.014, 0.155)	2.96 (0.82, 10.69)	
	T-DM1 (N=104)	3 (2.9)				0.0822	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Yes	T-DXd (N=160)	19 (11.9)	4.10 (1.49, 11.26)	3.73 (1.43, 9.74)	0.087 (0.030, 0.144)	2.98 (1.11, 8.01)	0.9858
	T-DM1 (N=157)	5 (3.2)				0.0235	
No	T-DXd (N=97)	10 (10.3)	NE (NE, NE)	NE (NE, NE)	0.103 (0.043, 0.164)	NE (NE, NE)	
	T-DM1 (N=104)	0				0.0043	
Dry mouth							
Yes	T-DXd (N=160)	1 (0.6)	0.09 (0.01, 0.73)	0.10 (0.01, 0.76)	-0.057 (-0.098, -0.017)	0.09 (0.01, 0.67)	0.1591
	T-DM1 (N=157)	10 (6.4)				0.0030	
No	T-DXd (N=97)	7 (7.2)	0.46 (0.18, 1.19)	0.50 (0.21, 1.17)	-0.072 (-0.157, 0.013)	0.36 (0.14, 0.88)	
	T-DM1 (N=104)	15 (14.4)				0.0205	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Yes	T-DXd (N=160)	88 (55.0)	0.59 (0.37, 0.93)	0.81 (0.68, 0.97)	-0.125 (-0.232, -0.019)	0.49 (0.36, 0.65)	0.0065
	T-DM1 (N=157)	106 (67.5)				<.0001	
No	T-DXd (N=97)	74 (76.3)	1.37 (0.73, 2.56)	1.09 (0.92, 1.28)	0.061 (-0.061, 0.183)	0.87 (0.63, 1.21)	
	T-DM1 (N=104)	73 (70.2)				0.5689	
Neutrophil count decreased							
Yes	T-DXd (N=160)	40 (25.0)	4.03 (2.02, 8.02)	3.27 (1.78, 6.00)	0.174 (0.095, 0.252)	2.96 (1.55, 5.64)	0.9354
	T-DM1 (N=157)	12 (7.6)				0.0006	
No	T-DXd (N=97)	35 (36.1)	3.95 (1.94, 8.07)	2.89 (1.63, 5.12)	0.236 (0.121, 0.351)	2.85 (1.51, 5.39)	
	T-DM1 (N=104)	13 (12.5)				0.0008	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
Yes	T-DXd (N=160)	27 (16.9)	0.34 (0.20, 0.57)	0.45 (0.30, 0.67)	-0.207 (-0.302, -0.112)	0.29 (0.18, 0.46)	0.0052
	T-DM1 (N=157)	59 (37.6)				<.0001	
No	T-DXd (N=97)	39 (40.2)	0.85 (0.48, 1.49)	0.91 (0.66, 1.26)	-0.040 (-0.177, 0.096)	0.69 (0.45, 1.06)	
	T-DM1 (N=104)	46 (44.2)				0.1003	
White blood cell count decreased							
Yes	T-DXd (N=160)	21 (13.1)	5.78 (1.94, 17.25)	5.15 (1.81, 14.67)	0.106 (0.048, 0.164)	4.52 (1.55, 13.21)	0.8265
	T-DM1 (N=157)	4 (2.5)				0.0025	
No	T-DXd (N=97)	37 (38.1)	5.80 (2.68, 12.52)	3.97 (2.09, 7.53)	0.285 (0.173, 0.397)	3.67 (1.82, 7.38)	
	T-DM1 (N=104)	10 (9.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
Yes	T-DXd (N=160)	27 (16.9)	0.46 (0.27, 0.79)	0.55 (0.36, 0.84)	-0.137 (-0.230, -0.044)	0.39 (0.24, 0.63)	0.0142
	T-DM1 (N=157)	48 (30.6)				<.0001	
No	T-DXd (N=97)	29 (29.9)	1.10 (0.60, 2.03)	1.07 (0.69, 1.65)	0.020 (-0.105, 0.146)	0.95 (0.57, 1.60)	
	T-DM1 (N=104)	29 (27.9)				0.8485	
Platelet count decreased							
Yes	T-DXd (N=160)	18 (11.3)	0.17 (0.10, 0.31)	0.26 (0.16, 0.42)	-0.314 (-0.406, -0.223)	0.17 (0.10, 0.30)	0.0002
	T-DM1 (N=157)	67 (42.7)				<.0001	
No	T-DXd (N=97)	36 (37.1)	0.77 (0.44, 1.36)	0.86 (0.61, 1.20)	-0.062 (-0.197, 0.074)	0.59 (0.38, 0.93)	
	T-DM1 (N=104)	45 (43.3)				0.0275	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
Yes	T-DXd (N=160)	17 (10.6)	2.99 (1.15, 7.80)	2.78 (1.13, 6.87)	0.068 (0.012, 0.124)	2.30 (0.90, 5.85)	0.8603
	T-DM1 (N=157)	6 (3.8)				0.0725	
No	T-DXd (N=97)	26 (26.8)	3.44 (1.56, 7.60)	2.79 (1.42, 5.47)	0.172 (0.067, 0.277)	2.18 (1.05, 4.53)	
	T-DM1 (N=104)	10 (9.6)				0.0326	
Blood lactate dehydrogenase increased							
Yes	T-DXd (N=160)	1 (0.6)	0.08 (0.01, 0.65)	0.09 (0.01, 0.68)	-0.064 (-0.106, -0.022)	0.08 (0.01, 0.63)	0.0601
	T-DM1 (N=157)	11 (7.0)				0.0020	
No	T-DXd (N=97)	16 (16.5)	0.66 (0.33, 1.33)	0.71 (0.40, 1.26)	-0.066 (-0.175, 0.044)	0.51 (0.27, 0.96)	
	T-DM1 (N=104)	24 (23.1)				0.0359	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
Yes	T-DXd (N=160)	6 (3.8)	3.02 (0.60, 15.19)	2.94 (0.60, 14.36)	0.025 (-0.010, 0.059)	2.20 (0.44, 10.99)	0.4124
	T-DM1 (N=157)	2 (1.3)				0.3226	
No	T-DXd (N=97)	8 (8.2)	9.26 (1.14, 75.43)	8.58 (1.09, 67.32)	0.073 (0.015, 0.131)	6.38 (0.79, 51.37)	
	T-DM1 (N=104)	1 (1.0)				0.0462	
General disorders and administration site conditions							
Any PT							
Yes	T-DXd (N=160)	103 (64.4)	1.61 (1.03, 2.53)	1.22 (1.01, 1.47)	0.115 (0.007, 0.223)	1.08 (0.81, 1.45)	0.8814
	T-DM1 (N=157)	83 (52.9)				0.5898	
No	T-DXd (N=97)	56 (57.7)	1.48 (0.85, 2.57)	1.20 (0.92, 1.56)	0.097 (-0.041, 0.234)	0.96 (0.65, 1.41)	
	T-DM1 (N=104)	50 (48.1)				0.8401	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Yes	T-DXd (N=160)	18 (11.3)	2.36 (1.00, 5.60)	2.21 (0.99, 4.93)	0.062 (0.002, 0.121)	1.86 (0.80, 4.31)	0.2248
	T-DM1 (N=157)	8 (5.1)				0.1447	
No	T-DXd (N=97)	11 (11.3)	6.52 (1.41, 30.24)	5.90 (1.34, 25.93)	0.094 (0.026, 0.163)	5.70 (1.26, 25.74)	
	T-DM1 (N=104)	2 (1.9)				0.0106	
Pyrexia							
Yes	T-DXd (N=160)	13 (8.1)	0.73 (0.34, 1.55)	0.75 (0.38, 1.49)	-0.027 (-0.091, 0.037)	0.49 (0.23, 1.02)	0.9166
	T-DM1 (N=157)	17 (10.8)				0.0524	
No	T-DXd (N=97)	14 (14.4)	0.63 (0.30, 1.31)	0.68 (0.37, 1.26)	-0.067 (-0.172, 0.038)	0.43 (0.22, 0.86)	
	T-DM1 (N=104)	22 (21.2)				0.0135	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Yes	T-DXd (N=160)	90 (56.3)	4.03 (2.49, 6.51)	2.32 (1.71, 3.16)	0.320 (0.218, 0.422)	2.59 (1.77, 3.79)	0.0388
	T-DM1 (N=157)	38 (24.2)				<.0001	
No	T-DXd (N=97)	49 (50.5)	1.85 (1.05, 3.25)	1.42 (1.03, 1.97)	0.149 (0.014, 0.285)	1.31 (0.85, 2.02)	
	T-DM1 (N=104)	37 (35.6)				0.2209	
Alopecia							
Yes	T-DXd (N=160)	58 (36.3)	29.19 (8.91, 95.67)	18.97 (6.07, 59.28)	0.343 (0.266, 0.421)	21.25 (6.66, 67.85)	0.2608
	T-DM1 (N=157)	3 (1.9)				<.0001	
No	T-DXd (N=97)	37 (38.1)	12.21 (4.55, 32.77)	7.93 (3.25, 19.36)	0.333 (0.228, 0.438)	8.80 (3.45, 22.40)	
	T-DM1 (N=104)	5 (4.8)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
Yes	T-DXd (N=160)	11 (6.9)	1.09 (0.45, 2.63)	1.08 (0.47, 2.47)	0.005 (-0.050, 0.060)	0.83 (0.35, 1.98)	0.1120
	T-DM1 (N=157)	10 (6.4)				0.6773	
No	T-DXd (N=97)	5 (5.2)	0.35 (0.12, 1.01)	0.38 (0.14, 1.02)	-0.083 (-0.162, -0.004)	0.24 (0.08, 0.67)	
	T-DM1 (N=104)	14 (13.5)				0.0032	
Skin hyperpigmentation							
Yes	T-DXd (N=160)	6 (3.8)	NE (NE, NE)	NE (NE, NE)	0.038 (0.008, 0.067)	NE (NE, NE)	0.9999
	T-DM1 (N=157)	0				0.0276	
No	T-DXd (N=97)	5 (5.2)	NE (NE, NE)	NE (NE, NE)	0.052 (0.008, 0.096)	NE (NE, NE)	
	T-DM1 (N=104)	0				0.0459	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Yes	T-DXd (N=160)	65 (40.6)	1.94 (1.20, 3.11)	1.56 (1.13, 2.15)	0.145 (0.043, 0.248)	1.50 (1.01, 2.22)	0.5607
	T-DM1 (N=157)	41 (26.1)				0.0433	
No	T-DXd (N=97)	57 (58.8)	2.37 (1.35, 4.19)	1.57 (1.16, 2.11)	0.213 (0.078, 0.348)	1.74 (1.15, 2.61)	
	T-DM1 (N=104)	39 (37.5)				0.0084	
Decreased appetite							
Yes	T-DXd (N=160)	41 (25.6)	1.74 (1.00, 3.01)	1.55 (1.00, 2.40)	0.091 (0.001, 0.180)	1.47 (0.90, 2.40)	0.3279
	T-DM1 (N=157)	26 (16.6)				0.1274	
No	T-DXd (N=97)	34 (35.1)	2.58 (1.34, 4.98)	2.03 (1.23, 3.34)	0.177 (0.058, 0.297)	2.06 (1.16, 3.66)	
	T-DM1 (N=104)	18 (17.3)				0.0134	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
Yes	T-DXd (N=160)	8 (5.0)	NE (NE, NE)	NE (NE, NE)	0.050 (0.016, 0.084)	NE (NE, NE)	0.9999
	T-DM1 (N=157)	0				0.0055	
No	T-DXd (N=97)	3 (3.1)	NE (NE, NE)	NE (NE, NE)	0.031 (-0.004, 0.065)	NE (NE, NE)	
	T-DM1 (N=104)	0				0.0714	
Nervous system disorders							
Any PT							
Yes	T-DXd (N=160)	75 (46.9)	1.59 (1.01, 2.50)	1.31 (1.01, 1.72)	0.112 (0.004, 0.220)	1.05 (0.74, 1.50)	0.3150
	T-DM1 (N=157)	56 (35.7)				0.7625	
No	T-DXd (N=97)	41 (42.3)	1.08 (0.62, 1.90)	1.05 (0.75, 1.46)	0.019 (-0.117, 0.155)	0.79 (0.51, 1.22)	
	T-DM1 (N=104)	42 (40.4)				0.2854	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
Yes	T-DXd (N=160)	16 (10.0)	0.86 (0.42, 1.75)	0.87 (0.46, 1.65)	-0.015 (-0.083, 0.054)	0.63 (0.32, 1.26)	0.4736
	T-DM1 (N=157)	18 (11.5)				0.1891	
No	T-DXd (N=97)	3 (3.1)	0.44 (0.11, 1.76)	0.46 (0.12, 1.73)	-0.036 (-0.096, 0.023)	0.30 (0.08, 1.19)	
	T-DM1 (N=104)	7 (6.7)				0.0715	
Infections and infestations							
Any PT							
Yes	T-DXd (N=160)	68 (42.5)	1.78 (1.12, 2.84)	1.45 (1.07, 1.96)	0.132 (0.027, 0.237)	1.15 (0.79, 1.68)	0.4171
	T-DM1 (N=157)	46 (29.3)				0.4763	
No	T-DXd (N=97)	44 (45.4)	1.38 (0.79, 2.43)	1.21 (0.87, 1.68)	0.079 (-0.057, 0.215)	0.86 (0.56, 1.33)	
	T-DM1 (N=104)	39 (37.5)				0.5008	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Yes	T-DXd (N=160)	63 (39.4)	1.52 (0.95, 2.42)	1.32 (0.97, 1.79)	0.094 (-0.010, 0.199)	0.92 (0.63, 1.35)	0.7440
	T-DM1 (N=157)	47 (29.9)				0.6745	
No	T-DXd (N=97)	44 (45.4)	1.87 (1.05, 3.33)	1.47 (1.03, 2.12)	0.146 (0.013, 0.279)	1.01 (0.64, 1.60)	
	T-DM1 (N=104)	32 (30.8)				0.9599	
Epistaxis							
Yes	T-DXd (N=160)	17 (10.6)	0.57 (0.30, 1.10)	0.62 (0.35, 1.09)	-0.066 (-0.142, 0.010)	0.35 (0.19, 0.67)	0.4189
	T-DM1 (N=157)	27 (17.2)				0.0008	
No	T-DXd (N=97)	12 (12.4)	0.84 (0.37, 1.89)	0.86 (0.42, 1.74)	-0.021 (-0.115, 0.074)	0.51 (0.23, 1.09)	
	T-DM1 (N=104)	15 (14.4)				0.0783	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
Yes	T-DXd (N=160)	10 (6.3)	10.40 (1.32, 82.24)	9.81 (1.27, 75.75)	0.056 (0.017, 0.096)	5.00 (0.64, 39.42)	0.9908
	T-DM1 (N=157)	1 (0.6)				0.0899	
No	T-DXd (N=97)	8 (8.2)	NE (NE, NE)	NE (NE, NE)	0.082 (0.028, 0.137)	NE (NE, NE)	
	T-DM1 (N=104)	0				0.0139	
Blood and lymphatic system disorders							
Any PT							
Yes	T-DXd (N=160)	43 (26.9)	1.01 (0.61, 1.65)	1.00 (0.70, 1.45)	0.001 (-0.096, 0.099)	0.77 (0.50, 1.18)	0.0010
	T-DM1 (N=157)	42 (26.8)				0.2375	
No	T-DXd (N=97)	60 (61.9)	3.49 (1.95, 6.24)	1.95 (1.41, 2.69)	0.301 (0.170, 0.433)	1.99 (1.30, 3.05)	
	T-DM1 (N=104)	33 (31.7)				0.0012	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
Yes	T-DXd (N=160)	33 (20.6)	1.44 (0.81, 2.57)	1.35 (0.84, 2.17)	0.053 (-0.031, 0.138)	1.07 (0.63, 1.81)	0.0083
	T-DM1 (N=157)	24 (15.3)				0.8155	
No	T-DXd (N=97)	50 (51.5)	4.47 (2.38, 8.39)	2.68 (1.73, 4.16)	0.323 (0.198, 0.448)	2.70 (1.61, 4.54)	
	T-DM1 (N=104)	20 (19.2)				<.0001	
Neutropenia							
Yes	T-DXd (N=160)	17 (10.6)	9.21 (2.09, 40.57)	8.34 (1.96, 35.50)	0.094 (0.043, 0.144)	6.93 (1.59, 30.14)	0.6640
	T-DM1 (N=157)	2 (1.3)				0.0028	
No	T-DXd (N=97)	24 (24.7)	6.51 (2.37, 17.87)	5.15 (2.04, 12.95)	0.199 (0.104, 0.295)	4.02 (1.53, 10.58)	
	T-DM1 (N=104)	5 (4.8)				0.0023	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
Yes	T-DXd (N=160)	3 (1.9)	0.15 (0.04, 0.51)	0.16 (0.05, 0.54)	-0.096 (-0.150, -0.042)	0.12 (0.04, 0.42)	0.0254
	T-DM1 (N=157)	18 (11.5)				<.0001	
No	T-DXd (N=97)	10 (10.3)	0.80 (0.34, 1.93)	0.82 (0.38, 1.79)	-0.022 (-0.110, 0.066)	0.60 (0.26, 1.40)	
	T-DM1 (N=104)	13 (12.5)				0.2322	
Musculoskeletal and connective tissue disorders							
Any PT							
Yes	T-DXd (N=160)	67 (41.9)	1.45 (0.92, 2.30)	1.26 (0.95, 1.69)	0.088 (-0.019, 0.194)	0.99 (0.69, 1.42)	0.1033
	T-DM1 (N=157)	52 (33.1)				0.9509	
No	T-DXd (N=97)	27 (27.8)	0.76 (0.42, 1.39)	0.83 (0.54, 1.26)	-0.058 (-0.185, 0.069)	0.53 (0.31, 0.88)	
	T-DM1 (N=104)	35 (33.7)				0.0133	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
Yes	T-DXd (N=160)	33 (20.6)	3.14 (1.56, 6.34)	2.70 (1.45, 5.03)	0.130 (0.055, 0.205)	2.06 (1.05, 4.02)	0.2501
	T-DM1 (N=157)	12 (7.6)				0.0319	
No	T-DXd (N=97)	12 (12.4)	1.49 (0.60, 3.71)	1.43 (0.63, 3.24)	0.037 (-0.048, 0.122)	1.08 (0.45, 2.59)	
	T-DM1 (N=104)	9 (8.7)				0.8558	
Eye disorders							
Any PT							
Yes	T-DXd (N=160)	28 (17.5)	1.54 (0.82, 2.89)	1.45 (0.84, 2.48)	0.054 (-0.024, 0.132)	0.96 (0.53, 1.74)	0.7801
	T-DM1 (N=157)	19 (12.1)				0.8903	
No	T-DXd (N=97)	13 (13.4)	1.31 (0.56, 3.08)	1.27 (0.60, 2.69)	0.028 (-0.062, 0.118)	0.81 (0.36, 1.83)	
	T-DM1 (N=104)	11 (10.6)				0.6063	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
Yes	T-DXd (N=160)	22 (13.8)	1.40 (0.71, 2.79)	1.35 (0.74, 2.47)	0.036 (-0.036, 0.107)	0.93 (0.48, 1.78)	0.5315
	T-DM1 (N=157)	16 (10.2)				0.8197	
No	T-DXd (N=97)	17 (17.5)	0.95 (0.46, 1.96)	0.96 (0.53, 1.74)	-0.007 (-0.113, 0.099)	0.70 (0.36, 1.35)	
	T-DM1 (N=104)	19 (18.3)				0.2865	
Insomnia							
Yes	T-DXd (N=160)	5 (3.1)	0.47 (0.16, 1.42)	0.49 (0.17, 1.40)	-0.032 (-0.079, 0.014)	0.32 (0.11, 0.95)	0.4931
	T-DM1 (N=157)	10 (6.4)				0.0318	
No	T-DXd (N=97)	10 (10.3)	0.74 (0.31, 1.75)	0.77 (0.36, 1.64)	-0.032 (-0.121, 0.058)	0.57 (0.25, 1.29)	
	T-DM1 (N=104)	14 (13.5)				0.1695	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Yes	T-DXd (N=160)	25 (15.6)	1.43 (0.75, 2.74)	1.36 (0.78, 2.40)	0.042 (-0.034, 0.117)	0.85 (0.46, 1.59)	0.4558
	T-DM1 (N=157)	18 (11.5)				0.6166	
No	T-DXd (N=97)	7 (7.2)	0.82 (0.29, 2.30)	0.83 (0.32, 2.15)	-0.014 (-0.089, 0.060)	0.55 (0.20, 1.49)	
	T-DM1 (N=104)	9 (8.7)				0.2300	
Cardiac disorders							
Any PT							
Yes	T-DXd (N=160)	7 (4.4)	1.15 (0.38, 3.51)	1.14 (0.39, 3.33)	0.006 (-0.038, 0.049)	0.73 (0.24, 2.23)	0.1509
	T-DM1 (N=157)	6 (3.8)				0.5752	
No	T-DXd (N=97)	14 (14.4)	3.34 (1.15, 9.66)	3.00 (1.12, 8.02)	0.096 (0.015, 0.177)	2.17 (0.77, 6.07)	
	T-DM1 (N=104)	5 (4.8)				0.1318	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
Yes	T-DXd (N=160)	18 (11.3)	2.72 (1.10, 6.70)	2.52 (1.08, 5.87)	0.068 (0.009, 0.127)	1.79 (0.74, 4.33)	0.6397
	T-DM1 (N=157)	7 (4.5)				0.1933	
No	T-DXd (N=97)	3 (3.1)	1.63 (0.27, 9.96)	1.61 (0.27, 9.42)	0.012 (-0.032, 0.055)	0.97 (0.16, 5.95)	
	T-DM1 (N=104)	2 (1.9)				0.9778	
Reproductive system and breast disorders							
Any PT							
Yes	T-DXd (N=160)	13 (8.1)	0.98 (0.44, 2.19)	0.98 (0.47, 2.05)	-0.002 (-0.062, 0.059)	0.58 (0.26, 1.28)	0.2048
	T-DM1 (N=157)	13 (8.3)				0.1705	
No	T-DXd (N=97)	8 (8.2)	2.25 (0.65, 7.72)	2.14 (0.67, 6.89)	0.044 (-0.022, 0.110)	1.70 (0.51, 5.67)	
	T-DM1 (N=104)	4 (3.8)				0.3859	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
Yes	T-DXd (N=160)	9 (5.6)	0.53 (0.22, 1.23)	0.55 (0.25, 1.21)	-0.046 (-0.105, 0.014)	0.40 (0.17, 0.93)	0.3281
	T-DM1 (N=157)	16 (10.2)				0.0293	
No	T-DXd (N=97)	11 (11.3)	0.90 (0.38, 2.11)	0.91 (0.43, 1.93)	-0.012 (-0.101, 0.078)	0.69 (0.31, 1.55)	
	T-DM1 (N=104)	13 (12.5)				0.3749	
Renal and urinary disorders							
Any PT							
Yes	T-DXd (N=160)	8 (5.0)	1.32 (0.45, 3.91)	1.31 (0.46, 3.68)	0.012 (-0.033, 0.057)	0.88 (0.30, 2.57)	0.8331
	T-DM1 (N=157)	6 (3.8)				0.8089	
No	T-DXd (N=97)	7 (7.2)	1.54 (0.47, 5.02)	1.50 (0.49, 4.57)	0.024 (-0.042, 0.090)	1.14 (0.36, 3.63)	
	T-DM1 (N=104)	5 (4.8)				0.8202	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
< 3 lines	T-DXd (N=186)	171 (91.9)	7.84 (4.29, 14.31)	1.55 (1.37, 1.76)	0.327 (0.247, 0.407)	2.81 (2.21, 3.59)	0.8184
	T-DM1 (N=189)	112 (59.3)				<.0001	
>= 3 lines	T-DXd (N=71)	66 (93.0)	10.56 (3.80, 29.32)	1.67 (1.35, 2.08)	0.374 (0.245, 0.503)	3.02 (2.02, 4.51)	
	T-DM1 (N=72)	40 (55.6)				<.0001	
Nausea							
< 3 lines	T-DXd (N=186)	144 (77.4)	7.74 (4.88, 12.29)	2.52 (2.01, 3.17)	0.467 (0.378, 0.556)	3.88 (2.85, 5.27)	0.7562
	T-DM1 (N=189)	58 (30.7)				<.0001	
>= 3 lines	T-DXd (N=71)	51 (71.8)	6.19 (3.00, 12.79)	2.46 (1.67, 3.63)	0.427 (0.278, 0.575)	3.42 (2.05, 5.69)	
	T-DM1 (N=72)	21 (29.2)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
< 3 lines	T-DXd (N=186)	91 (48.9)	9.69 (5.45, 17.23)	5.44 (3.38, 8.76)	0.399 (0.317, 0.482)	6.06 (3.61, 10.19)	0.4984
	T-DM1 (N=189)	17 (9.0)				<.0001	
>= 3 lines	T-DXd (N=71)	35 (49.3)	6.80 (2.94, 15.75)	3.94 (2.05, 7.59)	0.368 (0.229, 0.507)	4.39 (2.11, 9.16)	
	T-DM1 (N=72)	9 (12.5)				<.0001	
Constipation							
< 3 lines	T-DXd (N=186)	69 (37.1)	2.27 (1.43, 3.60)	1.80 (1.28, 2.52)	0.165 (0.074, 0.255)	1.58 (1.06, 2.34)	0.7785
	T-DM1 (N=189)	39 (20.6)				0.0220	
>= 3 lines	T-DXd (N=71)	19 (26.8)	1.83 (0.81, 4.12)	1.61 (0.84, 3.06)	0.101 (-0.033, 0.235)	1.35 (0.65, 2.81)	
	T-DM1 (N=72)	12 (16.7)				0.4237	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
< 3 lines	T-DXd (N=186)	60 (32.3)	7.02 (3.63, 13.60)	5.08 (2.83, 9.13)	0.259 (0.183, 0.335)	5.22 (2.81, 9.71)	0.1862
	T-DM1 (N=189)	12 (6.3)				<.0001	
>= 3 lines	T-DXd (N=71)	15 (21.1)	2.95 (1.07, 8.10)	2.54 (1.04, 6.16)	0.128 (0.014, 0.242)	2.25 (0.86, 5.84)	
	T-DM1 (N=72)	6 (8.3)				0.0888	
Stomatitis							
< 3 lines	T-DXd (N=186)	28 (15.1)	4.01 (1.78, 9.05)	3.56 (1.66, 7.60)	0.108 (0.049, 0.167)	3.06 (1.39, 6.74)	0.5698
	T-DM1 (N=189)	8 (4.2)				0.0034	
>= 3 lines	T-DXd (N=71)	12 (16.9)	7.12 (1.53, 33.09)	6.08 (1.41, 26.22)	0.141 (0.046, 0.236)	4.54 (1.01, 20.49)	
	T-DM1 (N=72)	2 (2.8)				0.0312	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
< 3 lines	T-DXd (N=186)	20 (10.8)	5.57 (1.87, 16.64)	5.08 (1.77, 14.58)	0.086 (0.037, 0.135)	3.98 (1.35, 11.69)	0.6799
	T-DM1 (N=189)	4 (2.1)				0.0068	
>= 3 lines	T-DXd (N=71)	9 (12.7)	10.30 (1.27, 83.59)	9.13 (1.19, 70.18)	0.113 (0.031, 0.195)	6.20 (0.77, 49.73)	
	T-DM1 (N=72)	1 (1.4)				0.0507	
Dry mouth							
< 3 lines	T-DXd (N=186)	5 (2.7)	0.28 (0.10, 0.77)	0.30 (0.11, 0.79)	-0.063 (-0.110, -0.016)	0.25 (0.09, 0.69)	0.8344
	T-DM1 (N=189)	17 (9.0)				0.0036	
>= 3 lines	T-DXd (N=71)	3 (4.2)	0.35 (0.09, 1.39)	0.38 (0.11, 1.38)	-0.069 (-0.155, 0.018)	0.20 (0.05, 0.81)	
	T-DM1 (N=72)	8 (11.1)				0.0150	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
< 3 lines	T-DXd (N=186)	108 (58.1)	0.66 (0.43, 1.01)	0.86 (0.73, 1.00)	-0.097 (-0.194, 0.001)	0.56 (0.43, 0.73)	0.1924
	T-DM1 (N=189)	128 (67.7)				<.0001	
>= 3 lines	T-DXd (N=71)	54 (76.1)	1.31 (0.62, 2.76)	1.07 (0.88, 1.31)	0.052 (-0.092, 0.197)	0.72 (0.49, 1.07)	
	T-DM1 (N=72)	51 (70.8)				0.1932	
Neutrophil count decreased							
< 3 lines	T-DXd (N=186)	52 (28.0)	4.85 (2.58, 9.12)	3.77 (2.17, 6.57)	0.205 (0.131, 0.280)	3.52 (1.95, 6.35)	0.2206
	T-DM1 (N=189)	14 (7.4)				<.0001	
>= 3 lines	T-DXd (N=71)	23 (32.4)	2.66 (1.18, 5.98)	2.12 (1.12, 4.02)	0.171 (0.034, 0.308)	1.92 (0.93, 3.96)	
	T-DM1 (N=72)	11 (15.3)				0.0738	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
< 3 lines	T-DXd (N=186)	40 (21.5)	0.42 (0.26, 0.66)	0.54 (0.39, 0.75)	-0.182 (-0.273, -0.090)	0.38 (0.26, 0.56)	0.1041
	T-DM1 (N=189)	75 (39.7)				<.0001	
>= 3 lines	T-DXd (N=71)	26 (36.6)	0.81 (0.41, 1.59)	0.88 (0.58, 1.32)	-0.050 (-0.210, 0.109)	0.56 (0.32, 0.96)	
	T-DM1 (N=72)	30 (41.7)				0.0394	
White blood cell count decreased							
< 3 lines	T-DXd (N=186)	35 (18.8)	7.07 (2.90, 17.26)	5.93 (2.55, 13.76)	0.156 (0.095, 0.218)	5.08 (2.13, 12.09)	0.2464
	T-DM1 (N=189)	6 (3.2)				<.0001	
>= 3 lines	T-DXd (N=71)	23 (32.4)	3.83 (1.58, 9.31)	2.92 (1.40, 6.08)	0.213 (0.082, 0.344)	2.62 (1.17, 5.90)	
	T-DM1 (N=72)	8 (11.1)				0.0151	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
< 3 lines	T-DXd (N=186)	39 (21.0)	0.57 (0.36, 0.91)	0.66 (0.47, 0.94)	-0.108 (-0.196, -0.019)	0.50 (0.34, 0.76)	0.1895
	T-DM1 (N=189)	60 (31.7)				0.0008	
>= 3 lines	T-DXd (N=71)	17 (23.9)	1.02 (0.47, 2.20)	1.01 (0.56, 1.82)	0.003 (-0.136, 0.143)	0.82 (0.41, 1.63)	
	T-DM1 (N=72)	17 (23.6)				0.5791	
Platelet count decreased							
< 3 lines	T-DXd (N=186)	29 (15.6)	0.25 (0.15, 0.40)	0.36 (0.25, 0.53)	-0.273 (-0.360, -0.185)	0.23 (0.15, 0.36)	0.0077
	T-DM1 (N=189)	81 (42.9)				<.0001	
>= 3 lines	T-DXd (N=71)	25 (35.2)	0.72 (0.37, 1.41)	0.82 (0.54, 1.24)	-0.078 (-0.238, 0.081)	0.57 (0.33, 0.97)	
	T-DM1 (N=72)	31 (43.1)				0.0462	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
< 3 lines	T-DXd (N=186)	26 (14.0)	3.68 (1.62, 8.35)	3.30 (1.53, 7.10)	0.097 (0.040, 0.155)	2.65 (1.20, 5.88)	0.4558
	T-DM1 (N=189)	8 (4.2)				0.0124	
>= 3 lines	T-DXd (N=71)	17 (23.9)	2.52 (1.01, 6.29)	2.15 (0.99, 4.67)	0.128 (0.005, 0.251)	1.44 (0.61, 3.41)	
	T-DM1 (N=72)	8 (11.1)				0.4002	
Blood lactate dehydrogenase increased							
< 3 lines	T-DXd (N=186)	7 (3.8)	0.30 (0.12, 0.71)	0.32 (0.14, 0.74)	-0.079 (-0.132, -0.025)	0.25 (0.11, 0.59)	0.1677
	T-DM1 (N=189)	22 (11.6)				0.0007	
>= 3 lines	T-DXd (N=71)	10 (14.1)	0.74 (0.30, 1.83)	0.78 (0.37, 1.66)	-0.040 (-0.160, 0.080)	0.55 (0.24, 1.29)	
	T-DM1 (N=72)	13 (18.1)				0.1678	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
< 3 lines	T-DXd (N=186)	6 (3.2)	6.27 (0.75, 52.56)	6.10 (0.74, 50.15)	0.027 (0.000, 0.054)	4.27 (0.51, 35.68)	0.7387
	T-DM1 (N=189)	1 (0.5)				0.1451	
>= 3 lines	T-DXd (N=71)	8 (11.3)	4.44 (0.91, 21.72)	4.06 (0.89, 18.44)	0.085 (0.002, 0.168)	2.93 (0.61, 14.03)	
	T-DM1 (N=72)	2 (2.8)				0.1598	
General disorders and administration site conditions							
Any PT							
< 3 lines	T-DXd (N=186)	120 (64.5)	1.69 (1.12, 2.55)	1.24 (1.05, 1.48)	0.127 (0.028, 0.226)	1.10 (0.84, 1.43)	0.4859
	T-DM1 (N=189)	98 (51.9)				0.4989	
>= 3 lines	T-DXd (N=71)	39 (54.9)	1.29 (0.67, 2.49)	1.13 (0.82, 1.55)	0.063 (-0.100, 0.227)	0.87 (0.55, 1.39)	
	T-DM1 (N=72)	35 (48.6)				0.5645	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
< 3 lines	T-DXd (N=186)	23 (12.4)	3.19 (1.39, 7.33)	2.92 (1.34, 6.36)	0.081 (0.026, 0.137)	2.57 (1.14, 5.77)	0.9636
	T-DM1 (N=189)	8 (4.2)				0.0177	
>= 3 lines	T-DXd (N=71)	6 (8.5)	3.23 (0.63, 16.58)	3.04 (0.64, 14.57)	0.057 (-0.018, 0.132)	2.99 (0.60, 14.84)	
	T-DM1 (N=72)	2 (2.8)				0.1604	
Pyrexia							
< 3 lines	T-DXd (N=186)	17 (9.1)	0.66 (0.34, 1.27)	0.69 (0.39, 1.24)	-0.041 (-0.105, 0.023)	0.45 (0.24, 0.84)	0.9134
	T-DM1 (N=189)	25 (13.2)				0.0104	
>= 3 lines	T-DXd (N=71)	10 (14.1)	0.68 (0.28, 1.65)	0.72 (0.34, 1.52)	-0.054 (-0.176, 0.068)	0.43 (0.19, 1.00)	
	T-DM1 (N=72)	14 (19.4)				0.0440	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
< 3 lines	T-DXd (N=186)	99 (53.2)	2.84 (1.86, 4.36)	1.86 (1.43, 2.42)	0.247 (0.150, 0.343)	1.93 (1.38, 2.69)	0.8950
	T-DM1 (N=189)	54 (28.6)				<.0001	
>= 3 lines	T-DXd (N=71)	40 (56.3)	3.13 (1.57, 6.26)	1.93 (1.28, 2.92)	0.272 (0.116, 0.428)	2.07 (1.22, 3.53)	
	T-DM1 (N=72)	21 (29.2)				0.0062	
Alopecia							
< 3 lines	T-DXd (N=186)	68 (36.6)	26.65 (9.47, 74.99)	17.27 (6.43, 46.39)	0.344 (0.272, 0.417)	19.21 (7.01, 52.65)	0.2250
	T-DM1 (N=189)	4 (2.1)				<.0001	
>= 3 lines	T-DXd (N=71)	27 (38.0)	10.43 (3.42, 31.86)	6.85 (2.52, 18.56)	0.325 (0.200, 0.449)	7.74 (2.71, 22.17)	
	T-DM1 (N=72)	4 (5.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
< 3 lines	T-DXd (N=186)	13 (7.0)	0.76 (0.36, 1.61)	0.78 (0.39, 1.55)	-0.020 (-0.075, 0.035)	0.56 (0.27, 1.17)	0.3540
	T-DM1 (N=189)	17 (9.0)				0.1169	
>= 3 lines	T-DXd (N=71)	3 (4.2)	0.41 (0.10, 1.65)	0.43 (0.12, 1.61)	-0.055 (-0.138, 0.028)	0.28 (0.07, 1.12)	
	T-DM1 (N=72)	7 (9.7)				0.0563	
Skin hyperpigmentation							
< 3 lines	T-DXd (N=186)	7 (3.8)	NE (NE, NE)	NE (NE, NE)	0.038 (0.010, 0.065)	NE (NE, NE)	0.9999
	T-DM1 (N=189)	0				0.0161	
>= 3 lines	T-DXd (N=71)	4 (5.6)	NE (NE, NE)	NE (NE, NE)	0.056 (0.003, 0.110)	NE (NE, NE)	
	T-DM1 (N=72)	0				0.0856	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
< 3 lines	T-DXd (N=186)	80 (43.0)	1.99 (1.29, 3.06)	1.56 (1.18, 2.08)	0.155 (0.059, 0.250)	1.56 (1.10, 2.22)	0.9569
	T-DM1 (N=189)	52 (27.5)				0.0120	
>= 3 lines	T-DXd (N=71)	42 (59.2)	2.28 (1.16, 4.45)	1.52 (1.07, 2.15)	0.203 (0.042, 0.363)	1.55 (0.96, 2.52)	
	T-DM1 (N=72)	28 (38.9)				0.0761	
Decreased appetite							
< 3 lines	T-DXd (N=186)	50 (26.9)	2.11 (1.26, 3.54)	1.81 (1.20, 2.75)	0.121 (0.039, 0.202)	1.79 (1.13, 2.85)	0.6591
	T-DM1 (N=189)	28 (14.8)				0.0129	
>= 3 lines	T-DXd (N=71)	25 (35.2)	1.90 (0.91, 3.98)	1.58 (0.93, 2.71)	0.130 (-0.017, 0.277)	1.47 (0.78, 2.76)	
	T-DM1 (N=72)	16 (22.2)				0.2431	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
< 3 lines	T-DXd (N=186)	5 (2.7)	NE (NE, NE)	NE (NE, NE)	0.027 (0.004, 0.050)	NE (NE, NE)	0.9997
	T-DM1 (N=189)	0				0.0249	
>= 3 lines	T-DXd (N=71)	6 (8.5)	NE (NE, NE)	NE (NE, NE)	0.085 (0.020, 0.149)	NE (NE, NE)	
	T-DM1 (N=72)	0				0.0134	
Nervous system disorders							
Any PT							
< 3 lines	T-DXd (N=186)	80 (43.0)	1.15 (0.76, 1.73)	1.08 (0.85, 1.38)	0.033 (-0.066, 0.133)	0.85 (0.62, 1.17)	0.2076
	T-DM1 (N=189)	75 (39.7)				0.3131	
>= 3 lines	T-DXd (N=71)	36 (50.7)	2.19 (1.11, 4.32)	1.59 (1.06, 2.39)	0.188 (0.029, 0.346)	1.19 (0.70, 2.02)	
	T-DM1 (N=72)	23 (31.9)				0.5144	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
< 3 lines	T-DXd (N=186)	15 (8.1)	0.67 (0.33, 1.33)	0.69 (0.37, 1.29)	-0.036 (-0.096, 0.024)	0.50 (0.26, 0.97)	0.4139
	T-DM1 (N=189)	22 (11.6)				0.0377	
>= 3 lines	T-DXd (N=71)	4 (5.6)	1.37 (0.30, 6.37)	1.35 (0.31, 5.83)	0.015 (-0.056, 0.085)	0.79 (0.17, 3.70)	
	T-DM1 (N=72)	3 (4.2)				0.7645	
Infections and infestations							
Any PT							
< 3 lines	T-DXd (N=186)	78 (41.9)	1.52 (0.99, 2.31)	1.30 (0.99, 1.70)	0.097 (-0.001, 0.194)	0.99 (0.71, 1.39)	0.9119
	T-DM1 (N=189)	61 (32.3)				0.9722	
>= 3 lines	T-DXd (N=71)	34 (47.9)	1.84 (0.93, 3.61)	1.44 (0.96, 2.16)	0.146 (-0.014, 0.305)	1.05 (0.62, 1.79)	
	T-DM1 (N=72)	24 (33.3)				0.8533	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
< 3 lines	T-DXd (N=186)	78 (41.9)	1.67 (1.09, 2.56)	1.39 (1.06, 1.83)	0.118 (0.021, 0.214)	1.02 (0.72, 1.44)	0.5564
	T-DM1 (N=189)	57 (30.2)				0.9251	
>= 3 lines	T-DXd (N=71)	29 (40.8)	1.57 (0.79, 3.13)	1.34 (0.86, 2.09)	0.103 (-0.053, 0.259)	0.80 (0.45, 1.41)	
	T-DM1 (N=72)	22 (30.6)				0.4362	
Epistaxis							
< 3 lines	T-DXd (N=186)	20 (10.8)	0.57 (0.31, 1.03)	0.62 (0.37, 1.03)	-0.067 (-0.137, 0.003)	0.38 (0.22, 0.67)	0.4248
	T-DM1 (N=189)	33 (17.5)				0.0006	
>= 3 lines	T-DXd (N=71)	9 (12.7)	1.02 (0.38, 2.73)	1.01 (0.43, 2.41)	0.002 (-0.107, 0.111)	0.45 (0.17, 1.20)	
	T-DM1 (N=72)	9 (12.5)				0.1035	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
< 3 lines	T-DXd (N=186)	16 (8.6)	17.69 (2.32, 134.84)	16.26 (2.18, 121.35)	0.081 (0.039, 0.122)	9.93 (1.31, 75.03)	0.9939
	T-DM1 (N=189)	1 (0.5)				0.0061	
>= 3 lines	T-DXd (N=71)	2 (2.8)	NE (NE, NE)	NE (NE, NE)	0.028 (-0.010, 0.067)	NE (NE, NE)	
	T-DM1 (N=72)	0				0.2034	
Blood and lymphatic system disorders							
Any PT							
< 3 lines	T-DXd (N=186)	57 (30.6)	1.05 (0.68, 1.63)	1.03 (0.76, 1.41)	0.010 (-0.083, 0.103)	0.78 (0.54, 1.14)	0.0003
	T-DM1 (N=189)	56 (29.6)				0.2054	
>= 3 lines	T-DXd (N=71)	46 (64.8)	5.13 (2.51, 10.50)	2.46 (1.61, 3.74)	0.384 (0.233, 0.535)	2.60 (1.52, 4.46)	
	T-DM1 (N=72)	19 (26.4)				0.0003	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
< 3 lines	T-DXd (N=186)	41 (22.0)	1.39 (0.83, 2.32)	1.30 (0.86, 1.97)	0.051 (-0.029, 0.131)	1.05 (0.66, 1.67)	0.0019
	T-DM1 (N=189)	32 (16.9)				0.8361	
>= 3 lines	T-DXd (N=71)	42 (59.2)	7.24 (3.32, 15.79)	3.55 (2.04, 6.16)	0.425 (0.282, 0.568)	3.55 (1.86, 6.79)	
	T-DM1 (N=72)	12 (16.7)				<.0001	
Neutropenia							
< 3 lines	T-DXd (N=186)	26 (14.0)	30.53 (4.10, 227.39)	26.42 (3.62, 192.70)	0.134 (0.084, 0.185)	20.32 (2.75, 150.14)	0.0334
	T-DM1 (N=189)	1 (0.5)				<.0001	
>= 3 lines	T-DXd (N=71)	15 (21.1)	2.95 (1.07, 8.10)	2.54 (1.04, 6.16)	0.128 (0.014, 0.242)	1.84 (0.70, 4.85)	
	T-DM1 (N=72)	6 (8.3)				0.2087	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
< 3 lines	T-DXd (N=186)	7 (3.8)	0.35 (0.14, 0.85)	0.37 (0.16, 0.87)	-0.063 (-0.114, -0.012)	0.28 (0.12, 0.67)	0.7428
	T-DM1 (N=189)	19 (10.1)				0.0024	
>= 3 lines	T-DXd (N=71)	6 (8.5)	0.46 (0.16, 1.31)	0.51 (0.20, 1.28)	-0.082 (-0.190, 0.026)	0.34 (0.12, 0.96)	
	T-DM1 (N=72)	12 (16.7)				0.0337	
Musculoskeletal and connective tissue disorders							
Any PT							
< 3 lines	T-DXd (N=186)	68 (36.6)	1.18 (0.77, 1.81)	1.11 (0.84, 1.47)	0.038 (-0.059, 0.134)	0.83 (0.59, 1.18)	0.8202
	T-DM1 (N=189)	62 (32.8)				0.2990	
>= 3 lines	T-DXd (N=71)	26 (36.6)	1.09 (0.55, 2.15)	1.05 (0.68, 1.64)	0.019 (-0.138, 0.176)	0.74 (0.42, 1.31)	
	T-DM1 (N=72)	25 (34.7)				0.3044	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
< 3 lines	T-DXd (N=186)	34 (18.3)	2.59 (1.36, 4.95)	2.30 (1.30, 4.08)	0.103 (0.036, 0.171)	1.77 (0.96, 3.27)	0.6208
	T-DM1 (N=189)	15 (7.9)				0.0651	
>= 3 lines	T-DXd (N=71)	11 (15.5)	2.02 (0.70, 5.79)	1.86 (0.73, 4.76)	0.072 (-0.034, 0.177)	1.41 (0.51, 3.88)	
	T-DM1 (N=72)	6 (8.3)				0.5058	
Eye disorders							
Any PT							
< 3 lines	T-DXd (N=186)	28 (15.1)	1.35 (0.74, 2.45)	1.29 (0.77, 2.18)	0.034 (-0.035, 0.103)	0.88 (0.50, 1.55)	0.7758
	T-DM1 (N=189)	22 (11.6)				0.6482	
>= 3 lines	T-DXd (N=71)	13 (18.3)	1.79 (0.69, 4.64)	1.65 (0.73, 3.73)	0.072 (-0.044, 0.188)	0.99 (0.40, 2.46)	
	T-DM1 (N=72)	8 (11.1)				0.9828	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
< 3 lines	T-DXd (N=186)	26 (14.0)	1.12 (0.62, 2.03)	1.10 (0.66, 1.85)	0.013 (-0.056, 0.082)	0.76 (0.43, 1.32)	0.9016
	T-DM1 (N=189)	24 (12.7)				0.3259	
>= 3 lines	T-DXd (N=71)	13 (18.3)	1.24 (0.52, 3.00)	1.20 (0.58, 2.49)	0.030 (-0.092, 0.153)	0.92 (0.41, 2.07)	
	T-DM1 (N=72)	11 (15.3)				0.8401	
Insomnia							
< 3 lines	T-DXd (N=186)	7 (3.8)	0.42 (0.17, 1.05)	0.44 (0.19, 1.06)	-0.047 (-0.095, 0.001)	0.31 (0.13, 0.76)	0.2311
	T-DM1 (N=189)	16 (8.5)				0.0067	
>= 3 lines	T-DXd (N=71)	8 (11.3)	1.02 (0.36, 2.87)	1.01 (0.40, 2.55)	0.002 (-0.102, 0.105)	0.78 (0.29, 2.09)	
	T-DM1 (N=72)	8 (11.1)				0.6158	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
< 3 lines	T-DXd (N=186)	24 (12.9)	1.72 (0.87, 3.39)	1.63 (0.88, 3.00)	0.050 (-0.012, 0.111)	1.13 (0.59, 2.18)	0.0585
	T-DM1 (N=189)	15 (7.9)				0.7056	
>= 3 lines	T-DXd (N=71)	8 (11.3)	0.63 (0.24, 1.66)	0.68 (0.29, 1.55)	-0.054 (-0.167, 0.059)	0.33 (0.13, 0.83)	
	T-DM1 (N=72)	12 (16.7)				0.0151	
Cardiac disorders							
Any PT							
< 3 lines	T-DXd (N=186)	11 (5.9)	1.42 (0.56, 3.62)	1.40 (0.57, 3.40)	0.017 (-0.028, 0.061)	0.97 (0.39, 2.45)	0.3050
	T-DM1 (N=189)	8 (4.2)				0.9530	
>= 3 lines	T-DXd (N=71)	10 (14.1)	3.77 (0.99, 14.33)	3.38 (0.97, 11.77)	0.099 (0.006, 0.192)	2.10 (0.56, 7.86)	
	T-DM1 (N=72)	3 (4.2)				0.2622	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
< 3 lines	T-DXd (N=186)	16 (8.6)	2.45 (0.98, 6.09)	2.32 (0.98, 5.52)	0.049 (0.001, 0.097)	1.70 (0.69, 4.16)	0.9691
	T-DM1 (N=189)	7 (3.7)				0.2417	
>= 3 lines	T-DXd (N=71)	5 (7.0)	2.65 (0.50, 14.14)	2.54 (0.51, 12.64)	0.043 (-0.028, 0.113)	1.50 (0.28, 8.05)	
	T-DM1 (N=72)	2 (2.8)				0.6356	
Reproductive system and breast disorders							
Any PT							
< 3 lines	T-DXd (N=186)	14 (7.5)	1.10 (0.50, 2.41)	1.09 (0.53, 2.26)	0.006 (-0.046, 0.059)	0.70 (0.33, 1.50)	0.5427
	T-DM1 (N=189)	13 (6.9)				0.3574	
>= 3 lines	T-DXd (N=71)	7 (9.9)	1.86 (0.52, 6.65)	1.77 (0.54, 5.80)	0.043 (-0.044, 0.130)	1.47 (0.42, 5.08)	
	T-DM1 (N=72)	4 (5.6)				0.5384	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
< 3 lines	T-DXd (N=186)	15 (8.1)	0.74 (0.37, 1.50)	0.76 (0.40, 1.44)	-0.025 (-0.084, 0.034)	0.59 (0.30, 1.16)	0.5223
	T-DM1 (N=189)	20 (10.6)				0.1256	
>= 3 lines	T-DXd (N=71)	5 (7.0)	0.53 (0.17, 1.67)	0.56 (0.20, 1.60)	-0.055 (-0.151, 0.042)	0.39 (0.12, 1.22)	
	T-DM1 (N=72)	9 (12.5)				0.0971	
Renal and urinary disorders							
Any PT							
< 3 lines	T-DXd (N=186)	10 (5.4)	1.73 (0.62, 4.87)	1.69 (0.63, 4.57)	0.022 (-0.019, 0.063)	1.30 (0.47, 3.60)	0.4623
	T-DM1 (N=189)	6 (3.2)				0.6129	
>= 3 lines	T-DXd (N=71)	5 (7.0)	1.02 (0.28, 3.67)	1.01 (0.31, 3.35)	0.001 (-0.083, 0.085)	0.60 (0.17, 2.17)	
	T-DM1 (N=72)	5 (6.9)				0.4323	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
< 3 lines	T-DXd (N=154)	147 (95.5)	15.87 (6.96, 36.17)	1.68 (1.45, 1.93)	0.385 (0.299, 0.471)	3.46 (2.62, 4.55)	0.7445
	T-DM1 (N=151)	86 (57.0)				<.0001	
>= 3 lines	T-DXd (N=6)	6 (100)	NE (NE, NE)	3.00 (0.97, 9.30)	0.667 (0.289, 1.000)	3.88 (0.77, 19.46)	
	T-DM1 (N=6)	2 (33.3)				0.0724	
Nausea							
< 3 lines	T-DXd (N=154)	125 (81.2)	9.54 (5.61, 16.22)	2.61 (2.03, 3.35)	0.500 (0.404, 0.597)	4.25 (3.03, 5.96)	0.7838
	T-DM1 (N=151)	47 (31.1)				<.0001	
>= 3 lines	T-DXd (N=6)	5 (83.3)	24.99 (1.20, 520.48)	5.00 (0.81, 31.00)	0.667 (0.245, 1.000)	5.22 (0.61, 44.79)	
	T-DM1 (N=6)	1 (16.7)				0.0880	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
< 3 lines	T-DXd (N=154)	79 (51.3)	11.18 (5.83, 21.43)	5.96 (3.47, 10.25)	0.427 (0.336, 0.518)	6.63 (3.68, 11.93)	0.9833
	T-DM1 (N=151)	13 (8.6)				<.0001	
>= 3 lines	T-DXd (N=6)	3 (50.0)	NE (NE, NE)	NE (NE, NE)	0.500 (0.100, 0.900)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.0947	
Constipation							
< 3 lines	T-DXd (N=154)	62 (40.3)	2.41 (1.46, 3.98)	1.84 (1.29, 2.63)	0.184 (0.082, 0.286)	1.63 (1.07, 2.50)	0.9799
	T-DM1 (N=151)	33 (21.9)				0.0224	
>= 3 lines	T-DXd (N=6)	3 (50.0)	NE (NE, NE)	NE (NE, NE)	0.500 (0.100, 0.900)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.1297	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
< 3 lines	T-DXd (N=154)	52 (33.8)	5.91 (3.00, 11.63)	4.25 (2.36, 7.64)	0.258 (0.172, 0.344)	4.45 (2.37, 8.34)	0.9854
	T-DM1 (N=151)	12 (7.9)				<.0001	
>= 3 lines	T-DXd (N=6)	2 (33.3)	NE (NE, NE)	NE (NE, NE)	0.333 (-0.044, 0.711)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.1803	
Stomatitis							
< 3 lines	T-DXd (N=154)	27 (17.5)	5.14 (2.06, 12.84)	4.41 (1.88, 10.38)	0.136 (0.068, 0.203)	3.69 (1.51, 8.99)	0.4726
	T-DM1 (N=151)	6 (4.0)				0.0021	
>= 3 lines	T-DXd (N=6)	2 (33.3)	2.50 (0.16, 38.60)	2.00 (0.24, 16.61)	0.167 (-0.314, 0.647)	1.60 (0.14, 17.84)	
	T-DM1 (N=6)	1 (16.7)				0.7002	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
< 3 lines	T-DXd (N=154)	19 (12.3)	4.11 (1.49, 11.31)	3.73 (1.43, 9.72)	0.090 (0.031, 0.150)	2.99 (1.11, 8.05)	0.9997
	T-DM1 (N=151)	5 (3.3)				0.0227	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	
Dry mouth							
< 3 lines	T-DXd (N=154)	1 (0.6)	0.09 (0.01, 0.73)	0.10 (0.01, 0.76)	-0.060 (-0.101, -0.018)	0.09 (0.01, 0.68)	0.9993
	T-DM1 (N=151)	10 (6.6)				0.0031	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
< 3 lines	T-DXd (N=154)	83 (53.9)	0.53 (0.33, 0.84)	0.78 (0.65, 0.94)	-0.150 (-0.258, -0.042)	0.46 (0.35, 0.62)	0.0882
	T-DM1 (N=151)	104 (68.9)				<.0001	
>= 3 lines	T-DXd (N=6)	5 (83.3)	10.00 (0.65, 154.37)	2.50 (0.76, 8.19)	0.500 (0.019, 0.981)	0.84 (0.12, 6.14)	
	T-DM1 (N=6)	2 (33.3)				0.8626	
Neutrophil count decreased							
< 3 lines	T-DXd (N=154)	39 (25.3)	3.93 (1.97, 7.85)	3.19 (1.74, 5.85)	0.174 (0.093, 0.255)	2.90 (1.52, 5.55)	0.9876
	T-DM1 (N=151)	12 (7.9)				0.0007	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.4142	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
< 3 lines	T-DXd (N=154)	25 (16.2)	0.31 (0.18, 0.53)	0.42 (0.28, 0.64)	-0.222 (-0.319, -0.125)	0.28 (0.17, 0.45)	0.2021
	T-DM1 (N=151)	58 (38.4)				<.0001	
>= 3 lines	T-DXd (N=6)	2 (33.3)	2.50 (0.16, 38.60)	2.00 (0.24, 16.61)	0.167 (-0.314, 0.647)	0.91 (0.06, 14.63)	
	T-DM1 (N=6)	1 (16.7)				0.9486	
White blood cell count decreased							
< 3 lines	T-DXd (N=154)	21 (13.6)	7.79 (2.27, 26.71)	6.86 (2.09, 22.53)	0.116 (0.058, 0.175)	6.13 (1.83, 20.61)	0.9875
	T-DM1 (N=151)	3 (2.0)				0.0008	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	-0.167 (-0.465, 0.132)	NE (NE, NE)	
	T-DM1 (N=6)	1 (16.7)				0.1967	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
< 3 lines	T-DXd (N=154)	25 (16.2)	0.43 (0.25, 0.74)	0.52 (0.34, 0.80)	-0.149 (-0.243, -0.055)	0.37 (0.23, 0.61)	0.2990
	T-DM1 (N=151)	47 (31.1)				<.0001	
>= 3 lines	T-DXd (N=6)	2 (33.3)	2.50 (0.16, 38.60)	2.00 (0.24, 16.61)	0.167 (-0.314, 0.647)	0.91 (0.06, 14.63)	
	T-DM1 (N=6)	1 (16.7)				0.9486	
Platelet count decreased							
< 3 lines	T-DXd (N=154)	17 (11.0)	0.16 (0.09, 0.28)	0.25 (0.15, 0.40)	-0.333 (-0.427, -0.240)	0.16 (0.09, 0.28)	0.9875
	T-DM1 (N=151)	67 (44.4)				<.0001	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.3173	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
< 3 lines	T-DXd (N=154)	16 (10.4)	2.80 (1.07, 7.37)	2.61 (1.05, 6.50)	0.064 (0.007, 0.122)	2.21 (0.86, 5.67)	0.9914
	T-DM1 (N=151)	6 (4.0)				0.0896	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.5271	
Blood lactate dehydrogenase increased							
< 3 lines	T-DXd (N=154)	1 (0.6)	0.08 (0.01, 0.65)	0.09 (0.01, 0.68)	-0.066 (-0.110, -0.023)	0.08 (0.01, 0.63)	0.9995
	T-DM1 (N=151)	11 (7.3)				0.0020	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
< 3 lines	T-DXd (N=154)	6 (3.9)	6.08 (0.72, 51.13)	5.88 (0.72, 48.29)	0.032 (-0.001, 0.066)	4.62 (0.55, 38.55)	0.9935
	T-DM1 (N=151)	1 (0.7)				0.1197	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	-0.167 (-0.465, 0.132)	NE (NE, NE)	
	T-DM1 (N=6)	1 (16.7)				0.1138	
General disorders and administration site conditions							
Any PT							
< 3 lines	T-DXd (N=154)	99 (64.3)	1.68 (1.06, 2.67)	1.24 (1.02, 1.51)	0.126 (0.016, 0.236)	1.11 (0.83, 1.50)	0.2542
	T-DM1 (N=151)	78 (51.7)				0.4790	
>= 3 lines	T-DXd (N=6)	4 (66.7)	0.40 (0.03, 6.18)	0.80 (0.41, 1.56)	-0.167 (-0.647, 0.314)	0.67 (0.18, 2.51)	
	T-DM1 (N=6)	5 (83.3)				0.5301	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
< 3 lines	T-DXd (N=154)	17 (11.0)	2.22 (0.93, 5.31)	2.08 (0.93, 4.68)	0.057 (-0.004, 0.118)	1.74 (0.74, 4.08)	0.9900
	T-DM1 (N=151)	8 (5.3)				0.1981	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.4142	
Pyrexia							
< 3 lines	T-DXd (N=154)	12 (7.8)	0.71 (0.33, 1.56)	0.74 (0.36, 1.50)	-0.028 (-0.093, 0.037)	0.48 (0.22, 1.03)	0.9394
	T-DM1 (N=151)	16 (10.6)				0.0565	
>= 3 lines	T-DXd (N=6)	1 (16.7)	1.00 (0.05, 20.83)	1.00 (0.08, 12.56)	0.000 (-0.422, 0.422)	0.45 (0.02, 8.98)	
	T-DM1 (N=6)	1 (16.7)				0.5930	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
< 3 lines	T-DXd (N=154)	86 (55.8)	3.90 (2.39, 6.35)	2.28 (1.67, 3.12)	0.313 (0.209, 0.418)	2.57 (1.75, 3.78)	0.7331
	T-DM1 (N=151)	37 (24.5)				<.0001	
>= 3 lines	T-DXd (N=6)	4 (66.7)	10.00 (0.65, 154.37)	4.00 (0.61, 26.12)	0.500 (0.019, 0.981)	3.50 (0.39, 31.36)	
	T-DM1 (N=6)	1 (16.7)				0.2331	
Alopecia							
< 3 lines	T-DXd (N=154)	55 (35.7)	27.41 (8.34, 90.05)	17.98 (5.75, 56.22)	0.337 (0.258, 0.416)	20.45 (6.40, 65.39)	0.9889
	T-DM1 (N=151)	3 (2.0)				<.0001	
>= 3 lines	T-DXd (N=6)	3 (50.0)	NE (NE, NE)	NE (NE, NE)	0.500 (0.100, 0.900)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.1456	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
< 3 lines	T-DXd (N=154)	11 (7.1)	1.21 (0.49, 3.02)	1.20 (0.51, 2.81)	0.012 (-0.044, 0.067)	0.92 (0.38, 2.26)	0.9913
	T-DM1 (N=151)	9 (6.0)				0.8639	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	-0.167 (-0.465, 0.132)	NE (NE, NE)	
	T-DM1 (N=6)	1 (16.7)				0.3173	
Skin hyperpigmentation							
< 3 lines	T-DXd (N=154)	6 (3.9)	NE (NE, NE)	NE (NE, NE)	0.039 (0.008, 0.070)	NE (NE, NE)	0.9992
	T-DM1 (N=151)	0				0.0271	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
< 3 lines	T-DXd (N=154)	61 (39.6)	1.82 (1.12, 2.96)	1.50 (1.08, 2.08)	0.131 (0.027, 0.236)	1.44 (0.97, 2.16)	0.4690
	T-DM1 (N=151)	40 (26.5)				0.0715	
>= 3 lines	T-DXd (N=6)	4 (66.7)	10.00 (0.65, 154.37)	4.00 (0.61, 26.12)	0.500 (0.019, 0.981)	2.88 (0.31, 26.52)	
	T-DM1 (N=6)	1 (16.7)				0.3198	
Decreased appetite							
< 3 lines	T-DXd (N=154)	37 (24.0)	1.52 (0.87, 2.67)	1.40 (0.89, 2.19)	0.068 (-0.022, 0.159)	1.32 (0.80, 2.19)	0.9820
	T-DM1 (N=151)	26 (17.2)				0.2819	
>= 3 lines	T-DXd (N=6)	4 (66.7)	NE (NE, NE)	NE (NE, NE)	0.667 (0.289, 1.000)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.0634	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
< 3 lines	T-DXd (N=154)	8 (5.2)	NE (NE, NE)	NE (NE, NE)	0.052 (0.017, 0.087)	NE (NE, NE)	0.9991
	T-DM1 (N=151)	0				0.0053	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	
Nervous system disorders							
Any PT							
< 3 lines	T-DXd (N=154)	71 (46.1)	1.58 (1.00, 2.51)	1.31 (1.00, 1.73)	0.110 (0.001, 0.220)	1.07 (0.75, 1.54)	0.5132
	T-DM1 (N=151)	53 (35.1)				0.7001	
>= 3 lines	T-DXd (N=6)	4 (66.7)	2.00 (0.19, 20.61)	1.33 (0.50, 3.55)	0.167 (-0.383, 0.717)	0.44 (0.08, 2.31)	
	T-DM1 (N=6)	3 (50.0)				0.3215	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
< 3 lines	T-DXd (N=154)	15 (9.7)	0.80 (0.39, 1.65)	0.82 (0.43, 1.56)	-0.022 (-0.092, 0.048)	0.59 (0.29, 1.19)	0.9887
	T-DM1 (N=151)	18 (11.9)				0.1345	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.4142	
Infections and infestations							
Any PT							
< 3 lines	T-DXd (N=154)	65 (42.2)	1.72 (1.07, 2.76)	1.42 (1.04, 1.92)	0.124 (0.017, 0.231)	1.12 (0.76, 1.64)	0.5755
	T-DM1 (N=151)	45 (29.8)				0.5747	
>= 3 lines	T-DXd (N=6)	3 (50.0)	5.00 (0.34, 72.76)	3.00 (0.42, 21.30)	0.333 (-0.166, 0.832)	2.55 (0.26, 24.92)	
	T-DM1 (N=6)	1 (16.7)				0.4054	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
< 3 lines	T-DXd (N=154)	60 (39.0)	1.50 (0.93, 2.42)	1.31 (0.95, 1.79)	0.092 (-0.014, 0.198)	0.93 (0.63, 1.38)	0.9685
	T-DM1 (N=151)	45 (29.8)				0.7311	
>= 3 lines	T-DXd (N=6)	3 (50.0)	2.00 (0.19, 20.61)	1.50 (0.38, 6.00)	0.167 (-0.383, 0.717)	0.82 (0.13, 5.04)	
	T-DM1 (N=6)	2 (33.3)				0.8260	
Epistaxis							
< 3 lines	T-DXd (N=154)	15 (9.7)	0.54 (0.27, 1.08)	0.59 (0.32, 1.07)	-0.068 (-0.144, 0.007)	0.34 (0.17, 0.67)	0.5925
	T-DM1 (N=151)	25 (16.6)				0.0011	
>= 3 lines	T-DXd (N=6)	2 (33.3)	1.00 (0.09, 11.03)	1.00 (0.20, 4.95)	0.000 (-0.533, 0.533)	0.46 (0.06, 3.31)	
	T-DM1 (N=6)	2 (33.3)				0.4289	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
< 3 lines	T-DXd (N=154)	10 (6.5)	10.42 (1.32, 82.41)	9.81 (1.27, 75.66)	0.058 (0.017, 0.099)	5.03 (0.64, 39.62)	0.9997
	T-DM1 (N=151)	1 (0.7)				0.0886	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	
Blood and lymphatic system disorders							
Any PT							
< 3 lines	T-DXd (N=154)	39 (25.3)	1.01 (0.60, 1.69)	1.01 (0.68, 1.48)	0.002 (-0.096, 0.099)	0.77 (0.49, 1.22)	0.9435
	T-DM1 (N=151)	38 (25.2)				0.2684	
>= 3 lines	T-DXd (N=6)	4 (66.7)	1.00 (0.09, 11.03)	1.00 (0.45, 2.23)	0.000 (-0.533, 0.533)	0.70 (0.15, 3.14)	
	T-DM1 (N=6)	4 (66.7)				0.5954	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
< 3 lines	T-DXd (N=154)	30 (19.5)	1.50 (0.81, 2.75)	1.40 (0.84, 2.33)	0.056 (-0.028, 0.139)	1.14 (0.65, 2.01)	0.4029
	T-DM1 (N=151)	21 (13.9)				0.6373	
>= 3 lines	T-DXd (N=6)	3 (50.0)	1.00 (0.10, 9.61)	1.00 (0.32, 3.10)	0.000 (-0.566, 0.566)	0.18 (0.02, 1.80)	
	T-DM1 (N=6)	3 (50.0)				0.1036	
Neutropenia							
< 3 lines	T-DXd (N=154)	14 (9.1)	NE (NE, NE)	NE (NE, NE)	0.091 (0.046, 0.136)	NE (NE, NE)	0.9887
	T-DM1 (N=151)	0				0.0009	
>= 3 lines	T-DXd (N=6)	3 (50.0)	2.00 (0.19, 20.61)	1.50 (0.38, 6.00)	0.167 (-0.383, 0.717)	1.27 (0.20, 7.95)	
	T-DM1 (N=6)	2 (33.3)				0.7967	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
< 3 lines	T-DXd (N=154)	1 (0.6)	0.06 (0.01, 0.45)	0.07 (0.01, 0.49)	-0.093 (-0.142, -0.043)	0.05 (0.01, 0.41)	0.1028
	T-DM1 (N=151)	15 (9.9)				0.0001	
>= 3 lines	T-DXd (N=6)	2 (33.3)	0.50 (0.05, 5.15)	0.67 (0.17, 2.67)	-0.167 (-0.717, 0.383)	0.21 (0.02, 2.16)	
	T-DM1 (N=6)	3 (50.0)				0.1442	
Musculoskeletal and connective tissue disorders							
Any PT							
< 3 lines	T-DXd (N=154)	63 (40.9)	1.44 (0.90, 2.30)	1.26 (0.94, 1.70)	0.085 (-0.023, 0.192)	1.02 (0.70, 1.48)	0.3377
	T-DM1 (N=151)	49 (32.5)				0.9297	
>= 3 lines	T-DXd (N=6)	4 (66.7)	2.00 (0.19, 20.61)	1.33 (0.50, 3.55)	0.167 (-0.383, 0.717)	0.26 (0.03, 2.55)	
	T-DM1 (N=6)	3 (50.0)				0.2154	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
< 3 lines	T-DXd (N=154)	32 (20.8)	3.70 (1.75, 7.83)	3.14 (1.60, 6.15)	0.142 (0.066, 0.217)	2.39 (1.16, 4.91)	0.1116
	T-DM1 (N=151)	10 (6.6)				0.0149	
>= 3 lines	T-DXd (N=6)	1 (16.7)	0.40 (0.03, 6.18)	0.50 (0.06, 4.15)	-0.167 (-0.647, 0.314)	0.32 (0.03, 3.61)	
	T-DM1 (N=6)	2 (33.3)				0.3352	
Eye disorders							
Any PT							
< 3 lines	T-DXd (N=154)	28 (18.2)	1.64 (0.87, 3.11)	1.53 (0.88, 2.64)	0.063 (-0.017, 0.142)	1.01 (0.55, 1.86)	0.9886
	T-DM1 (N=151)	18 (11.9)				0.9620	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	-0.167 (-0.465, 0.132)	NE (NE, NE)	
	T-DM1 (N=6)	1 (16.7)				0.3173	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
< 3 lines	T-DXd (N=154)	21 (13.6)	1.33 (0.67, 2.66)	1.29 (0.70, 2.37)	0.030 (-0.043, 0.104)	0.89 (0.46, 1.72)	0.9885
	T-DM1 (N=151)	16 (10.6)				0.7274	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.4386	
Insomnia							
< 3 lines	T-DXd (N=154)	5 (3.2)	0.47 (0.16, 1.42)	0.49 (0.17, 1.40)	-0.034 (-0.082, 0.015)	0.32 (0.11, 0.95)	0.9997
	T-DM1 (N=151)	10 (6.6)				0.0318	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
< 3 lines	T-DXd (N=154)	25 (16.2)	1.53 (0.79, 2.96)	1.44 (0.81, 2.56)	0.050 (-0.027, 0.127)	0.91 (0.49, 1.72)	0.9889
	T-DM1 (N=151)	17 (11.3)				0.7792	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	-0.167 (-0.465, 0.132)	NE (NE, NE)	
	T-DM1 (N=6)	1 (16.7)				0.3173	
Cardiac disorders							
Any PT							
< 3 lines	T-DXd (N=154)	5 (3.2)	0.81 (0.24, 2.72)	0.82 (0.25, 2.62)	-0.007 (-0.049, 0.035)	0.59 (0.18, 1.96)	0.9924
	T-DM1 (N=151)	6 (4.0)				0.3821	
>= 3 lines	T-DXd (N=6)	2 (33.3)	NE (NE, NE)	NE (NE, NE)	0.333 (-0.044, 0.711)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.4795	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
< 3 lines	T-DXd (N=154)	17 (11.0)	2.55 (1.03, 6.35)	2.38 (1.02, 5.58)	0.064 (0.004, 0.124)	1.68 (0.69, 4.10)	0.9907
	T-DM1 (N=151)	7 (4.6)				0.2518	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.4386	
Reproductive system and breast disorders							
Any PT							
< 3 lines	T-DXd (N=154)	13 (8.4)	0.98 (0.44, 2.19)	0.98 (0.47, 2.05)	-0.002 (-0.064, 0.061)	0.58 (0.26, 1.29)	0.9998
	T-DM1 (N=151)	13 (8.6)				0.1775	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
< 3 lines	T-DXd (N=154)	9 (5.8)	0.52 (0.22, 1.22)	0.55 (0.25, 1.21)	-0.048 (-0.109, 0.014)	0.40 (0.17, 0.94)	0.9997
	T-DM1 (N=151)	16 (10.6)				0.0296	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	
Renal and urinary disorders							
Any PT							
< 3 lines	T-DXd (N=154)	7 (4.5)	1.39 (0.43, 4.48)	1.37 (0.45, 4.23)	0.012 (-0.031, 0.056)	0.96 (0.30, 3.06)	0.7505
	T-DM1 (N=151)	5 (3.3)				0.9390	
>= 3 lines	T-DXd (N=6)	1 (16.7)	1.00 (0.05, 20.83)	1.00 (0.08, 12.56)	0.000 (-0.422, 0.422)	0.58 (0.03, 10.25)	
	T-DM1 (N=6)	1 (16.7)				0.7055	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	122 (93.8)	11.54 (5.21, 25.56)	1.65 (1.41, 1.93)	0.369 (0.275, 0.464)	3.13 (2.33, 4.21)	0.4271
	T-DM1 (N=130)	74 (56.9)				<.0001	
Mild Impairment	T-DXd (N=92)	83 (90.2)	6.25 (2.83, 13.79)	1.51 (1.27, 1.80)	0.306 (0.194, 0.418)	2.54 (1.82, 3.55)	
	T-DM1 (N=104)	62 (59.6)				<.0001	
Moderate Impairment	T-DXd (N=30)	27 (90.0)	6.23 (1.44, 26.95)	1.52 (1.05, 2.20)	0.309 (0.077, 0.541)	2.56 (1.31, 5.00)	
	T-DM1 (N=22)	13 (59.1)				0.0043	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Nausea							
Within Normal Range	T-DXd (N=130)	103 (79.2)	6.74 (3.87, 11.73)	2.19 (1.72, 2.80)	0.431 (0.323, 0.539)	3.41 (2.41, 4.83)	0.8872
	T-DM1 (N=130)	47 (36.2)				<.0001	
Mild Impairment	T-DXd (N=92)	66 (71.7)	7.24 (3.85, 13.61)	2.76 (1.95, 3.92)	0.458 (0.333, 0.583)	3.80 (2.43, 5.96)	
	T-DM1 (N=104)	27 (26.0)				<.0001	
Moderate Impairment	T-DXd (N=30)	21 (70.0)	7.93 (2.24, 28.15)	3.08 (1.38, 6.89)	0.473 (0.233, 0.713)	4.73 (1.78, 12.61)	
	T-DM1 (N=22)	5 (22.7)				0.0006	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Within Normal Range	T-DXd (N=130)	69 (53.1)	8.67 (4.58, 16.43)	4.60 (2.78, 7.60)	0.415 (0.314, 0.517)	5.07 (2.89, 8.87)	0.9370
	T-DM1 (N=130)	15 (11.5)				<.0001	
Mild Impairment	T-DXd (N=92)	38 (41.3)	8.44 (3.67, 19.41)	5.37 (2.64, 10.91)	0.336 (0.223, 0.449)	5.61 (2.61, 12.05)	
	T-DM1 (N=104)	8 (7.7)				<.0001	
Moderate Impairment	T-DXd (N=30)	16 (53.3)	7.24 (1.76, 29.73)	3.91 (1.30, 11.79)	0.397 (0.168, 0.626)	4.69 (1.37, 16.12)	
	T-DM1 (N=22)	3 (13.6)				0.0066	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Constipation							
Within Normal Range	T-DXd (N=130)	47 (36.2)	2.38 (1.35, 4.18)	1.88 (1.24, 2.86)	0.169 (0.062, 0.276)	1.58 (0.97, 2.57)	0.9534
	T-DM1 (N=130)	25 (19.2)				0.0664	
Mild Impairment	T-DXd (N=92)	31 (33.7)	2.13 (1.11, 4.10)	1.75 (1.08, 2.85)	0.145 (0.022, 0.267)	1.65 (0.94, 2.89)	
	T-DM1 (N=104)	20 (19.2)				0.0805	
Moderate Impairment	T-DXd (N=30)	10 (33.3)	1.70 (0.49, 5.95)	1.47 (0.58, 3.69)	0.106 (-0.137, 0.349)	1.27 (0.43, 3.74)	
	T-DM1 (N=22)	5 (22.7)				0.6589	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Within Normal Range	T-DXd (N=130)	39 (30.0)	8.86 (3.60, 21.81)	6.50 (2.85, 14.82)	0.254 (0.167, 0.340)	6.41 (2.71, 15.18)	0.4202
	T-DM1 (N=130)	6 (4.6)				<.0001	
Mild Impairment	T-DXd (N=92)	26 (28.3)	4.16 (1.83, 9.44)	3.27 (1.61, 6.60)	0.196 (0.089, 0.303)	3.27 (1.53, 6.99)	
	T-DM1 (N=104)	9 (8.7)				0.0012	
Moderate Impairment	T-DXd (N=30)	7 (23.3)	3.04 (0.57, 16.36)	2.57 (0.59, 11.19)	0.142 (-0.051, 0.336)	2.66 (0.55, 12.79)	
	T-DM1 (N=22)	2 (9.1)				0.2063	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Stomatitis							
Within Normal Range	T-DXd (N=130)	15 (11.5)	4.11 (1.33, 12.74)	3.75 (1.28, 11.00)	0.085 (0.022, 0.147)	2.84 (0.93, 8.63)	0.8995
	T-DM1 (N=130)	4 (3.1)				0.0552	
Mild Impairment	T-DXd (N=92)	19 (20.7)	5.15 (1.84, 14.44)	4.30 (1.67, 11.04)	0.158 (0.066, 0.251)	3.95 (1.47, 10.60)	
	T-DM1 (N=104)	5 (4.8)				0.0033	
Moderate Impairment	T-DXd (N=30)	6 (20.0)	5.25 (0.58, 47.22)	4.40 (0.57, 33.98)	0.155 (-0.013, 0.322)	3.83 (0.46, 31.86)	
	T-DM1 (N=22)	1 (4.5)				0.1812	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Within Normal Range	T-DXd (N=130)	14 (10.8)	5.11 (1.43, 18.23)	4.67 (1.37, 15.85)	0.085 (0.025, 0.144)	3.33 (0.95, 11.74)	0.9284
	T-DM1 (N=130)	3 (2.3)				0.0474	
Mild Impairment	T-DXd (N=92)	10 (10.9)	6.22 (1.33, 29.18)	5.65 (1.27, 25.13)	0.089 (0.021, 0.158)	4.13 (0.90, 19.00)	
	T-DM1 (N=104)	2 (1.9)				0.0490	
Moderate Impairment	T-DXd (N=30)	3 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.007, 0.207)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.1903	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Dry mouth							
Within Normal Range	T-DXd (N=130)	4 (3.1)	0.29 (0.09, 0.90)	0.31 (0.10, 0.92)	-0.069 (-0.129, -0.010)	0.23 (0.07, 0.72)	0.3973
	T-DM1 (N=130)	13 (10.0)				0.0058	
Mild Impairment	T-DXd (N=92)	2 (2.2)	0.21 (0.04, 0.98)	0.23 (0.05, 1.01)	-0.074 (-0.138, -0.010)	0.20 (0.04, 0.91)	
	T-DM1 (N=104)	10 (9.6)				0.0211	
Moderate Impairment	T-DXd (N=30)	2 (6.7)	1.50 (0.13, 17.66)	1.47 (0.14, 15.17)	0.021 (-0.103, 0.146)	0.73 (0.06, 8.46)	
	T-DM1 (N=22)	1 (4.5)				0.8013	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Within Normal Range	T-DXd (N=130)	84 (64.6)	1.03 (0.62, 1.72)	1.01 (0.84, 1.21)	0.008 (-0.109, 0.124)	0.69 (0.51, 0.94)	0.2639
	T-DM1 (N=130)	83 (63.8)				0.0404	
Mild Impairment	T-DXd (N=92)	58 (63.0)	0.69 (0.38, 1.26)	0.89 (0.73, 1.08)	-0.081 (-0.213, 0.050)	0.60 (0.43, 0.85)	
	T-DM1 (N=104)	74 (71.2)				0.0090	
Moderate Impairment	T-DXd (N=30)	18 (60.0)	0.33 (0.09, 1.23)	0.73 (0.52, 1.04)	-0.218 (-0.456, 0.020)	0.36 (0.19, 0.71)	
	T-DM1 (N=22)	18 (81.8)				0.0032	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
Within Normal Range	T-DXd (N=130)	42 (32.3)	9.86 (4.02, 24.21)	7.00 (3.08, 15.90)	0.277 (0.189, 0.365)	6.30 (2.67, 14.82)	0.0220
	T-DM1 (N=130)	6 (4.6)				<.0001	
Mild Impairment	T-DXd (N=92)	28 (30.4)	2.60 (1.28, 5.25)	2.11 (1.20, 3.70)	0.160 (0.044, 0.276)	2.11 (1.13, 3.96)	
	T-DM1 (N=104)	15 (14.4)				0.0174	
Moderate Impairment	T-DXd (N=30)	5 (16.7)	0.90 (0.21, 3.83)	0.92 (0.28, 3.03)	-0.015 (-0.224, 0.194)	0.82 (0.22, 3.08)	
	T-DM1 (N=22)	4 (18.2)				0.7741	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
Within Normal Range	T-DXd (N=130)	37 (28.5)	0.68 (0.40, 1.14)	0.77 (0.54, 1.10)	-0.085 (-0.198, 0.029)	0.56 (0.36, 0.87)	0.2764
	T-DM1 (N=130)	48 (36.9)				0.0098	
Mild Impairment	T-DXd (N=92)	18 (19.6)	0.33 (0.17, 0.63)	0.46 (0.29, 0.74)	-0.227 (-0.352, -0.103)	0.30 (0.17, 0.52)	
	T-DM1 (N=104)	44 (42.3)				<.0001	
Moderate Impairment	T-DXd (N=30)	10 (33.3)	0.60 (0.19, 1.86)	0.73 (0.37, 1.45)	-0.121 (-0.389, 0.147)	0.56 (0.23, 1.34)	
	T-DM1 (N=22)	10 (45.5)				0.1952	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
Within Normal Range	T-DXd (N=130)	35 (26.9)	9.21 (3.48, 24.40)	7.00 (2.83, 17.30)	0.231 (0.148, 0.314)	5.73 (2.23, 14.67)	0.1744
	T-DM1 (N=130)	5 (3.8)				<.0001	
Mild Impairment	T-DXd (N=92)	20 (21.7)	3.85 (1.54, 9.59)	3.23 (1.43, 7.29)	0.150 (0.053, 0.247)	3.10 (1.31, 7.35)	
	T-DM1 (N=104)	7 (6.7)				0.0067	
Moderate Impairment	T-DXd (N=30)	3 (10.0)	1.11 (0.17, 7.28)	1.10 (0.20, 6.04)	0.009 (-0.152, 0.170)	0.91 (0.15, 5.51)	
	T-DM1 (N=22)	2 (9.1)				0.9187	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
Within Normal Range	T-DXd (N=130)	34 (26.2)	1.00 (0.58, 1.74)	1.00 (0.66, 1.50)	0.000 (-0.107, 0.107)	0.80 (0.50, 1.30)	0.1079
	T-DM1 (N=130)	34 (26.2)				0.3735	
Mild Impairment	T-DXd (N=92)	15 (16.3)	0.38 (0.19, 0.76)	0.48 (0.28, 0.83)	-0.173 (-0.292, -0.055)	0.35 (0.19, 0.65)	
	T-DM1 (N=104)	35 (33.7)				0.0006	
Moderate Impairment	T-DXd (N=30)	6 (20.0)	0.44 (0.13, 1.52)	0.55 (0.22, 1.36)	-0.164 (-0.410, 0.083)	0.42 (0.15, 1.23)	
	T-DM1 (N=22)	8 (36.4)				0.1087	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Within Normal Range	T-DXd (N=130)	26 (20.0)	0.43 (0.24, 0.75)	0.54 (0.36, 0.82)	-0.169 (-0.277, -0.061)	0.34 (0.21, 0.56)	0.5114
	T-DM1 (N=130)	48 (36.9)				<.0001	
Mild Impairment	T-DXd (N=92)	23 (25.0)	0.33 (0.18, 0.61)	0.50 (0.33, 0.75)	-0.250 (-0.381, -0.119)	0.34 (0.21, 0.57)	
	T-DM1 (N=104)	52 (50.0)				<.0001	
Moderate Impairment	T-DXd (N=30)	5 (16.7)	0.17 (0.05, 0.60)	0.31 (0.13, 0.74)	-0.379 (-0.626, -0.132)	0.20 (0.07, 0.56)	
	T-DM1 (N=22)	12 (54.5)				0.0011	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
Within Normal Range	T-DXd (N=130)	23 (17.7)	3.78 (1.56, 9.15)	3.29 (1.46, 7.39)	0.123 (0.047, 0.199)	2.30 (0.98, 5.41)	0.2186
	T-DM1 (N=130)	7 (5.4)				0.0494	
Mild Impairment	T-DXd (N=92)	15 (16.3)	3.86 (1.34, 11.08)	3.39 (1.28, 8.97)	0.115 (0.029, 0.201)	2.88 (1.04, 7.94)	
	T-DM1 (N=104)	5 (4.8)				0.0327	
Moderate Impairment	T-DXd (N=30)	5 (16.7)	0.90 (0.21, 3.83)	0.92 (0.28, 3.03)	-0.015 (-0.224, 0.194)	0.66 (0.18, 2.47)	
	T-DM1 (N=22)	4 (18.2)				0.5418	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Blood lactate dehydrogenase increased							
Within Normal Range	T-DXd (N=130)	10 (7.7)	0.46 (0.21, 1.02)	0.50 (0.24, 1.03)	-0.077 (-0.154, 0.000)	0.33 (0.15, 0.72)	0.7781
	T-DM1 (N=130)	20 (15.4)				0.0040	
Mild Impairment	T-DXd (N=92)	7 (7.6)	0.63 (0.24, 1.68)	0.66 (0.27, 1.60)	-0.039 (-0.121, 0.043)	0.55 (0.22, 1.41)	
	T-DM1 (N=104)	12 (11.5)				0.2093	
Moderate Impairment	T-DXd (N=30)	0	NE (NE, NE)	NE (NE, NE)	-0.136 (-0.280, 0.007)	NE (NE, NE)	
	T-DM1 (N=22)	3 (13.6)				0.0386	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
Within Normal Range	T-DXd (N=130)	8 (6.2)	8.46 (1.04, 68.61)	8.00 (1.01, 63.06)	0.054 (0.010, 0.098)	5.72 (0.70, 46.38)	0.2929
	T-DM1 (N=130)	1 (0.8)				0.0662	
Mild Impairment	T-DXd (N=92)	4 (4.3)	NE (NE, NE)	NE (NE, NE)	0.043 (0.002, 0.085)	NE (NE, NE)	
	T-DM1 (N=104)	0				0.0843	
Moderate Impairment	T-DXd (N=30)	2 (6.7)	0.71 (0.09, 5.51)	0.73 (0.11, 4.81)	-0.024 (-0.174, 0.125)	0.59 (0.08, 4.27)	
	T-DM1 (N=22)	2 (9.1)				0.5998	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
Within Normal Range	T-DXd (N=130)	81 (62.3)	1.46 (0.89, 2.40)	1.17 (0.95, 1.45)	0.092 (-0.027, 0.212)	0.88 (0.63, 1.21)	0.2931
	T-DM1 (N=130)	69 (53.1)				0.4234	
Mild Impairment	T-DXd (N=92)	57 (62.0)	1.98 (1.12, 3.50)	1.37 (1.05, 1.79)	0.168 (0.030, 0.305)	1.35 (0.92, 1.99)	
	T-DM1 (N=104)	47 (45.2)				0.1269	
Moderate Impairment	T-DXd (N=30)	19 (63.3)	1.20 (0.39, 3.70)	1.07 (0.69, 1.67)	0.042 (-0.226, 0.311)	0.97 (0.48, 1.97)	
	T-DM1 (N=22)	13 (59.1)				0.9300	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Within Normal Range	T-DXd (N=130)	17 (13.1)	6.37 (1.82, 22.30)	5.67 (1.70, 18.87)	0.108 (0.044, 0.171)	4.35 (1.26, 15.02)	0.5414
	T-DM1 (N=130)	3 (2.3)				0.0114	
Mild Impairment	T-DXd (N=92)	11 (12.0)	2.22 (0.79, 6.26)	2.07 (0.80, 5.38)	0.062 (-0.018, 0.142)	2.12 (0.78, 5.73)	
	T-DM1 (N=104)	6 (5.8)				0.1300	
Moderate Impairment	T-DXd (N=30)	1 (3.3)	NE (NE, NE)	NE (NE, NE)	0.033 (-0.031, 0.098)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.3918	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Pyrexia							
Within Normal Range	T-DXd (N=130)	17 (13.1)	0.74 (0.37, 1.47)	0.77 (0.43, 1.39)	-0.038 (-0.125, 0.048)	0.45 (0.23, 0.87)	0.1690
	T-DM1 (N=130)	22 (16.9)				0.0150	
Mild Impairment	T-DXd (N=92)	9 (9.8)	1.02 (0.40, 2.63)	1.02 (0.43, 2.39)	0.002 (-0.081, 0.085)	0.74 (0.30, 1.85)	
	T-DM1 (N=104)	10 (9.6)				0.5215	
Moderate Impairment	T-DXd (N=30)	1 (3.3)	0.09 (0.01, 0.83)	0.12 (0.02, 0.94)	-0.239 (-0.436, -0.043)	0.07 (0.01, 0.57)	
	T-DM1 (N=22)	6 (27.3)				0.0013	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	73 (56.2)	3.62 (2.14, 6.10)	2.15 (1.55, 2.98)	0.300 (0.186, 0.414)	2.26 (1.50, 3.40)	0.0976
	T-DM1 (N=130)	34 (26.2)				<.0001	
Mild Impairment	T-DXd (N=92)	54 (58.7)	3.20 (1.78, 5.75)	1.91 (1.36, 2.67)	0.279 (0.145, 0.413)	2.20 (1.42, 3.42)	
	T-DM1 (N=104)	32 (30.8)				0.0003	
Moderate Impairment	T-DXd (N=30)	10 (33.3)	0.87 (0.28, 2.77)	0.92 (0.43, 1.94)	-0.030 (-0.293, 0.232)	0.58 (0.21, 1.57)	
	T-DM1 (N=22)	8 (36.4)				0.2779	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Alopecia							
Within Normal Range	T-DXd (N=130)	51 (39.2)	20.34 (7.07, 58.45)	12.75 (4.75, 34.25)	0.362 (0.273, 0.451)	13.94 (5.03, 38.58)	0.9964
	T-DM1 (N=130)	4 (3.1)				<.0001	
Mild Impairment	T-DXd (N=92)	39 (42.4)	18.39 (6.24, 54.22)	11.02 (4.10, 29.66)	0.385 (0.278, 0.493)	13.28 (4.74, 37.17)	
	T-DM1 (N=104)	4 (3.8)				<.0001	
Moderate Impairment	T-DXd (N=30)	5 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (0.033, 0.300)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.0517	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
Within Normal Range	T-DXd (N=130)	11 (8.5)	1.00 (0.42, 2.40)	1.00 (0.45, 2.22)	0.000 (-0.068, 0.068)	0.65 (0.28, 1.54)	0.3162
	T-DM1 (N=130)	11 (8.5)				0.3231	
Mild Impairment	T-DXd (N=92)	3 (3.3)	0.32 (0.08, 1.19)	0.34 (0.10, 1.19)	-0.064 (-0.131, 0.004)	0.24 (0.07, 0.90)	
	T-DM1 (N=104)	10 (9.6)				0.0222	
Moderate Impairment	T-DXd (N=30)	1 (3.3)	0.22 (0.02, 2.26)	0.24 (0.03, 2.20)	-0.103 (-0.260, 0.054)	0.18 (0.02, 1.72)	
	T-DM1 (N=22)	3 (13.6)				0.0934	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Skin hyperpigmentation							
Within Normal Range	T-DXd (N=130)	8 (6.2)	NE (NE, NE)	NE (NE, NE)	0.062 (0.020, 0.103)	NE (NE, NE)	1.0000
	T-DM1 (N=130)	0				0.0113	
Mild Impairment	T-DXd (N=92)	3 (3.3)	NE (NE, NE)	NE (NE, NE)	0.033 (-0.004, 0.069)	NE (NE, NE)	
	T-DM1 (N=104)	0				0.1185	
Moderate Impairment	T-DXd (N=30)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=22)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	69 (53.1)	2.64 (1.59, 4.39)	1.77 (1.30, 2.41)	0.231 (0.114, 0.347)	1.82 (1.22, 2.70)	0.1150
	T-DM1 (N=130)	39 (30.0)				0.0029	
Mild Impairment	T-DXd (N=92)	38 (41.3)	1.91 (1.05, 3.48)	1.53 (1.03, 2.29)	0.144 (0.012, 0.276)	1.59 (0.98, 2.60)	
	T-DM1 (N=104)	28 (26.9)				0.0622	
Moderate Impairment	T-DXd (N=30)	13 (43.3)	0.76 (0.25, 2.31)	0.87 (0.48, 1.56)	-0.067 (-0.341, 0.207)	0.62 (0.28, 1.40)	
	T-DM1 (N=22)	11 (50.0)				0.2499	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Decreased appetite							
Within Normal Range	T-DXd (N=130)	45 (34.6)	2.60 (1.45, 4.66)	2.05 (1.31, 3.20)	0.177 (0.073, 0.281)	2.03 (1.22, 3.40)	0.1523
	T-DM1 (N=130)	22 (16.9)				0.0064	
Mild Impairment	T-DXd (N=92)	24 (26.1)	2.27 (1.09, 4.71)	1.94 (1.07, 3.52)	0.126 (0.015, 0.237)	1.93 (1.00, 3.74)	
	T-DM1 (N=104)	14 (13.5)				0.0473	
Moderate Impairment	T-DXd (N=30)	6 (20.0)	0.67 (0.18, 2.44)	0.73 (0.27, 1.97)	-0.073 (-0.308, 0.162)	0.53 (0.17, 1.67)	
	T-DM1 (N=22)	6 (27.3)				0.2741	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
Within Normal Range	T-DXd (N=130)	4 (3.1)	NE (NE, NE)	NE (NE, NE)	0.031 (0.001, 0.060)	NE (NE, NE)	1.0000
	T-DM1 (N=130)	0				0.0530	
Mild Impairment	T-DXd (N=92)	5 (5.4)	NE (NE, NE)	NE (NE, NE)	0.054 (0.008, 0.101)	NE (NE, NE)	
	T-DM1 (N=104)	0				0.0167	
Moderate Impairment	T-DXd (N=30)	2 (6.7)	NE (NE, NE)	NE (NE, NE)	0.067 (-0.023, 0.156)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.2219	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	58 (44.6)	1.06 (0.65, 1.74)	1.04 (0.79, 1.36)	0.015 (-0.105, 0.136)	0.65 (0.44, 0.95)	0.0490
	T-DM1 (N=130)	56 (43.1)				0.0243	
Mild Impairment	T-DXd (N=92)	42 (45.7)	1.59 (0.89, 2.82)	1.32 (0.93, 1.86)	0.110 (-0.026, 0.247)	1.21 (0.77, 1.88)	
	T-DM1 (N=104)	36 (34.6)				0.4073	
Moderate Impairment	T-DXd (N=30)	13 (43.3)	2.60 (0.76, 8.91)	1.91 (0.80, 4.56)	0.206 (-0.043, 0.455)	1.73 (0.62, 4.87)	
	T-DM1 (N=22)	5 (22.7)				0.2904	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
Within Normal Range	T-DXd (N=130)	13 (10.0)	0.79 (0.36, 1.72)	0.81 (0.41, 1.62)	-0.023 (-0.100, 0.053)	0.46 (0.21, 1.00)	0.9958
	T-DM1 (N=130)	16 (12.3)				0.0441	
Mild Impairment	T-DXd (N=92)	5 (5.4)	0.61 (0.20, 1.88)	0.63 (0.22, 1.81)	-0.032 (-0.103, 0.039)	0.52 (0.17, 1.56)	
	T-DM1 (N=104)	9 (8.7)				0.2356	
Moderate Impairment	T-DXd (N=30)	1 (3.3)	NE (NE, NE)	NE (NE, NE)	0.033 (-0.031, 0.098)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.3918	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
Within Normal Range	T-DXd (N=130)	63 (48.5)	1.97 (1.19, 3.26)	1.50 (1.11, 2.04)	0.162 (0.044, 0.279)	1.10 (0.74, 1.64)	0.9003
	T-DM1 (N=130)	42 (32.3)				0.6403	
Mild Impairment	T-DXd (N=92)	36 (39.1)	1.38 (0.77, 2.49)	1.23 (0.84, 1.80)	0.074 (-0.060, 0.208)	0.98 (0.61, 1.58)	
	T-DM1 (N=104)	33 (31.7)				0.9406	
Moderate Impairment	T-DXd (N=30)	11 (36.7)	1.24 (0.39, 3.98)	1.15 (0.53, 2.49)	0.048 (-0.212, 0.309)	0.91 (0.35, 2.37)	
	T-DM1 (N=22)	7 (31.8)				0.8515	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	55 (42.3)	1.84 (1.10, 3.09)	1.49 (1.06, 2.09)	0.138 (0.023, 0.253)	1.02 (0.67, 1.56)	0.0310
	T-DM1 (N=130)	37 (28.5)				0.9186	
Mild Impairment	T-DXd (N=92)	32 (34.8)	1.01 (0.56, 1.82)	1.00 (0.68, 1.48)	0.002 (-0.132, 0.135)	0.68 (0.42, 1.11)	
	T-DM1 (N=104)	36 (34.6)				0.1249	
Moderate Impairment	T-DXd (N=30)	20 (66.7)	9.00 (2.40, 33.79)	3.67 (1.46, 9.22)	0.485 (0.252, 0.718)	2.92 (1.00, 8.57)	
	T-DM1 (N=22)	4 (18.2)				0.0410	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Epistaxis							
Within Normal Range	T-DXd (N=130)	15 (11.5)	0.76 (0.37, 1.57)	0.79 (0.42, 1.49)	-0.031 (-0.113, 0.051)	0.47 (0.23, 0.94)	0.8057
	T-DM1 (N=130)	19 (14.6)				0.0284	
Mild Impairment	T-DXd (N=92)	10 (10.9)	0.55 (0.24, 1.24)	0.59 (0.29, 1.21)	-0.074 (-0.172, 0.024)	0.35 (0.16, 0.77)	
	T-DM1 (N=104)	19 (18.3)				0.0065	
Moderate Impairment	T-DXd (N=30)	4 (13.3)	0.97 (0.19, 4.87)	0.98 (0.24, 3.93)	-0.003 (-0.191, 0.185)	0.53 (0.11, 2.43)	
	T-DM1 (N=22)	3 (13.6)				0.4040	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
Within Normal Range	T-DXd (N=130)	7 (5.4)	NE (NE, NE)	NE (NE, NE)	0.054 (0.015, 0.093)	NE (NE, NE)	0.9999
	T-DM1 (N=130)	0				0.0409	
Mild Impairment	T-DXd (N=92)	6 (6.5)	7.19 (0.85, 60.85)	6.78 (0.83, 55.30)	0.056 (0.002, 0.109)	4.22 (0.51, 35.24)	
	T-DM1 (N=104)	1 (1.0)				0.1477	
Moderate Impairment	T-DXd (N=30)	5 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (0.033, 0.300)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.1124	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	57 (43.8)	1.82 (1.09, 3.04)	1.46 (1.05, 2.03)	0.138 (0.022, 0.255)	1.05 (0.69, 1.59)	0.4233
	T-DM1 (N=130)	39 (30.0)				0.8211	
Mild Impairment	T-DXd (N=92)	36 (39.1)	1.83 (1.00, 3.36)	1.51 (1.00, 2.28)	0.132 (0.001, 0.262)	1.42 (0.86, 2.35)	
	T-DM1 (N=104)	27 (26.0)				0.1649	
Moderate Impairment	T-DXd (N=30)	8 (26.7)	0.78 (0.23, 2.61)	0.84 (0.36, 1.97)	-0.052 (-0.302, 0.199)	0.75 (0.27, 2.08)	
	T-DM1 (N=22)	7 (31.8)				0.5747	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
Within Normal Range	T-DXd (N=130)	48 (36.9)	3.04 (1.69, 5.47)	2.29 (1.46, 3.59)	0.208 (0.103, 0.312)	1.73 (1.03, 2.91)	0.8563
	T-DM1 (N=130)	21 (16.2)				0.0371	
Mild Impairment	T-DXd (N=92)	26 (28.3)	1.88 (0.95, 3.72)	1.63 (0.96, 2.78)	0.110 (-0.008, 0.227)	1.53 (0.84, 2.79)	
	T-DM1 (N=104)	18 (17.3)				0.1670	
Moderate Impairment	T-DXd (N=30)	7 (23.3)	1.93 (0.44, 8.49)	1.71 (0.50, 5.89)	0.097 (-0.112, 0.305)	1.71 (0.44, 6.64)	
	T-DM1 (N=22)	3 (13.6)				0.4328	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Neutropenia							
Within Normal Range	T-DXd (N=130)	18 (13.8)	4.02 (1.44, 11.18)	3.60 (1.38, 9.41)	0.100 (0.032, 0.168)	2.09 (0.76, 5.72)	0.2081
	T-DM1 (N=130)	5 (3.8)				0.1437	
Mild Impairment	T-DXd (N=92)	18 (19.6)	25.05 (3.27, 191.83)	20.35 (2.77, 149.46)	0.186 (0.103, 0.269)	18.74 (2.50, 140.70)	
	T-DM1 (N=104)	1 (1.0)				<.0001	
Moderate Impairment	T-DXd (N=30)	4 (13.3)	3.23 (0.34, 31.12)	2.93 (0.35, 24.47)	0.088 (-0.062, 0.237)	2.45 (0.27, 22.16)	
	T-DM1 (N=22)	1 (4.5)				0.4086	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
Within Normal Range	T-DXd (N=130)	8 (6.2)	0.38 (0.16, 0.91)	0.42 (0.19, 0.93)	-0.085 (-0.158, -0.011)	0.28 (0.12, 0.65)	0.7401
	T-DM1 (N=130)	19 (14.6)				0.0018	
Mild Impairment	T-DXd (N=92)	4 (4.3)	0.55 (0.16, 1.87)	0.57 (0.18, 1.82)	-0.033 (-0.099, 0.033)	0.48 (0.14, 1.61)	
	T-DM1 (N=104)	8 (7.7)				0.2224	
Moderate Impairment	T-DXd (N=30)	1 (3.3)	0.22 (0.02, 2.26)	0.24 (0.03, 2.20)	-0.103 (-0.260, 0.054)	0.17 (0.02, 1.74)	
	T-DM1 (N=22)	3 (13.6)				0.0975	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Musculoskeletal and connective tissue disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	52 (40.0)	1.14 (0.69, 1.88)	1.08 (0.80, 1.47)	0.031 (-0.087, 0.149)	0.76 (0.51, 1.14)	0.8281
	T-DM1 (N=130)	48 (36.9)				0.1856	
Mild Impairment	T-DXd (N=92)	29 (31.5)	1.14 (0.62, 2.09)	1.09 (0.71, 1.67)	0.027 (-0.102, 0.156)	0.78 (0.47, 1.31)	
	T-DM1 (N=104)	30 (28.8)				0.3445	
Moderate Impairment	T-DXd (N=30)	9 (30.0)	1.14 (0.34, 3.87)	1.10 (0.46, 2.64)	0.027 (-0.221, 0.275)	1.02 (0.35, 2.92)	
	T-DM1 (N=22)	6 (27.3)				0.9744	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	20 (15.4)	2.77 (1.17, 6.55)	2.50 (1.14, 5.47)	0.092 (0.018, 0.167)	1.55 (0.66, 3.62)	0.6203
	T-DM1 (N=130)	8 (6.2)				0.3076	
Mild Impairment	T-DXd (N=92)	17 (18.5)	2.13 (0.92, 4.93)	1.92 (0.93, 3.98)	0.089 (-0.009, 0.186)	1.56 (0.71, 3.42)	
	T-DM1 (N=104)	10 (9.6)				0.2614	
Moderate Impairment	T-DXd (N=30)	7 (23.3)	6.39 (0.72, 56.38)	5.13 (0.68, 38.77)	0.188 (0.013, 0.362)	5.40 (0.66, 43.90)	
	T-DM1 (N=22)	1 (4.5)				0.0769	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Eye disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	24 (18.5)	1.74 (0.86, 3.49)	1.60 (0.88, 2.91)	0.069 (-0.017, 0.156)	0.96 (0.49, 1.86)	0.8580
	T-DM1 (N=130)	15 (11.5)				0.9006	
Mild Impairment	T-DXd (N=92)	12 (13.0)	1.15 (0.49, 2.70)	1.13 (0.53, 2.39)	0.015 (-0.077, 0.107)	0.81 (0.36, 1.81)	
	T-DM1 (N=104)	12 (11.5)				0.5986	
Moderate Impairment	T-DXd (N=30)	4 (13.3)	0.97 (0.19, 4.87)	0.98 (0.24, 3.93)	-0.003 (-0.191, 0.185)	0.68 (0.15, 3.05)	
	T-DM1 (N=22)	3 (13.6)				0.6090	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	24 (18.5)	1.05 (0.56, 1.98)	1.04 (0.62, 1.75)	0.008 (-0.086, 0.101)	0.66 (0.37, 1.20)	0.9891
	T-DM1 (N=130)	23 (17.7)				0.1698	
Mild Impairment	T-DXd (N=92)	10 (10.9)	0.93 (0.38, 2.28)	0.94 (0.43, 2.08)	-0.007 (-0.095, 0.082)	0.67 (0.29, 1.57)	
	T-DM1 (N=104)	12 (11.5)				0.3552	
Moderate Impairment	T-DXd (N=30)	3 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.007, 0.207)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.2190	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Insomnia							
Within Normal Range	T-DXd (N=130)	12 (9.2)	0.68 (0.31, 1.48)	0.71 (0.35, 1.42)	-0.038 (-0.115, 0.038)	0.46 (0.21, 0.97)	0.5198
	T-DM1 (N=130)	17 (13.1)				0.0380	
Mild Impairment	T-DXd (N=92)	1 (1.1)	0.15 (0.02, 1.26)	0.16 (0.02, 1.29)	-0.056 (-0.109, -0.004)	0.12 (0.01, 0.96)	
	T-DM1 (N=104)	7 (6.7)				0.0170	
Moderate Impairment	T-DXd (N=30)	1 (3.3)	NE (NE, NE)	NE (NE, NE)	0.033 (-0.031, 0.098)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.4872	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Within Normal Range	T-DXd (N=130)	21 (16.2)	1.73 (0.83, 3.63)	1.62 (0.85, 3.09)	0.062 (-0.020, 0.143)	1.01 (0.49, 2.06)	0.6495
	T-DM1 (N=130)	13 (10.0)				0.9857	
Mild Impairment	T-DXd (N=92)	7 (7.6)	0.87 (0.31, 2.44)	0.88 (0.34, 2.27)	-0.010 (-0.087, 0.066)	0.59 (0.22, 1.60)	
	T-DM1 (N=104)	9 (8.7)				0.2942	
Moderate Impairment	T-DXd (N=30)	4 (13.3)	0.69 (0.15, 3.14)	0.73 (0.21, 2.62)	-0.048 (-0.250, 0.153)	0.59 (0.14, 2.45)	
	T-DM1 (N=22)	4 (18.2)				0.4610	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Cardiac disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	16 (12.3)	8.98 (2.02, 39.90)	8.00 (1.88, 34.10)	0.108 (0.047, 0.168)	5.53 (1.26, 24.35)	0.0131
	T-DM1 (N=130)	2 (1.5)				0.0113	
Mild Impairment	T-DXd (N=92)	3 (3.3)	0.36 (0.09, 1.36)	0.38 (0.11, 1.35)	-0.054 (-0.119, 0.011)	0.26 (0.07, 0.96)	
	T-DM1 (N=104)	9 (8.7)				0.0306	
Moderate Impairment	T-DXd (N=30)	2 (6.7)	NE (NE, NE)	NE (NE, NE)	0.067 (-0.023, 0.156)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.3670	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	9 (6.9)	3.15 (0.83, 11.91)	3.00 (0.83, 10.83)	0.046 (-0.005, 0.097)	2.14 (0.57, 8.05)	0.8265
	T-DM1 (N=130)	3 (2.3)				0.2479	
Mild Impairment	T-DXd (N=92)	8 (8.7)	1.56 (0.52, 4.66)	1.51 (0.54, 4.18)	0.029 (-0.044, 0.102)	1.10 (0.38, 3.19)	
	T-DM1 (N=104)	6 (5.8)				0.8637	
Moderate Impairment	T-DXd (N=30)	2 (6.7)	NE (NE, NE)	NE (NE, NE)	0.067 (-0.023, 0.156)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.3173	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Reproductive system and breast disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	15 (11.5)	1.17 (0.53, 2.58)	1.15 (0.57, 2.33)	0.015 (-0.060, 0.091)	0.68 (0.32, 1.47)	0.6485
	T-DM1 (N=130)	13 (10.0)				0.3258	
Mild Impairment	T-DXd (N=92)	3 (3.3)	1.72 (0.28, 10.52)	1.70 (0.29, 9.93)	0.013 (-0.031, 0.058)	1.27 (0.21, 7.76)	
	T-DM1 (N=104)	2 (1.9)				0.7927	
Moderate Impairment	T-DXd (N=30)	3 (10.0)	2.33 (0.23, 24.08)	2.20 (0.24, 19.76)	0.055 (-0.084, 0.193)	1.81 (0.19, 17.59)	
	T-DM1 (N=22)	1 (4.5)				0.6021	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	10 (7.7)	0.75 (0.32, 1.78)	0.77 (0.35, 1.69)	-0.023 (-0.092, 0.046)	0.63 (0.27, 1.44)	0.8534
	T-DM1 (N=130)	13 (10.0)				0.2734	
Mild Impairment	T-DXd (N=92)	8 (8.7)	0.73 (0.28, 1.87)	0.75 (0.32, 1.76)	-0.028 (-0.113, 0.056)	0.62 (0.25, 1.53)	
	T-DM1 (N=104)	12 (11.5)				0.2985	
Moderate Impairment	T-DXd (N=30)	2 (6.7)	0.45 (0.07, 2.97)	0.49 (0.09, 2.68)	-0.070 (-0.239, 0.099)	0.28 (0.04, 1.76)	
	T-DM1 (N=22)	3 (13.6)				0.1505	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Renal and urinary disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	8 (6.2)	2.07 (0.61, 7.04)	2.00 (0.62, 6.48)	0.031 (-0.020, 0.082)	1.54 (0.46, 5.17)	0.4596
	T-DM1 (N=130)	4 (3.1)				0.4827	
Mild Impairment	T-DXd (N=92)	5 (5.4)	1.44 (0.37, 5.52)	1.41 (0.39, 5.11)	0.016 (-0.043, 0.075)	0.93 (0.25, 3.48)	
	T-DM1 (N=104)	4 (3.8)				0.9095	
Moderate Impairment	T-DXd (N=30)	2 (6.7)	0.45 (0.07, 2.97)	0.49 (0.09, 2.68)	-0.070 (-0.239, 0.099)	0.37 (0.06, 2.25)	
	T-DM1 (N=22)	3 (13.6)				0.2640	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	192 (92.3)	8.19 (4.59, 14.61)	1.55 (1.38, 1.75)	0.329 (0.253, 0.404)	2.78 (2.21, 3.50)	0.4407
	T-DM1 (N=212)	126 (59.4)				<.0001	
Mild Impairment	T-DXd (N=49)	45 (91.8)	9.95 (3.10, 31.95)	1.73 (1.31, 2.28)	0.388 (0.228, 0.547)	3.31 (2.02, 5.43)	
	T-DM1 (N=49)	26 (53.1)				<.0001	
Nausea							
Within Normal Range	T-DXd (N=208)	160 (76.9)	7.71 (4.98, 11.92)	2.55 (2.05, 3.17)	0.467 (0.383, 0.552)	3.80 (2.84, 5.09)	0.8278
	T-DM1 (N=212)	64 (30.2)				<.0001	
Mild Impairment	T-DXd (N=49)	35 (71.4)	5.67 (2.38, 13.50)	2.33 (1.48, 3.69)	0.408 (0.227, 0.589)	3.29 (1.79, 6.05)	
	T-DM1 (N=49)	15 (30.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Within Normal Range	T-DXd (N=208)	103 (49.5)	9.42 (5.52, 16.08)	5.25 (3.38, 8.14)	0.401 (0.322, 0.479)	5.90 (3.65, 9.53)	0.4563
	T-DM1 (N=212)	20 (9.4)				<.0001	
Mild Impairment	T-DXd (N=49)	23 (46.9)	6.34 (2.28, 17.61)	3.83 (1.71, 8.59)	0.347 (0.180, 0.514)	4.10 (1.67, 10.10)	
	T-DM1 (N=49)	6 (12.2)				0.0009	
Constipation							
Within Normal Range	T-DXd (N=208)	77 (37.0)	2.38 (1.53, 3.69)	1.87 (1.35, 2.58)	0.172 (0.087, 0.257)	1.69 (1.16, 2.47)	0.2181
	T-DM1 (N=212)	42 (19.8)				0.0057	
Mild Impairment	T-DXd (N=49)	11 (22.4)	1.29 (0.48, 3.45)	1.22 (0.56, 2.68)	0.041 (-0.119, 0.200)	0.92 (0.38, 2.24)	
	T-DM1 (N=49)	9 (18.4)				0.8530	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Within Normal Range	T-DXd (N=208)	62 (29.8)	6.50 (3.45, 12.27)	4.86 (2.76, 8.57)	0.237 (0.167, 0.307)	4.93 (2.71, 8.98)	0.2490
	T-DM1 (N=212)	13 (6.1)				<.0001	
Mild Impairment	T-DXd (N=49)	13 (26.5)	3.18 (1.04, 9.75)	2.60 (1.00, 6.74)	0.163 (0.013, 0.313)	2.34 (0.83, 6.61)	
	T-DM1 (N=49)	5 (10.2)				0.1001	
Stomatitis							
Within Normal Range	T-DXd (N=208)	33 (15.9)	4.25 (1.98, 9.13)	3.74 (1.83, 7.62)	0.116 (0.060, 0.173)	3.06 (1.46, 6.43)	0.6199
	T-DM1 (N=212)	9 (4.2)				0.0019	
Mild Impairment	T-DXd (N=49)	7 (14.3)	8.00 (0.95, 67.70)	7.00 (0.89, 54.79)	0.122 (0.017, 0.228)	6.15 (0.75, 50.19)	
	T-DM1 (N=49)	1 (2.0)				0.0528	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Within Normal Range	T-DXd (N=208)	24 (11.5)	6.78 (2.31, 19.91)	6.12 (2.16, 17.32)	0.097 (0.049, 0.144)	4.81 (1.66, 13.92)	0.8118
	T-DM1 (N=212)	4 (1.9)				0.0014	
Mild Impairment	T-DXd (N=49)	5 (10.2)	5.45 (0.61, 48.53)	5.00 (0.61, 41.25)	0.082 (-0.012, 0.175)	3.92 (0.45, 34.11)	
	T-DM1 (N=49)	1 (2.0)				0.1818	
Dry mouth							
Within Normal Range	T-DXd (N=208)	6 (2.9)	0.29 (0.11, 0.73)	0.31 (0.13, 0.75)	-0.065 (-0.111, -0.020)	0.25 (0.10, 0.62)	0.8710
	T-DM1 (N=212)	20 (9.4)				0.0014	
Mild Impairment	T-DXd (N=49)	2 (4.1)	0.37 (0.07, 2.03)	0.40 (0.08, 1.96)	-0.061 (-0.162, 0.040)	0.22 (0.04, 1.18)	
	T-DM1 (N=49)	5 (10.2)				0.0562	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Within Normal Range	T-DXd (N=208)	122 (58.7)	0.67 (0.45, 1.00)	0.86 (0.75, 1.00)	-0.093 (-0.185, -0.001)	0.56 (0.44, 0.72)	0.2066
	T-DM1 (N=212)	144 (67.9)				<.0001	
Mild Impairment	T-DXd (N=49)	40 (81.6)	1.78 (0.69, 4.61)	1.14 (0.92, 1.43)	0.102 (-0.065, 0.269)	0.76 (0.47, 1.22)	
	T-DM1 (N=49)	35 (71.4)				0.3159	
Neutrophil count decreased							
Within Normal Range	T-DXd (N=208)	62 (29.8)	3.49 (2.06, 5.90)	2.75 (1.77, 4.26)	0.190 (0.115, 0.265)	2.57 (1.59, 4.16)	0.3112
	T-DM1 (N=212)	23 (10.8)				<.0001	
Mild Impairment	T-DXd (N=49)	13 (26.5)	8.49 (1.80, 40.01)	6.50 (1.55, 27.30)	0.224 (0.089, 0.360)	6.02 (1.35, 26.85)	
	T-DM1 (N=49)	2 (4.1)				0.0076	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
Within Normal Range	T-DXd (N=208)	47 (22.6)	0.43 (0.28, 0.65)	0.56 (0.41, 0.75)	-0.180 (-0.267, -0.093)	0.39 (0.27, 0.55)	0.1165
	T-DM1 (N=212)	86 (40.6)				<.0001	
Mild Impairment	T-DXd (N=49)	19 (38.8)	1.00 (0.44, 2.25)	1.00 (0.61, 1.64)	0.000 (-0.193, 0.193)	0.67 (0.35, 1.29)	
	T-DM1 (N=49)	19 (38.8)				0.2467	
White blood cell count decreased							
Within Normal Range	T-DXd (N=208)	46 (22.1)	4.35 (2.27, 8.32)	3.61 (2.01, 6.47)	0.160 (0.095, 0.225)	3.11 (1.68, 5.78)	0.2931
	T-DM1 (N=212)	13 (6.1)				0.0001	
Mild Impairment	T-DXd (N=49)	12 (24.5)	15.57 (1.94, 125.18)	12.00 (1.62, 88.77)	0.224 (0.098, 0.351)	11.36 (1.47, 87.62)	
	T-DM1 (N=49)	1 (2.0)				0.0032	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
Within Normal Range	T-DXd (N=208)	42 (20.2)	0.57 (0.37, 0.89)	0.66 (0.47, 0.92)	-0.105 (-0.187, -0.022)	0.51 (0.34, 0.75)	0.1988
	T-DM1 (N=212)	65 (30.7)				0.0006	
Mild Impairment	T-DXd (N=49)	14 (28.6)	1.23 (0.50, 3.03)	1.17 (0.60, 2.26)	0.041 (-0.134, 0.215)	0.94 (0.43, 2.04)	
	T-DM1 (N=49)	12 (24.5)				0.8908	
Platelet count decreased							
Within Normal Range	T-DXd (N=208)	38 (18.3)	0.28 (0.18, 0.43)	0.41 (0.29, 0.56)	-0.265 (-0.351, -0.180)	0.27 (0.18, 0.39)	0.0121
	T-DM1 (N=212)	95 (44.8)				<.0001	
Mild Impairment	T-DXd (N=49)	16 (32.7)	0.91 (0.39, 2.11)	0.94 (0.54, 1.64)	-0.020 (-0.207, 0.167)	0.66 (0.33, 1.32)	
	T-DM1 (N=49)	17 (34.7)				0.2392	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
Within Normal Range	T-DXd (N=208)	31 (14.9)	2.48 (1.28, 4.81)	2.26 (1.24, 4.12)	0.083 (0.024, 0.142)	1.74 (0.92, 3.28)	0.2821
	T-DM1 (N=212)	14 (6.6)				0.0842	
Mild Impairment	T-DXd (N=49)	12 (24.5)	7.62 (1.61, 36.19)	6.00 (1.42, 25.42)	0.204 (0.072, 0.337)	4.58 (1.02, 20.64)	
	T-DM1 (N=49)	2 (4.1)				0.0300	
Blood lactate dehydrogenase increased							
Within Normal Range	T-DXd (N=208)	7 (3.4)	0.29 (0.12, 0.68)	0.31 (0.14, 0.71)	-0.075 (-0.123, -0.026)	0.23 (0.10, 0.55)	0.1550
	T-DM1 (N=212)	23 (10.8)				0.0003	
Mild Impairment	T-DXd (N=49)	10 (20.4)	0.79 (0.31, 2.05)	0.83 (0.40, 1.75)	-0.041 (-0.206, 0.124)	0.56 (0.24, 1.33)	
	T-DM1 (N=49)	12 (24.5)				0.1894	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
Within Normal Range	T-DXd (N=208)	9 (4.3)	3.15 (0.84, 11.80)	3.06 (0.84, 11.14)	0.029 (-0.003, 0.061)	2.27 (0.61, 8.47)	0.9911
	T-DM1 (N=212)	3 (1.4)				0.2093	
Mild Impairment	T-DXd (N=49)	5 (10.2)	NE (NE, NE)	NE (NE, NE)	0.102 (0.017, 0.187)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.0676	
General disorders and administration site conditions							
Any PT							
Within Normal Range	T-DXd (N=208)	133 (63.9)	1.77 (1.20, 2.62)	1.28 (1.08, 1.51)	0.139 (0.046, 0.233)	1.15 (0.89, 1.49)	0.0640
	T-DM1 (N=212)	106 (50.0)				0.2764	
Mild Impairment	T-DXd (N=49)	26 (53.1)	0.92 (0.42, 2.04)	0.96 (0.67, 1.39)	-0.020 (-0.218, 0.177)	0.60 (0.34, 1.05)	
	T-DM1 (N=49)	27 (55.1)				0.0700	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Within Normal Range	T-DXd (N=208)	24 (11.5)	2.94 (1.33, 6.49)	2.72 (1.29, 5.71)	0.073 (0.022, 0.124)	2.42 (1.12, 5.23)	0.6032
	T-DM1 (N=212)	9 (4.2)				0.0207	
Mild Impairment	T-DXd (N=49)	5 (10.2)	5.45 (0.61, 48.53)	5.00 (0.61, 41.25)	0.082 (-0.012, 0.175)	4.42 (0.51, 37.98)	
	T-DM1 (N=49)	1 (2.0)				0.1395	
Pyrexia							
Within Normal Range	T-DXd (N=208)	19 (9.1)	0.66 (0.36, 1.22)	0.69 (0.40, 1.20)	-0.041 (-0.101, 0.019)	0.45 (0.25, 0.81)	0.8497
	T-DM1 (N=212)	28 (13.2)				0.0064	
Mild Impairment	T-DXd (N=49)	8 (16.3)	0.67 (0.25, 1.85)	0.73 (0.32, 1.65)	-0.061 (-0.217, 0.095)	0.42 (0.16, 1.07)	
	T-DM1 (N=49)	11 (22.4)				0.0634	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	109 (52.4)	2.66 (1.78, 3.98)	1.79 (1.40, 2.29)	0.232 (0.140, 0.323)	1.86 (1.36, 2.54)	0.4481
	T-DM1 (N=212)	62 (29.2)				<.0001	
Mild Impairment	T-DXd (N=49)	30 (61.2)	4.37 (1.86, 10.29)	2.31 (1.38, 3.87)	0.347 (0.163, 0.531)	2.40 (1.25, 4.61)	
	T-DM1 (N=49)	13 (26.5)				0.0067	
Alopecia							
Within Normal Range	T-DXd (N=208)	75 (36.1)	14.38 (6.72, 30.77)	9.56 (4.73, 19.31)	0.323 (0.253, 0.393)	10.71 (5.16, 22.22)	0.9846
	T-DM1 (N=212)	8 (3.8)				<.0001	
Mild Impairment	T-DXd (N=49)	20 (40.8)	NE (NE, NE)	NE (NE, NE)	0.408 (0.271, 0.546)	NE (NE, NE)	
	T-DM1 (N=49)	0				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
Within Normal Range	T-DXd (N=208)	13 (6.3)	0.68 (0.33, 1.41)	0.70 (0.35, 1.38)	-0.027 (-0.078, 0.023)	0.49 (0.24, 1.01)	0.7448
	T-DM1 (N=212)	19 (9.0)				0.0475	
Mild Impairment	T-DXd (N=49)	3 (6.1)	0.57 (0.13, 2.55)	0.60 (0.15, 2.37)	-0.041 (-0.149, 0.067)	0.42 (0.10, 1.78)	
	T-DM1 (N=49)	5 (10.2)				0.2229	
Skin hyperpigmentation							
Within Normal Range	T-DXd (N=208)	8 (3.8)	NE (NE, NE)	NE (NE, NE)	0.038 (0.012, 0.065)	NE (NE, NE)	0.9999
	T-DM1 (N=212)	0				0.0102	
Mild Impairment	T-DXd (N=49)	3 (6.1)	NE (NE, NE)	NE (NE, NE)	0.061 (-0.006, 0.128)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.1574	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	99 (47.6)	2.35 (1.57, 3.53)	1.71 (1.32, 2.22)	0.198 (0.107, 0.288)	1.79 (1.29, 2.47)	0.0901
	T-DM1 (N=212)	59 (27.8)				0.0004	
Mild Impairment	T-DXd (N=49)	23 (46.9)	1.18 (0.53, 2.62)	1.10 (0.71, 1.70)	0.041 (-0.156, 0.238)	0.87 (0.48, 1.60)	
	T-DM1 (N=49)	21 (42.9)				0.6578	
Decreased appetite							
Within Normal Range	T-DXd (N=208)	63 (30.3)	2.36 (1.47, 3.79)	1.95 (1.34, 2.83)	0.147 (0.068, 0.226)	2.00 (1.31, 3.05)	0.1088
	T-DM1 (N=212)	33 (15.6)				0.0011	
Mild Impairment	T-DXd (N=49)	12 (24.5)	1.12 (0.44, 2.85)	1.09 (0.53, 2.23)	0.020 (-0.147, 0.188)	0.75 (0.33, 1.74)	
	T-DM1 (N=49)	11 (22.4)				0.5025	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
Within Normal Range	T-DXd (N=208)	10 (4.8)	NE (NE, NE)	NE (NE, NE)	0.048 (0.019, 0.077)	NE (NE, NE)	0.9998
	T-DM1 (N=212)	0				0.0014	
Mild Impairment	T-DXd (N=49)	1 (2.0)	NE (NE, NE)	NE (NE, NE)	0.020 (-0.019, 0.060)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.3173	
Nervous system disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	97 (46.6)	1.50 (1.02, 2.22)	1.27 (1.01, 1.59)	0.098 (0.005, 0.192)	1.02 (0.76, 1.38)	0.1344
	T-DM1 (N=212)	78 (36.8)				0.8914	
Mild Impairment	T-DXd (N=49)	19 (38.8)	0.92 (0.41, 2.06)	0.95 (0.58, 1.55)	-0.020 (-0.214, 0.173)	0.61 (0.32, 1.16)	
	T-DM1 (N=49)	20 (40.8)				0.1321	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
Within Normal Range	T-DXd (N=208)	16 (7.7)	0.76 (0.38, 1.50)	0.78 (0.42, 1.45)	-0.022 (-0.076, 0.032)	0.54 (0.28, 1.05)	0.8459
	T-DM1 (N=212)	21 (9.9)				0.0650	
Mild Impairment	T-DXd (N=49)	3 (6.1)	0.73 (0.16, 3.46)	0.75 (0.18, 3.18)	-0.020 (-0.122, 0.081)	0.53 (0.12, 2.40)	
	T-DM1 (N=49)	4 (8.2)				0.4012	
Infections and infestations							
Any PT							
Within Normal Range	T-DXd (N=208)	89 (42.8)	1.58 (1.06, 2.36)	1.33 (1.04, 1.71)	0.107 (0.015, 0.199)	1.03 (0.75, 1.42)	0.7982
	T-DM1 (N=212)	68 (32.1)				0.8586	
Mild Impairment	T-DXd (N=49)	23 (46.9)	1.67 (0.74, 3.75)	1.35 (0.83, 2.20)	0.122 (-0.071, 0.316)	0.95 (0.50, 1.80)	
	T-DM1 (N=49)	17 (34.7)				0.8734	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	85 (40.9)	1.56 (1.05, 2.34)	1.33 (1.03, 1.73)	0.102 (0.011, 0.193)	0.95 (0.68, 1.31)	0.9476
	T-DM1 (N=212)	65 (30.7)				0.7431	
Mild Impairment	T-DXd (N=49)	22 (44.9)	2.04 (0.88, 4.71)	1.57 (0.92, 2.70)	0.163 (-0.025, 0.351)	0.90 (0.45, 1.78)	
	T-DM1 (N=49)	14 (28.6)				0.7625	
Epistaxis							
Within Normal Range	T-DXd (N=208)	24 (11.5)	0.68 (0.39, 1.20)	0.72 (0.44, 1.17)	-0.045 (-0.111, 0.021)	0.42 (0.24, 0.72)	0.7061
	T-DM1 (N=212)	34 (16.0)				0.0012	
Mild Impairment	T-DXd (N=49)	5 (10.2)	0.58 (0.18, 1.93)	0.63 (0.22, 1.78)	-0.061 (-0.195, 0.073)	0.33 (0.10, 1.02)	
	T-DM1 (N=49)	8 (16.3)				0.0442	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
Within Normal Range	T-DXd (N=208)	16 (7.7)	17.58 (2.31, 133.84)	16.31 (2.18, 121.86)	0.072 (0.035, 0.110)	10.30 (1.36, 77.97)	0.9925
	T-DM1 (N=212)	1 (0.5)				0.0052	
Mild Impairment	T-DXd (N=49)	2 (4.1)	NE (NE, NE)	NE (NE, NE)	0.041 (-0.015, 0.096)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.3437	
Blood and lymphatic system disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	81 (38.9)	1.73 (1.15, 2.62)	1.45 (1.09, 1.92)	0.121 (0.031, 0.210)	1.21 (0.86, 1.70)	0.5969
	T-DM1 (N=212)	57 (26.9)				0.2666	
Mild Impairment	T-DXd (N=49)	22 (44.9)	1.40 (0.62, 3.15)	1.22 (0.76, 1.98)	0.082 (-0.112, 0.276)	1.01 (0.54, 1.89)	
	T-DM1 (N=49)	18 (36.7)				0.9888	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
Within Normal Range	T-DXd (N=208)	62 (29.8)	2.39 (1.48, 3.86)	1.97 (1.35, 2.89)	0.147 (0.068, 0.226)	1.72 (1.12, 2.65)	0.6650
	T-DM1 (N=212)	32 (15.1)				0.0121	
Mild Impairment	T-DXd (N=49)	21 (42.9)	2.31 (0.98, 5.48)	1.75 (0.97, 3.15)	0.184 (0.000, 0.367)	1.36 (0.66, 2.79)	
	T-DM1 (N=49)	12 (24.5)				0.3989	
Neutropenia							
Within Normal Range	T-DXd (N=208)	33 (15.9)	7.81 (2.98, 20.43)	6.73 (2.68, 16.90)	0.135 (0.081, 0.189)	5.06 (1.96, 13.02)	0.5226
	T-DM1 (N=212)	5 (2.4)				0.0002	
Mild Impairment	T-DXd (N=49)	8 (16.3)	4.59 (0.92, 22.83)	4.00 (0.89, 17.89)	0.122 (0.005, 0.240)	3.31 (0.70, 15.75)	
	T-DM1 (N=49)	2 (4.1)				0.1115	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
Within Normal Range	T-DXd (N=208)	8 (3.8)	0.31 (0.14, 0.71)	0.34 (0.16, 0.74)	-0.075 (-0.125, -0.025)	0.25 (0.11, 0.56)	0.3246
	T-DM1 (N=212)	24 (11.3)				0.0003	
Mild Impairment	T-DXd (N=49)	5 (10.2)	0.68 (0.20, 2.32)	0.71 (0.24, 2.10)	-0.041 (-0.170, 0.089)	0.51 (0.16, 1.65)	
	T-DM1 (N=49)	7 (14.3)				0.2459	
Musculoskeletal and connective tissue disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	78 (37.5)	1.30 (0.87, 1.94)	1.19 (0.91, 1.55)	0.059 (-0.032, 0.150)	0.88 (0.63, 1.23)	0.0731
	T-DM1 (N=212)	67 (31.6)				0.4565	
Mild Impairment	T-DXd (N=49)	16 (32.7)	0.70 (0.31, 1.60)	0.80 (0.47, 1.35)	-0.082 (-0.272, 0.109)	0.56 (0.29, 1.11)	
	T-DM1 (N=49)	20 (40.8)				0.0934	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	39 (18.8)	3.03 (1.61, 5.69)	2.65 (1.51, 4.66)	0.117 (0.053, 0.180)	1.99 (1.09, 3.63)	0.1068
	T-DM1 (N=212)	15 (7.1)				0.0227	
Mild Impairment	T-DXd (N=49)	6 (12.2)	1.00 (0.30, 3.35)	1.00 (0.35, 2.89)	0.000 (-0.130, 0.130)	0.86 (0.27, 2.70)	
	T-DM1 (N=49)	6 (12.2)				0.7949	
Eye disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	35 (16.8)	1.45 (0.84, 2.50)	1.37 (0.86, 2.20)	0.046 (-0.022, 0.113)	0.92 (0.55, 1.55)	0.9652
	T-DM1 (N=212)	26 (12.3)				0.7562	
Mild Impairment	T-DXd (N=49)	6 (12.2)	1.57 (0.41, 5.95)	1.50 (0.45, 4.99)	0.041 (-0.079, 0.160)	0.91 (0.25, 3.24)	
	T-DM1 (N=49)	4 (8.2)				0.8798	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	34 (16.3)	1.23 (0.72, 2.11)	1.19 (0.76, 1.89)	0.027 (-0.042, 0.095)	0.87 (0.53, 1.44)	0.4572
	T-DM1 (N=212)	29 (13.7)				0.5879	
Mild Impairment	T-DXd (N=49)	5 (10.2)	0.81 (0.23, 2.87)	0.83 (0.27, 2.55)	-0.020 (-0.145, 0.105)	0.51 (0.15, 1.69)	
	T-DM1 (N=49)	6 (12.2)				0.2632	
Insomnia							
Within Normal Range	T-DXd (N=208)	12 (5.8)	0.56 (0.27, 1.16)	0.58 (0.29, 1.15)	-0.041 (-0.093, 0.010)	0.43 (0.21, 0.89)	0.6164
	T-DM1 (N=212)	21 (9.9)				0.0193	
Mild Impairment	T-DXd (N=49)	3 (6.1)	1.00 (0.19, 5.22)	1.00 (0.21, 4.71)	0.000 (-0.095, 0.095)	0.60 (0.12, 3.01)	
	T-DM1 (N=49)	3 (6.1)				0.5295	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Within Normal Range	T-DXd (N=208)	28 (13.5)	1.28 (0.71, 2.30)	1.24 (0.74, 2.08)	0.026 (-0.036, 0.089)	0.81 (0.46, 1.42)	0.6229
	T-DM1 (N=212)	23 (10.8)				0.4666	
Mild Impairment	T-DXd (N=49)	4 (8.2)	1.00 (0.24, 4.25)	1.00 (0.26, 3.77)	0.000 (-0.108, 0.108)	0.66 (0.16, 2.73)	
	T-DM1 (N=49)	4 (8.2)				0.5713	
Cardiac disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	16 (7.7)	1.88 (0.81, 4.35)	1.81 (0.82, 4.01)	0.034 (-0.011, 0.080)	1.25 (0.55, 2.87)	0.7954
	T-DM1 (N=212)	9 (4.2)				0.5977	
Mild Impairment	T-DXd (N=49)	5 (10.2)	2.67 (0.49, 14.48)	2.50 (0.51, 12.28)	0.061 (-0.040, 0.162)	1.55 (0.29, 8.15)	
	T-DM1 (N=49)	2 (4.1)				0.6021	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	18 (8.7)	2.77 (1.13, 6.79)	2.62 (1.12, 6.14)	0.054 (0.008, 0.099)	1.81 (0.75, 4.38)	0.5013
	T-DM1 (N=212)	7 (3.3)				0.1809	
Mild Impairment	T-DXd (N=49)	3 (6.1)	1.53 (0.24, 9.60)	1.50 (0.26, 8.59)	0.020 (-0.067, 0.107)	0.99 (0.16, 5.99)	
	T-DM1 (N=49)	2 (4.1)				0.9879	
Reproductive system and breast disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	20 (9.6)	1.50 (0.74, 3.06)	1.46 (0.76, 2.80)	0.030 (-0.022, 0.082)	0.99 (0.50, 1.99)	0.1848
	T-DM1 (N=212)	14 (6.6)				0.9864	
Mild Impairment	T-DXd (N=49)	1 (2.0)	0.32 (0.03, 3.18)	0.33 (0.04, 3.09)	-0.041 (-0.119, 0.037)	0.27 (0.03, 2.67)	
	T-DM1 (N=49)	3 (6.1)				0.2319	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	13 (6.3)	0.68 (0.33, 1.41)	0.70 (0.35, 1.38)	-0.027 (-0.078, 0.023)	0.54 (0.26, 1.10)	0.8094
	T-DM1 (N=212)	19 (9.0)				0.0856	
Mild Impairment	T-DXd (N=49)	7 (14.3)	0.65 (0.23, 1.88)	0.70 (0.29, 1.69)	-0.061 (-0.211, 0.088)	0.44 (0.16, 1.18)	
	T-DM1 (N=49)	10 (20.4)				0.0990	
Renal and urinary disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	12 (5.8)	1.79 (0.69, 4.65)	1.75 (0.70, 4.35)	0.025 (-0.015, 0.064)	1.34 (0.52, 3.43)	0.2378
	T-DM1 (N=212)	7 (3.3)				0.5402	
Mild Impairment	T-DXd (N=49)	3 (6.1)	0.73 (0.16, 3.46)	0.75 (0.18, 3.18)	-0.020 (-0.122, 0.081)	0.40 (0.09, 1.88)	
	T-DM1 (N=49)	4 (8.2)				0.2345	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Yes	T-DXd (N=192)	176 (91.7)	7.63 (4.24, 13.75)	1.55 (1.37, 1.76)	0.326 (0.246, 0.407)	2.68 (2.10, 3.41)	0.3725
	T-DM1 (N=188)	111 (59.0)				<.0001	
No	T-DXd (N=65)	61 (93.8)	11.90 (3.91, 36.20)	1.67 (1.35, 2.07)	0.377 (0.249, 0.505)	3.42 (2.28, 5.14)	
	T-DM1 (N=73)	41 (56.2)				<.0001	
Nausea							
Yes	T-DXd (N=192)	144 (75.0)	7.44 (4.73, 11.73)	2.61 (2.05, 3.32)	0.463 (0.374, 0.552)	3.75 (2.74, 5.14)	0.9824
	T-DM1 (N=188)	54 (28.7)				<.0001	
No	T-DXd (N=65)	51 (78.5)	6.99 (3.26, 15.01)	2.29 (1.63, 3.23)	0.442 (0.294, 0.590)	3.81 (2.35, 6.18)	
	T-DM1 (N=73)	25 (34.2)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Yes	T-DXd (N=192)	100 (52.1)	9.67 (5.57, 16.80)	5.15 (3.29, 8.06)	0.420 (0.337, 0.503)	5.96 (3.65, 9.75)	0.5140
	T-DM1 (N=188)	19 (10.1)				<.0001	
No	T-DXd (N=65)	26 (40.0)	6.29 (2.50, 15.83)	4.17 (1.94, 8.96)	0.304 (0.167, 0.441)	4.15 (1.80, 9.58)	
	T-DM1 (N=73)	7 (9.6)				0.0003	
Constipation							
Yes	T-DXd (N=192)	68 (35.4)	2.78 (1.71, 4.51)	2.15 (1.48, 3.12)	0.189 (0.103, 0.275)	1.92 (1.25, 2.94)	0.0649
	T-DM1 (N=188)	31 (16.5)				0.0024	
No	T-DXd (N=65)	20 (30.8)	1.18 (0.56, 2.46)	1.12 (0.67, 1.89)	0.034 (-0.118, 0.186)	0.94 (0.50, 1.75)	
	T-DM1 (N=73)	20 (27.4)				0.8366	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Yes	T-DXd (N=192)	52 (27.1)	5.98 (3.01, 11.88)	4.63 (2.49, 8.59)	0.212 (0.141, 0.284)	4.46 (2.32, 8.56)	0.8620
	T-DM1 (N=188)	11 (5.9)				<.0001	
No	T-DXd (N=65)	23 (35.4)	5.16 (2.04, 13.09)	3.69 (1.70, 8.03)	0.258 (0.124, 0.392)	4.08 (1.75, 9.53)	
	T-DM1 (N=73)	7 (9.6)				0.0004	
Stomatitis							
Yes	T-DXd (N=192)	26 (13.5)	3.11 (1.42, 6.84)	2.83 (1.36, 5.87)	0.088 (0.030, 0.145)	2.31 (1.08, 4.96)	0.1056
	T-DM1 (N=188)	9 (4.8)				0.0270	
No	T-DXd (N=65)	14 (21.5)	19.76 (2.52, 155.11)	15.72 (2.13, 116.30)	0.202 (0.098, 0.305)	13.52 (1.77, 103.06)	
	T-DM1 (N=73)	1 (1.4)				0.0011	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Yes	T-DXd (N=192)	22 (11.5)	5.95 (2.01, 17.63)	5.39 (1.89, 15.33)	0.093 (0.044, 0.143)	4.03 (1.38, 11.79)	0.7285
	T-DM1 (N=188)	4 (2.1)				0.0060	
No	T-DXd (N=65)	7 (10.8)	8.69 (1.04, 72.64)	7.86 (0.99, 62.21)	0.094 (0.014, 0.174)	5.78 (0.71, 47.34)	
	T-DM1 (N=73)	1 (1.4)				0.0650	
Dry mouth							
Yes	T-DXd (N=192)	7 (3.6)	0.34 (0.14, 0.82)	0.36 (0.16, 0.84)	-0.065 (-0.115, -0.014)	0.28 (0.12, 0.68)	0.6108
	T-DM1 (N=188)	19 (10.1)				0.0027	
No	T-DXd (N=65)	1 (1.5)	0.17 (0.02, 1.49)	0.19 (0.02, 1.51)	-0.067 (-0.137, 0.003)	0.13 (0.02, 1.09)	
	T-DM1 (N=73)	6 (8.2)				0.0270	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Yes	T-DXd (N=192)	128 (66.7)	0.91 (0.60, 1.41)	0.97 (0.85, 1.12)	-0.020 (-0.114, 0.075)	0.68 (0.53, 0.87)	0.0876
	T-DM1 (N=188)	129 (68.6)				0.0064	
No	T-DXd (N=65)	34 (52.3)	0.50 (0.25, 1.01)	0.76 (0.58, 1.01)	-0.162 (-0.323, 0.000)	0.44 (0.28, 0.69)	
	T-DM1 (N=73)	50 (68.5)				0.0004	
Neutrophil count decreased							
Yes	T-DXd (N=192)	59 (30.7)	4.77 (2.62, 8.66)	3.61 (2.16, 6.04)	0.222 (0.146, 0.299)	3.39 (1.95, 5.90)	0.2225
	T-DM1 (N=188)	16 (8.5)				<.0001	
No	T-DXd (N=65)	16 (24.6)	2.32 (0.95, 5.70)	2.00 (0.95, 4.21)	0.123 (-0.006, 0.252)	1.78 (0.78, 4.03)	
	T-DM1 (N=73)	9 (12.3)				0.1628	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
Yes	T-DXd (N=192)	53 (27.6)	0.56 (0.37, 0.86)	0.68 (0.51, 0.91)	-0.128 (-0.223, -0.034)	0.46 (0.32, 0.65)	0.4463
	T-DM1 (N=188)	76 (40.4)				<.0001	
No	T-DXd (N=65)	13 (20.0)	0.38 (0.18, 0.82)	0.50 (0.29, 0.88)	-0.197 (-0.346, -0.049)	0.38 (0.19, 0.73)	
	T-DM1 (N=73)	29 (39.7)				0.0028	
White blood cell count decreased							
Yes	T-DXd (N=192)	48 (25.0)	5.93 (2.90, 12.14)	4.70 (2.45, 9.01)	0.197 (0.128, 0.266)	4.12 (2.08, 8.17)	0.4353
	T-DM1 (N=188)	10 (5.3)				<.0001	
No	T-DXd (N=65)	10 (15.4)	3.14 (0.93, 10.54)	2.81 (0.93, 8.52)	0.099 (-0.003, 0.201)	2.35 (0.73, 7.54)	
	T-DM1 (N=73)	4 (5.5)				0.1380	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
Yes	T-DXd (N=192)	43 (22.4)	0.68 (0.43, 1.08)	0.75 (0.53, 1.06)	-0.074 (-0.162, 0.014)	0.57 (0.38, 0.85)	0.8527
	T-DM1 (N=188)	56 (29.8)				0.0060	
No	T-DXd (N=65)	13 (20.0)	0.62 (0.28, 1.37)	0.70 (0.38, 1.27)	-0.088 (-0.230, 0.055)	0.56 (0.28, 1.13)	
	T-DM1 (N=73)	21 (28.8)				0.1011	
Platelet count decreased							
Yes	T-DXd (N=192)	42 (21.9)	0.36 (0.23, 0.57)	0.50 (0.37, 0.69)	-0.217 (-0.309, -0.126)	0.33 (0.23, 0.49)	0.5804
	T-DM1 (N=188)	82 (43.6)				<.0001	
No	T-DXd (N=65)	12 (18.5)	0.32 (0.15, 0.71)	0.45 (0.25, 0.80)	-0.226 (-0.373, -0.079)	0.30 (0.15, 0.60)	
	T-DM1 (N=73)	30 (41.1)				0.0004	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
Yes	T-DXd (N=192)	36 (18.8)	4.59 (2.14, 9.83)	3.92 (1.94, 7.90)	0.140 (0.077, 0.203)	3.17 (1.52, 6.59)	0.0457
	T-DM1 (N=188)	9 (4.8)				0.0012	
No	T-DXd (N=65)	7 (10.8)	1.14 (0.38, 3.44)	1.12 (0.42, 3.03)	0.012 (-0.089, 0.113)	0.73 (0.25, 2.11)	
	T-DM1 (N=73)	7 (9.6)				0.5619	
Blood lactate dehydrogenase increased							
Yes	T-DXd (N=192)	16 (8.3)	0.62 (0.32, 1.21)	0.65 (0.36, 1.19)	-0.044 (-0.106, 0.017)	0.49 (0.26, 0.93)	0.0859
	T-DM1 (N=188)	24 (12.8)				0.0262	
No	T-DXd (N=65)	1 (1.5)	0.09 (0.01, 0.70)	0.10 (0.01, 0.77)	-0.135 (-0.223, -0.048)	0.08 (0.01, 0.65)	
	T-DM1 (N=73)	11 (15.1)				0.0026	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
Yes	T-DXd (N=192)	13 (6.8)	6.75 (1.50, 30.35)	6.36 (1.46, 27.82)	0.057 (0.019, 0.096)	4.86 (1.09, 21.65)	0.2846
	T-DM1 (N=188)	2 (1.1)				0.0218	
No	T-DXd (N=65)	1 (1.5)	1.13 (0.07, 18.36)	1.12 (0.07, 17.60)	0.002 (-0.038, 0.042)	0.60 (0.04, 9.86)	
	T-DM1 (N=73)	1 (1.4)				0.7200	
General disorders and administration site conditions							
Any PT							
Yes	T-DXd (N=192)	114 (59.4)	1.56 (1.04, 2.34)	1.23 (1.02, 1.48)	0.110 (0.010, 0.209)	1.01 (0.76, 1.33)	0.5785
	T-DM1 (N=188)	91 (48.4)				0.9602	
No	T-DXd (N=65)	45 (69.2)	1.66 (0.82, 3.35)	1.20 (0.93, 1.55)	0.117 (-0.043, 0.276)	1.15 (0.75, 1.75)	
	T-DM1 (N=73)	42 (57.5)				0.5283	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Yes	T-DXd (N=192)	21 (10.9)	3.18 (1.32, 7.66)	2.94 (1.28, 6.75)	0.072 (0.020, 0.124)	2.73 (1.16, 6.45)	0.9913
	T-DM1 (N=188)	7 (3.7)				0.0169	
No	T-DXd (N=65)	8 (12.3)	3.27 (0.83, 12.91)	2.99 (0.83, 10.82)	0.082 (-0.010, 0.174)	2.45 (0.64, 9.34)	
	T-DM1 (N=73)	3 (4.1)				0.1758	
Pyrexia							
Yes	T-DXd (N=192)	23 (12.0)	0.93 (0.50, 1.71)	0.94 (0.55, 1.60)	-0.008 (-0.074, 0.058)	0.60 (0.33, 1.08)	0.1026
	T-DM1 (N=188)	24 (12.8)				0.0886	
No	T-DXd (N=65)	4 (6.2)	0.25 (0.08, 0.81)	0.30 (0.10, 0.86)	-0.144 (-0.254, -0.034)	0.19 (0.06, 0.59)	
	T-DM1 (N=73)	15 (20.5)				0.0014	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Yes	T-DXd (N=192)	108 (56.3)	3.55 (2.31, 5.46)	2.12 (1.62, 2.77)	0.297 (0.202, 0.391)	2.32 (1.66, 3.25)	0.0502
	T-DM1 (N=188)	50 (26.6)				<.0001	
No	T-DXd (N=65)	31 (47.7)	1.75 (0.88, 3.48)	1.39 (0.93, 2.09)	0.134 (-0.029, 0.298)	1.24 (0.73, 2.11)	
	T-DM1 (N=73)	25 (34.2)				0.4169	
Alopecia							
Yes	T-DXd (N=192)	76 (39.6)	19.87 (8.38, 47.11)	12.40 (5.54, 27.78)	0.364 (0.290, 0.438)	14.26 (6.21, 32.75)	0.7603
	T-DM1 (N=188)	6 (3.2)				<.0001	
No	T-DXd (N=65)	19 (29.2)	14.66 (3.26, 65.89)	10.67 (2.58, 44.06)	0.265 (0.148, 0.382)	10.87 (2.53, 46.70)	
	T-DM1 (N=73)	2 (2.7)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
Yes	T-DXd (N=192)	12 (6.3)	0.63 (0.29, 1.35)	0.65 (0.32, 1.32)	-0.033 (-0.087, 0.021)	0.45 (0.22, 0.96)	0.7857
	T-DM1 (N=188)	18 (9.6)				0.0335	
No	T-DXd (N=65)	4 (6.2)	0.73 (0.20, 2.72)	0.75 (0.22, 2.54)	-0.021 (-0.107, 0.065)	0.52 (0.14, 1.88)	
	T-DM1 (N=73)	6 (8.2)				0.3105	
Skin hyperpigmentation							
Yes	T-DXd (N=192)	11 (5.7)	NE (NE, NE)	NE (NE, NE)	0.057 (0.024, 0.090)	NE (NE, NE)	0.9974
	T-DM1 (N=188)	0				0.0038	
No	T-DXd (N=65)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=73)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Yes	T-DXd (N=192)	92 (47.9)	1.92 (1.26, 2.90)	1.48 (1.15, 1.90)	0.155 (0.057, 0.252)	1.48 (1.07, 2.05)	0.5565
	T-DM1 (N=188)	61 (32.4)				0.0187	
No	T-DXd (N=65)	30 (46.2)	2.44 (1.19, 4.98)	1.77 (1.11, 2.83)	0.201 (0.044, 0.359)	1.80 (1.01, 3.22)	
	T-DM1 (N=73)	19 (26.0)				0.0429	
Decreased appetite							
Yes	T-DXd (N=192)	57 (29.7)	2.14 (1.30, 3.51)	1.80 (1.22, 2.65)	0.132 (0.048, 0.216)	1.77 (1.14, 2.75)	0.7017
	T-DM1 (N=188)	31 (16.5)				0.0108	
No	T-DXd (N=65)	18 (27.7)	1.77 (0.79, 3.97)	1.56 (0.83, 2.92)	0.099 (-0.041, 0.239)	1.46 (0.71, 3.01)	
	T-DM1 (N=73)	13 (17.8)				0.2970	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
Yes	T-DXd (N=192)	9 (4.7)	NE (NE, NE)	NE (NE, NE)	0.047 (0.017, 0.077)	NE (NE, NE)	0.9999
	T-DM1 (N=188)	0				0.0033	
No	T-DXd (N=65)	2 (3.1)	NE (NE, NE)	NE (NE, NE)	0.031 (-0.011, 0.073)	NE (NE, NE)	
	T-DM1 (N=73)	0				0.1324	
Nervous system disorders							
Any PT							
Yes	T-DXd (N=192)	86 (44.8)	1.31 (0.87, 1.97)	1.17 (0.92, 1.49)	0.065 (-0.034, 0.164)	0.88 (0.64, 1.20)	0.5114
	T-DM1 (N=188)	72 (38.3)				0.4199	
No	T-DXd (N=65)	30 (46.2)	1.55 (0.78, 3.07)	1.30 (0.86, 1.94)	0.105 (-0.058, 0.269)	1.09 (0.64, 1.85)	
	T-DM1 (N=73)	26 (35.6)				0.7473	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
Yes	T-DXd (N=192)	15 (7.8)	0.91 (0.44, 1.90)	0.92 (0.47, 1.80)	-0.007 (-0.062, 0.048)	0.63 (0.31, 1.29)	0.3743
	T-DM1 (N=188)	16 (8.5)				0.2003	
No	T-DXd (N=65)	4 (6.2)	0.47 (0.14, 1.59)	0.50 (0.16, 1.54)	-0.062 (-0.157, 0.034)	0.36 (0.11, 1.18)	
	T-DM1 (N=73)	9 (12.3)				0.0799	
Infections and infestations							
Any PT							
Yes	T-DXd (N=192)	87 (45.3)	2.00 (1.31, 3.06)	1.55 (1.18, 2.03)	0.161 (0.065, 0.256)	1.20 (0.86, 1.69)	0.0733
	T-DM1 (N=188)	55 (29.3)				0.2873	
No	T-DXd (N=65)	25 (38.5)	0.90 (0.45, 1.77)	0.94 (0.62, 1.41)	-0.026 (-0.190, 0.137)	0.65 (0.38, 1.11)	
	T-DM1 (N=73)	30 (41.1)				0.1127	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Yes	T-DXd (N=192)	85 (44.3)	2.02 (1.32, 3.10)	1.57 (1.19, 2.07)	0.161 (0.066, 0.256)	1.12 (0.79, 1.58)	0.0901
	T-DM1 (N=188)	53 (28.2)				0.5329	
No	T-DXd (N=65)	22 (33.8)	0.92 (0.46, 1.87)	0.95 (0.60, 1.50)	-0.018 (-0.177, 0.141)	0.62 (0.35, 1.11)	
	T-DM1 (N=73)	26 (35.6)				0.1036	
Epistaxis							
Yes	T-DXd (N=192)	22 (11.5)	0.77 (0.42, 1.41)	0.80 (0.47, 1.35)	-0.029 (-0.096, 0.038)	0.51 (0.29, 0.90)	0.3968
	T-DM1 (N=188)	27 (14.4)				0.0189	
No	T-DXd (N=65)	7 (10.8)	0.47 (0.18, 1.23)	0.52 (0.23, 1.21)	-0.098 (-0.217, 0.022)	0.26 (0.10, 0.66)	
	T-DM1 (N=73)	15 (20.5)				0.0023	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
Yes	T-DXd (N=192)	11 (5.7)	NE (NE, NE)	NE (NE, NE)	0.057 (0.024, 0.090)	NE (NE, NE)	0.9926
	T-DM1 (N=188)	0				0.0164	
No	T-DXd (N=65)	7 (10.8)	8.69 (1.04, 72.64)	7.86 (0.99, 62.21)	0.094 (0.014, 0.174)	5.42 (0.66, 44.37)	
	T-DM1 (N=73)	1 (1.4)				0.0778	
Blood and lymphatic system disorders							
Any PT							
Yes	T-DXd (N=192)	79 (41.1)	1.93 (1.25, 2.97)	1.55 (1.16, 2.07)	0.146 (0.052, 0.239)	1.29 (0.90, 1.84)	0.2528
	T-DM1 (N=188)	50 (26.6)				0.1568	
No	T-DXd (N=65)	24 (36.9)	1.12 (0.56, 2.26)	1.08 (0.69, 1.69)	0.027 (-0.133, 0.187)	0.90 (0.51, 1.58)	
	T-DM1 (N=73)	25 (34.2)				0.7074	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
Yes	T-DXd (N=192)	64 (33.3)	2.74 (1.67, 4.50)	2.16 (1.46, 3.19)	0.179 (0.095, 0.263)	1.88 (1.21, 2.92)	0.2803
	T-DM1 (N=188)	29 (15.4)				0.0045	
No	T-DXd (N=65)	19 (29.2)	1.60 (0.73, 3.48)	1.42 (0.79, 2.56)	0.087 (-0.057, 0.231)	1.15 (0.58, 2.28)	
	T-DM1 (N=73)	15 (20.5)				0.6811	
Neutropenia							
Yes	T-DXd (N=192)	29 (15.1)	6.51 (2.46, 17.22)	5.68 (2.25, 14.36)	0.124 (0.069, 0.180)	4.28 (1.65, 11.12)	0.8009
	T-DM1 (N=188)	5 (2.7)				0.0012	
No	T-DXd (N=65)	12 (18.5)	8.04 (1.73, 37.44)	6.74 (1.57, 28.99)	0.157 (0.056, 0.259)	5.50 (1.22, 24.67)	
	T-DM1 (N=73)	2 (2.7)				0.0126	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
Yes	T-DXd (N=192)	9 (4.7)	0.37 (0.17, 0.83)	0.40 (0.19, 0.85)	-0.070 (-0.125, -0.015)	0.28 (0.13, 0.62)	0.7119
	T-DM1 (N=188)	22 (11.7)				0.0009	
No	T-DXd (N=65)	4 (6.2)	0.47 (0.14, 1.59)	0.50 (0.16, 1.54)	-0.062 (-0.157, 0.034)	0.40 (0.12, 1.30)	
	T-DM1 (N=73)	9 (12.3)				0.1139	
Musculoskeletal and connective tissue disorders							
Any PT							
Yes	T-DXd (N=192)	73 (38.0)	1.28 (0.84, 1.95)	1.17 (0.89, 1.54)	0.056 (-0.040, 0.152)	0.85 (0.60, 1.21)	0.4001
	T-DM1 (N=188)	61 (32.4)				0.3747	
No	T-DXd (N=65)	21 (32.3)	0.86 (0.43, 1.75)	0.91 (0.57, 1.45)	-0.033 (-0.191, 0.125)	0.64 (0.36, 1.15)	
	T-DM1 (N=73)	26 (35.6)				0.1317	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
Yes	T-DXd (N=192)	30 (15.6)	2.72 (1.35, 5.48)	2.45 (1.29, 4.64)	0.092 (0.030, 0.155)	1.91 (0.97, 3.77)	0.6888
	T-DM1 (N=188)	12 (6.4)				0.0573	
No	T-DXd (N=65)	15 (23.1)	2.13 (0.86, 5.28)	1.87 (0.88, 3.99)	0.107 (-0.020, 0.235)	1.41 (0.61, 3.25)	
	T-DM1 (N=73)	9 (12.3)				0.4180	
Eye disorders							
Any PT							
Yes	T-DXd (N=192)	31 (16.1)	1.38 (0.77, 2.47)	1.32 (0.80, 2.18)	0.039 (-0.031, 0.109)	0.91 (0.52, 1.57)	0.6792
	T-DM1 (N=188)	23 (12.2)				0.7279	
No	T-DXd (N=65)	10 (15.4)	1.71 (0.61, 4.80)	1.60 (0.65, 3.97)	0.058 (-0.053, 0.169)	0.97 (0.36, 2.59)	
	T-DM1 (N=73)	7 (9.6)				0.9556	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
Yes	T-DXd (N=192)	28 (14.6)	1.22 (0.68, 2.21)	1.19 (0.71, 1.99)	0.023 (-0.045, 0.092)	0.85 (0.49, 1.49)	0.7643
	T-DM1 (N=188)	23 (12.2)				0.5767	
No	T-DXd (N=65)	11 (16.9)	1.04 (0.42, 2.54)	1.03 (0.49, 2.17)	0.005 (-0.120, 0.129)	0.70 (0.30, 1.60)	
	T-DM1 (N=73)	12 (16.4)				0.3939	
Insomnia							
Yes	T-DXd (N=192)	13 (6.8)	0.90 (0.41, 1.98)	0.91 (0.44, 1.88)	-0.007 (-0.058, 0.045)	0.69 (0.32, 1.48)	0.0961
	T-DM1 (N=188)	14 (7.4)				0.3420	
No	T-DXd (N=65)	2 (3.1)	0.20 (0.04, 0.95)	0.22 (0.05, 0.99)	-0.106 (-0.196, -0.017)	0.14 (0.03, 0.66)	
	T-DM1 (N=73)	10 (13.7)				0.0039	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Yes	T-DXd (N=192)	21 (10.9)	1.09 (0.57, 2.10)	1.08 (0.60, 1.95)	0.008 (-0.053, 0.070)	0.68 (0.36, 1.28)	0.4590
	T-DM1 (N=188)	19 (10.1)				0.2314	
No	T-DXd (N=65)	11 (16.9)	1.66 (0.62, 4.41)	1.54 (0.66, 3.60)	0.060 (-0.056, 0.176)	1.05 (0.41, 2.67)	
	T-DM1 (N=73)	8 (11.0)				0.9211	
Cardiac disorders							
Any PT							
Yes	T-DXd (N=192)	18 (9.4)	2.06 (0.90, 4.70)	1.96 (0.90, 4.25)	0.046 (-0.005, 0.097)	1.31 (0.58, 2.96)	0.9007
	T-DM1 (N=188)	9 (4.8)				0.5139	
No	T-DXd (N=65)	3 (4.6)	1.72 (0.28, 10.62)	1.68 (0.29, 9.77)	0.019 (-0.045, 0.082)	1.28 (0.21, 7.72)	
	T-DM1 (N=73)	2 (2.7)				0.7881	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
Yes	T-DXd (N=192)	18 (9.4)	2.67 (1.09, 6.56)	2.52 (1.08, 5.89)	0.057 (0.007, 0.106)	1.80 (0.74, 4.34)	0.7011
	T-DM1 (N=188)	7 (3.7)				0.1871	
No	T-DXd (N=65)	3 (4.6)	1.72 (0.28, 10.62)	1.68 (0.29, 9.77)	0.019 (-0.045, 0.082)	1.07 (0.18, 6.49)	
	T-DM1 (N=73)	2 (2.7)				0.9407	
Reproductive system and breast disorders							
Any PT							
Yes	T-DXd (N=192)	17 (8.9)	1.73 (0.77, 3.88)	1.66 (0.78, 3.54)	0.035 (-0.016, 0.087)	1.10 (0.49, 2.43)	0.2247
	T-DM1 (N=188)	10 (5.3)				0.8195	
No	T-DXd (N=65)	4 (6.2)	0.62 (0.17, 2.22)	0.64 (0.20, 2.09)	-0.034 (-0.124, 0.055)	0.48 (0.14, 1.65)	
	T-DM1 (N=73)	7 (9.6)				0.2360	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
Yes	T-DXd (N=192)	17 (8.9)	0.77 (0.39, 1.52)	0.79 (0.43, 1.45)	-0.023 (-0.084, 0.037)	0.61 (0.32, 1.16)	0.3593
	T-DM1 (N=188)	21 (11.2)				0.1335	
No	T-DXd (N=65)	3 (4.6)	0.39 (0.10, 1.55)	0.42 (0.12, 1.52)	-0.063 (-0.151, 0.025)	0.30 (0.08, 1.15)	
	T-DM1 (N=73)	8 (11.0)				0.0642	
Renal and urinary disorders							
Any PT							
Yes	T-DXd (N=192)	10 (5.2)	1.24 (0.48, 3.20)	1.22 (0.49, 3.03)	0.010 (-0.033, 0.052)	0.91 (0.36, 2.34)	0.5837
	T-DM1 (N=188)	8 (4.3)				0.8515	
No	T-DXd (N=65)	5 (7.7)	1.94 (0.45, 8.48)	1.87 (0.47, 7.53)	0.036 (-0.043, 0.115)	1.30 (0.31, 5.51)	
	T-DM1 (N=73)	3 (4.1)				0.7202	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Yes	T-DXd (N=41)	38 (92.7)	9.79 (2.58, 37.19)	1.64 (1.23, 2.19)	0.363 (0.188, 0.538)	2.81 (1.65, 4.79)	0.9297
	T-DM1 (N=39)	22 (56.4)				<.0001	
No	T-DXd (N=216)	199 (92.1)	8.28 (4.72, 14.54)	1.57 (1.40, 1.77)	0.336 (0.262, 0.410)	2.90 (2.31, 3.63)	
	T-DM1 (N=222)	130 (58.6)				<.0001	
Nausea							
Yes	T-DXd (N=41)	31 (75.6)	7.89 (2.91, 21.39)	2.68 (1.58, 4.55)	0.474 (0.281, 0.667)	3.84 (1.92, 7.67)	0.8573
	T-DM1 (N=39)	11 (28.2)				<.0001	
No	T-DXd (N=216)	164 (75.9)	7.14 (4.68, 10.90)	2.48 (2.01, 3.06)	0.453 (0.370, 0.536)	3.73 (2.81, 4.96)	
	T-DM1 (N=222)	68 (30.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Yes	T-DXd (N=41)	21 (51.2)	9.19 (2.76, 30.57)	4.99 (1.88, 13.24)	0.410 (0.229, 0.590)	6.22 (2.13, 18.16)	0.8562
	T-DM1 (N=39)	4 (10.3)				0.0001	
No	T-DXd (N=216)	105 (48.6)	8.60 (5.14, 14.39)	4.91 (3.22, 7.46)	0.387 (0.310, 0.464)	5.36 (3.38, 8.49)	
	T-DM1 (N=222)	22 (9.9)				<.0001	
Constipation							
Yes	T-DXd (N=41)	13 (31.7)	5.57 (1.45, 21.47)	4.12 (1.27, 13.37)	0.240 (0.075, 0.405)	3.01 (0.84, 10.84)	0.1735
	T-DM1 (N=39)	3 (7.7)				0.0782	
No	T-DXd (N=216)	75 (34.7)	1.93 (1.26, 2.95)	1.61 (1.18, 2.19)	0.131 (0.048, 0.214)	1.43 (0.99, 2.06)	
	T-DM1 (N=222)	48 (21.6)				0.0527	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Yes	T-DXd (N=41)	13 (31.7)	8.59 (1.79, 41.18)	6.18 (1.49, 25.65)	0.266 (0.107, 0.424)	5.69 (1.28, 25.42)	0.6787
	T-DM1 (N=39)	2 (5.1)				0.0103	
No	T-DXd (N=216)	62 (28.7)	5.18 (2.88, 9.33)	3.98 (2.38, 6.68)	0.215 (0.146, 0.284)	4.03 (2.32, 6.99)	
	T-DM1 (N=222)	16 (7.2)				<.0001	
Stomatitis							
Yes	T-DXd (N=41)	5 (12.2)	1.22 (0.30, 4.90)	1.19 (0.34, 4.11)	0.019 (-0.119, 0.158)	0.91 (0.24, 3.50)	0.0231
	T-DM1 (N=39)	4 (10.3)				0.8903	
No	T-DXd (N=216)	35 (16.2)	6.96 (2.86, 16.92)	6.00 (2.57, 13.96)	0.135 (0.081, 0.189)	5.05 (2.12, 12.04)	
	T-DM1 (N=222)	6 (2.7)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Yes	T-DXd (N=41)	6 (14.6)	NE (NE, NE)	NE (NE, NE)	0.146 (0.038, 0.255)	NE (NE, NE)	0.9877
	T-DM1 (N=39)	0				0.0324	
No	T-DXd (N=216)	23 (10.6)	5.17 (1.93, 13.87)	4.73 (1.83, 12.21)	0.084 (0.038, 0.129)	3.55 (1.34, 9.38)	
	T-DM1 (N=222)	5 (2.3)				0.0065	
Dry mouth							
Yes	T-DXd (N=41)	1 (2.4)	0.17 (0.02, 1.53)	0.19 (0.02, 1.56)	-0.104 (-0.219, 0.011)	0.12 (0.01, 1.13)	0.5010
	T-DM1 (N=39)	5 (12.8)				0.0329	
No	T-DXd (N=216)	7 (3.2)	0.34 (0.14, 0.82)	0.36 (0.16, 0.83)	-0.058 (-0.102, -0.013)	0.28 (0.12, 0.66)	
	T-DM1 (N=222)	20 (9.0)				0.0021	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Yes	T-DXd (N=41)	24 (58.5)	0.55 (0.22, 1.41)	0.82 (0.59, 1.13)	-0.133 (-0.339, 0.074)	0.46 (0.26, 0.80)	0.2434
	T-DM1 (N=39)	28 (71.8)				0.0073	
No	T-DXd (N=216)	138 (63.9)	0.83 (0.56, 1.24)	0.94 (0.82, 1.07)	-0.041 (-0.130, 0.047)	0.64 (0.51, 0.81)	
	T-DM1 (N=222)	151 (68.0)				0.0008	
Neutrophil count decreased							
Yes	T-DXd (N=41)	6 (14.6)	0.94 (0.28, 3.22)	0.95 (0.34, 2.70)	-0.008 (-0.164, 0.149)	0.68 (0.22, 2.15)	0.0083
	T-DM1 (N=39)	6 (15.4)				0.5127	
No	T-DXd (N=216)	69 (31.9)	5.01 (2.89, 8.69)	3.73 (2.33, 5.98)	0.234 (0.162, 0.306)	3.62 (2.18, 6.02)	
	T-DM1 (N=222)	19 (8.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
Yes	T-DXd (N=41)	16 (39.0)	0.92 (0.38, 2.25)	0.95 (0.56, 1.63)	-0.020 (-0.235, 0.195)	0.62 (0.30, 1.26)	0.2056
	T-DM1 (N=39)	16 (41.0)				0.1971	
No	T-DXd (N=216)	50 (23.1)	0.45 (0.30, 0.68)	0.58 (0.43, 0.77)	-0.169 (-0.255, -0.084)	0.40 (0.28, 0.57)	
	T-DM1 (N=222)	89 (40.1)				<.0001	
White blood cell count decreased							
Yes	T-DXd (N=41)	7 (17.1)	2.47 (0.59, 10.34)	2.22 (0.62, 7.98)	0.094 (-0.049, 0.236)	1.58 (0.40, 6.27)	0.1917
	T-DM1 (N=39)	3 (7.7)				0.5069	
No	T-DXd (N=216)	51 (23.6)	5.93 (3.00, 11.73)	4.77 (2.55, 8.89)	0.187 (0.123, 0.250)	4.30 (2.24, 8.27)	
	T-DM1 (N=222)	11 (5.0)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
Yes	T-DXd (N=41)	13 (31.7)	0.93 (0.36, 2.37)	0.95 (0.51, 1.79)	-0.016 (-0.222, 0.189)	0.64 (0.29, 1.44)	0.4624
	T-DM1 (N=39)	13 (33.3)				0.2889	
No	T-DXd (N=216)	43 (19.9)	0.61 (0.39, 0.96)	0.69 (0.49, 0.97)	-0.089 (-0.169, -0.009)	0.54 (0.37, 0.80)	
	T-DM1 (N=222)	64 (28.8)				0.0019	
Platelet count decreased							
Yes	T-DXd (N=41)	12 (29.3)	0.44 (0.17, 1.09)	0.60 (0.34, 1.07)	-0.194 (-0.404, 0.015)	0.35 (0.17, 0.75)	0.6166
	T-DM1 (N=39)	19 (48.7)				0.0051	
No	T-DXd (N=216)	42 (19.4)	0.33 (0.22, 0.51)	0.46 (0.34, 0.63)	-0.224 (-0.308, -0.141)	0.31 (0.21, 0.45)	
	T-DM1 (N=222)	93 (41.9)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
Yes	T-DXd (N=41)	8 (19.5)	4.48 (0.89, 22.64)	3.80 (0.86, 16.82)	0.144 (0.004, 0.284)	2.42 (0.50, 11.81)	0.8109
	T-DM1 (N=39)	2 (5.1)				0.2595	
No	T-DXd (N=216)	35 (16.2)	2.87 (1.50, 5.51)	2.57 (1.42, 4.64)	0.099 (0.040, 0.158)	2.04 (1.09, 3.80)	
	T-DM1 (N=222)	14 (6.3)				0.0221	
Blood lactate dehydrogenase increased							
Yes	T-DXd (N=41)	5 (12.2)	0.76 (0.21, 2.74)	0.79 (0.26, 2.39)	-0.032 (-0.183, 0.119)	0.70 (0.21, 2.30)	0.4323
	T-DM1 (N=39)	6 (15.4)				0.5614	
No	T-DXd (N=216)	12 (5.6)	0.39 (0.19, 0.79)	0.43 (0.22, 0.81)	-0.075 (-0.129, -0.021)	0.31 (0.16, 0.62)	
	T-DM1 (N=222)	29 (13.1)				0.0005	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
Yes	T-DXd (N=41)	3 (7.3)	3.00 (0.30, 30.14)	2.85 (0.31, 26.28)	0.048 (-0.046, 0.141)	1.67 (0.17, 16.78)	0.5087
	T-DM1 (N=39)	1 (2.6)				0.6577	
No	T-DXd (N=216)	11 (5.1)	5.90 (1.29, 26.95)	5.65 (1.27, 25.21)	0.042 (0.010, 0.074)	4.34 (0.96, 19.71)	
	T-DM1 (N=222)	2 (0.9)				0.0380	
General disorders and administration site conditions							
Any PT							
Yes	T-DXd (N=41)	24 (58.5)	2.52 (1.02, 6.21)	1.63 (1.00, 2.67)	0.226 (0.013, 0.439)	1.41 (0.72, 2.75)	0.2976
	T-DM1 (N=39)	14 (35.9)				0.3019	
No	T-DXd (N=216)	135 (62.5)	1.44 (0.99, 2.11)	1.17 (0.99, 1.37)	0.089 (-0.003, 0.181)	0.98 (0.77, 1.26)	
	T-DM1 (N=222)	119 (53.6)				0.9022	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Yes	T-DXd (N=41)	3 (7.3)	1.46 (0.23, 9.25)	1.43 (0.25, 8.09)	0.022 (-0.084, 0.127)	1.42 (0.24, 8.52)	0.3573
	T-DM1 (N=39)	2 (5.1)				0.6970	
No	T-DXd (N=216)	26 (12.0)	3.66 (1.62, 8.28)	3.34 (1.55, 7.21)	0.084 (0.034, 0.134)	2.98 (1.34, 6.61)	
	T-DM1 (N=222)	8 (3.6)				0.0048	
Pyrexia							
Yes	T-DXd (N=41)	4 (9.8)	1.30 (0.27, 6.21)	1.27 (0.30, 5.31)	0.021 (-0.103, 0.144)	0.79 (0.17, 3.73)	0.5908
	T-DM1 (N=39)	3 (7.7)				0.7695	
No	T-DXd (N=216)	23 (10.6)	0.62 (0.35, 1.08)	0.66 (0.40, 1.07)	-0.056 (-0.119, 0.008)	0.43 (0.25, 0.73)	
	T-DM1 (N=222)	36 (16.2)				0.0014	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Yes	T-DXd (N=41)	22 (53.7)	3.36 (1.30, 8.64)	2.09 (1.14, 3.83)	0.280 (0.075, 0.485)	1.91 (0.89, 4.08)	0.9354
	T-DM1 (N=39)	10 (25.6)				0.0918	
No	T-DXd (N=216)	117 (54.2)	2.85 (1.93, 4.23)	1.85 (1.46, 2.35)	0.249 (0.159, 0.338)	1.97 (1.45, 2.67)	
	T-DM1 (N=222)	65 (29.3)				<.0001	
Alopecia							
Yes	T-DXd (N=41)	12 (29.3)	4.97 (1.28, 19.28)	3.80 (1.16, 12.47)	0.216 (0.053, 0.378)	3.91 (1.09, 13.95)	0.0502
	T-DM1 (N=39)	3 (7.7)				0.0241	
No	T-DXd (N=216)	83 (38.4)	27.08 (10.71, 68.51)	17.06 (7.06, 41.25)	0.362 (0.294, 0.429)	19.36 (7.85, 47.75)	
	T-DM1 (N=222)	5 (2.3)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
Yes	T-DXd (N=41)	2 (4.9)	0.62 (0.10, 3.90)	0.63 (0.11, 3.59)	-0.028 (-0.135, 0.078)	0.38 (0.06, 2.42)	0.7745
	T-DM1 (N=39)	3 (7.7)				0.2877	
No	T-DXd (N=216)	14 (6.5)	0.66 (0.33, 1.34)	0.69 (0.36, 1.31)	-0.030 (-0.080, 0.021)	0.49 (0.25, 0.98)	
	T-DM1 (N=222)	21 (9.5)				0.0389	
Skin hyperpigmentation							
Yes	T-DXd (N=41)	2 (4.9)	NE (NE, NE)	NE (NE, NE)	0.049 (-0.017, 0.115)	NE (NE, NE)	1.0000
	T-DM1 (N=39)	0				0.2410	
No	T-DXd (N=216)	9 (4.2)	NE (NE, NE)	NE (NE, NE)	0.042 (0.015, 0.068)	NE (NE, NE)	
	T-DM1 (N=222)	0				0.0065	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Yes	T-DXd (N=41)	19 (46.3)	1.24 (0.51, 3.01)	1.13 (0.69, 1.86)	0.053 (-0.164, 0.270)	1.04 (0.53, 2.05)	0.1692
	T-DM1 (N=39)	16 (41.0)				0.9253	
No	T-DXd (N=216)	103 (47.7)	2.25 (1.52, 3.34)	1.65 (1.29, 2.12)	0.189 (0.099, 0.278)	1.70 (1.24, 2.32)	
	T-DM1 (N=222)	64 (28.8)				0.0008	
Decreased appetite							
Yes	T-DXd (N=41)	11 (26.8)	1.22 (0.44, 3.38)	1.16 (0.54, 2.50)	0.038 (-0.152, 0.227)	1.03 (0.42, 2.50)	0.1981
	T-DM1 (N=39)	9 (23.1)				0.9551	
No	T-DXd (N=216)	64 (29.6)	2.25 (1.41, 3.58)	1.88 (1.30, 2.71)	0.139 (0.061, 0.216)	1.87 (1.23, 2.82)	
	T-DM1 (N=222)	35 (15.8)				0.0029	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
Yes	T-DXd (N=41)	1 (2.4)	NE (NE, NE)	NE (NE, NE)	0.024 (-0.023, 0.072)	NE (NE, NE)	0.9999
	T-DM1 (N=39)	0				0.3294	
No	T-DXd (N=216)	10 (4.6)	NE (NE, NE)	NE (NE, NE)	0.046 (0.018, 0.074)	NE (NE, NE)	
	T-DM1 (N=222)	0				0.0014	
Nervous system disorders							
Any PT							
Yes	T-DXd (N=41)	21 (51.2)	2.10 (0.85, 5.19)	1.54 (0.90, 2.62)	0.179 (-0.034, 0.392)	1.06 (0.51, 2.17)	0.5192
	T-DM1 (N=39)	13 (33.3)				0.8772	
No	T-DXd (N=216)	95 (44.0)	1.27 (0.86, 1.85)	1.15 (0.92, 1.44)	0.057 (-0.035, 0.149)	0.90 (0.67, 1.21)	
	T-DM1 (N=222)	85 (38.3)				0.4979	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
Yes	T-DXd (N=41)	1 (2.4)	0.46 (0.04, 5.32)	0.48 (0.04, 5.04)	-0.027 (-0.111, 0.057)	0.31 (0.03, 3.66)	0.5995
	T-DM1 (N=39)	2 (5.1)				0.3320	
No	T-DXd (N=216)	18 (8.3)	0.79 (0.41, 1.50)	0.80 (0.45, 1.45)	-0.020 (-0.075, 0.034)	0.58 (0.31, 1.08)	
	T-DM1 (N=222)	23 (10.4)				0.0809	
Infections and infestations							
Any PT							
Yes	T-DXd (N=41)	24 (58.5)	2.52 (1.02, 6.21)	1.63 (1.00, 2.67)	0.226 (0.013, 0.439)	1.24 (0.63, 2.46)	0.6641
	T-DM1 (N=39)	14 (35.9)				0.5295	
No	T-DXd (N=216)	88 (40.7)	1.46 (0.99, 2.16)	1.27 (0.99, 1.64)	0.088 (-0.002, 0.177)	0.96 (0.70, 1.32)	
	T-DM1 (N=222)	71 (32.0)				0.7967	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Yes	T-DXd (N=41)	17 (41.5)	2.74 (1.01, 7.42)	2.02 (0.99, 4.14)	0.210 (0.013, 0.406)	1.11 (0.47, 2.63)	0.5155
	T-DM1 (N=39)	8 (20.5)				0.8207	
No	T-DXd (N=216)	90 (41.7)	1.52 (1.03, 2.25)	1.30 (1.02, 1.67)	0.097 (0.007, 0.187)	0.95 (0.69, 1.30)	
	T-DM1 (N=222)	71 (32.0)				0.7276	
Epistaxis							
Yes	T-DXd (N=41)	5 (12.2)	2.57 (0.47, 14.10)	2.38 (0.49, 11.55)	0.071 (-0.051, 0.192)	1.34 (0.25, 7.17)	0.1557
	T-DM1 (N=39)	2 (5.1)				0.7323	
No	T-DXd (N=216)	24 (11.1)	0.57 (0.33, 0.98)	0.62 (0.39, 0.99)	-0.069 (-0.135, -0.003)	0.37 (0.22, 0.62)	
	T-DM1 (N=222)	40 (18.0)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
Yes	T-DXd (N=41)	5 (12.2)	NE (NE, NE)	NE (NE, NE)	0.122 (0.022, 0.222)	NE (NE, NE)	0.9929
	T-DM1 (N=39)	0				0.2341	
No	T-DXd (N=216)	13 (6.0)	14.15 (1.84, 109.15)	13.36 (1.76, 101.26)	0.056 (0.023, 0.089)	8.86 (1.16, 68.01)	
	T-DM1 (N=222)	1 (0.5)				0.0113	
Blood and lymphatic system disorders							
Any PT							
Yes	T-DXd (N=41)	20 (48.8)	2.76 (1.07, 7.10)	1.90 (1.02, 3.54)	0.231 (0.026, 0.437)	1.59 (0.74, 3.42)	0.4332
	T-DM1 (N=39)	10 (25.6)				0.2207	
No	T-DXd (N=216)	83 (38.4)	1.51 (1.01, 2.25)	1.31 (1.01, 1.71)	0.091 (0.003, 0.180)	1.09 (0.79, 1.51)	
	T-DM1 (N=222)	65 (29.3)				0.5937	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
Yes	T-DXd (N=41)	18 (43.9)	3.03 (1.12, 8.18)	2.14 (1.05, 4.34)	0.234 (0.036, 0.432)	1.85 (0.80, 4.28)	0.8909
	T-DM1 (N=39)	8 (20.5)				0.1418	
No	T-DXd (N=216)	65 (30.1)	2.22 (1.40, 3.52)	1.86 (1.29, 2.66)	0.139 (0.061, 0.217)	1.58 (1.05, 2.38)	
	T-DM1 (N=222)	36 (16.2)				0.0274	
Neutropenia							
Yes	T-DXd (N=41)	7 (17.1)	NE (NE, NE)	NE (NE, NE)	0.171 (0.056, 0.286)	NE (NE, NE)	0.9855
	T-DM1 (N=39)	0				0.0289	
No	T-DXd (N=216)	34 (15.7)	5.74 (2.48, 13.25)	4.99 (2.26, 11.02)	0.126 (0.072, 0.180)	3.91 (1.72, 8.85)	
	T-DM1 (N=222)	7 (3.2)				0.0004	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
Yes	T-DXd (N=41)	1 (2.4)	0.46 (0.04, 5.32)	0.48 (0.04, 5.04)	-0.027 (-0.111, 0.057)	0.30 (0.02, 3.65)	0.9887
	T-DM1 (N=39)	2 (5.1)				0.3253	
No	T-DXd (N=216)	12 (5.6)	0.39 (0.19, 0.79)	0.43 (0.22, 0.81)	-0.075 (-0.129, -0.021)	0.32 (0.16, 0.63)	
	T-DM1 (N=222)	29 (13.1)				0.0006	
Musculoskeletal and connective tissue disorders							
Any PT							
Yes	T-DXd (N=41)	18 (43.9)	3.58 (1.28, 9.96)	2.45 (1.15, 5.20)	0.260 (0.066, 0.453)	1.92 (0.78, 4.70)	0.0434
	T-DM1 (N=39)	7 (17.9)				0.1472	
No	T-DXd (N=216)	76 (35.2)	0.96 (0.65, 1.42)	0.98 (0.76, 1.26)	-0.009 (-0.098, 0.081)	0.70 (0.51, 0.96)	
	T-DM1 (N=222)	80 (36.0)				0.0280	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
Yes	T-DXd (N=41)	5 (12.2)	1.67 (0.37, 7.50)	1.59 (0.41, 6.19)	0.045 (-0.085, 0.176)	0.59 (0.12, 2.94)	0.4120
	T-DM1 (N=39)	3 (7.7)				0.5146	
No	T-DXd (N=216)	40 (18.5)	2.58 (1.43, 4.65)	2.28 (1.35, 3.86)	0.104 (0.041, 0.167)	1.85 (1.05, 3.24)	
	T-DM1 (N=222)	18 (8.1)				0.0297	
Eye disorders							
Any PT							
Yes	T-DXd (N=41)	8 (19.5)	2.91 (0.71, 11.90)	2.54 (0.73, 8.87)	0.118 (-0.029, 0.266)	1.52 (0.39, 5.87)	0.4659
	T-DM1 (N=39)	3 (7.7)				0.5377	
No	T-DXd (N=216)	33 (15.3)	1.30 (0.75, 2.25)	1.26 (0.78, 2.02)	0.031 (-0.033, 0.096)	0.85 (0.51, 1.42)	
	T-DM1 (N=222)	27 (12.2)				0.5279	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
Yes	T-DXd (N=41)	6 (14.6)	1.17 (0.33, 4.18)	1.14 (0.38, 3.44)	0.018 (-0.133, 0.169)	0.66 (0.19, 2.26)	0.7954
	T-DM1 (N=39)	5 (12.8)				0.5075	
No	T-DXd (N=216)	33 (15.3)	1.15 (0.68, 1.97)	1.13 (0.72, 1.79)	0.018 (-0.048, 0.083)	0.82 (0.50, 1.36)	
	T-DM1 (N=222)	30 (13.5)				0.4451	
Insomnia							
Yes	T-DXd (N=41)	3 (7.3)	0.95 (0.18, 5.00)	0.95 (0.20, 4.43)	-0.004 (-0.119, 0.112)	0.61 (0.12, 3.26)	0.7127
	T-DM1 (N=39)	3 (7.7)				0.5644	
No	T-DXd (N=216)	12 (5.6)	0.56 (0.27, 1.17)	0.59 (0.30, 1.16)	-0.039 (-0.088, 0.010)	0.43 (0.21, 0.88)	
	T-DM1 (N=222)	21 (9.5)				0.0182	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Yes	T-DXd (N=41)	5 (12.2)	0.94 (0.25, 3.55)	0.95 (0.30, 3.03)	-0.006 (-0.151, 0.139)	0.51 (0.14, 1.87)	0.4328
	T-DM1 (N=39)	5 (12.8)				0.2985	
No	T-DXd (N=216)	27 (12.5)	1.30 (0.71, 2.36)	1.26 (0.74, 2.14)	0.026 (-0.033, 0.085)	0.85 (0.48, 1.51)	
	T-DM1 (N=222)	22 (9.9)				0.5889	
Cardiac disorders							
Any PT							
Yes	T-DXd (N=41)	6 (14.6)	2.06 (0.48, 8.87)	1.90 (0.51, 7.08)	0.069 (-0.067, 0.206)	1.19 (0.28, 5.06)	0.7578
	T-DM1 (N=39)	3 (7.7)				0.8119	
No	T-DXd (N=216)	15 (6.9)	2.00 (0.83, 4.81)	1.93 (0.83, 4.45)	0.033 (-0.008, 0.075)	1.32 (0.56, 3.15)	
	T-DM1 (N=222)	8 (3.6)				0.5272	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
Yes	T-DXd (N=41)	8 (19.5)	9.21 (1.09, 77.54)	7.61 (1.00, 58.06)	0.169 (0.038, 0.301)	5.85 (0.72, 47.69)	0.2339
	T-DM1 (N=39)	1 (2.6)				0.0622	
No	T-DXd (N=216)	13 (6.0)	1.71 (0.70, 4.22)	1.67 (0.71, 3.95)	0.024 (-0.016, 0.064)	1.13 (0.46, 2.75)	
	T-DM1 (N=222)	8 (3.6)				0.7870	
Reproductive system and breast disorders							
Any PT							
Yes	T-DXd (N=41)	4 (9.8)	4.11 (0.44, 38.50)	3.80 (0.44, 32.57)	0.072 (-0.032, 0.175)	2.40 (0.25, 23.21)	0.3719
	T-DM1 (N=39)	1 (2.6)				0.4356	
No	T-DXd (N=216)	17 (7.9)	1.10 (0.54, 2.24)	1.09 (0.57, 2.11)	0.007 (-0.043, 0.056)	0.76 (0.38, 1.52)	
	T-DM1 (N=222)	16 (7.2)				0.4438	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
Yes	T-DXd (N=41)	5 (12.2)	0.54 (0.16, 1.82)	0.59 (0.21, 1.66)	-0.083 (-0.245, 0.078)	0.40 (0.13, 1.25)	0.6083
	T-DM1 (N=39)	8 (20.5)				0.1063	
No	T-DXd (N=216)	15 (6.9)	0.71 (0.36, 1.43)	0.73 (0.39, 1.39)	-0.025 (-0.076, 0.026)	0.55 (0.28, 1.09)	
	T-DM1 (N=222)	21 (9.5)				0.0833	
Renal and urinary disorders							
Any PT							
Yes	T-DXd (N=41)	4 (9.8)	NE (NE, NE)	NE (NE, NE)	0.098 (0.007, 0.188)	NE (NE, NE)	0.9874
	T-DM1 (N=39)	0				0.1145	
No	T-DXd (N=216)	11 (5.1)	1.03 (0.44, 2.43)	1.03 (0.46, 2.32)	0.001 (-0.040, 0.042)	0.76 (0.33, 1.78)	
	T-DM1 (N=222)	11 (5.0)				0.5324	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Yes	T-DXd (N=60)	55 (91.7)	8.72 (3.00, 25.35)	1.64 (1.28, 2.12)	0.359 (0.207, 0.511)	2.68 (1.70, 4.22)	0.8471
	T-DM1 (N=52)	29 (55.8)				<.0001	
No	T-DXd (N=197)	182 (92.4)	8.48 (4.68, 15.37)	1.57 (1.39, 1.77)	0.335 (0.259, 0.412)	2.92 (2.31, 3.69)	
	T-DM1 (N=209)	123 (58.9)				<.0001	
Nausea							
Yes	T-DXd (N=60)	44 (73.3)	6.19 (2.72, 14.06)	2.38 (1.54, 3.68)	0.426 (0.258, 0.594)	3.35 (1.89, 5.96)	0.7600
	T-DM1 (N=52)	16 (30.8)				<.0001	
No	T-DXd (N=197)	151 (76.6)	7.61 (4.88, 11.85)	2.54 (2.04, 3.17)	0.465 (0.379, 0.551)	3.87 (2.88, 5.20)	
	T-DM1 (N=209)	63 (30.1)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Vomiting							
Yes	T-DXd (N=60)	29 (48.3)	6.01 (2.34, 15.45)	3.59 (1.72, 7.50)	0.349 (0.192, 0.506)	3.94 (1.72, 9.02)	0.4047
	T-DM1 (N=52)	7 (13.5)				0.0005	
No	T-DXd (N=197)	97 (49.2)	9.70 (5.61, 16.78)	5.42 (3.45, 8.51)	0.401 (0.322, 0.481)	6.01 (3.67, 9.84)	
	T-DM1 (N=209)	19 (9.1)				<.0001	
Constipation							
Yes	T-DXd (N=60)	18 (30.0)	3.29 (1.19, 9.06)	2.60 (1.12, 6.06)	0.185 (0.040, 0.329)	2.08 (0.81, 5.32)	0.3751
	T-DM1 (N=52)	6 (11.5)				0.1208	
No	T-DXd (N=197)	70 (35.5)	2.01 (1.29, 3.12)	1.65 (1.20, 2.27)	0.140 (0.053, 0.227)	1.46 (1.00, 2.13)	
	T-DM1 (N=209)	45 (21.5)				0.0476	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Diarrhoea							
Yes	T-DXd (N=60)	17 (28.3)	4.74 (1.48, 15.20)	3.68 (1.32, 10.25)	0.206 (0.071, 0.341)	3.61 (1.21, 10.76)	0.7153
	T-DM1 (N=52)	4 (7.7)				0.0141	
No	T-DXd (N=197)	58 (29.4)	5.81 (3.12, 10.83)	4.40 (2.54, 7.62)	0.227 (0.155, 0.300)	4.41 (2.46, 7.92)	
	T-DM1 (N=209)	14 (6.7)				<.0001	
Stomatitis							
Yes	T-DXd (N=60)	7 (11.7)	1.58 (0.44, 5.75)	1.52 (0.47, 4.89)	0.040 (-0.069, 0.149)	1.22 (0.35, 4.25)	0.0561
	T-DM1 (N=52)	4 (7.7)				0.7510	
No	T-DXd (N=197)	33 (16.8)	6.81 (2.78, 16.64)	5.84 (2.50, 13.62)	0.139 (0.082, 0.196)	4.89 (2.04, 11.69)	
	T-DM1 (N=209)	6 (2.9)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Abdominal pain							
Yes	T-DXd (N=60)	7 (11.7)	NE (NE, NE)	NE (NE, NE)	0.117 (0.035, 0.198)	NE (NE, NE)	0.9857
	T-DM1 (N=52)	0				0.0272	
No	T-DXd (N=197)	22 (11.2)	5.13 (1.90, 13.83)	4.67 (1.80, 12.09)	0.088 (0.039, 0.136)	3.49 (1.31, 9.26)	
	T-DM1 (N=209)	5 (2.4)				0.0077	
Dry mouth							
Yes	T-DXd (N=60)	2 (3.3)	0.26 (0.05, 1.37)	0.29 (0.06, 1.37)	-0.082 (-0.180, 0.016)	0.21 (0.04, 1.09)	0.7953
	T-DM1 (N=52)	6 (11.5)				0.0434	
No	T-DXd (N=197)	6 (3.0)	0.31 (0.12, 0.80)	0.34 (0.14, 0.82)	-0.060 (-0.106, -0.015)	0.26 (0.10, 0.65)	
	T-DM1 (N=209)	19 (9.1)				0.0020	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Yes	T-DXd (N=60)	33 (55.0)	0.54 (0.25, 1.18)	0.79 (0.59, 1.06)	-0.142 (-0.320, 0.035)	0.48 (0.30, 0.78)	0.2634
	T-DM1 (N=52)	36 (69.2)				0.0031	
No	T-DXd (N=197)	129 (65.5)	0.88 (0.58, 1.32)	0.96 (0.83, 1.10)	-0.029 (-0.121, 0.062)	0.65 (0.51, 0.83)	
	T-DM1 (N=209)	143 (68.4)				0.0021	
Neutrophil count decreased							
Yes	T-DXd (N=60)	8 (13.3)	0.99 (0.33, 2.94)	0.99 (0.39, 2.55)	-0.001 (-0.128, 0.125)	0.84 (0.30, 2.32)	0.0063
	T-DM1 (N=52)	7 (13.5)				0.7287	
No	T-DXd (N=197)	67 (34.0)	5.47 (3.10, 9.63)	3.95 (2.44, 6.40)	0.254 (0.178, 0.330)	3.82 (2.27, 6.43)	
	T-DM1 (N=209)	18 (8.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Aspartate aminotransferase increased							
Yes	T-DXd (N=60)	17 (28.3)	0.63 (0.29, 1.40)	0.74 (0.43, 1.25)	-0.101 (-0.276, 0.073)	0.48 (0.24, 0.93)	0.6579
	T-DM1 (N=52)	20 (38.5)				0.0306	
No	T-DXd (N=197)	49 (24.9)	0.48 (0.32, 0.74)	0.61 (0.46, 0.82)	-0.158 (-0.248, -0.068)	0.43 (0.30, 0.61)	
	T-DM1 (N=209)	85 (40.7)				<.0001	
White blood cell count decreased							
Yes	T-DXd (N=60)	8 (13.3)	1.45 (0.44, 4.73)	1.39 (0.48, 3.98)	0.037 (-0.080, 0.155)	1.21 (0.40, 3.72)	0.0183
	T-DM1 (N=52)	5 (9.6)				0.7330	
No	T-DXd (N=197)	50 (25.4)	7.56 (3.60, 15.86)	5.89 (2.98, 11.66)	0.211 (0.144, 0.277)	5.23 (2.57, 10.64)	
	T-DM1 (N=209)	9 (4.3)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Alanine aminotransferase increased							
Yes	T-DXd (N=60)	13 (21.7)	0.52 (0.23, 1.21)	0.63 (0.34, 1.15)	-0.129 (-0.296, 0.037)	0.41 (0.20, 0.87)	0.5455
	T-DM1 (N=52)	18 (34.6)				0.0176	
No	T-DXd (N=197)	43 (21.8)	0.71 (0.45, 1.12)	0.77 (0.55, 1.09)	-0.064 (-0.148, 0.020)	0.61 (0.41, 0.91)	
	T-DM1 (N=209)	59 (28.2)				0.0153	
Platelet count decreased							
Yes	T-DXd (N=60)	15 (25.0)	0.42 (0.19, 0.94)	0.57 (0.33, 0.96)	-0.192 (-0.366, -0.018)	0.37 (0.19, 0.72)	0.4908
	T-DM1 (N=52)	23 (44.2)				0.0025	
No	T-DXd (N=197)	39 (19.8)	0.33 (0.21, 0.52)	0.46 (0.34, 0.64)	-0.228 (-0.315, -0.141)	0.31 (0.21, 0.45)	
	T-DM1 (N=209)	89 (42.6)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Weight decreased							
Yes	T-DXd (N=60)	12 (20.0)	4.08 (1.08, 15.37)	3.47 (1.03, 11.62)	0.142 (0.023, 0.262)	2.44 (0.68, 8.79)	0.7322
	T-DM1 (N=52)	3 (5.8)				0.1594	
No	T-DXd (N=197)	31 (15.7)	2.82 (1.43, 5.56)	2.53 (1.36, 4.69)	0.095 (0.035, 0.156)	1.98 (1.03, 3.79)	
	T-DM1 (N=209)	13 (6.2)				0.0366	
Blood lactate dehydrogenase increased							
Yes	T-DXd (N=60)	4 (6.7)	0.39 (0.11, 1.39)	0.43 (0.14, 1.36)	-0.087 (-0.204, 0.029)	0.39 (0.12, 1.31)	0.7698
	T-DM1 (N=52)	8 (15.4)				0.1154	
No	T-DXd (N=197)	13 (6.6)	0.48 (0.24, 0.95)	0.51 (0.27, 0.96)	-0.063 (-0.120, -0.006)	0.37 (0.19, 0.73)	
	T-DM1 (N=209)	27 (12.9)				0.0029	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Lymphocyte count decreased							
Yes	T-DXd (N=60)	6 (10.0)	5.67 (0.66, 48.71)	5.20 (0.65, 41.80)	0.081 (-0.004, 0.165)	3.57 (0.42, 30.10)	0.9264
	T-DM1 (N=52)	1 (1.9)				0.2119	
No	T-DXd (N=197)	8 (4.1)	4.38 (0.92, 20.89)	4.24 (0.91, 19.74)	0.031 (0.000, 0.062)	3.17 (0.67, 15.04)	
	T-DM1 (N=209)	2 (1.0)				0.1265	
General disorders and administration site conditions							
Any PT							
Yes	T-DXd (N=60)	37 (61.7)	1.61 (0.76, 3.41)	1.23 (0.88, 1.73)	0.117 (-0.067, 0.300)	1.02 (0.61, 1.70)	0.9321
	T-DM1 (N=52)	26 (50.0)				0.9368	
No	T-DXd (N=197)	122 (61.9)	1.55 (1.04, 2.30)	1.21 (1.02, 1.44)	0.107 (0.011, 0.203)	1.03 (0.79, 1.34)	
	T-DM1 (N=209)	107 (51.2)				0.8143	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Malaise							
Yes	T-DXd (N=60)	6 (10.0)	2.78 (0.54, 14.40)	2.60 (0.55, 12.33)	0.062 (-0.031, 0.154)	2.67 (0.54, 13.21)	0.8555
	T-DM1 (N=52)	2 (3.8)				0.2118	
No	T-DXd (N=197)	23 (11.7)	3.32 (1.45, 7.61)	3.05 (1.40, 6.66)	0.078 (0.027, 0.130)	2.66 (1.19, 5.98)	
	T-DM1 (N=209)	8 (3.8)				0.0137	
Pyrexia							
Yes	T-DXd (N=60)	7 (11.7)	1.58 (0.44, 5.75)	1.52 (0.47, 4.89)	0.040 (-0.069, 0.149)	0.95 (0.27, 3.35)	0.2373
	T-DM1 (N=52)	4 (7.7)				0.9412	
No	T-DXd (N=197)	20 (10.2)	0.56 (0.31, 1.01)	0.61 (0.36, 1.01)	-0.066 (-0.132, 0.000)	0.39 (0.22, 0.69)	
	T-DM1 (N=209)	35 (16.7)				0.0007	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Any PT							
Yes	T-DXd (N=60)	26 (43.3)	2.29 (1.02, 5.15)	1.73 (1.00, 3.01)	0.183 (0.011, 0.355)	1.60 (0.81, 3.14)	0.5780
	T-DM1 (N=52)	13 (25.0)				0.1702	
No	T-DXd (N=197)	113 (57.4)	3.19 (2.12, 4.80)	1.93 (1.52, 2.46)	0.277 (0.184, 0.370)	2.09 (1.53, 2.85)	
	T-DM1 (N=209)	62 (29.7)				<.0001	
Alopecia							
Yes	T-DXd (N=60)	15 (25.0)	5.44 (1.48, 20.06)	4.33 (1.33, 14.14)	0.192 (0.066, 0.319)	4.19 (1.21, 14.58)	0.0642
	T-DM1 (N=52)	3 (5.8)				0.0145	
No	T-DXd (N=197)	80 (40.6)	27.90 (10.99, 70.82)	16.97 (7.02, 41.02)	0.382 (0.311, 0.454)	19.61 (7.95, 48.40)	
	T-DM1 (N=209)	5 (2.4)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Skin and subcutaneous tissue disorders							
Rash							
Yes	T-DXd (N=60)	3 (5.0)	0.63 (0.13, 2.96)	0.65 (0.15, 2.77)	-0.027 (-0.118, 0.064)	0.46 (0.10, 2.12)	0.8777
	T-DM1 (N=52)	4 (7.7)				0.3073	
No	T-DXd (N=197)	13 (6.6)	0.67 (0.32, 1.38)	0.69 (0.35, 1.35)	-0.030 (-0.083, 0.023)	0.48 (0.24, 0.98)	
	T-DM1 (N=209)	20 (9.6)				0.0407	
Skin hyperpigmentation							
Yes	T-DXd (N=60)	2 (3.3)	NE (NE, NE)	NE (NE, NE)	0.033 (-0.012, 0.079)	NE (NE, NE)	0.9999
	T-DM1 (N=52)	0				0.2497	
No	T-DXd (N=197)	9 (4.6)	NE (NE, NE)	NE (NE, NE)	0.046 (0.017, 0.075)	NE (NE, NE)	
	T-DM1 (N=209)	0				0.0059	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Yes	T-DXd (N=60)	29 (48.3)	1.62 (0.76, 3.47)	1.32 (0.85, 2.06)	0.118 (-0.064, 0.300)	1.26 (0.70, 2.27)	0.4494
	T-DM1 (N=52)	19 (36.5)				0.4488	
No	T-DXd (N=197)	93 (47.2)	2.17 (1.44, 3.27)	1.62 (1.25, 2.09)	0.180 (0.087, 0.273)	1.65 (1.20, 2.28)	
	T-DM1 (N=209)	61 (29.2)				0.0022	
Decreased appetite							
Yes	T-DXd (N=60)	16 (26.7)	1.36 (0.56, 3.26)	1.26 (0.64, 2.47)	0.055 (-0.102, 0.213)	1.13 (0.52, 2.46)	0.2631
	T-DM1 (N=52)	11 (21.2)				0.7553	
No	T-DXd (N=197)	59 (29.9)	2.28 (1.41, 3.69)	1.90 (1.30, 2.77)	0.142 (0.061, 0.222)	1.88 (1.23, 2.89)	
	T-DM1 (N=209)	33 (15.8)				0.0034	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Dehydration							
Yes	T-DXd (N=60)	3 (5.0)	NE (NE, NE)	NE (NE, NE)	0.050 (-0.005, 0.105)	NE (NE, NE)	1.0000
	T-DM1 (N=52)	0				0.1062	
No	T-DXd (N=197)	8 (4.1)	NE (NE, NE)	NE (NE, NE)	0.041 (0.013, 0.068)	NE (NE, NE)	
	T-DM1 (N=209)	0				0.0039	
Nervous system disorders							
Any PT							
Yes	T-DXd (N=60)	31 (51.7)	1.71 (0.80, 3.64)	1.34 (0.88, 2.05)	0.132 (-0.051, 0.315)	0.92 (0.51, 1.64)	0.7503
	T-DM1 (N=52)	20 (38.5)				0.7752	
No	T-DXd (N=197)	85 (43.1)	1.27 (0.86, 1.90)	1.16 (0.91, 1.47)	0.058 (-0.037, 0.154)	0.91 (0.67, 1.25)	
	T-DM1 (N=209)	78 (37.3)				0.5749	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Nervous system disorders							
Peripheral sensory neuropathy							
Yes	T-DXd (N=60)	2 (3.3)	0.32 (0.06, 1.75)	0.35 (0.07, 1.71)	-0.063 (-0.155, 0.029)	0.27 (0.05, 1.41)	0.2468
	T-DM1 (N=52)	5 (9.6)				0.0965	
No	T-DXd (N=197)	17 (8.6)	0.89 (0.45, 1.76)	0.90 (0.49, 1.67)	-0.009 (-0.065, 0.047)	0.64 (0.33, 1.22)	
	T-DM1 (N=209)	20 (9.6)				0.1715	
Infections and infestations							
Any PT							
Yes	T-DXd (N=60)	32 (53.3)	2.35 (1.09, 5.08)	1.63 (1.03, 2.57)	0.206 (0.027, 0.386)	1.21 (0.66, 2.23)	0.4066
	T-DM1 (N=52)	17 (32.7)				0.5295	
No	T-DXd (N=197)	80 (40.6)	1.42 (0.94, 2.13)	1.25 (0.96, 1.62)	0.081 (-0.013, 0.174)	0.93 (0.67, 1.29)	
	T-DM1 (N=209)	68 (32.5)				0.6841	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Any PT							
Yes	T-DXd (N=60)	24 (40.0)	2.48 (1.07, 5.77)	1.89 (1.03, 3.48)	0.188 (0.022, 0.355)	1.10 (0.53, 2.31)	0.4146
	T-DM1 (N=52)	11 (21.2)				0.7958	
No	T-DXd (N=197)	83 (42.1)	1.51 (1.01, 2.26)	1.29 (1.00, 1.67)	0.096 (0.002, 0.190)	0.93 (0.68, 1.29)	
	T-DM1 (N=209)	68 (32.5)				0.6825	
Epistaxis							
Yes	T-DXd (N=60)	6 (10.0)	1.33 (0.35, 5.01)	1.30 (0.39, 4.36)	0.023 (-0.082, 0.128)	0.73 (0.20, 2.69)	0.3225
	T-DM1 (N=52)	4 (7.7)				0.6394	
No	T-DXd (N=197)	23 (11.7)	0.59 (0.34, 1.04)	0.64 (0.40, 1.04)	-0.065 (-0.134, 0.004)	0.38 (0.23, 0.65)	
	T-DM1 (N=209)	38 (18.2)				0.0002	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Respiratory, thoracic and mediastinal disorders							
Pneumonitis							
Yes	T-DXd (N=60)	5 (8.3)	NE (NE, NE)	NE (NE, NE)	0.083 (0.013, 0.153)	NE (NE, NE)	0.9912
	T-DM1 (N=52)	0				0.1759	
No	T-DXd (N=197)	13 (6.6)	14.70 (1.90, 113.43)	13.79 (1.82, 104.45)	0.061 (0.025, 0.097)	8.88 (1.16, 68.14)	
	T-DM1 (N=209)	1 (0.5)				0.0112	
Blood and lymphatic system disorders							
Any PT							
Yes	T-DXd (N=60)	27 (45.0)	1.84 (0.85, 4.01)	1.46 (0.89, 2.40)	0.142 (-0.035, 0.320)	1.19 (0.64, 2.22)	0.9248
	T-DM1 (N=52)	16 (30.8)				0.5723	
No	T-DXd (N=197)	76 (38.6)	1.60 (1.05, 2.42)	1.37 (1.03, 1.81)	0.103 (0.012, 0.195)	1.14 (0.81, 1.61)	
	T-DM1 (N=209)	59 (28.2)				0.4483	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Anaemia							
Yes	T-DXd (N=60)	23 (38.3)	1.86 (0.83, 4.21)	1.53 (0.87, 2.71)	0.133 (-0.037, 0.304)	1.19 (0.59, 2.37)	0.3269
	T-DM1 (N=52)	13 (25.0)				0.6232	
No	T-DXd (N=197)	60 (30.5)	2.51 (1.54, 4.09)	2.05 (1.39, 3.02)	0.156 (0.076, 0.237)	1.78 (1.15, 2.76)	
	T-DM1 (N=209)	31 (14.8)				0.0084	
Neutropenia							
Yes	T-DXd (N=60)	10 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (0.072, 0.261)	NE (NE, NE)	0.9829
	T-DM1 (N=52)	0				0.0063	
No	T-DXd (N=197)	31 (15.7)	5.39 (2.31, 12.55)	4.70 (2.12, 10.42)	0.124 (0.067, 0.180)	3.54 (1.55, 8.09)	
	T-DM1 (N=209)	7 (3.3)				0.0014	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
Yes	T-DXd (N=60)	3 (5.0)	0.86 (0.17, 4.45)	0.87 (0.18, 4.11)	-0.008 (-0.092, 0.076)	0.53 (0.10, 2.93)	0.3858
	T-DM1 (N=52)	3 (5.8)				0.4659	
No	T-DXd (N=197)	10 (5.1)	0.35 (0.16, 0.73)	0.38 (0.19, 0.76)	-0.083 (-0.139, -0.028)	0.29 (0.14, 0.59)	
	T-DM1 (N=209)	28 (13.4)				0.0003	
Musculoskeletal and connective tissue disorders							
Any PT							
Yes	T-DXd (N=60)	24 (40.0)	2.00 (0.89, 4.51)	1.60 (0.91, 2.81)	0.150 (-0.021, 0.321)	1.10 (0.55, 2.21)	0.2478
	T-DM1 (N=52)	13 (25.0)				0.7915	
No	T-DXd (N=197)	70 (35.5)	1.01 (0.67, 1.51)	1.00 (0.77, 1.30)	0.001 (-0.092, 0.094)	0.73 (0.52, 1.02)	
	T-DM1 (N=209)	74 (35.4)				0.0616	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Vascular disorders							
Any PT							
Yes	T-DXd (N=60)	11 (18.3)	2.11 (0.68, 6.53)	1.91 (0.71, 5.13)	0.087 (-0.039, 0.214)	1.25 (0.41, 3.79)	0.6330
	T-DM1 (N=52)	5 (9.6)				0.6910	
No	T-DXd (N=197)	34 (17.3)	2.52 (1.34, 4.72)	2.25 (1.29, 3.95)	0.096 (0.032, 0.160)	1.75 (0.96, 3.19)	
	T-DM1 (N=209)	16 (7.7)				0.0642	
Eye disorders							
Any PT							
Yes	T-DXd (N=60)	9 (15.0)	1.66 (0.52, 5.31)	1.56 (0.56, 4.36)	0.054 (-0.067, 0.175)	1.08 (0.36, 3.28)	0.9304
	T-DM1 (N=52)	5 (9.6)				0.8870	
No	T-DXd (N=197)	32 (16.2)	1.43 (0.81, 2.51)	1.36 (0.84, 2.21)	0.043 (-0.025, 0.111)	0.90 (0.53, 1.53)	
	T-DM1 (N=209)	25 (12.0)				0.6910	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Psychiatric disorders							
Any PT							
Yes	T-DXd (N=60)	9 (15.0)	1.13 (0.39, 3.29)	1.11 (0.45, 2.78)	0.015 (-0.114, 0.145)	0.76 (0.28, 2.10)	0.8825
	T-DM1 (N=52)	7 (13.5)				0.5988	
No	T-DXd (N=197)	30 (15.2)	1.16 (0.67, 2.03)	1.14 (0.71, 1.83)	0.018 (-0.050, 0.087)	0.81 (0.48, 1.37)	
	T-DM1 (N=209)	28 (13.4)				0.4336	
Insomnia							
Yes	T-DXd (N=60)	4 (6.7)	1.17 (0.25, 5.47)	1.16 (0.27, 4.93)	0.009 (-0.080, 0.098)	0.77 (0.17, 3.64)	0.4263
	T-DM1 (N=52)	3 (5.8)				0.7456	
No	T-DXd (N=197)	11 (5.6)	0.53 (0.25, 1.13)	0.56 (0.28, 1.12)	-0.045 (-0.096, 0.007)	0.41 (0.19, 0.85)	
	T-DM1 (N=209)	21 (10.0)				0.0132	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Injury, poisoning and procedural complications							
Any PT							
Yes	T-DXd (N=60)	7 (11.7)	0.85 (0.28, 2.60)	0.87 (0.33, 2.31)	-0.018 (-0.141, 0.105)	0.47 (0.15, 1.42)	0.3152
	T-DM1 (N=52)	7 (13.5)				0.1710	
No	T-DXd (N=197)	25 (12.7)	1.37 (0.74, 2.56)	1.33 (0.76, 2.31)	0.031 (-0.030, 0.092)	0.90 (0.50, 1.63)	
	T-DM1 (N=209)	20 (9.6)				0.7314	
Cardiac disorders							
Any PT							
Yes	T-DXd (N=60)	5 (8.3)	1.09 (0.28, 4.30)	1.08 (0.31, 3.82)	0.006 (-0.094, 0.107)	0.75 (0.19, 2.97)	0.2340
	T-DM1 (N=52)	4 (7.7)				0.6833	
No	T-DXd (N=197)	16 (8.1)	2.55 (1.03, 6.34)	2.42 (1.02, 5.77)	0.048 (0.002, 0.093)	1.63 (0.67, 4.00)	
	T-DM1 (N=209)	7 (3.3)				0.2791	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Ear and labyrinth disorders							
Any PT							
Yes	T-DXd (N=60)	7 (11.7)	2.16 (0.53, 8.81)	2.02 (0.55, 7.42)	0.059 (-0.044, 0.162)	1.72 (0.44, 6.69)	0.7230
	T-DM1 (N=52)	3 (5.8)				0.4298	
No	T-DXd (N=197)	14 (7.1)	2.59 (0.97, 6.88)	2.48 (0.97, 6.31)	0.042 (0.000, 0.085)	1.60 (0.61, 4.21)	
	T-DM1 (N=209)	6 (2.9)				0.3340	
Reproductive system and breast disorders							
Any PT							
Yes	T-DXd (N=60)	5 (8.3)	2.27 (0.42, 12.24)	2.17 (0.44, 10.70)	0.045 (-0.042, 0.132)	1.14 (0.20, 6.45)	0.5541
	T-DM1 (N=52)	2 (3.8)				0.8782	
No	T-DXd (N=197)	16 (8.1)	1.14 (0.55, 2.38)	1.13 (0.58, 2.23)	0.009 (-0.042, 0.061)	0.80 (0.39, 1.64)	
	T-DM1 (N=209)	15 (7.2)				0.5442	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 35 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term with incidence >= 1% in at least one arm and observed for >= 10 patients by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Hepatobiliary disorders							
Any PT							
Yes	T-DXd (N=60)	4 (6.7)	0.34 (0.10, 1.18)	0.39 (0.13, 1.18)	-0.106 (-0.227, 0.014)	0.29 (0.09, 0.94)	0.2062
	T-DM1 (N=52)	9 (17.3)				0.0282	
No	T-DXd (N=197)	16 (8.1)	0.84 (0.42, 1.66)	0.85 (0.45, 1.59)	-0.014 (-0.070, 0.041)	0.64 (0.33, 1.25)	
	T-DM1 (N=209)	20 (9.6)				0.1941	
Renal and urinary disorders							
Any PT							
Yes	T-DXd (N=60)	4 (6.7)	3.64 (0.39, 33.67)	3.47 (0.40, 30.05)	0.047 (-0.026, 0.121)	1.45 (0.14, 14.53)	0.4032
	T-DM1 (N=52)	1 (1.9)				0.7525	
No	T-DXd (N=197)	11 (5.6)	1.18 (0.49, 2.84)	1.17 (0.51, 2.69)	0.008 (-0.035, 0.051)	0.91 (0.38, 2.15)	
	T-DM1 (N=209)	10 (4.8)				0.8286	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Protocol DS8201-A-U302 Supplementary analyses - Germany

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
<65	T-DXd (N=209)	7 (3.3)	0.85 (0.30, 2.39)	0.85 (0.32, 2.31)	-0.006 (-0.042, 0.030)	0.64 (0.23, 1.81)	0.2586
	T-DM1 (N=204)	8 (3.9)				0.3994	
>=65	T-DXd (N=48)	6 (12.5)	1.89 (0.50, 7.15)	1.78 (0.53, 5.95)	0.055 (-0.060, 0.170)	1.26 (0.35, 4.49)	
	T-DM1 (N=57)	4 (7.0)				0.7228	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
<75	T-DXd (N=250)	13 (5.2)	1.10 (0.49, 2.46)	1.10 (0.51, 2.36)	0.005 (-0.033, 0.043)	0.77 (0.34, 1.70)	0.9999
	T-DM1 (N=253)	12 (4.7)				0.5094	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
Asia	T-DXd (N=147)	6 (4.1)	0.92 (0.30, 2.82)	0.93 (0.32, 2.70)	-0.003 (-0.048, 0.042)	0.58 (0.19, 1.78)	0.7407
	T-DM1 (N=159)	7 (4.4)				0.3353	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	1 (1.9)	0.46 (0.04, 5.25)	0.47 (0.04, 5.03)	-0.022 (-0.088, 0.045)	0.41 (0.04, 4.50)	
	T-DM1 (N=49)	2 (4.1)				0.4472	
Rest of World	T-DXd (N=41)	6 (14.6)	1.89 (0.44, 8.16)	1.76 (0.47, 6.52)	0.063 (-0.078, 0.204)	1.42 (0.35, 5.74)	
	T-DM1 (N=36)	3 (8.3)				0.6187	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
White	T-DXd (N=71)	4 (5.6)	1.00 (0.24, 4.16)	1.00 (0.26, 3.84)	0.000 (-0.076, 0.076)	0.75 (0.19, 3.07)	0.9967
	T-DM1 (N=71)	4 (5.6)				0.6924	
Black or African American	T-DXd (N=10)	1 (10.0)	0.89 (0.05, 16.66)	0.90 (0.07, 12.38)	-0.011 (-0.288, 0.266)	0.95 (0.06, 15.18)	
	T-DM1 (N=9)	1 (11.1)				0.9703	
Asian	T-DXd (N=149)	6 (4.0)	0.92 (0.30, 2.81)	0.93 (0.32, 2.69)	-0.003 (-0.048, 0.041)	0.58 (0.19, 1.78)	
	T-DM1 (N=161)	7 (4.3)				0.3385	
Other	T-DXd (N=27)	2 (7.4)	NE (NE, NE)	NE (NE, NE)	0.074 (-0.025, 0.173)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.3125	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
0	T-DXd (N=152)	8 (5.3)	2.36 (0.70, 8.00)	2.29 (0.70, 7.45)	0.030 (-0.012, 0.072)	1.32 (0.39, 4.51)	0.0921
	T-DM1 (N=174)	4 (2.3)				0.6549	
1	T-DXd (N=105)	5 (4.8)	0.49 (0.16, 1.57)	0.52 (0.18, 1.53)	-0.044 (-0.117, 0.029)	0.42 (0.14, 1.30)	
	T-DM1 (N=87)	8 (9.2)				0.1225	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
Positive	T-DXd (N=133)	7 (5.3)	1.49 (0.46, 4.81)	1.46 (0.48, 4.50)	0.017 (-0.032, 0.066)	0.97 (0.30, 3.09)	0.5018
	T-DM1 (N=139)	5 (3.6)				0.9524	
Negative	T-DXd (N=123)	6 (4.9)	0.84 (0.27, 2.56)	0.84 (0.29, 2.44)	-0.009 (-0.065, 0.047)	0.63 (0.21, 1.93)	
	T-DM1 (N=121)	7 (5.8)				0.4178	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
Positive	T-DXd (N=129)	6 (4.7)	1.24 (0.37, 4.17)	1.23 (0.38, 3.92)	0.009 (-0.040, 0.057)	0.80 (0.24, 2.69)	0.8042
	T-DM1 (N=132)	5 (3.8)				0.7214	
Negative	T-DXd (N=127)	7 (5.5)	1.00 (0.34, 2.94)	1.00 (0.36, 2.77)	0.000 (-0.056, 0.056)	0.75 (0.26, 2.17)	
	T-DM1 (N=127)	7 (5.5)				0.5913	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
Positive	T-DXd (N=81)	3 (3.7)	1.14 (0.22, 5.82)	1.14 (0.24, 5.47)	0.004 (-0.050, 0.059)	0.78 (0.15, 3.99)	0.9927
	T-DM1 (N=92)	3 (3.3)				0.7677	
Negative	T-DXd (N=174)	10 (5.7)	1.07 (0.42, 2.70)	1.07 (0.44, 2.56)	0.004 (-0.045, 0.052)	0.76 (0.30, 1.90)	
	T-DM1 (N=167)	9 (5.4)				0.5545	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
Yes	T-DXd (N=160)	8 (5.0)	1.60 (0.51, 5.00)	1.57 (0.52, 4.70)	0.018 (-0.025, 0.062)	0.97 (0.31, 3.06)	0.4001
	T-DM1 (N=157)	5 (3.2)				0.9651	
No	T-DXd (N=97)	5 (5.2)	0.75 (0.23, 2.46)	0.77 (0.25, 2.33)	-0.016 (-0.081, 0.049)	0.58 (0.18, 1.87)	
	T-DM1 (N=104)	7 (6.7)				0.3604	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
< 3 lines	T-DXd (N=186)	8 (4.3)	0.90 (0.34, 2.38)	0.90 (0.36, 2.29)	-0.005 (-0.047, 0.037)	0.63 (0.24, 1.66)	0.5542
	T-DM1 (N=189)	9 (4.8)				0.3468	
>= 3 lines	T-DXd (N=71)	5 (7.0)	1.74 (0.40, 7.58)	1.69 (0.42, 6.81)	0.029 (-0.047, 0.104)	1.10 (0.25, 4.88)	
	T-DM1 (N=72)	3 (4.2)				0.8968	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

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Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
< 3 lines	T-DXd (N=154)	5 (3.2)	0.98 (0.28, 3.46)	0.98 (0.29, 3.32)	-0.001 (-0.041, 0.039)	0.59 (0.16, 2.12)	0.9922
	T-DM1 (N=151)	5 (3.3)				0.4145	
>= 3 lines	T-DXd (N=6)	3 (50.0)	NE (NE, NE)	NE (NE, NE)	0.500 (0.100, 0.900)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.1762	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
Within Normal Range	T-DXd (N=130)	8 (6.2)	1.36 (0.46, 4.02)	1.33 (0.48, 3.74)	0.015 (-0.039, 0.070)	0.78 (0.26, 2.34)	0.7082
	T-DM1 (N=130)	6 (4.6)				0.6545	
Mild Impairment	T-DXd (N=92)	3 (3.3)	0.84 (0.18, 3.87)	0.85 (0.19, 3.69)	-0.006 (-0.058, 0.046)	0.71 (0.16, 3.18)	
	T-DM1 (N=104)	4 (3.8)				0.6471	
Moderate Impairment	T-DXd (N=30)	1 (3.3)	0.34 (0.03, 4.06)	0.37 (0.04, 3.79)	-0.058 (-0.194, 0.079)	0.26 (0.02, 2.91)	
	T-DM1 (N=22)	2 (9.1)				0.2402	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
Within Normal Range	T-DXd (N=208)	8 (3.8)	1.17 (0.42, 3.29)	1.16 (0.43, 3.15)	0.005 (-0.030, 0.041)	0.74 (0.26, 2.07)	0.8086
	T-DM1 (N=212)	7 (3.3)				0.5585	
Mild Impairment	T-DXd (N=49)	5 (10.2)	1.00 (0.27, 3.70)	1.00 (0.31, 3.24)	0.000 (-0.120, 0.120)	0.79 (0.22, 2.78)	
	T-DM1 (N=49)	5 (10.2)				0.7101	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
Yes	T-DXd (N=192)	9 (4.7)	1.80 (0.59, 5.47)	1.76 (0.60, 5.16)	0.020 (-0.017, 0.058)	1.23 (0.40, 3.75)	0.2474
	T-DM1 (N=188)	5 (2.7)				0.7210	
No	T-DXd (N=65)	4 (6.2)	0.62 (0.17, 2.22)	0.64 (0.20, 2.09)	-0.034 (-0.124, 0.055)	0.45 (0.13, 1.57)	
	T-DM1 (N=73)	7 (9.6)				0.2005	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
Yes	T-DXd (N=41)	4 (9.8)	2.00 (0.34, 11.60)	1.90 (0.37, 9.81)	0.046 (-0.068, 0.160)	1.00 (0.17, 5.99)	0.5782
	T-DM1 (N=39)	2 (5.1)				0.9968	
No	T-DXd (N=216)	9 (4.2)	0.92 (0.37, 2.31)	0.93 (0.38, 2.23)	-0.003 (-0.042, 0.035)	0.67 (0.27, 1.67)	
	T-DM1 (N=222)	10 (4.5)				0.3876	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 37 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Infections and infestations							
Any PT							
Yes	T-DXd (N=60)	5 (8.3)	2.27 (0.42, 12.24)	2.17 (0.44, 10.70)	0.045 (-0.042, 0.132)	1.05 (0.19, 5.97)	0.3755
	T-DM1 (N=52)	2 (3.8)				0.9523	
No	T-DXd (N=197)	8 (4.1)	0.84 (0.33, 2.18)	0.85 (0.34, 2.11)	-0.007 (-0.047, 0.033)	0.63 (0.25, 1.63)	
	T-DM1 (N=209)	10 (4.8)				0.3397	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

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Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
<65	T-DXd (N=209)	47 (22.5)	0.65 (0.42, 1.01)	0.73 (0.53, 1.01)	-0.084 (-0.169, 0.001)	0.51 (0.35, 0.75)	0.0168
	T-DM1 (N=204)	63 (30.9)				0.0007	
>=65	T-DXd (N=48)	18 (37.5)	1.84 (0.80, 4.27)	1.53 (0.85, 2.74)	0.129 (-0.047, 0.306)	1.35 (0.67, 2.72)	
	T-DM1 (N=57)	14 (24.6)				0.3658	
Neutrophil count decreased							
<65	T-DXd (N=209)	29 (13.9)	6.41 (2.43, 16.92)	5.66 (2.24, 14.34)	0.114 (0.063, 0.166)	4.27 (1.64, 11.09)	0.7741
	T-DM1 (N=204)	5 (2.5)				0.0012	
>=65	T-DXd (N=48)	10 (20.8)	7.24 (1.50, 34.91)	5.94 (1.37, 25.79)	0.173 (0.049, 0.298)	5.52 (1.21, 25.21)	
	T-DM1 (N=57)	2 (3.5)				0.0133	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
<65	T-DXd (N=209)	12 (5.7)	0.26 (0.13, 0.51)	0.30 (0.16, 0.56)	-0.134 (-0.196, -0.071)	0.24 (0.13, 0.47)	0.4772
	T-DM1 (N=204)	39 (19.1)				<.0001	
>=65	T-DXd (N=48)	5 (10.4)	0.39 (0.13, 1.20)	0.46 (0.18, 1.19)	-0.124 (-0.263, 0.015)	0.39 (0.14, 1.09)	
	T-DM1 (N=57)	13 (22.8)				0.0665	
White blood cell count decreased							
<65	T-DXd (N=209)	12 (5.7)	12.37 (1.59, 96.00)	11.71 (1.54, 89.26)	0.053 (0.020, 0.085)	7.65 (0.99, 59.27)	0.9931
	T-DM1 (N=204)	1 (0.5)				0.0219	
>=65	T-DXd (N=48)	3 (6.3)	NE (NE, NE)	NE (NE, NE)	0.063 (-0.006, 0.131)	NE (NE, NE)	
	T-DM1 (N=57)	0				0.0641	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
<65	T-DXd (N=209)	32 (15.3)	1.76 (0.96, 3.22)	1.64 (0.96, 2.80)	0.060 (-0.003, 0.123)	1.12 (0.63, 2.00)	0.0324
	T-DM1 (N=204)	19 (9.3)				0.6968	
>=65	T-DXd (N=48)	5 (10.4)	0.36 (0.12, 1.08)	0.42 (0.16, 1.09)	-0.141 (-0.283, 0.000)	0.32 (0.11, 0.89)	
	T-DM1 (N=57)	14 (24.6)				0.0211	
Thrombocytopenia							
<65	T-DXd (N=209)	2 (1.0)	0.24 (0.05, 1.13)	0.24 (0.05, 1.14)	-0.030 (-0.059, 0.000)	0.21 (0.04, 1.00)	0.9897
	T-DM1 (N=204)	8 (3.9)				0.0305	
>=65	T-DXd (N=48)	0	NE (NE, NE)	NE (NE, NE)	-0.123 (-0.208, -0.038)	NE (NE, NE)	
	T-DM1 (N=57)	7 (12.3)				0.0091	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
<65	T-DXd (N=209)	20 (9.6)	5.29 (1.78, 15.76)	4.88 (1.70, 14.03)	0.076 (0.032, 0.120)	4.24 (1.44, 12.47)	0.8278
	T-DM1 (N=204)	4 (2.0)				0.0044	
>=65	T-DXd (N=48)	6 (12.5)	3.93 (0.75, 20.45)	3.56 (0.75, 16.84)	0.090 (-0.015, 0.195)	2.71 (0.54, 13.53)	
	T-DM1 (N=57)	2 (3.5)				0.2054	
Nausea							
<65	T-DXd (N=209)	13 (6.2)	NE (NE, NE)	NE (NE, NE)	0.062 (0.029, 0.095)	NE (NE, NE)	0.9914
	T-DM1 (N=204)	0				0.0004	
>=65	T-DXd (N=48)	4 (8.3)	5.09 (0.55, 47.18)	4.75 (0.55, 41.08)	0.066 (-0.020, 0.151)	3.68 (0.41, 33.16)	
	T-DM1 (N=57)	1 (1.8)				0.2145	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
<65	T-DXd (N=209)	16 (7.7)	4.15 (1.36, 12.62)	3.90 (1.33, 11.48)	0.057 (0.016, 0.098)	2.94 (0.97, 8.88)	0.9904
	T-DM1 (N=204)	4 (2.0)				0.0450	
>=65	T-DXd (N=48)	7 (14.6)	NE (NE, NE)	NE (NE, NE)	0.146 (0.046, 0.246)	NE (NE, NE)	
	T-DM1 (N=57)	0				0.0108	
Metabolism and nutrition disorders							
Any PT							
<65	T-DXd (N=209)	13 (6.2)	2.19 (0.82, 5.87)	2.11 (0.82, 5.46)	0.033 (-0.007, 0.073)	1.59 (0.60, 4.22)	0.8471
	T-DM1 (N=204)	6 (2.9)				0.3481	
>=65	T-DXd (N=48)	5 (10.4)	1.54 (0.39, 6.09)	1.48 (0.42, 5.22)	0.034 (-0.075, 0.143)	1.31 (0.35, 4.89)	
	T-DM1 (N=57)	4 (7.0)				0.6862	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
<75	T-DXd (N=250)	63 (25.2)	0.80 (0.54, 1.18)	0.85 (0.64, 1.13)	-0.044 (-0.122, 0.033)	0.63 (0.45, 0.88)	0.7032
	T-DM1 (N=253)	75 (29.6)				0.0091	
>=75	T-DXd (N=7)	2 (28.6)	1.20 (0.12, 11.87)	1.14 (0.21, 6.11)	0.036 (-0.414, 0.485)	0.93 (0.13, 6.61)	
	T-DM1 (N=8)	2 (25.0)				0.9647	
Neutrophil count decreased							
<75	T-DXd (N=250)	37 (14.8)	6.10 (2.67, 13.98)	5.35 (2.43, 11.77)	0.120 (0.072, 0.169)	4.24 (1.88, 9.54)	0.9889
	T-DM1 (N=253)	7 (2.8)				0.0002	
>=75	T-DXd (N=7)	2 (28.6)	NE (NE, NE)	NE (NE, NE)	0.286 (-0.049, 0.620)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.1710	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
<75	T-DXd (N=250)	17 (6.8)	0.30 (0.17, 0.53)	0.34 (0.20, 0.58)	-0.130 (-0.188, -0.071)	0.28 (0.16, 0.49)	0.9859
	T-DM1 (N=253)	50 (19.8)				<.0001	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	-0.250 (-0.550, 0.050)	NE (NE, NE)	
	T-DM1 (N=8)	2 (25.0)				0.1698	
White blood cell count decreased							
<75	T-DXd (N=250)	15 (6.0)	16.08 (2.11, 122.72)	15.18 (2.02, 114.05)	0.056 (0.026, 0.086)	11.22 (1.48, 85.24)	0.9992
	T-DM1 (N=253)	1 (0.4)				0.0033	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
<75	T-DXd (N=250)	37 (14.8)	1.16 (0.70, 1.92)	1.13 (0.73, 1.75)	0.018 (-0.043, 0.078)	0.79 (0.49, 1.27)	0.9999
	T-DM1 (N=253)	33 (13.0)				0.3279	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	
Thrombocytopenia							
<75	T-DXd (N=250)	2 (0.8)	0.13 (0.03, 0.57)	0.13 (0.03, 0.58)	-0.051 (-0.082, -0.020)	0.11 (0.02, 0.48)	0.9992
	T-DM1 (N=253)	15 (5.9)				0.0004	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
<75	T-DXd (N=250)	24 (9.6)	4.37 (1.76, 10.89)	4.05 (1.68, 9.73)	0.072 (0.031, 0.113)	3.40 (1.38, 8.37)	0.9910
	T-DM1 (N=253)	6 (2.4)				0.0047	
>=75	T-DXd (N=7)	2 (28.6)	NE (NE, NE)	NE (NE, NE)	0.286 (-0.049, 0.620)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.2850	
Nausea							
<75	T-DXd (N=250)	15 (6.0)	16.08 (2.11, 122.72)	15.18 (2.02, 114.05)	0.056 (0.026, 0.086)	14.29 (1.89, 108.26)	0.9928
	T-DM1 (N=253)	1 (0.4)				0.0007	
>=75	T-DXd (N=7)	2 (28.6)	NE (NE, NE)	NE (NE, NE)	0.286 (-0.049, 0.620)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.2850	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Protocol DS8201-A-U302 Supplementary analyses - Germany

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
<75	T-DXd (N=250)	20 (8.0)	5.41 (1.82, 16.07)	5.06 (1.75, 14.59)	0.064 (0.027, 0.101)	3.81 (1.29, 11.24)	0.9880
	T-DM1 (N=253)	4 (1.6)				0.0092	
>=75	T-DXd (N=7)	3 (42.9)	NE (NE, NE)	NE (NE, NE)	0.429 (0.062, 0.795)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.1287	
Metabolism and nutrition disorders							
Any PT							
<75	T-DXd (N=250)	17 (6.8)	1.77 (0.80, 3.95)	1.72 (0.80, 3.68)	0.028 (-0.011, 0.068)	1.32 (0.60, 2.90)	0.9898
	T-DM1 (N=253)	10 (4.0)				0.4864	
>=75	T-DXd (N=7)	1 (14.3)	NE (NE, NE)	NE (NE, NE)	0.143 (-0.116, 0.402)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.2850	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Protocol DS8201-A-U302 Supplementary analyses - Germany

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Asia	T-DXd (N=147)	49 (33.3)	0.78 (0.49, 1.25)	0.85 (0.63, 1.15)	-0.057 (-0.164, 0.051)	0.59 (0.40, 0.86)	0.4159
	T-DM1 (N=159)	62 (39.0)				0.0093	
North America	T-DXd (N=17)	3 (17.6)	3.43 (0.32, 36.82)	3.00 (0.35, 26.04)	0.118 (-0.095, 0.331)	2.41 (0.25, 23.29)	
	T-DM1 (N=17)	1 (5.9)				0.4315	
Europe	T-DXd (N=52)	8 (15.4)	1.30 (0.42, 4.07)	1.26 (0.47, 3.36)	0.031 (-0.103, 0.166)	0.95 (0.33, 2.76)	
	T-DM1 (N=49)	6 (12.2)				0.9323	
Rest of World	T-DXd (N=41)	5 (12.2)	0.49 (0.14, 1.65)	0.55 (0.20, 1.53)	-0.100 (-0.269, 0.068)	0.45 (0.15, 1.38)	
	T-DM1 (N=36)	8 (22.2)				0.1519	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Protocol DS8201-A-U302 Supplementary analyses - Germany

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
Asia	T-DXd (N=147)	33 (22.4)	6.29 (2.68, 14.72)	5.10 (2.33, 11.17)	0.180 (0.106, 0.255)	4.10 (1.80, 9.31)	1.0000
	T-DM1 (N=159)	7 (4.4)				0.0003	
North America	T-DXd (N=17)	1 (5.9)	NE (NE, NE)	NE (NE, NE)	0.059 (-0.053, 0.171)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.4008	
Europe	T-DXd (N=52)	4 (7.7)	NE (NE, NE)	NE (NE, NE)	0.077 (0.004, 0.149)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.0865	
Rest of World	T-DXd (N=41)	1 (2.4)	NE (NE, NE)	NE (NE, NE)	0.024 (-0.023, 0.072)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.5637	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Asia	T-DXd (N=147)	17 (11.6)	0.30 (0.16, 0.56)	0.38 (0.23, 0.64)	-0.186 (-0.274, -0.098)	0.29 (0.16, 0.50)	1.0000
	T-DM1 (N=159)	48 (30.2)				<.0001	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	0	NE (NE, NE)	NE (NE, NE)	-0.061 (-0.128, 0.006)	NE (NE, NE)	
	T-DM1 (N=49)	3 (6.1)				0.0714	
Rest of World	T-DXd (N=41)	0	NE (NE, NE)	NE (NE, NE)	-0.028 (-0.081, 0.026)	NE (NE, NE)	
	T-DM1 (N=36)	1 (2.8)				0.2859	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
Asia	T-DXd (N=147)	14 (9.5)	16.63 (2.16, 128.14)	15.14 (2.02, 113.73)	0.089 (0.040, 0.138)	11.43 (1.50, 87.20)	1.0000
	T-DM1 (N=159)	1 (0.6)				0.0031	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=49)	0				NE	
Rest of World	T-DXd (N=41)	1 (2.4)	NE (NE, NE)	NE (NE, NE)	0.024 (-0.023, 0.072)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.4945	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Asia	T-DXd (N=147)	20 (13.6)	1.23 (0.62, 2.44)	1.20 (0.66, 2.18)	0.023 (-0.051, 0.097)	0.81 (0.42, 1.56)	0.5465
	T-DM1 (N=159)	18 (11.3)				0.5322	
North America	T-DXd (N=17)	4 (23.5)	2.31 (0.36, 14.72)	2.00 (0.42, 9.50)	0.118 (-0.136, 0.371)	1.51 (0.28, 8.33)	
	T-DM1 (N=17)	2 (11.8)				0.6305	
Europe	T-DXd (N=52)	5 (9.6)	0.55 (0.17, 1.80)	0.59 (0.21, 1.68)	-0.067 (-0.198, 0.064)	0.41 (0.13, 1.25)	
	T-DM1 (N=49)	8 (16.3)				0.1058	
Rest of World	T-DXd (N=41)	8 (19.5)	1.50 (0.44, 5.09)	1.40 (0.50, 3.91)	0.056 (-0.110, 0.222)	1.11 (0.36, 3.41)	
	T-DM1 (N=36)	5 (13.9)				0.8579	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
Asia	T-DXd (N=147)	1 (0.7)	0.13 (0.02, 1.05)	0.14 (0.02, 1.07)	-0.044 (-0.080, -0.007)	0.11 (0.01, 0.92)	0.8965
	T-DM1 (N=159)	8 (5.0)				0.0144	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	-0.059 (-0.171, 0.053)	NE (NE, NE)	
	T-DM1 (N=17)	1 (5.9)				0.3173	
Europe	T-DXd (N=52)	0	NE (NE, NE)	NE (NE, NE)	-0.082 (-0.158, -0.005)	NE (NE, NE)	
	T-DM1 (N=49)	4 (8.2)				0.0307	
Rest of World	T-DXd (N=41)	1 (2.4)	0.43 (0.04, 4.89)	0.44 (0.04, 4.64)	-0.031 (-0.120, 0.057)	0.32 (0.03, 3.63)	
	T-DM1 (N=36)	2 (5.6)				0.3331	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Asia	T-DXd (N=147)	14 (9.5)	3.24 (1.14, 9.24)	3.03 (1.12, 8.20)	0.064 (0.009, 0.118)	2.00 (0.71, 5.65)	0.9979
	T-DM1 (N=159)	5 (3.1)				0.1827	
North America	T-DXd (N=17)	2 (11.8)	NE (NE, NE)	NE (NE, NE)	0.118 (-0.036, 0.271)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.1869	
Europe	T-DXd (N=52)	6 (11.5)	NE (NE, NE)	NE (NE, NE)	0.115 (0.029, 0.202)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.0168	
Rest of World	T-DXd (N=41)	4 (9.8)	3.78 (0.40, 35.52)	3.51 (0.41, 30.00)	0.070 (-0.036, 0.175)	3.53 (0.40, 31.63)	
	T-DM1 (N=36)	1 (2.8)				0.2279	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Nausea							
Asia	T-DXd (N=147)	6 (4.1)	6.72 (0.80, 56.52)	6.49 (0.79, 53.27)	0.035 (0.000, 0.069)	4.82 (0.57, 40.66)	1.0000
	T-DM1 (N=159)	1 (0.6)				0.1118	
North America	T-DXd (N=17)	2 (11.8)	NE (NE, NE)	NE (NE, NE)	0.118 (-0.036, 0.271)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.1869	
Europe	T-DXd (N=52)	6 (11.5)	NE (NE, NE)	NE (NE, NE)	0.115 (0.029, 0.202)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.0168	
Rest of World	T-DXd (N=41)	3 (7.3)	NE (NE, NE)	NE (NE, NE)	0.073 (-0.007, 0.153)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.1053	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
Asia	T-DXd (N=147)	15 (10.2)	17.95 (2.34, 137.72)	16.22 (2.17, 121.30)	0.096 (0.045, 0.146)	11.21 (1.47, 85.65)	0.2553
	T-DM1 (N=159)	1 (0.6)				0.0036	
North America	T-DXd (N=17)	1 (5.9)	NE (NE, NE)	NE (NE, NE)	0.059 (-0.053, 0.171)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.4212	
Europe	T-DXd (N=52)	5 (9.6)	5.11 (0.57, 45.37)	4.71 (0.57, 38.91)	0.076 (-0.014, 0.165)	4.18 (0.49, 35.92)	
	T-DM1 (N=49)	1 (2.0)				0.1571	
Rest of World	T-DXd (N=41)	2 (4.9)	0.87 (0.12, 6.53)	0.88 (0.13, 5.92)	-0.007 (-0.107, 0.093)	0.74 (0.10, 5.25)	
	T-DM1 (N=36)	2 (5.6)				0.7586	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Asia	T-DXd (N=147)	8 (5.4)	1.47 (0.50, 4.33)	1.44 (0.51, 4.06)	0.017 (-0.030, 0.064)	1.04 (0.36, 3.03)	0.7975
	T-DM1 (N=159)	6 (3.8)				0.9391	
North America	T-DXd (N=17)	3 (17.6)	3.43 (0.32, 36.82)	3.00 (0.35, 26.04)	0.118 (-0.095, 0.331)	2.51 (0.26, 24.22)	
	T-DM1 (N=17)	1 (5.9)				0.4114	
Europe	T-DXd (N=52)	4 (7.7)	4.00 (0.43, 37.11)	3.77 (0.44, 32.56)	0.057 (-0.026, 0.139)	3.53 (0.39, 31.58)	
	T-DM1 (N=49)	1 (2.0)				0.2290	
Rest of World	T-DXd (N=41)	3 (7.3)	1.34 (0.21, 8.52)	1.32 (0.23, 7.45)	0.018 (-0.092, 0.127)	0.90 (0.15, 5.52)	
	T-DM1 (N=36)	2 (5.6)				0.9066	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
White	T-DXd (N=71)	10 (14.1)	1.13 (0.43, 2.97)	1.11 (0.48, 2.57)	0.014 (-0.098, 0.126)	0.85 (0.34, 2.11)	0.7038
	T-DM1 (N=71)	9 (12.7)				0.7280	
Black or African American	T-DXd (N=10)	2 (20.0)	0.31 (0.04, 2.38)	0.45 (0.11, 1.90)	-0.244 (-0.653, 0.164)	0.34 (0.06, 1.90)	
	T-DM1 (N=9)	4 (44.4)				0.1972	
Asian	T-DXd (N=149)	50 (33.6)	0.81 (0.51, 1.28)	0.87 (0.65, 1.17)	-0.050 (-0.156, 0.057)	0.61 (0.42, 0.89)	
	T-DM1 (N=161)	62 (38.5)				0.0139	
Other	T-DXd (N=27)	3 (11.1)	1.12 (0.17, 7.45)	1.11 (0.20, 6.04)	0.011 (-0.166, 0.188)	0.89 (0.15, 5.38)	
	T-DM1 (N=20)	2 (10.0)				0.8997	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
White	T-DXd (N=71)	2 (2.8)	NE (NE, NE)	NE (NE, NE)	0.028 (-0.010, 0.067)	NE (NE, NE)	1.0000
	T-DM1 (N=71)	0				0.2287	
Black or African American	T-DXd (N=10)	1 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.086, 0.286)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.5403	
Asian	T-DXd (N=149)	34 (22.8)	6.50 (2.78, 15.20)	5.25 (2.40, 11.48)	0.185 (0.110, 0.259)	4.28 (1.89, 9.69)	
	T-DM1 (N=161)	7 (4.3)				0.0002	
Other	T-DXd (N=27)	2 (7.4)	NE (NE, NE)	NE (NE, NE)	0.074 (-0.025, 0.173)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.2650	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
White	T-DXd (N=71)	0	NE (NE, NE)	NE (NE, NE)	-0.042 (-0.089, 0.005)	NE (NE, NE)	1.0000
	T-DM1 (N=71)	3 (4.2)				0.0811	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	17 (11.4)	0.30 (0.17, 0.56)	0.38 (0.23, 0.63)	-0.184 (-0.271, -0.097)	0.29 (0.16, 0.50)	
	T-DM1 (N=161)	48 (29.8)				<.0001	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	-0.050 (-0.146, 0.046)	NE (NE, NE)	
	T-DM1 (N=20)	1 (5.0)				0.2453	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
White	T-DXd (N=71)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	1.0000
	T-DM1 (N=71)	0				NE	
Black or African American	T-DXd (N=10)	1 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.086, 0.286)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.4292	
Asian	T-DXd (N=149)	14 (9.4)	16.59 (2.15, 127.81)	15.13 (2.01, 113.64)	0.088 (0.039, 0.136)	11.44 (1.50, 87.30)	
	T-DM1 (N=161)	1 (0.6)				0.0030	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=20)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
White	T-DXd (N=71)	11 (15.5)	1.44 (0.54, 3.83)	1.38 (0.59, 3.21)	0.042 (-0.070, 0.154)	1.04 (0.42, 2.61)	0.4349
	T-DM1 (N=71)	8 (11.3)				0.9277	
Black or African American	T-DXd (N=10)	2 (20.0)	2.00 (0.15, 26.73)	1.80 (0.19, 16.66)	0.089 (-0.233, 0.411)	1.38 (0.12, 15.49)	
	T-DM1 (N=9)	1 (11.1)				0.7913	
Asian	T-DXd (N=149)	21 (14.1)	1.23 (0.63, 2.38)	1.19 (0.67, 2.13)	0.023 (-0.052, 0.098)	0.82 (0.44, 1.55)	
	T-DM1 (N=161)	19 (11.8)				0.5436	
Other	T-DXd (N=27)	3 (11.1)	0.38 (0.08, 1.80)	0.44 (0.12, 1.65)	-0.139 (-0.363, 0.085)	0.31 (0.07, 1.33)	
	T-DM1 (N=20)	5 (25.0)				0.0961	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
White	T-DXd (N=71)	1 (1.4)	0.32 (0.03, 3.19)	0.33 (0.04, 3.13)	-0.028 (-0.082, 0.026)	0.22 (0.02, 2.24)	0.9225
	T-DM1 (N=71)	3 (4.2)				0.1677	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	-0.111 (-0.316, 0.094)	NE (NE, NE)	
	T-DM1 (N=9)	1 (11.1)				0.2918	
Asian	T-DXd (N=149)	1 (0.7)	0.11 (0.01, 0.91)	0.12 (0.02, 0.94)	-0.049 (-0.087, -0.011)	0.10 (0.01, 0.82)	
	T-DM1 (N=161)	9 (5.6)				0.0085	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	-0.100 (-0.231, 0.031)	NE (NE, NE)	
	T-DM1 (N=20)	2 (10.0)				0.0960	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
White	T-DXd (N=71)	7 (9.9)	7.66 (0.92, 63.94)	7.00 (0.88, 55.44)	0.085 (0.010, 0.159)	7.01 (0.86, 56.95)	0.8973
	T-DM1 (N=71)	1 (1.4)				0.0338	
Black or African American	T-DXd (N=10)	2 (20.0)	NE (NE, NE)	NE (NE, NE)	0.200 (-0.048, 0.448)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.2117	
Asian	T-DXd (N=149)	14 (9.4)	3.24 (1.14, 9.22)	3.03 (1.12, 8.20)	0.063 (0.009, 0.117)	2.01 (0.71, 5.68)	
	T-DM1 (N=161)	5 (3.1)				0.1787	
Other	T-DXd (N=27)	3 (11.1)	NE (NE, NE)	NE (NE, NE)	0.111 (-0.007, 0.230)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.1319	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Nausea							
White	T-DXd (N=71)	7 (9.9)	NE (NE, NE)	NE (NE, NE)	0.099 (0.029, 0.168)	NE (NE, NE)	1.0000
	T-DM1 (N=71)	0				0.0082	
Black or African American	T-DXd (N=10)	2 (20.0)	NE (NE, NE)	NE (NE, NE)	0.200 (-0.048, 0.448)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.2117	
Asian	T-DXd (N=149)	6 (4.0)	6.71 (0.80, 56.43)	6.48 (0.79, 53.22)	0.034 (0.000, 0.068)	4.85 (0.58, 40.89)	
	T-DM1 (N=161)	1 (0.6)				0.1098	
Other	T-DXd (N=27)	2 (7.4)	NE (NE, NE)	NE (NE, NE)	0.074 (-0.025, 0.173)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.2251	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
White	T-DXd (N=71)	4 (5.6)	2.06 (0.37, 11.62)	2.00 (0.38, 10.57)	0.028 (-0.038, 0.094)	1.72 (0.31, 9.42)	0.5131
	T-DM1 (N=71)	2 (2.8)				0.5273	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	-0.111 (-0.316, 0.094)	NE (NE, NE)	
	T-DM1 (N=9)	1 (11.1)				0.2918	
Asian	T-DXd (N=149)	15 (10.1)	17.91 (2.34, 137.35)	16.21 (2.17, 121.20)	0.094 (0.045, 0.144)	11.21 (1.47, 85.65)	
	T-DM1 (N=161)	1 (0.6)				0.0036	
Other	T-DXd (N=27)	4 (14.8)	NE (NE, NE)	NE (NE, NE)	0.148 (0.014, 0.282)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.1290	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
White	T-DXd (N=71)	5 (7.0)	1.72 (0.39, 7.47)	1.67 (0.41, 6.71)	0.028 (-0.048, 0.104)	1.44 (0.34, 6.06)	0.9835
	T-DM1 (N=71)	3 (4.2)				0.6184	
Black or African American	T-DXd (N=10)	2 (20.0)	NE (NE, NE)	NE (NE, NE)	0.200 (-0.048, 0.448)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.2262	
Asian	T-DXd (N=149)	8 (5.4)	1.47 (0.50, 4.33)	1.44 (0.51, 4.05)	0.016 (-0.030, 0.063)	1.05 (0.36, 3.05)	
	T-DM1 (N=161)	6 (3.7)				0.9286	
Other	T-DXd (N=27)	3 (11.1)	2.37 (0.23, 24.70)	2.22 (0.25, 19.82)	0.061 (-0.091, 0.213)	1.89 (0.20, 18.17)	
	T-DM1 (N=20)	1 (5.0)				0.5769	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
0	T-DXd (N=152)	32 (21.1)	0.58 (0.35, 0.96)	0.67 (0.46, 0.97)	-0.106 (-0.200, -0.011)	0.47 (0.30, 0.73)	0.0377
	T-DM1 (N=174)	55 (31.6)				0.0007	
1	T-DXd (N=105)	33 (31.4)	1.35 (0.72, 2.56)	1.24 (0.79, 1.97)	0.061 (-0.066, 0.189)	0.98 (0.57, 1.69)	
	T-DM1 (N=87)	22 (25.3)				0.9892	
Neutrophil count decreased							
0	T-DXd (N=152)	22 (14.5)	7.19 (2.42, 21.38)	6.30 (2.22, 17.86)	0.122 (0.062, 0.182)	4.89 (1.68, 14.25)	0.7789
	T-DM1 (N=174)	4 (2.3)				0.0013	
1	T-DXd (N=105)	17 (16.2)	5.41 (1.53, 19.13)	4.70 (1.42, 15.50)	0.127 (0.047, 0.208)	3.76 (1.10, 12.92)	
	T-DM1 (N=87)	3 (3.4)				0.0241	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
0	T-DXd (N=152)	6 (3.9)	0.15 (0.06, 0.37)	0.19 (0.08, 0.43)	-0.173 (-0.241, -0.105)	0.15 (0.06, 0.36)	0.0379
	T-DM1 (N=174)	37 (21.3)				<.0001	
1	T-DXd (N=105)	11 (10.5)	0.56 (0.24, 1.30)	0.61 (0.29, 1.25)	-0.068 (-0.166, 0.031)	0.50 (0.23, 1.09)	
	T-DM1 (N=87)	15 (17.2)				0.0839	
White blood cell count decreased							
0	T-DXd (N=152)	6 (3.9)	NE (NE, NE)	NE (NE, NE)	0.039 (0.009, 0.070)	NE (NE, NE)	0.9904
	T-DM1 (N=174)	0				0.0373	
1	T-DXd (N=105)	9 (8.6)	8.06 (1.00, 64.93)	7.46 (0.96, 57.72)	0.074 (0.016, 0.132)	5.99 (0.76, 47.42)	
	T-DM1 (N=87)	1 (1.1)				0.0536	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
0	T-DXd (N=152)	19 (12.5)	1.32 (0.66, 2.64)	1.28 (0.69, 2.37)	0.027 (-0.041, 0.096)	0.89 (0.46, 1.72)	0.5536
	T-DM1 (N=174)	17 (9.8)				0.7287	
1	T-DXd (N=105)	18 (17.1)	0.92 (0.44, 1.93)	0.93 (0.51, 1.72)	-0.012 (-0.121, 0.096)	0.61 (0.30, 1.23)	
	T-DM1 (N=87)	16 (18.4)				0.1615	
Thrombocytopenia							
0	T-DXd (N=152)	1 (0.7)	0.14 (0.02, 1.11)	0.14 (0.02, 1.13)	-0.039 (-0.073, -0.006)	0.13 (0.02, 1.07)	0.8996
	T-DM1 (N=174)	8 (4.6)				0.0256	
1	T-DXd (N=105)	1 (1.0)	0.11 (0.01, 0.91)	0.12 (0.01, 0.94)	-0.071 (-0.131, -0.011)	0.08 (0.01, 0.66)	
	T-DM1 (N=87)	7 (8.0)				0.0034	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
0	T-DXd (N=152)	17 (11.2)	5.35 (1.76, 16.28)	4.87 (1.67, 14.14)	0.089 (0.034, 0.144)	4.06 (1.36, 12.15)	0.7888
	T-DM1 (N=174)	4 (2.3)				0.0067	
1	T-DXd (N=105)	9 (8.6)	3.98 (0.84, 18.96)	3.73 (0.83, 16.80)	0.063 (0.001, 0.125)	3.04 (0.65, 14.22)	
	T-DM1 (N=87)	2 (2.3)				0.1390	
Nausea							
0	T-DXd (N=152)	12 (7.9)	14.83 (1.90, 115.43)	13.74 (1.81, 104.42)	0.073 (0.029, 0.118)	12.78 (1.66, 98.44)	0.9922
	T-DM1 (N=174)	1 (0.6)				0.0016	
1	T-DXd (N=105)	5 (4.8)	NE (NE, NE)	NE (NE, NE)	0.048 (0.007, 0.088)	NE (NE, NE)	
	T-DM1 (N=87)	0				0.0653	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
0	T-DXd (N=152)	12 (7.9)	7.37 (1.62, 33.48)	6.87 (1.56, 30.20)	0.067 (0.022, 0.113)	4.29 (0.95, 19.51)	0.7514
	T-DM1 (N=174)	2 (1.1)				0.0407	
1	T-DXd (N=105)	11 (10.5)	4.97 (1.07, 23.08)	4.56 (1.04, 20.01)	0.082 (0.015, 0.148)	4.00 (0.88, 18.07)	
	T-DM1 (N=87)	2 (2.3)				0.0516	
Metabolism and nutrition disorders							
Any PT							
0	T-DXd (N=152)	6 (3.9)	2.34 (0.58, 9.53)	2.29 (0.58, 9.00)	0.022 (-0.014, 0.059)	1.46 (0.36, 5.95)	0.6380
	T-DM1 (N=174)	3 (1.7)				0.5970	
1	T-DXd (N=105)	12 (11.4)	1.47 (0.55, 3.92)	1.42 (0.58, 3.45)	0.034 (-0.050, 0.117)	1.21 (0.47, 3.07)	
	T-DM1 (N=87)	7 (8.0)				0.6929	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Positive	T-DXd (N=133)	35 (26.3)	0.80 (0.47, 1.35)	0.85 (0.58, 1.24)	-0.046 (-0.153, 0.061)	0.63 (0.40, 0.98)	0.8658
	T-DM1 (N=139)	43 (30.9)				0.0468	
Negative	T-DXd (N=123)	30 (24.4)	0.83 (0.47, 1.46)	0.87 (0.57, 1.32)	-0.037 (-0.147, 0.073)	0.66 (0.40, 1.08)	
	T-DM1 (N=121)	34 (28.1)				0.1063	
Neutrophil count decreased							
Positive	T-DXd (N=133)	23 (17.3)	7.06 (2.37, 21.01)	6.01 (2.14, 16.91)	0.144 (0.074, 0.214)	4.86 (1.67, 14.10)	0.8689
	T-DM1 (N=139)	4 (2.9)				0.0013	
Negative	T-DXd (N=123)	16 (13.0)	5.88 (1.67, 20.75)	5.25 (1.57, 17.55)	0.105 (0.040, 0.171)	4.06 (1.18, 14.03)	
	T-DM1 (N=121)	3 (2.5)				0.0166	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Positive	T-DXd (N=133)	8 (6.0)	0.31 (0.13, 0.71)	0.35 (0.16, 0.75)	-0.113 (-0.187, -0.038)	0.29 (0.13, 0.65)	0.8188
	T-DM1 (N=139)	24 (17.3)				0.0016	
Negative	T-DXd (N=123)	9 (7.3)	0.26 (0.12, 0.58)	0.32 (0.16, 0.64)	-0.158 (-0.246, -0.070)	0.26 (0.12, 0.55)	
	T-DM1 (N=121)	28 (23.1)				0.0002	
White blood cell count decreased							
Positive	T-DXd (N=133)	6 (4.5)	6.52 (0.77, 54.90)	6.27 (0.77, 51.39)	0.038 (0.000, 0.076)	4.30 (0.51, 35.83)	0.9906
	T-DM1 (N=139)	1 (0.7)				0.1423	
Negative	T-DXd (N=123)	9 (7.3)	NE (NE, NE)	NE (NE, NE)	0.073 (0.027, 0.119)	NE (NE, NE)	
	T-DM1 (N=121)	0				0.0091	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Positive	T-DXd (N=133)	18 (13.5)	1.29 (0.62, 2.69)	1.25 (0.66, 2.38)	0.027 (-0.050, 0.105)	0.90 (0.45, 1.81)	0.6877
	T-DM1 (N=139)	15 (10.8)				0.7774	
Negative	T-DXd (N=123)	19 (15.4)	1.05 (0.52, 2.10)	1.04 (0.57, 1.88)	0.006 (-0.084, 0.096)	0.70 (0.36, 1.35)	
	T-DM1 (N=121)	18 (14.9)				0.2833	
Thrombocytopenia							
Positive	T-DXd (N=133)	1 (0.8)	0.14 (0.02, 1.18)	0.15 (0.02, 1.20)	-0.043 (-0.082, -0.004)	0.13 (0.02, 1.06)	0.9109
	T-DM1 (N=139)	7 (5.0)				0.0250	
Negative	T-DXd (N=123)	1 (0.8)	0.12 (0.01, 0.94)	0.12 (0.02, 0.97)	-0.058 (-0.105, -0.011)	0.09 (0.01, 0.75)	
	T-DM1 (N=121)	8 (6.6)				0.0063	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Positive	T-DXd (N=133)	12 (9.0)	13.69 (1.75, 106.80)	12.54 (1.65, 95.12)	0.083 (0.032, 0.134)	11.11 (1.44, 85.76)	0.1924
	T-DM1 (N=139)	1 (0.7)				0.0037	
Negative	T-DXd (N=123)	14 (11.4)	2.98 (1.04, 8.55)	2.75 (1.02, 7.41)	0.072 (0.006, 0.139)	2.14 (0.76, 6.02)	
	T-DM1 (N=121)	5 (4.1)				0.1388	
Nausea							
Positive	T-DXd (N=133)	9 (6.8)	NE (NE, NE)	NE (NE, NE)	0.068 (0.025, 0.110)	NE (NE, NE)	0.9890
	T-DM1 (N=139)	0				0.0031	
Negative	T-DXd (N=123)	8 (6.5)	8.35 (1.03, 67.78)	7.87 (1.00, 61.97)	0.057 (0.010, 0.103)	6.86 (0.85, 55.16)	
	T-DM1 (N=121)	1 (0.8)				0.0361	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
Positive	T-DXd (N=133)	10 (7.5)	3.68 (0.99, 13.69)	3.48 (0.98, 12.38)	0.054 (0.003, 0.105)	2.38 (0.64, 8.81)	0.2759
	T-DM1 (N=139)	3 (2.2)				0.1816	
Negative	T-DXd (N=123)	13 (10.6)	14.18 (1.83, 110.20)	12.79 (1.70, 96.25)	0.097 (0.041, 0.154)	10.53 (1.37, 80.76)	
	T-DM1 (N=121)	1 (0.8)				0.0049	
Metabolism and nutrition disorders							
Any PT							
Positive	T-DXd (N=133)	8 (6.0)	1.72 (0.55, 5.38)	1.67 (0.56, 4.98)	0.024 (-0.027, 0.075)	1.43 (0.47, 4.39)	0.8165
	T-DM1 (N=139)	5 (3.6)				0.5301	
Negative	T-DXd (N=123)	10 (8.1)	2.05 (0.68, 6.19)	1.97 (0.69, 5.59)	0.040 (-0.020, 0.100)	1.41 (0.48, 4.16)	
	T-DM1 (N=121)	5 (4.1)				0.5315	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Positive	T-DXd (N=129)	34 (26.4)	0.74 (0.43, 1.26)	0.81 (0.55, 1.18)	-0.062 (-0.173, 0.048)	0.59 (0.37, 0.93)	0.6063
	T-DM1 (N=132)	43 (32.6)				0.0252	
Negative	T-DXd (N=127)	31 (24.4)	0.88 (0.50, 1.55)	0.91 (0.60, 1.39)	-0.024 (-0.131, 0.084)	0.69 (0.42, 1.13)	
	T-DM1 (N=127)	34 (26.8)				0.1544	
Neutrophil count decreased							
Positive	T-DXd (N=129)	23 (17.8)	6.94 (2.33, 20.70)	5.88 (2.09, 16.54)	0.148 (0.076, 0.220)	4.79 (1.65, 13.91)	0.8888
	T-DM1 (N=132)	4 (3.0)				0.0015	
Negative	T-DXd (N=127)	16 (12.6)	5.96 (1.69, 20.99)	5.33 (1.59, 17.86)	0.102 (0.039, 0.166)	4.09 (1.18, 14.12)	
	T-DM1 (N=127)	3 (2.4)				0.0161	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Positive	T-DXd (N=129)	7 (5.4)	0.26 (0.11, 0.62)	0.30 (0.13, 0.67)	-0.128 (-0.204, -0.051)	0.25 (0.11, 0.58)	0.7786
	T-DM1 (N=132)	24 (18.2)				0.0006	
Negative	T-DXd (N=127)	10 (7.9)	0.30 (0.14, 0.65)	0.36 (0.18, 0.70)	-0.142 (-0.228, -0.056)	0.29 (0.14, 0.60)	
	T-DM1 (N=127)	28 (22.0)				0.0004	
White blood cell count decreased							
Positive	T-DXd (N=129)	6 (4.7)	6.39 (0.76, 53.84)	6.14 (0.75, 50.29)	0.039 (0.000, 0.078)	4.25 (0.51, 35.47)	0.9903
	T-DM1 (N=132)	1 (0.8)				0.1456	
Negative	T-DXd (N=127)	9 (7.1)	NE (NE, NE)	NE (NE, NE)	0.071 (0.026, 0.115)	NE (NE, NE)	
	T-DM1 (N=127)	0				0.0091	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Positive	T-DXd (N=129)	17 (13.2)	1.18 (0.56, 2.48)	1.16 (0.61, 2.22)	0.018 (-0.061, 0.098)	0.84 (0.42, 1.70)	0.9084
	T-DM1 (N=132)	15 (11.4)				0.6279	
Negative	T-DXd (N=127)	20 (15.7)	1.13 (0.57, 2.26)	1.11 (0.62, 2.00)	0.016 (-0.072, 0.103)	0.74 (0.39, 1.42)	
	T-DM1 (N=127)	18 (14.2)				0.3733	
Thrombocytopenia							
Positive	T-DXd (N=129)	1 (0.8)	0.14 (0.02, 1.15)	0.15 (0.02, 1.17)	-0.045 (-0.086, -0.004)	0.13 (0.02, 1.05)	0.9325
	T-DM1 (N=132)	7 (5.3)				0.0234	
Negative	T-DXd (N=127)	1 (0.8)	0.12 (0.01, 0.96)	0.13 (0.02, 0.98)	-0.055 (-0.100, -0.010)	0.09 (0.01, 0.77)	
	T-DM1 (N=127)	8 (6.3)				0.0069	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Positive	T-DXd (N=129)	11 (8.5)	12.21 (1.55, 96.02)	11.26 (1.47, 85.93)	0.078 (0.027, 0.128)	9.83 (1.26, 76.43)	0.2590
	T-DM1 (N=132)	1 (0.8)				0.0073	
Negative	T-DXd (N=127)	15 (11.8)	3.27 (1.15, 9.28)	3.00 (1.12, 8.01)	0.079 (0.013, 0.144)	2.38 (0.85, 6.61)	
	T-DM1 (N=127)	5 (3.9)				0.0878	
Nausea							
Positive	T-DXd (N=129)	8 (6.2)	NE (NE, NE)	NE (NE, NE)	0.062 (0.020, 0.104)	NE (NE, NE)	0.9894
	T-DM1 (N=132)	0				0.0061	
Negative	T-DXd (N=127)	9 (7.1)	9.61 (1.20, 76.96)	9.00 (1.16, 70.00)	0.063 (0.016, 0.110)	8.00 (1.01, 63.45)	
	T-DM1 (N=127)	1 (0.8)				0.0196	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
Positive	T-DXd (N=129)	10 (7.8)	3.61 (0.97, 13.44)	3.41 (0.96, 12.11)	0.055 (0.002, 0.107)	2.31 (0.62, 8.57)	0.2643
	T-DM1 (N=132)	3 (2.3)				0.1976	
Negative	T-DXd (N=127)	13 (10.2)	14.37 (1.85, 111.57)	13.00 (1.73, 97.90)	0.094 (0.040, 0.149)	10.57 (1.38, 81.15)	
	T-DM1 (N=127)	1 (0.8)				0.0048	
Metabolism and nutrition disorders							
Any PT							
Positive	T-DXd (N=129)	7 (5.4)	1.46 (0.45, 4.72)	1.43 (0.47, 4.40)	0.016 (-0.034, 0.067)	1.24 (0.39, 3.91)	0.5843
	T-DM1 (N=132)	5 (3.8)				0.7198	
Negative	T-DXd (N=127)	11 (8.7)	2.31 (0.78, 6.86)	2.20 (0.79, 6.15)	0.047 (-0.012, 0.107)	1.57 (0.54, 4.55)	
	T-DM1 (N=127)	5 (3.9)				0.4034	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Positive	T-DXd (N=81)	22 (27.2)	0.85 (0.44, 1.65)	0.89 (0.56, 1.43)	-0.033 (-0.168, 0.102)	0.64 (0.36, 1.13)	0.9612
	T-DM1 (N=92)	28 (30.4)				0.1336	
Negative	T-DXd (N=174)	43 (24.7)	0.79 (0.49, 1.28)	0.84 (0.59, 1.20)	-0.046 (-0.141, 0.048)	0.64 (0.42, 0.97)	
	T-DM1 (N=167)	49 (29.3)				0.0389	
Neutrophil count decreased							
Positive	T-DXd (N=81)	14 (17.3)	9.40 (2.07, 42.77)	7.95 (1.86, 33.93)	0.151 (0.064, 0.239)	6.37 (1.44, 28.19)	0.6131
	T-DM1 (N=92)	2 (2.2)				0.0053	
Negative	T-DXd (N=174)	25 (14.4)	5.44 (2.03, 14.57)	4.80 (1.88, 12.24)	0.114 (0.056, 0.172)	3.81 (1.45, 9.98)	
	T-DM1 (N=167)	5 (3.0)				0.0035	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Positive	T-DXd (N=81)	5 (6.2)	0.27 (0.10, 0.77)	0.32 (0.12, 0.81)	-0.134 (-0.230, -0.037)	0.26 (0.10, 0.71)	0.8977
	T-DM1 (N=92)	18 (19.6)				0.0051	
Negative	T-DXd (N=174)	12 (6.9)	0.29 (0.14, 0.58)	0.34 (0.18, 0.63)	-0.135 (-0.206, -0.063)	0.28 (0.15, 0.54)	
	T-DM1 (N=167)	34 (20.4)				<.0001	
White blood cell count decreased							
Positive	T-DXd (N=81)	2 (2.5)	NE (NE, NE)	NE (NE, NE)	0.025 (-0.009, 0.058)	NE (NE, NE)	0.9931
	T-DM1 (N=92)	0				0.2575	
Negative	T-DXd (N=174)	13 (7.5)	13.40 (1.73, 103.65)	12.48 (1.65, 94.32)	0.069 (0.028, 0.110)	9.80 (1.28, 75.17)	
	T-DM1 (N=167)	1 (0.6)				0.0071	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Positive	T-DXd (N=81)	9 (11.1)	1.15 (0.43, 3.06)	1.14 (0.47, 2.72)	0.013 (-0.078, 0.105)	0.78 (0.31, 1.99)	0.9797
	T-DM1 (N=92)	9 (9.8)				0.6103	
Negative	T-DXd (N=174)	28 (16.1)	1.14 (0.63, 2.07)	1.12 (0.68, 1.85)	0.017 (-0.059, 0.093)	0.79 (0.46, 1.38)	
	T-DM1 (N=167)	24 (14.4)				0.4127	
Thrombocytopenia							
Positive	T-DXd (N=81)	1 (1.2)	0.28 (0.03, 2.51)	0.28 (0.03, 2.49)	-0.031 (-0.079, 0.017)	0.23 (0.03, 2.07)	0.4449
	T-DM1 (N=92)	4 (4.3)				0.1535	
Negative	T-DXd (N=174)	1 (0.6)	0.08 (0.01, 0.64)	0.09 (0.01, 0.67)	-0.060 (-0.099, -0.021)	0.07 (0.01, 0.55)	
	T-DM1 (N=167)	11 (6.6)				0.0010	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Positive	T-DXd (N=81)	6 (7.4)	7.28 (0.86, 61.81)	6.81 (0.84, 55.42)	0.063 (0.002, 0.124)	6.43 (0.77, 53.43)	0.6565
	T-DM1 (N=92)	1 (1.1)				0.0476	
Negative	T-DXd (N=174)	20 (11.5)	4.21 (1.54, 11.49)	3.84 (1.47, 9.99)	0.085 (0.031, 0.139)	3.08 (1.15, 8.28)	
	T-DM1 (N=167)	5 (3.0)				0.0188	
Nausea							
Positive	T-DXd (N=81)	6 (7.4)	NE (NE, NE)	NE (NE, NE)	0.074 (0.017, 0.131)	NE (NE, NE)	0.9913
	T-DM1 (N=92)	0				0.0108	
Negative	T-DXd (N=174)	11 (6.3)	11.20 (1.43, 87.76)	10.56 (1.38, 80.88)	0.057 (0.019, 0.095)	9.34 (1.20, 72.65)	
	T-DM1 (N=167)	1 (0.6)				0.0093	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
Positive	T-DXd (N=81)	4 (4.9)	1.54 (0.33, 7.10)	1.51 (0.35, 6.57)	0.017 (-0.043, 0.076)	1.05 (0.23, 4.86)	0.0441
	T-DM1 (N=92)	3 (3.3)				0.9477	
Negative	T-DXd (N=174)	19 (10.9)	20.35 (2.69, 153.80)	18.24 (2.47, 134.70)	0.103 (0.055, 0.151)	14.33 (1.91, 107.44)	
	T-DM1 (N=167)	1 (0.6)				0.0007	
Metabolism and nutrition disorders							
Any PT							
Positive	T-DXd (N=81)	6 (7.4)	1.39 (0.41, 4.74)	1.36 (0.43, 4.30)	0.020 (-0.054, 0.093)	1.19 (0.36, 3.92)	0.4772
	T-DM1 (N=92)	5 (5.4)				0.7756	
Negative	T-DXd (N=174)	12 (6.9)	2.40 (0.83, 6.97)	2.30 (0.83, 6.40)	0.039 (-0.007, 0.085)	1.70 (0.59, 4.84)	
	T-DM1 (N=167)	5 (3.0)				0.3179	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Yes	T-DXd (N=160)	35 (21.9)	0.72 (0.43, 1.20)	0.78 (0.53, 1.15)	-0.062 (-0.157, 0.034)	0.58 (0.37, 0.91)	0.4258
	T-DM1 (N=157)	44 (28.0)				0.0196	
No	T-DXd (N=97)	30 (30.9)	0.96 (0.53, 1.75)	0.97 (0.65, 1.47)	-0.008 (-0.136, 0.120)	0.73 (0.44, 1.20)	
	T-DM1 (N=104)	33 (31.7)				0.2325	
Neutrophil count decreased							
Yes	T-DXd (N=160)	24 (15.0)	6.75 (2.28, 19.94)	5.89 (2.09, 16.58)	0.125 (0.064, 0.185)	4.89 (1.69, 14.15)	0.9127
	T-DM1 (N=157)	4 (2.5)				0.0012	
No	T-DXd (N=97)	15 (15.5)	6.16 (1.72, 22.00)	5.36 (1.60, 17.95)	0.126 (0.047, 0.205)	3.93 (1.13, 13.68)	
	T-DM1 (N=104)	3 (2.9)				0.0208	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Yes	T-DXd (N=160)	5 (3.1)	0.14 (0.05, 0.38)	0.17 (0.07, 0.43)	-0.153 (-0.220, -0.087)	0.15 (0.06, 0.38)	0.0442
	T-DM1 (N=157)	29 (18.5)				<.0001	
No	T-DXd (N=97)	12 (12.4)	0.50 (0.23, 1.06)	0.56 (0.29, 1.06)	-0.097 (-0.201, 0.006)	0.45 (0.22, 0.90)	
	T-DM1 (N=104)	23 (22.1)				0.0232	
White blood cell count decreased							
Yes	T-DXd (N=160)	6 (3.8)	NE (NE, NE)	NE (NE, NE)	0.038 (0.008, 0.067)	NE (NE, NE)	0.9915
	T-DM1 (N=157)	0				0.0317	
No	T-DXd (N=97)	9 (9.3)	10.53 (1.31, 84.71)	9.65 (1.25, 74.76)	0.083 (0.022, 0.144)	6.97 (0.88, 55.24)	
	T-DM1 (N=104)	1 (1.0)				0.0326	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Yes	T-DXd (N=160)	17 (10.6)	0.69 (0.35, 1.35)	0.73 (0.40, 1.30)	-0.040 (-0.113, 0.033)	0.48 (0.25, 0.91)	0.0129
	T-DM1 (N=157)	23 (14.6)				0.0211	
No	T-DXd (N=97)	20 (20.6)	2.44 (1.08, 5.53)	2.14 (1.06, 4.35)	0.110 (0.012, 0.208)	1.65 (0.77, 3.56)	
	T-DM1 (N=104)	10 (9.6)				0.1934	
Thrombocytopenia							
Yes	T-DXd (N=160)	0	NE (NE, NE)	NE (NE, NE)	-0.064 (-0.102, -0.025)	NE (NE, NE)	0.9916
	T-DM1 (N=157)	10 (6.4)				0.0010	
No	T-DXd (N=97)	2 (2.1)	0.42 (0.08, 2.20)	0.43 (0.09, 2.16)	-0.027 (-0.077, 0.022)	0.31 (0.06, 1.65)	
	T-DM1 (N=104)	5 (4.8)				0.1489	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Yes	T-DXd (N=160)	15 (9.4)	3.14 (1.11, 8.87)	2.94 (1.10, 7.91)	0.062 (0.009, 0.115)	2.58 (0.93, 7.12)	0.2276
	T-DM1 (N=157)	5 (3.2)				0.0589	
No	T-DXd (N=97)	11 (11.3)	13.17 (1.67, 104.10)	11.79 (1.55, 89.65)	0.104 (0.038, 0.170)	9.02 (1.15, 70.52)	
	T-DM1 (N=104)	1 (1.0)				0.0115	
Nausea							
Yes	T-DXd (N=160)	12 (7.5)	12.65 (1.62, 98.48)	11.78 (1.55, 89.48)	0.069 (0.026, 0.111)	10.33 (1.34, 79.81)	0.9911
	T-DM1 (N=157)	1 (0.6)				0.0056	
No	T-DXd (N=97)	5 (5.2)	NE (NE, NE)	NE (NE, NE)	0.052 (0.008, 0.096)	NE (NE, NE)	
	T-DM1 (N=104)	0				0.0229	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
Yes	T-DXd (N=160)	15 (9.4)	16.14 (2.11, 123.71)	14.72 (1.97, 110.10)	0.087 (0.041, 0.134)	10.31 (1.35, 78.69)	0.1907
	T-DM1 (N=157)	1 (0.6)				0.0055	
No	T-DXd (N=97)	8 (8.2)	3.03 (0.78, 11.76)	2.86 (0.78, 10.47)	0.054 (-0.010, 0.117)	2.32 (0.61, 8.82)	
	T-DM1 (N=104)	3 (2.9)				0.2040	
Metabolism and nutrition disorders							
Any PT							
Yes	T-DXd (N=160)	9 (5.6)	1.28 (0.46, 3.52)	1.26 (0.48, 3.30)	0.012 (-0.036, 0.060)	0.96 (0.35, 2.62)	0.2386
	T-DM1 (N=157)	7 (4.5)				0.9411	
No	T-DXd (N=97)	9 (9.3)	3.44 (0.90, 13.11)	3.22 (0.90, 11.53)	0.064 (-0.002, 0.130)	2.51 (0.67, 9.30)	
	T-DM1 (N=104)	3 (2.9)				0.1556	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
< 3 lines	T-DXd (N=186)	43 (23.1)	0.71 (0.45, 1.13)	0.78 (0.55, 1.10)	-0.065 (-0.154, 0.024)	0.58 (0.39, 0.86)	0.3348
	T-DM1 (N=189)	56 (29.6)				0.0083	
>= 3 lines	T-DXd (N=71)	22 (31.0)	1.09 (0.53, 2.23)	1.06 (0.64, 1.75)	0.018 (-0.132, 0.169)	0.79 (0.43, 1.46)	
	T-DM1 (N=72)	21 (29.2)				0.4629	
Neutrophil count decreased							
< 3 lines	T-DXd (N=186)	30 (16.1)	7.08 (2.68, 18.68)	6.10 (2.42, 15.37)	0.135 (0.077, 0.192)	4.95 (1.92, 12.78)	0.6728
	T-DM1 (N=189)	5 (2.6)				0.0003	
>= 3 lines	T-DXd (N=71)	9 (12.7)	5.08 (1.06, 24.42)	4.56 (1.02, 20.38)	0.099 (0.013, 0.185)	3.41 (0.72, 16.13)	
	T-DM1 (N=72)	2 (2.8)				0.1010	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
< 3 lines	T-DXd (N=186)	9 (4.8)	0.19 (0.09, 0.40)	0.23 (0.11, 0.46)	-0.163 (-0.229, -0.097)	0.19 (0.09, 0.39)	0.0514
	T-DM1 (N=189)	40 (21.2)				<.0001	
>= 3 lines	T-DXd (N=71)	8 (11.3)	0.63 (0.24, 1.66)	0.68 (0.29, 1.55)	-0.054 (-0.167, 0.059)	0.57 (0.23, 1.41)	
	T-DM1 (N=72)	12 (16.7)				0.2200	
White blood cell count decreased							
< 3 lines	T-DXd (N=186)	10 (5.4)	NE (NE, NE)	NE (NE, NE)	0.054 (0.021, 0.086)	NE (NE, NE)	0.9922
	T-DM1 (N=189)	0				0.0051	
>= 3 lines	T-DXd (N=71)	5 (7.0)	5.38 (0.61, 47.25)	5.07 (0.61, 42.32)	0.057 (-0.009, 0.122)	3.13 (0.35, 27.60)	
	T-DM1 (N=72)	1 (1.4)				0.2806	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
< 3 lines	T-DXd (N=186)	22 (11.8)	0.92 (0.50, 1.71)	0.93 (0.54, 1.60)	-0.009 (-0.075, 0.058)	0.65 (0.36, 1.17)	0.2410
	T-DM1 (N=189)	24 (12.7)				0.1531	
>= 3 lines	T-DXd (N=71)	15 (21.1)	1.87 (0.76, 4.62)	1.69 (0.79, 3.61)	0.086 (-0.036, 0.208)	1.06 (0.45, 2.49)	
	T-DM1 (N=72)	9 (12.5)				0.8974	
Thrombocytopenia							
< 3 lines	T-DXd (N=186)	0	NE (NE, NE)	NE (NE, NE)	-0.048 (-0.078, -0.017)	NE (NE, NE)	0.9919
	T-DM1 (N=189)	9 (4.8)				0.0022	
>= 3 lines	T-DXd (N=71)	2 (2.8)	0.32 (0.06, 1.64)	0.34 (0.07, 1.62)	-0.055 (-0.130, 0.019)	0.22 (0.04, 1.16)	
	T-DM1 (N=72)	6 (8.3)				0.0531	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
< 3 lines	T-DXd (N=186)	16 (8.6)	5.84 (1.67, 20.38)	5.42 (1.61, 18.29)	0.070 (0.026, 0.114)	4.72 (1.37, 16.27)	0.5649
	T-DM1 (N=189)	3 (1.6)				0.0069	
>= 3 lines	T-DXd (N=71)	10 (14.1)	3.77 (0.99, 14.33)	3.38 (0.97, 11.77)	0.099 (0.006, 0.192)	2.47 (0.67, 9.15)	
	T-DM1 (N=72)	3 (4.2)				0.1636	
Nausea							
< 3 lines	T-DXd (N=186)	12 (6.5)	12.97 (1.67, 100.75)	12.19 (1.60, 92.84)	0.059 (0.022, 0.096)	11.11 (1.44, 85.66)	0.9924
	T-DM1 (N=189)	1 (0.5)				0.0037	
>= 3 lines	T-DXd (N=71)	5 (7.0)	NE (NE, NE)	NE (NE, NE)	0.070 (0.011, 0.130)	NE (NE, NE)	
	T-DM1 (N=72)	0				0.0340	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
< 3 lines	T-DXd (N=186)	15 (8.1)	8.20 (1.85, 36.38)	7.62 (1.77, 32.86)	0.070 (0.028, 0.112)	5.87 (1.33, 25.79)	0.5332
	T-DM1 (N=189)	2 (1.1)				0.0080	
>= 3 lines	T-DXd (N=71)	8 (11.3)	4.44 (0.91, 21.72)	4.06 (0.89, 18.44)	0.085 (0.002, 0.168)	2.76 (0.57, 13.45)	
	T-DM1 (N=72)	2 (2.8)				0.1910	
Metabolism and nutrition disorders							
Any PT							
< 3 lines	T-DXd (N=186)	12 (6.5)	2.10 (0.77, 5.73)	2.03 (0.78, 5.30)	0.033 (-0.010, 0.076)	1.60 (0.60, 4.28)	0.6814
	T-DM1 (N=189)	6 (3.2)				0.3471	
>= 3 lines	T-DXd (N=71)	6 (8.5)	1.57 (0.42, 5.82)	1.52 (0.45, 5.16)	0.029 (-0.055, 0.113)	1.13 (0.31, 4.06)	
	T-DM1 (N=72)	4 (5.6)				0.8545	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Protocol DS8201-A-U302 Supplementary analyses - Germany

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
< 3 lines	T-DXd (N=154)	34 (22.1)	0.74 (0.44, 1.24)	0.79 (0.54, 1.18)	-0.057 (-0.154, 0.040)	0.59 (0.38, 0.94)	0.7134
	T-DM1 (N=151)	42 (27.8)				0.0279	
>= 3 lines	T-DXd (N=6)	1 (16.7)	0.40 (0.03, 6.18)	0.50 (0.06, 4.15)	-0.167 (-0.647, 0.314)	0.29 (0.02, 3.71)	
	T-DM1 (N=6)	2 (33.3)				0.3075	
Neutrophil count decreased							
< 3 lines	T-DXd (N=154)	24 (15.6)	6.78 (2.29, 20.07)	5.88 (2.09, 16.55)	0.129 (0.067, 0.192)	4.93 (1.70, 14.26)	0.9995
	T-DM1 (N=151)	4 (2.6)				0.0011	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
< 3 lines	T-DXd (N=154)	4 (2.6)	0.11 (0.04, 0.33)	0.14 (0.05, 0.38)	-0.166 (-0.234, -0.098)	0.12 (0.04, 0.33)	0.9870
	T-DM1 (N=151)	29 (19.2)				<.0001	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.3173	
White blood cell count decreased							
< 3 lines	T-DXd (N=154)	6 (3.9)	NE (NE, NE)	NE (NE, NE)	0.039 (0.008, 0.070)	NE (NE, NE)	0.9992
	T-DM1 (N=151)	0				0.0309	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
< 3 lines	T-DXd (N=154)	16 (10.4)	0.81 (0.40, 1.63)	0.83 (0.44, 1.54)	-0.022 (-0.093, 0.050)	0.56 (0.28, 1.09)	0.1116
	T-DM1 (N=151)	19 (12.6)				0.0861	
>= 3 lines	T-DXd (N=6)	1 (16.7)	0.10 (0.01, 1.54)	0.25 (0.04, 1.63)	-0.500 (-0.981, -0.019)	0.00 (0.00, NE)	
	T-DM1 (N=6)	4 (66.7)				0.0080	
Thrombocytopenia							
< 3 lines	T-DXd (N=154)	0	NE (NE, NE)	NE (NE, NE)	-0.053 (-0.089, -0.017)	NE (NE, NE)	0.9997
	T-DM1 (N=151)	8 (5.3)				0.0032	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	-0.333 (-0.711, 0.044)	NE (NE, NE)	
	T-DM1 (N=6)	2 (33.3)				0.1161	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
< 3 lines	T-DXd (N=154)	13 (8.4)	2.69 (0.94, 7.75)	2.55 (0.93, 6.98)	0.051 (-0.001, 0.104)	2.26 (0.80, 6.37)	0.9898
	T-DM1 (N=151)	5 (3.3)				0.1136	
>= 3 lines	T-DXd (N=6)	2 (33.3)	NE (NE, NE)	NE (NE, NE)	0.333 (-0.044, 0.711)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.2253	
Nausea							
< 3 lines	T-DXd (N=154)	10 (6.5)	10.42 (1.32, 82.41)	9.81 (1.27, 75.66)	0.058 (0.017, 0.099)	8.75 (1.11, 68.69)	0.9930
	T-DM1 (N=151)	1 (0.7)				0.0130	
>= 3 lines	T-DXd (N=6)	2 (33.3)	NE (NE, NE)	NE (NE, NE)	0.333 (-0.044, 0.711)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.2253	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
< 3 lines	T-DXd (N=154)	12 (7.8)	12.68 (1.63, 98.75)	11.77 (1.55, 89.38)	0.071 (0.027, 0.116)	8.61 (1.11, 66.83)	0.9934
	T-DM1 (N=151)	1 (0.7)				0.0136	
>= 3 lines	T-DXd (N=6)	3 (50.0)	NE (NE, NE)	NE (NE, NE)	0.500 (0.100, 0.900)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.1762	
Metabolism and nutrition disorders							
Any PT							
< 3 lines	T-DXd (N=154)	8 (5.2)	1.13 (0.40, 3.19)	1.12 (0.42, 3.01)	0.006 (-0.043, 0.054)	0.86 (0.31, 2.39)	0.9922
	T-DM1 (N=151)	7 (4.6)				0.7681	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.4142	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Within Normal Range	T-DXd (N=130)	30 (23.1)	0.81 (0.46, 1.43)	0.86 (0.56, 1.31)	-0.038 (-0.144, 0.067)	0.62 (0.38, 1.02)	0.5201
	T-DM1 (N=130)	35 (26.9)				0.0690	
Mild Impairment	T-DXd (N=92)	30 (32.6)	1.00 (0.55, 1.81)	1.00 (0.67, 1.49)	-0.001 (-0.132, 0.131)	0.75 (0.46, 1.24)	
	T-DM1 (N=104)	34 (32.7)				0.2834	
Moderate Impairment	T-DXd (N=30)	5 (16.7)	0.43 (0.12, 1.59)	0.52 (0.19, 1.43)	-0.152 (-0.387, 0.084)	0.42 (0.13, 1.33)	
	T-DM1 (N=22)	7 (31.8)				0.1317	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Protocol DS8201-A-U302 Supplementary analyses - Germany

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Neutrophil count decreased							
Within Normal Range	T-DXd (N=130)	21 (16.2)	24.85 (3.29, 187.72)	21.00 (2.87, 153.83)	0.154 (0.089, 0.219)	14.60 (1.95, 108.99)	0.2991
	T-DM1 (N=130)	1 (0.8)				0.0006	
Mild Impairment	T-DXd (N=92)	16 (17.4)	3.44 (1.28, 9.21)	3.01 (1.23, 7.38)	0.116 (0.027, 0.206)	2.63 (1.03, 6.76)	
	T-DM1 (N=104)	6 (5.8)				0.0373	
Moderate Impairment	T-DXd (N=30)	2 (6.7)	NE (NE, NE)	NE (NE, NE)	0.067 (-0.023, 0.156)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.2388	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Within Normal Range	T-DXd (N=130)	6 (4.6)	0.24 (0.09, 0.61)	0.27 (0.11, 0.65)	-0.123 (-0.197, -0.049)	0.22 (0.09, 0.55)	0.3613
	T-DM1 (N=130)	22 (16.9)				0.0005	
Mild Impairment	T-DXd (N=92)	10 (10.9)	0.41 (0.18, 0.90)	0.47 (0.24, 0.93)	-0.122 (-0.225, -0.019)	0.39 (0.18, 0.81)	
	T-DM1 (N=104)	24 (23.1)				0.0097	
Moderate Impairment	T-DXd (N=30)	1 (3.3)	0.09 (0.01, 0.83)	0.12 (0.02, 0.94)	-0.239 (-0.436, -0.043)	0.11 (0.01, 0.89)	
	T-DM1 (N=22)	6 (27.3)				0.0118	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
White blood cell count decreased							
Within Normal Range	T-DXd (N=130)	8 (6.2)	NE (NE, NE)	NE (NE, NE)	0.062 (0.020, 0.103)	NE (NE, NE)	1.0000
	T-DM1 (N=130)	0				0.0300	
Mild Impairment	T-DXd (N=92)	7 (7.6)	8.48 (1.02, 70.29)	7.91 (0.99, 63.11)	0.066 (0.009, 0.124)	7.09 (0.87, 57.74)	
	T-DM1 (N=104)	1 (1.0)				0.0326	
Moderate Impairment	T-DXd (N=30)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=22)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	19 (14.6)	1.31 (0.64, 2.71)	1.27 (0.67, 2.38)	0.031 (-0.051, 0.113)	0.77 (0.38, 1.54)	0.1083
	T-DM1 (N=130)	15 (11.5)				0.4576	
Mild Impairment	T-DXd (N=92)	16 (17.4)	1.61 (0.72, 3.62)	1.51 (0.75, 3.02)	0.059 (-0.040, 0.157)	1.23 (0.58, 2.62)	
	T-DM1 (N=104)	12 (11.5)				0.5831	
Moderate Impairment	T-DXd (N=30)	1 (3.3)	0.12 (0.01, 1.09)	0.15 (0.02, 1.17)	-0.194 (-0.380, -0.007)	0.11 (0.01, 0.93)	
	T-DM1 (N=22)	5 (22.7)				0.0144	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Thrombocytopenia							
Within Normal Range	T-DXd (N=130)	1 (0.8)	0.14 (0.02, 1.12)	0.14 (0.02, 1.14)	-0.046 (-0.088, -0.005)	0.11 (0.01, 0.93)	0.9310
	T-DM1 (N=130)	7 (5.4)				0.0147	
Mild Impairment	T-DXd (N=92)	1 (1.1)	0.22 (0.02, 1.90)	0.23 (0.03, 1.90)	-0.037 (-0.083, 0.009)	0.22 (0.03, 1.86)	
	T-DM1 (N=104)	5 (4.8)				0.1253	
Moderate Impairment	T-DXd (N=30)	0	NE (NE, NE)	NE (NE, NE)	-0.136 (-0.280, 0.007)	NE (NE, NE)	
	T-DM1 (N=22)	3 (13.6)				0.0263	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	13 (10.0)	7.11 (1.57, 32.18)	6.50 (1.50, 28.23)	0.085 (0.029, 0.140)	5.96 (1.34, 26.47)	0.5328
	T-DM1 (N=130)	2 (1.5)				0.0077	
Mild Impairment	T-DXd (N=92)	7 (7.6)	2.06 (0.58, 7.27)	1.98 (0.60, 6.54)	0.038 (-0.028, 0.103)	1.41 (0.41, 4.89)	
	T-DM1 (N=104)	4 (3.8)				0.5853	
Moderate Impairment	T-DXd (N=30)	6 (20.0)	NE (NE, NE)	NE (NE, NE)	0.200 (0.057, 0.343)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.0493	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Nausea							
Within Normal Range	T-DXd (N=130)	9 (6.9)	NE (NE, NE)	NE (NE, NE)	0.069 (0.026, 0.113)	NE (NE, NE)	0.9999
	T-DM1 (N=130)	0				0.0033	
Mild Impairment	T-DXd (N=92)	3 (3.3)	3.47 (0.35, 33.96)	3.39 (0.36, 32.04)	0.023 (-0.018, 0.064)	2.62 (0.27, 25.69)	
	T-DM1 (N=104)	1 (1.0)				0.3912	
Moderate Impairment	T-DXd (N=30)	5 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (0.033, 0.300)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.0665	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
Within Normal Range	T-DXd (N=130)	10 (7.7)	5.33 (1.15, 24.84)	5.00 (1.12, 22.38)	0.062 (0.011, 0.112)	3.31 (0.71, 15.37)	0.9296
	T-DM1 (N=130)	2 (1.5)				0.1072	
Mild Impairment	T-DXd (N=92)	11 (12.0)	6.93 (1.49, 32.13)	6.22 (1.41, 27.32)	0.100 (0.029, 0.172)	5.29 (1.16, 23.99)	
	T-DM1 (N=104)	2 (1.9)				0.0160	
Moderate Impairment	T-DXd (N=30)	2 (6.7)	NE (NE, NE)	NE (NE, NE)	0.067 (-0.023, 0.156)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.3398	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Metabolism and nutrition disorders							
Any PT							
Within Normal Range	T-DXd (N=130)	8 (6.2)	2.78 (0.72, 10.71)	2.67 (0.72, 9.83)	0.038 (-0.010, 0.087)	1.65 (0.43, 6.38)	0.7430
	T-DM1 (N=130)	3 (2.3)				0.4603	
Mild Impairment	T-DXd (N=92)	5 (5.4)	1.14 (0.32, 4.06)	1.13 (0.34, 3.78)	0.006 (-0.056, 0.068)	1.00 (0.29, 3.46)	
	T-DM1 (N=104)	5 (4.8)				0.9979	
Moderate Impairment	T-DXd (N=30)	4 (13.3)	1.54 (0.26, 9.25)	1.47 (0.29, 7.31)	0.042 (-0.129, 0.213)	1.19 (0.22, 6.52)	
	T-DM1 (N=22)	2 (9.1)				0.8426	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Within Normal Range	T-DXd (N=208)	47 (22.6)	0.68 (0.44, 1.05)	0.75 (0.54, 1.04)	-0.076 (-0.160, 0.008)	0.55 (0.38, 0.80)	0.1124
	T-DM1 (N=212)	64 (30.2)				0.0024	
Mild Impairment	T-DXd (N=49)	18 (36.7)	1.61 (0.68, 3.80)	1.38 (0.76, 2.51)	0.102 (-0.081, 0.285)	1.05 (0.51, 2.16)	
	T-DM1 (N=49)	13 (26.5)				0.8723	
Neutrophil count decreased							
Within Normal Range	T-DXd (N=208)	30 (14.4)	5.79 (2.35, 14.22)	5.10 (2.17, 11.99)	0.116 (0.063, 0.169)	4.13 (1.71, 9.97)	0.6778
	T-DM1 (N=212)	6 (2.8)				0.0006	
Mild Impairment	T-DXd (N=49)	9 (18.4)	10.80 (1.31, 88.87)	9.00 (1.18, 68.37)	0.163 (0.048, 0.279)	6.56 (0.82, 52.35)	
	T-DM1 (N=49)	1 (2.0)				0.0417	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Within Normal Range	T-DXd (N=208)	11 (5.3)	0.20 (0.10, 0.40)	0.24 (0.13, 0.46)	-0.164 (-0.227, -0.101)	0.20 (0.11, 0.39)	0.0290
	T-DM1 (N=212)	46 (21.7)				<.0001	
Mild Impairment	T-DXd (N=49)	6 (12.2)	1.00 (0.30, 3.35)	1.00 (0.35, 2.89)	0.000 (-0.130, 0.130)	0.78 (0.25, 2.45)	
	T-DM1 (N=49)	6 (12.2)				0.6729	
White blood cell count decreased							
Within Normal Range	T-DXd (N=208)	10 (4.8)	10.66 (1.35, 84.01)	10.19 (1.32, 78.91)	0.043 (0.013, 0.074)	8.07 (1.03, 63.32)	0.9928
	T-DM1 (N=212)	1 (0.5)				0.0183	
Mild Impairment	T-DXd (N=49)	5 (10.2)	NE (NE, NE)	NE (NE, NE)	0.102 (0.017, 0.187)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.0836	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	26 (12.5)	1.07 (0.59, 1.92)	1.06 (0.63, 1.77)	0.007 (-0.055, 0.070)	0.70 (0.40, 1.23)	0.7158
	T-DM1 (N=212)	25 (11.8)				0.2108	
Mild Impairment	T-DXd (N=49)	11 (22.4)	1.48 (0.54, 4.08)	1.38 (0.61, 3.12)	0.061 (-0.095, 0.217)	1.00 (0.40, 2.52)	
	T-DM1 (N=49)	8 (16.3)				0.9913	
Thrombocytopenia							
Within Normal Range	T-DXd (N=208)	1 (0.5)	0.10 (0.01, 0.77)	0.10 (0.01, 0.79)	-0.042 (-0.072, -0.012)	0.08 (0.01, 0.61)	0.6932
	T-DM1 (N=212)	10 (4.7)				0.0020	
Mild Impairment	T-DXd (N=49)	1 (2.0)	0.18 (0.02, 1.63)	0.20 (0.02, 1.65)	-0.082 (-0.175, 0.012)	0.18 (0.02, 1.54)	
	T-DM1 (N=49)	5 (10.2)				0.0779	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	21 (10.1)	4.65 (1.72, 12.58)	4.28 (1.65, 11.14)	0.077 (0.032, 0.123)	3.61 (1.35, 9.64)	0.9300
	T-DM1 (N=212)	5 (2.4)				0.0061	
Mild Impairment	T-DXd (N=49)	5 (10.2)	5.45 (0.61, 48.53)	5.00 (0.61, 41.25)	0.082 (-0.012, 0.175)	4.25 (0.49, 36.81)	
	T-DM1 (N=49)	1 (2.0)				0.1543	
Nausea							
Within Normal Range	T-DXd (N=208)	16 (7.7)	17.58 (2.31, 133.84)	16.31 (2.18, 121.86)	0.072 (0.035, 0.110)	14.91 (1.97, 112.65)	0.9921
	T-DM1 (N=212)	1 (0.5)				0.0005	
Mild Impairment	T-DXd (N=49)	1 (2.0)	NE (NE, NE)	NE (NE, NE)	0.020 (-0.019, 0.060)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.3173	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
Within Normal Range	T-DXd (N=208)	19 (9.1)	10.55 (2.43, 45.88)	9.68 (2.28, 41.05)	0.082 (0.041, 0.123)	7.25 (1.68, 31.33)	0.1302
	T-DM1 (N=212)	2 (0.9)				0.0020	
Mild Impairment	T-DXd (N=49)	4 (8.2)	2.09 (0.36, 11.97)	2.00 (0.38, 10.42)	0.041 (-0.054, 0.135)	1.43 (0.26, 8.00)	
	T-DM1 (N=49)	2 (4.1)				0.6790	
Metabolism and nutrition disorders							
Any PT							
Within Normal Range	T-DXd (N=208)	12 (5.8)	1.79 (0.69, 4.65)	1.75 (0.70, 4.35)	0.025 (-0.015, 0.064)	1.37 (0.54, 3.52)	0.9784
	T-DM1 (N=212)	7 (3.3)				0.5051	
Mild Impairment	T-DXd (N=49)	6 (12.2)	2.14 (0.50, 9.09)	2.00 (0.53, 7.55)	0.061 (-0.052, 0.175)	1.40 (0.35, 5.65)	
	T-DM1 (N=49)	3 (6.1)				0.6367	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Yes	T-DXd (N=192)	54 (28.1)	0.90 (0.58, 1.40)	0.93 (0.68, 1.27)	-0.022 (-0.113, 0.069)	0.68 (0.47, 1.00)	0.3278
	T-DM1 (N=188)	57 (30.3)				0.0584	
No	T-DXd (N=65)	11 (16.9)	0.54 (0.24, 1.23)	0.62 (0.32, 1.19)	-0.105 (-0.242, 0.032)	0.46 (0.22, 0.96)	
	T-DM1 (N=73)	20 (27.4)				0.0382	
Neutrophil count decreased							
Yes	T-DXd (N=192)	30 (15.6)	6.78 (2.57, 17.88)	5.88 (2.33, 14.82)	0.130 (0.073, 0.186)	4.83 (1.86, 12.49)	0.8661
	T-DM1 (N=188)	5 (2.7)				0.0003	
No	T-DXd (N=65)	9 (13.8)	5.71 (1.18, 27.47)	5.05 (1.13, 22.54)	0.111 (0.019, 0.203)	3.55 (0.76, 16.54)	
	T-DM1 (N=73)	2 (2.7)				0.0844	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Yes	T-DXd (N=192)	15 (7.8)	0.32 (0.17, 0.61)	0.38 (0.22, 0.66)	-0.129 (-0.199, -0.060)	0.30 (0.17, 0.56)	0.3486
	T-DM1 (N=188)	39 (20.7)				<.0001	
No	T-DXd (N=65)	2 (3.1)	0.15 (0.03, 0.68)	0.17 (0.04, 0.74)	-0.147 (-0.245, -0.050)	0.15 (0.03, 0.66)	
	T-DM1 (N=73)	13 (17.8)				0.0038	
White blood cell count decreased							
Yes	T-DXd (N=192)	13 (6.8)	13.58 (1.76, 104.89)	12.73 (1.68, 96.34)	0.062 (0.025, 0.099)	9.59 (1.25, 73.66)	0.9931
	T-DM1 (N=188)	1 (0.5)				0.0079	
No	T-DXd (N=65)	2 (3.1)	NE (NE, NE)	NE (NE, NE)	0.031 (-0.011, 0.073)	NE (NE, NE)	
	T-DM1 (N=73)	0				0.2255	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Yes	T-DXd (N=192)	29 (15.1)	1.49 (0.81, 2.75)	1.42 (0.83, 2.42)	0.045 (-0.022, 0.112)	1.02 (0.57, 1.81)	0.1681
	T-DM1 (N=188)	20 (10.6)				0.9541	
No	T-DXd (N=65)	8 (12.3)	0.65 (0.25, 1.68)	0.69 (0.31, 1.56)	-0.055 (-0.174, 0.064)	0.45 (0.18, 1.09)	
	T-DM1 (N=73)	13 (17.8)				0.0680	
Thrombocytopenia							
Yes	T-DXd (N=192)	1 (0.5)	0.08 (0.01, 0.66)	0.09 (0.01, 0.68)	-0.053 (-0.088, -0.018)	0.08 (0.01, 0.61)	0.4531
	T-DM1 (N=188)	11 (5.9)				0.0017	
No	T-DXd (N=65)	1 (1.5)	0.27 (0.03, 2.48)	0.28 (0.03, 2.45)	-0.039 (-0.100, 0.021)	0.20 (0.02, 1.87)	
	T-DM1 (N=73)	4 (5.5)				0.1224	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Yes	T-DXd (N=192)	16 (8.3)	3.33 (1.19, 9.27)	3.13 (1.17, 8.38)	0.057 (0.011, 0.102)	2.52 (0.91, 6.94)	0.2583
	T-DM1 (N=188)	5 (2.7)				0.0649	
No	T-DXd (N=65)	10 (15.4)	13.09 (1.63, 105.35)	11.23 (1.48, 85.36)	0.140 (0.048, 0.232)	9.75 (1.24, 76.55)	
	T-DM1 (N=73)	1 (1.4)				0.0080	
Nausea							
Yes	T-DXd (N=192)	8 (4.2)	8.13 (1.01, 65.63)	7.83 (0.99, 62.02)	0.036 (0.006, 0.066)	7.32 (0.91, 58.67)	0.9920
	T-DM1 (N=188)	1 (0.5)				0.0279	
No	T-DXd (N=65)	9 (13.8)	NE (NE, NE)	NE (NE, NE)	0.138 (0.054, 0.222)	NE (NE, NE)	
	T-DM1 (N=73)	0				0.0026	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
Yes	T-DXd (N=192)	16 (8.3)	8.45 (1.92, 37.29)	7.83 (1.83, 33.60)	0.073 (0.031, 0.114)	5.83 (1.33, 25.57)	0.5615
	T-DM1 (N=188)	2 (1.1)				0.0082	
No	T-DXd (N=65)	7 (10.8)	4.28 (0.86, 21.42)	3.93 (0.85, 18.25)	0.080 (-0.004, 0.164)	3.09 (0.64, 15.02)	
	T-DM1 (N=73)	2 (2.7)				0.1416	
Metabolism and nutrition disorders							
Any PT							
Yes	T-DXd (N=192)	15 (7.8)	2.19 (0.87, 5.50)	2.10 (0.88, 5.03)	0.041 (-0.006, 0.088)	1.65 (0.67, 4.08)	0.5105
	T-DM1 (N=188)	7 (3.7)				0.2731	
No	T-DXd (N=65)	3 (4.6)	1.13 (0.22, 5.80)	1.12 (0.23, 5.37)	0.005 (-0.063, 0.073)	0.81 (0.16, 4.04)	
	T-DM1 (N=73)	3 (4.1)				0.7997	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Yes	T-DXd (N=41)	7 (17.1)	0.60 (0.20, 1.77)	0.67 (0.28, 1.57)	-0.086 (-0.265, 0.093)	0.41 (0.15, 1.16)	0.4060
	T-DM1 (N=39)	10 (25.6)				0.0876	
No	T-DXd (N=216)	58 (26.9)	0.85 (0.56, 1.29)	0.89 (0.66, 1.20)	-0.033 (-0.118, 0.051)	0.68 (0.47, 0.96)	
	T-DM1 (N=222)	67 (30.2)				0.0364	
Neutrophil count decreased							
Yes	T-DXd (N=41)	1 (2.4)	0.95 (0.06, 15.73)	0.95 (0.06, 14.69)	-0.001 (-0.070, 0.067)	0.65 (0.04, 10.93)	0.1392
	T-DM1 (N=39)	1 (2.6)				0.7634	
No	T-DXd (N=216)	38 (17.6)	7.69 (3.18, 18.59)	6.51 (2.81, 15.08)	0.149 (0.094, 0.204)	5.36 (2.26, 12.71)	
	T-DM1 (N=222)	6 (2.7)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Yes	T-DXd (N=41)	3 (7.3)	0.26 (0.07, 1.06)	0.32 (0.09, 1.09)	-0.158 (-0.312, -0.003)	0.26 (0.07, 0.98)	0.8607
	T-DM1 (N=39)	9 (23.1)				0.0338	
No	T-DXd (N=216)	14 (6.5)	0.29 (0.15, 0.54)	0.33 (0.19, 0.59)	-0.129 (-0.190, -0.067)	0.28 (0.15, 0.51)	
	T-DM1 (N=222)	43 (19.4)				<.0001	
White blood cell count decreased							
Yes	T-DXd (N=41)	1 (2.4)	0.95 (0.06, 15.73)	0.95 (0.06, 14.69)	-0.001 (-0.070, 0.067)	0.53 (0.03, 8.49)	0.9905
	T-DM1 (N=39)	1 (2.6)				0.6492	
No	T-DXd (N=216)	14 (6.5)	NE (NE, NE)	NE (NE, NE)	0.065 (0.032, 0.098)	NE (NE, NE)	
	T-DM1 (N=222)	0				0.0010	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Yes	T-DXd (N=41)	7 (17.1)	3.81 (0.74, 19.61)	3.33 (0.74, 15.06)	0.119 (-0.015, 0.254)	1.45 (0.29, 7.27)	0.2062
	T-DM1 (N=39)	2 (5.1)				0.6508	
No	T-DXd (N=216)	30 (13.9)	0.99 (0.58, 1.71)	0.99 (0.62, 1.58)	-0.001 (-0.066, 0.064)	0.73 (0.44, 1.21)	
	T-DM1 (N=222)	31 (14.0)				0.2188	
Thrombocytopenia							
Yes	T-DXd (N=41)	0	NE (NE, NE)	NE (NE, NE)	-0.026 (-0.075, 0.024)	NE (NE, NE)	0.9912
	T-DM1 (N=39)	1 (2.6)				0.1283	
No	T-DXd (N=216)	2 (0.9)	0.14 (0.03, 0.62)	0.15 (0.03, 0.64)	-0.054 (-0.088, -0.019)	0.12 (0.03, 0.55)	
	T-DM1 (N=222)	14 (6.3)				0.0011	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Yes	T-DXd (N=41)	3 (7.3)	3.00 (0.30, 30.14)	2.85 (0.31, 26.28)	0.048 (-0.046, 0.141)	1.22 (0.12, 12.77)	0.6106
	T-DM1 (N=39)	1 (2.6)				0.8692	
No	T-DXd (N=216)	23 (10.6)	5.17 (1.93, 13.87)	4.73 (1.83, 12.21)	0.084 (0.038, 0.129)	4.11 (1.56, 10.86)	
	T-DM1 (N=222)	5 (2.3)				0.0020	
Nausea							
Yes	T-DXd (N=41)	1 (2.4)	0.95 (0.06, 15.73)	0.95 (0.06, 14.69)	-0.001 (-0.070, 0.067)	0.63 (0.04, 10.68)	0.9901
	T-DM1 (N=39)	1 (2.6)				0.7468	
No	T-DXd (N=216)	16 (7.4)	NE (NE, NE)	NE (NE, NE)	0.074 (0.039, 0.109)	NE (NE, NE)	
	T-DM1 (N=222)	0				0.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
Yes	T-DXd (N=41)	5 (12.2)	NE (NE, NE)	NE (NE, NE)	0.122 (0.022, 0.222)	NE (NE, NE)	0.9890
	T-DM1 (N=39)	0				0.0498	
No	T-DXd (N=216)	18 (8.3)	4.95 (1.65, 14.89)	4.63 (1.59, 13.44)	0.065 (0.025, 0.106)	3.42 (1.15, 10.18)	
	T-DM1 (N=222)	4 (1.8)				0.0189	
Metabolism and nutrition disorders							
Any PT							
Yes	T-DXd (N=41)	6 (14.6)	6.51 (0.75, 56.84)	5.71 (0.72, 45.28)	0.121 (0.002, 0.240)	4.16 (0.49, 35.23)	0.2453
	T-DM1 (N=39)	1 (2.6)				0.1566	
No	T-DXd (N=216)	12 (5.6)	1.39 (0.57, 3.37)	1.37 (0.59, 3.19)	0.015 (-0.025, 0.055)	1.08 (0.45, 2.57)	
	T-DM1 (N=222)	9 (4.1)				0.8673	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Any PT							
Yes	T-DXd (N=60)	11 (18.3)	0.84 (0.33, 2.13)	0.87 (0.41, 1.83)	-0.028 (-0.176, 0.120)	0.61 (0.26, 1.45)	0.9947
	T-DM1 (N=52)	11 (21.2)				0.2655	
No	T-DXd (N=197)	54 (27.4)	0.82 (0.53, 1.26)	0.87 (0.64, 1.17)	-0.042 (-0.130, 0.047)	0.65 (0.45, 0.93)	
	T-DM1 (N=209)	66 (31.6)				0.0250	
Neutrophil count decreased							
Yes	T-DXd (N=60)	3 (5.0)	1.32 (0.21, 8.19)	1.30 (0.23, 7.48)	0.012 (-0.064, 0.088)	1.08 (0.18, 6.55)	0.0623
	T-DM1 (N=52)	2 (3.8)				0.9293	
No	T-DXd (N=197)	36 (18.3)	9.12 (3.50, 23.78)	7.64 (3.06, 19.07)	0.159 (0.101, 0.217)	6.21 (2.43, 15.86)	
	T-DM1 (N=209)	5 (2.4)				<.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Investigations							
Platelet count decreased							
Yes	T-DXd (N=60)	3 (5.0)	0.25 (0.06, 0.99)	0.29 (0.08, 1.01)	-0.123 (-0.240, -0.006)	0.26 (0.07, 0.95)	0.8207
	T-DM1 (N=52)	9 (17.3)				0.0282	
No	T-DXd (N=197)	14 (7.1)	0.30 (0.16, 0.56)	0.35 (0.20, 0.61)	-0.135 (-0.200, -0.069)	0.28 (0.15, 0.52)	
	T-DM1 (N=209)	43 (20.6)				<.0001	
White blood cell count decreased							
Yes	T-DXd (N=60)	1 (1.7)	0.86 (0.05, 14.17)	0.87 (0.06, 13.51)	-0.003 (-0.052, 0.047)	0.55 (0.03, 8.83)	0.9910
	T-DM1 (N=52)	1 (1.9)				0.6700	
No	T-DXd (N=197)	14 (7.1)	NE (NE, NE)	NE (NE, NE)	0.071 (0.035, 0.107)	NE (NE, NE)	
	T-DM1 (N=209)	0				0.0008	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Blood and lymphatic system disorders							
Any PT							
Yes	T-DXd (N=60)	11 (18.3)	2.69 (0.80, 9.05)	2.38 (0.81, 7.04)	0.106 (-0.015, 0.228)	1.26 (0.38, 4.09)	0.1862
	T-DM1 (N=52)	4 (7.7)				0.7058	
No	T-DXd (N=197)	26 (13.2)	0.94 (0.53, 1.67)	0.95 (0.58, 1.56)	-0.007 (-0.073, 0.060)	0.69 (0.41, 1.19)	
	T-DM1 (N=209)	29 (13.9)				0.1802	
Thrombocytopenia							
Yes	T-DXd (N=60)	1 (1.7)	0.86 (0.05, 14.17)	0.87 (0.06, 13.51)	-0.003 (-0.052, 0.047)	0.49 (0.03, 7.89)	0.1661
	T-DM1 (N=52)	1 (1.9)				0.6097	
No	T-DXd (N=197)	1 (0.5)	0.07 (0.01, 0.55)	0.08 (0.01, 0.57)	-0.062 (-0.097, -0.027)	0.06 (0.01, 0.49)	
	T-DM1 (N=209)	14 (6.7)				0.0004	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Gastrointestinal disorders							
Any PT							
Yes	T-DXd (N=60)	5 (8.3)	4.64 (0.52, 41.04)	4.33 (0.52, 35.91)	0.064 (-0.015, 0.143)	2.88 (0.32, 25.52)	0.9405
	T-DM1 (N=52)	1 (1.9)				0.3222	
No	T-DXd (N=197)	21 (10.7)	4.87 (1.80, 13.18)	4.46 (1.71, 11.59)	0.083 (0.035, 0.130)	3.82 (1.43, 10.17)	
	T-DM1 (N=209)	5 (2.4)				0.0040	
Nausea							
Yes	T-DXd (N=60)	2 (3.3)	1.76 (0.15, 19.97)	1.73 (0.16, 18.57)	0.014 (-0.045, 0.073)	1.44 (0.13, 16.24)	0.9907
	T-DM1 (N=52)	1 (1.9)				0.7660	
No	T-DXd (N=197)	15 (7.6)	NE (NE, NE)	NE (NE, NE)	0.076 (0.039, 0.113)	NE (NE, NE)	
	T-DM1 (N=209)	0				0.0001	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 39 Severe Treatment-Emergent Adverse Events (CTCAE grade >=3) by System Organ Class, Preferred Term with incidence >= 5% in at least one arm by pre-specified subgroup - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
General disorders and administration site conditions							
Any PT							
Yes	T-DXd (N=60)	8 (13.3)	NE (NE, NE)	NE (NE, NE)	0.133 (0.047, 0.219)	NE (NE, NE)	0.9874
	T-DM1 (N=52)	0				0.0283	
No	T-DXd (N=197)	15 (7.6)	4.22 (1.38, 12.96)	3.98 (1.34, 11.78)	0.057 (0.016, 0.098)	3.00 (0.99, 9.11)	
	T-DM1 (N=209)	4 (1.9)				0.0422	
Metabolism and nutrition disorders							
Any PT							
Yes	T-DXd (N=60)	9 (15.0)	9.00 (1.10, 73.63)	7.80 (1.02, 59.53)	0.131 (0.033, 0.229)	6.09 (0.77, 48.40)	0.0834
	T-DM1 (N=52)	1 (1.9)				0.0518	
No	T-DXd (N=197)	9 (4.6)	1.06 (0.41, 2.74)	1.06 (0.43, 2.62)	0.003 (-0.037, 0.043)	0.83 (0.33, 2.10)	
	T-DM1 (N=209)	9 (4.3)				0.6899	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0.
[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test
[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
<65	T-DXd (N=209)	18 (8.6)	4.71 (1.57, 14.18)	4.39 (1.51, 12.76)	0.067 (0.024, 0.109)	2.60 (0.87, 7.75)	0.3245
	T-DM1 (N=204)	4 (2.0)				0.0746	
>=65	T-DXd (N=48)	9 (18.8)	12.92 (1.57, 106.06)	10.69 (1.40, 81.37)	0.170 (0.054, 0.286)	9.06 (1.15, 71.53)	
	T-DM1 (N=57)	1 (1.8)				0.0112	
LVEF decrease							
<65	T-DXd (N=209)	7 (3.3)	7.03 (0.86, 57.69)	6.83 (0.85, 55.04)	0.029 (0.002, 0.055)	5.00 (0.61, 40.81)	0.9996
	T-DM1 (N=204)	1 (0.5)				0.0955	
>=65	T-DXd (N=48)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=57)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Age							
Adjudicated drug-related ILD/Pneumonitis							
<75	T-DXd (N=250)	26 (10.4)	5.76 (2.17, 15.25)	5.26 (2.05, 13.49)	0.084 (0.043, 0.126)	3.37 (1.29, 8.80)	0.9910
	T-DM1 (N=253)	5 (2.0)				0.0086	
>=75	T-DXd (N=7)	1 (14.3)	NE (NE, NE)	NE (NE, NE)	0.143 (-0.116, 0.402)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.2850	
LVEF decrease							
<75	T-DXd (N=250)	7 (2.8)	7.26 (0.89, 59.43)	7.08 (0.88, 57.16)	0.024 (0.002, 0.046)	5.33 (0.65, 43.51)	0.9996
	T-DM1 (N=253)	1 (0.4)				0.0803	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Region	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Asia	T-DXd (N=147)	16 (10.9)	4.73 (1.54, 14.51)	4.33 (1.48, 12.64)	0.084 (0.028, 0.140)	2.32 (0.77, 7.01)	0.9988
	T-DM1 (N=159)	4 (2.5)				0.1236	
North America	T-DXd (N=17)	1 (5.9)	NE (NE, NE)	NE (NE, NE)	0.059 (-0.053, 0.171)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.4054	
Europe	T-DXd (N=52)	5 (9.6)	NE (NE, NE)	NE (NE, NE)	0.096 (0.016, 0.176)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.0562	
Rest of World	T-DXd (N=41)	5 (12.2)	4.86 (0.54, 43.73)	4.39 (0.54, 35.85)	0.094 (-0.019, 0.208)	3.81 (0.45, 32.62)	
	T-DM1 (N=36)	1 (2.8)				0.1888	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Region	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
LVEF decrease							
Asia	T-DXd (N=147)	6 (4.1)	NE (NE, NE)	NE (NE, NE)	0.041 (0.009, 0.073)	NE (NE, NE)	1.0000
	T-DM1 (N=159)	0				0.0361	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	0	NE (NE, NE)	NE (NE, NE)	-0.020 (-0.060, 0.019)	NE (NE, NE)	
	T-DM1 (N=49)	1 (2.0)				0.2770	
Rest of World	T-DXd (N=41)	1 (2.4)	NE (NE, NE)	NE (NE, NE)	0.024 (-0.023, 0.072)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.3625	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
White	T-DXd (N=71)	6 (8.5)	6.46 (0.76, 55.12)	6.00 (0.74, 48.57)	0.070 (0.000, 0.141)	4.42 (0.53, 36.82)	0.9857
	T-DM1 (N=71)	1 (1.4)				0.1322	
Black or African American	T-DXd (N=10)	1 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.086, 0.286)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.3711	
Asian	T-DXd (N=149)	16 (10.7)	4.72 (1.54, 14.47)	4.32 (1.48, 12.64)	0.083 (0.027, 0.138)	2.34 (0.78, 7.07)	
	T-DM1 (N=161)	4 (2.5)				0.1198	
Other	T-DXd (N=27)	4 (14.8)	NE (NE, NE)	NE (NE, NE)	0.148 (0.014, 0.282)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.1140	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Race							
LVEF decrease							
White	T-DXd (N=71)	0	NE (NE, NE)	NE (NE, NE)	-0.014 (-0.041, 0.013)	NE (NE, NE)	1.0000
	T-DM1 (N=71)	1 (1.4)				0.2760	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	6 (4.0)	NE (NE, NE)	NE (NE, NE)	0.040 (0.009, 0.072)	NE (NE, NE)	
	T-DM1 (N=161)	0				0.0355	
Other	T-DXd (N=27)	1 (3.7)	NE (NE, NE)	NE (NE, NE)	0.037 (-0.034, 0.108)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.4015	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
0	T-DXd (N=152)	18 (11.8)	5.71 (1.89, 17.27)	5.15 (1.78, 14.89)	0.095 (0.039, 0.151)	3.05 (1.03, 9.06)	0.7402
	T-DM1 (N=174)	4 (2.3)				0.0347	
1	T-DXd (N=105)	9 (8.6)	8.06 (1.00, 64.93)	7.46 (0.96, 57.72)	0.074 (0.016, 0.132)	5.71 (0.72, 45.22)	
	T-DM1 (N=87)	1 (1.1)				0.0626	
LVEF decrease							
0	T-DXd (N=152)	3 (2.0)	3.48 (0.36, 33.83)	3.43 (0.36, 32.67)	0.014 (-0.011, 0.039)	2.59 (0.26, 25.35)	0.9941
	T-DM1 (N=174)	1 (0.6)				0.3967	
1	T-DXd (N=105)	4 (3.8)	NE (NE, NE)	NE (NE, NE)	0.038 (0.001, 0.075)	NE (NE, NE)	
	T-DM1 (N=87)	0				0.1199	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Positive	T-DXd (N=133)	14 (10.5)	8.06 (1.79, 36.18)	7.32 (1.69, 31.58)	0.091 (0.035, 0.147)	4.79 (1.08, 21.18)	0.6090
	T-DM1 (N=139)	2 (1.4)				0.0229	
Negative	T-DXd (N=123)	13 (10.6)	4.65 (1.29, 16.75)	4.26 (1.25, 14.58)	0.081 (0.020, 0.142)	2.80 (0.79, 9.91)	
	T-DM1 (N=121)	3 (2.5)				0.0947	
LVEF decrease							
Positive	T-DXd (N=133)	3 (2.3)	3.18 (0.33, 30.99)	3.14 (0.33, 29.77)	0.015 (-0.014, 0.044)	2.40 (0.25, 23.11)	0.9926
	T-DM1 (N=139)	1 (0.7)				0.4341	
Negative	T-DXd (N=123)	4 (3.3)	NE (NE, NE)	NE (NE, NE)	0.033 (0.001, 0.064)	NE (NE, NE)	
	T-DM1 (N=121)	0				0.0912	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Positive	T-DXd (N=129)	14 (10.9)	7.91 (1.76, 35.56)	7.16 (1.66, 30.89)	0.093 (0.036, 0.151)	4.70 (1.06, 20.81)	0.6222
	T-DM1 (N=132)	2 (1.5)				0.0248	
Negative	T-DXd (N=127)	13 (10.2)	4.71 (1.31, 16.97)	4.33 (1.27, 14.84)	0.079 (0.020, 0.138)	2.80 (0.79, 9.90)	
	T-DM1 (N=127)	3 (2.4)				0.0949	
LVEF decrease							
Positive	T-DXd (N=129)	3 (2.3)	3.12 (0.32, 30.37)	3.07 (0.32, 29.13)	0.016 (-0.014, 0.046)	2.39 (0.25, 22.98)	0.9925
	T-DM1 (N=132)	1 (0.8)				0.4370	
Negative	T-DXd (N=127)	4 (3.1)	NE (NE, NE)	NE (NE, NE)	0.031 (0.001, 0.062)	NE (NE, NE)	
	T-DM1 (N=127)	0				0.0912	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Positive	T-DXd (N=81)	8 (9.9)	9.97 (1.22, 81.52)	9.09 (1.16, 71.10)	0.088 (0.020, 0.156)	5.54 (0.69, 44.35)	0.6106
	T-DM1 (N=92)	1 (1.1)				0.0696	
Negative	T-DXd (N=174)	19 (10.9)	5.00 (1.66, 15.01)	4.56 (1.58, 13.12)	0.085 (0.033, 0.137)	3.07 (1.04, 9.07)	
	T-DM1 (N=167)	4 (2.4)				0.0332	
LVEF decrease							
Positive	T-DXd (N=81)	2 (2.5)	2.30 (0.21, 25.89)	2.27 (0.21, 24.59)	0.014 (-0.026, 0.054)	1.62 (0.15, 17.87)	0.9942
	T-DM1 (N=92)	1 (1.1)				0.6925	
Negative	T-DXd (N=174)	5 (2.9)	NE (NE, NE)	NE (NE, NE)	0.029 (0.004, 0.054)	NE (NE, NE)	
	T-DM1 (N=167)	0				0.0550	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=160)	16 (10.0)	3.38 (1.21, 9.46)	3.14 (1.18, 8.36)	0.068 (0.014, 0.122)	1.90 (0.69, 5.24)	0.9863
	T-DM1 (N=157)	5 (3.2)				0.2077	
No	T-DXd (N=97)	11 (11.3)	NE (NE, NE)	NE (NE, NE)	0.113 (0.050, 0.177)	NE (NE, NE)	
	T-DM1 (N=104)	0				0.0039	
LVEF decrease							
Yes	T-DXd (N=160)	1 (0.6)	NE (NE, NE)	NE (NE, NE)	0.006 (-0.006, 0.018)	NE (NE, NE)	0.9935
	T-DM1 (N=157)	0				0.3977	
No	T-DXd (N=97)	6 (6.2)	6.79 (0.80, 57.47)	6.43 (0.79, 52.47)	0.052 (0.001, 0.104)	4.90 (0.59, 40.86)	
	T-DM1 (N=104)	1 (1.0)				0.1042	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
< 3 lines	T-DXd (N=186)	20 (10.8)	5.57 (1.87, 16.64)	5.08 (1.77, 14.58)	0.086 (0.037, 0.135)	3.37 (1.15, 9.91)	0.8654
	T-DM1 (N=189)	4 (2.1)				0.0189	
>= 3 lines	T-DXd (N=71)	7 (9.9)	7.77 (0.93, 64.84)	7.10 (0.90, 56.23)	0.085 (0.010, 0.159)	4.29 (0.52, 35.50)	
	T-DM1 (N=72)	1 (1.4)				0.1417	
LVEF decrease							
< 3 lines	T-DXd (N=186)	3 (1.6)	NE (NE, NE)	NE (NE, NE)	0.016 (-0.002, 0.034)	NE (NE, NE)	0.9936
	T-DM1 (N=189)	0				0.1109	
>= 3 lines	T-DXd (N=71)	4 (5.6)	4.24 (0.46, 38.90)	4.06 (0.46, 35.41)	0.042 (-0.018, 0.103)	2.66 (0.29, 24.35)	
	T-DM1 (N=72)	1 (1.4)				0.3672	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
< 3 lines	T-DXd (N=154)	16 (10.4)	3.38 (1.21, 9.49)	3.14 (1.18, 8.35)	0.071 (0.015, 0.127)	1.91 (0.69, 5.26)	0.9998
	T-DM1 (N=151)	5 (3.3)				0.2054	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	
LVEF decrease							
< 3 lines	T-DXd (N=154)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE
	T-DM1 (N=151)	0				NE	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.4142	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Within Normal Range	T-DXd (N=130)	12 (9.2)	13.12 (1.68, 102.44)	12.00 (1.58, 90.95)	0.085 (0.033, 0.137)	6.00 (0.77, 46.56)	0.3630
	T-DM1 (N=130)	1 (0.8)				0.0514	
Mild Impairment	T-DXd (N=92)	6 (6.5)	1.74 (0.48, 6.38)	1.70 (0.49, 5.82)	0.027 (-0.036, 0.089)	1.19 (0.34, 4.24)	
	T-DM1 (N=104)	4 (3.8)				0.7850	
Moderate Impairment	T-DXd (N=30)	9 (30.0)	NE (NE, NE)	NE (NE, NE)	0.300 (0.136, 0.464)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.0189	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
LVEF decrease							
Within Normal Range	T-DXd (N=130)	6 (4.6)	NE (NE, NE)	NE (NE, NE)	0.046 (0.010, 0.082)	NE (NE, NE)	1.0000
	T-DM1 (N=130)	0				0.0393	
Mild Impairment	T-DXd (N=92)	1 (1.1)	1.13 (0.07, 18.36)	1.13 (0.07, 17.82)	0.001 (-0.027, 0.030)	0.93 (0.06, 14.94)	
	T-DM1 (N=104)	1 (1.0)				0.9609	
Moderate Impairment	T-DXd (N=30)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=22)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Within Normal Range	T-DXd (N=208)	21 (10.1)	5.84 (1.97, 17.32)	5.35 (1.87, 15.32)	0.082 (0.037, 0.127)	3.64 (1.24, 10.67)	0.9448
	T-DM1 (N=212)	4 (1.9)				0.0119	
Mild Impairment	T-DXd (N=49)	6 (12.2)	6.70 (0.78, 57.88)	6.00 (0.75, 48.01)	0.102 (0.002, 0.202)	2.95 (0.36, 24.54)	
	T-DM1 (N=49)	1 (2.0)				0.2929	
LVEF decrease							
Within Normal Range	T-DXd (N=208)	5 (2.4)	5.20 (0.60, 44.87)	5.10 (0.60, 43.25)	0.019 (-0.003, 0.042)	4.28 (0.50, 36.66)	0.9940
	T-DM1 (N=212)	1 (0.5)				0.1485	
Mild Impairment	T-DXd (N=49)	2 (4.1)	NE (NE, NE)	NE (NE, NE)	0.041 (-0.015, 0.096)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.3345	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=192)	20 (10.4)	21.74 (2.89, 163.72)	19.58 (2.65, 144.45)	0.099 (0.054, 0.143)	12.26 (1.64, 91.65)	0.0646
	T-DM1 (N=188)	1 (0.5)				0.0018	
No	T-DXd (N=65)	7 (10.8)	2.08 (0.58, 7.47)	1.97 (0.60, 6.41)	0.053 (-0.039, 0.145)	1.37 (0.40, 4.73)	
	T-DM1 (N=73)	4 (5.5)				0.6183	
LVEF decrease							
Yes	T-DXd (N=192)	5 (2.6)	5.00 (0.58, 43.21)	4.90 (0.58, 41.51)	0.021 (-0.004, 0.046)	3.67 (0.42, 31.64)	0.9942
	T-DM1 (N=188)	1 (0.5)				0.2061	
No	T-DXd (N=65)	2 (3.1)	NE (NE, NE)	NE (NE, NE)	0.031 (-0.011, 0.073)	NE (NE, NE)	
	T-DM1 (N=73)	0				0.1943	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=41)	7 (17.1)	NE (NE, NE)	NE (NE, NE)	0.171 (0.056, 0.286)	NE (NE, NE)	0.9889
	T-DM1 (N=39)	0				0.0924	
No	T-DXd (N=216)	20 (9.3)	4.43 (1.63, 12.02)	4.11 (1.57, 10.76)	0.070 (0.027, 0.113)	2.84 (1.06, 7.60)	
	T-DM1 (N=222)	5 (2.3)				0.0302	
LVEF decrease							
Yes	T-DXd (N=41)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.9997
	T-DM1 (N=39)	0				NE	
No	T-DXd (N=216)	7 (3.2)	7.40 (0.90, 60.67)	7.19 (0.89, 57.99)	0.028 (0.003, 0.053)	5.56 (0.68, 45.29)	
	T-DM1 (N=222)	1 (0.5)				0.0713	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 41 Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified Subgroups - Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=60)	9 (15.0)	NE (NE, NE)	NE (NE, NE)	0.150 (0.060, 0.240)	NE (NE, NE)	0.9866
	T-DM1 (N=52)	0				0.0383	
No	T-DXd (N=197)	18 (9.1)	4.10 (1.49, 11.28)	3.82 (1.45, 10.09)	0.067 (0.022, 0.113)	2.56 (0.95, 6.93)	
	T-DM1 (N=209)	5 (2.4)				0.0551	
LVEF decrease							
Yes	T-DXd (N=60)	1 (1.7)	0.86 (0.05, 14.17)	0.87 (0.06, 13.51)	-0.003 (-0.052, 0.047)	0.75 (0.05, 11.92)	0.9934
	T-DM1 (N=52)	1 (1.9)				0.8350	
No	T-DXd (N=197)	6 (3.0)	NE (NE, NE)	NE (NE, NE)	0.030 (0.006, 0.054)	NE (NE, NE)	
	T-DM1 (N=209)	0				0.0298	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
<65	T-DXd (N=209)	2 (1.0)	1.96 (0.18, 21.80)	1.95 (0.18, 21.36)	0.005 (-0.012, 0.021)	0.99 (0.09, 11.38)	0.9929
	T-DM1 (N=204)	1 (0.5)				0.9957	
>=65	T-DXd (N=48)	4 (8.3)	NE (NE, NE)	NE (NE, NE)	0.083 (0.005, 0.162)	NE (NE, NE)	
	T-DM1 (N=57)	0				0.0440	
LVEF decrease							
<65	T-DXd (N=209)	1 (0.5)	NE (NE, NE)	NE (NE, NE)	0.005 (-0.005, 0.014)	NE (NE, NE)	0.9993
	T-DM1 (N=204)	0				0.5197	
>=65	T-DXd (N=48)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=57)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
<75	T-DXd (N=250)	5 (2.0)	5.14 (0.60, 44.34)	5.06 (0.60, 43.00)	0.016 (-0.003, 0.035)	3.20 (0.37, 27.71)	0.9951
	T-DM1 (N=253)	1 (0.4)				0.2640	
>=75	T-DXd (N=7)	1 (14.3)	NE (NE, NE)	NE (NE, NE)	0.143 (-0.116, 0.402)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.2850	
LVEF decrease							
<75	T-DXd (N=250)	1 (0.4)	NE (NE, NE)	NE (NE, NE)	0.004 (-0.004, 0.012)	NE (NE, NE)	0.9997
	T-DM1 (N=253)	0				0.4973	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Region	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Asia	T-DXd (N=147)	2 (1.4)	NE (NE, NE)	NE (NE, NE)	0.014 (-0.005, 0.032)	NE (NE, NE)	1.0000
	T-DM1 (N=159)	0				0.3725	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	4 (7.7)	NE (NE, NE)	NE (NE, NE)	0.077 (0.004, 0.149)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.0781	
Rest of World	T-DXd (N=41)	0	NE (NE, NE)	NE (NE, NE)	-0.028 (-0.081, 0.026)	NE (NE, NE)	
	T-DM1 (N=36)	1 (2.8)				0.2482	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Region	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
LVEF decrease							
Asia	T-DXd (N=147)	1 (0.7)	NE (NE, NE)	NE (NE, NE)	0.007 (-0.006, 0.020)	NE (NE, NE)	1.0000
	T-DM1 (N=159)	0				0.5182	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=49)	0				NE	
Rest of World	T-DXd (N=41)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=36)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
White	T-DXd (N=71)	2 (2.8)	2.03 (0.18, 22.89)	2.00 (0.19, 21.56)	0.014 (-0.033, 0.061)	1.56 (0.14, 17.24)	1.0000
	T-DM1 (N=71)	1 (1.4)				0.7140	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	2 (1.3)	NE (NE, NE)	NE (NE, NE)	0.013 (-0.005, 0.032)	NE (NE, NE)	
	T-DM1 (N=161)	0				0.3737	
Other	T-DXd (N=27)	2 (7.4)	NE (NE, NE)	NE (NE, NE)	0.074 (-0.025, 0.173)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.2694	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
LVEF decrease							
White	T-DXd (N=71)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	1.0000
	T-DM1 (N=71)	0				NE	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	1 (0.7)	NE (NE, NE)	NE (NE, NE)	0.007 (-0.006, 0.020)	NE (NE, NE)	
	T-DM1 (N=161)	0				0.5154	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=20)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
0	T-DXd (N=152)	4 (2.6)	NE (NE, NE)	NE (NE, NE)	0.026 (0.001, 0.052)	NE (NE, NE)	0.9944
	T-DM1 (N=174)	0				0.0885	
1	T-DXd (N=105)	2 (1.9)	1.67 (0.15, 18.73)	1.66 (0.15, 17.97)	0.008 (-0.027, 0.042)	1.24 (0.11, 13.85)	
	T-DM1 (N=87)	1 (1.1)				0.8637	
LVEF decrease							
0	T-DXd (N=152)	1 (0.7)	NE (NE, NE)	NE (NE, NE)	0.007 (-0.006, 0.019)	NE (NE, NE)	0.9992
	T-DM1 (N=174)	0				0.4872	
1	T-DXd (N=105)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=87)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Positive	T-DXd (N=133)	3 (2.3)	3.18 (0.33, 30.99)	3.14 (0.33, 29.77)	0.015 (-0.014, 0.044)	2.07 (0.21, 20.42)	0.9932
	T-DM1 (N=139)	1 (0.7)				0.5255	
Negative	T-DXd (N=123)	3 (2.4)	NE (NE, NE)	NE (NE, NE)	0.024 (-0.003, 0.052)	NE (NE, NE)	
	T-DM1 (N=121)	0				0.1388	
LVEF decrease							
Positive	T-DXd (N=133)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.9993
	T-DM1 (N=139)	0				NE	
Negative	T-DXd (N=123)	1 (0.8)	NE (NE, NE)	NE (NE, NE)	0.008 (-0.008, 0.024)	NE (NE, NE)	
	T-DM1 (N=121)	0				0.5102	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Positive	T-DXd (N=129)	3 (2.3)	3.12 (0.32, 30.37)	3.07 (0.32, 29.13)	0.016 (-0.014, 0.046)	2.01 (0.20, 19.87)	0.9930
	T-DM1 (N=132)	1 (0.8)				0.5447	
Negative	T-DXd (N=127)	3 (2.4)	NE (NE, NE)	NE (NE, NE)	0.024 (-0.003, 0.050)	NE (NE, NE)	
	T-DM1 (N=127)	0				0.1396	
LVEF decrease							
Positive	T-DXd (N=129)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.9993
	T-DM1 (N=132)	0				NE	
Negative	T-DXd (N=127)	1 (0.8)	NE (NE, NE)	NE (NE, NE)	0.008 (-0.007, 0.023)	NE (NE, NE)	
	T-DM1 (N=127)	0				0.5094	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Positive	T-DXd (N=81)	1 (1.2)	1.14 (0.07, 18.48)	1.14 (0.07, 17.87)	0.001 (-0.031, 0.034)	0.69 (0.04, 11.29)	0.9945
	T-DM1 (N=92)	1 (1.1)				0.7927	
Negative	T-DXd (N=174)	5 (2.9)	NE (NE, NE)	NE (NE, NE)	0.029 (0.004, 0.054)	NE (NE, NE)	
	T-DM1 (N=167)	0				0.0598	
LVEF decrease							
Positive	T-DXd (N=81)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.9992
	T-DM1 (N=92)	0				NE	
Negative	T-DXd (N=174)	1 (0.6)	NE (NE, NE)	NE (NE, NE)	0.006 (-0.005, 0.017)	NE (NE, NE)	
	T-DM1 (N=167)	0				0.4995	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=160)	3 (1.9)	2.98 (0.31, 28.96)	2.94 (0.31, 28.00)	0.012 (-0.012, 0.037)	1.93 (0.19, 19.34)	0.9936
	T-DM1 (N=157)	1 (0.6)				0.5685	
No	T-DXd (N=97)	3 (3.1)	NE (NE, NE)	NE (NE, NE)	0.031 (-0.004, 0.065)	NE (NE, NE)	
	T-DM1 (N=104)	0				0.1447	
LVEF decrease							
Yes	T-DXd (N=160)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.9994
	T-DM1 (N=157)	0				NE	
No	T-DXd (N=97)	1 (1.0)	NE (NE, NE)	NE (NE, NE)	0.010 (-0.010, 0.030)	NE (NE, NE)	
	T-DM1 (N=104)	0				0.4954	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
< 3 lines	T-DXd (N=186)	4 (2.2)	NE (NE, NE)	NE (NE, NE)	0.022 (0.001, 0.042)	NE (NE, NE)	0.9944
	T-DM1 (N=189)	0				0.0879	
>= 3 lines	T-DXd (N=71)	2 (2.8)	2.06 (0.18, 23.22)	2.03 (0.19, 21.87)	0.014 (-0.033, 0.061)	1.11 (0.10, 12.77)	
	T-DM1 (N=72)	1 (1.4)				0.9362	
LVEF decrease							
< 3 lines	T-DXd (N=186)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.9996
	T-DM1 (N=189)	0				NE	
>= 3 lines	T-DXd (N=71)	1 (1.4)	NE (NE, NE)	NE (NE, NE)	0.014 (-0.013, 0.041)	NE (NE, NE)	
	T-DM1 (N=72)	0				0.6065	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Lines of Systemic Therapy Prior to Pertuzumab Treatment							
Adjudicated drug-related ILD/Pneumonitis							
< 3 lines	T-DXd (N=154)	3 (1.9)	2.98 (0.31, 28.97)	2.94 (0.31, 27.96)	0.013 (-0.013, 0.038)	1.94 (0.19, 19.44)	0.9999
	T-DM1 (N=151)	1 (0.7)				0.5663	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	
LVEF decrease							
< 3 lines	T-DXd (N=154)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE
	T-DM1 (N=151)	0				NE	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Within Normal Range	T-DXd (N=130)	2 (1.5)	NE (NE, NE)	NE (NE, NE)	0.015 (-0.006, 0.037)	NE (NE, NE)	1.0000
	T-DM1 (N=130)	0				0.4261	
Mild Impairment	T-DXd (N=92)	1 (1.1)	1.13 (0.07, 18.36)	1.13 (0.07, 17.82)	0.001 (-0.027, 0.030)	0.88 (0.05, 14.10)	
	T-DM1 (N=104)	1 (1.0)				0.9262	
Moderate Impairment	T-DXd (N=30)	3 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.007, 0.207)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.1805	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
LVEF decrease							
Within Normal Range	T-DXd (N=130)	1 (0.8)	NE (NE, NE)	NE (NE, NE)	0.008 (-0.007, 0.023)	NE (NE, NE)	1.0000
	T-DM1 (N=130)	0				0.5343	
Mild Impairment	T-DXd (N=92)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=104)	0				NE	
Moderate Impairment	T-DXd (N=30)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=22)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Within Normal Range	T-DXd (N=208)	5 (2.4)	5.20 (0.60, 44.87)	5.10 (0.60, 43.25)	0.019 (-0.003, 0.042)	3.53 (0.41, 30.73)	0.9941
	T-DM1 (N=212)	1 (0.5)				0.2239	
Mild Impairment	T-DXd (N=49)	1 (2.0)	NE (NE, NE)	NE (NE, NE)	0.020 (-0.019, 0.060)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.4739	
LVEF decrease							
Within Normal Range	T-DXd (N=208)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.9996
	T-DM1 (N=212)	0				NE	
Mild Impairment	T-DXd (N=49)	1 (2.0)	NE (NE, NE)	NE (NE, NE)	0.020 (-0.019, 0.060)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.5448	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=192)	5 (2.6)	5.00 (0.58, 43.21)	4.90 (0.58, 41.51)	0.021 (-0.004, 0.046)	3.11 (0.36, 27.05)	0.9948
	T-DM1 (N=188)	1 (0.5)				0.2802	
No	T-DXd (N=65)	1 (1.5)	NE (NE, NE)	NE (NE, NE)	0.015 (-0.015, 0.045)	NE (NE, NE)	
	T-DM1 (N=73)	0				0.3367	
LVEF decrease							
Yes	T-DXd (N=192)	1 (0.5)	NE (NE, NE)	NE (NE, NE)	0.005 (-0.005, 0.015)	NE (NE, NE)	0.9992
	T-DM1 (N=188)	0				0.5233	
No	T-DXd (N=65)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=73)	0				NE	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=41)	1 (2.4)	NE (NE, NE)	NE (NE, NE)	0.024 (-0.023, 0.072)	NE (NE, NE)	0.9947
	T-DM1 (N=39)	0				0.5108	
No	T-DXd (N=216)	5 (2.3)	5.24 (0.61, 45.20)	5.14 (0.61, 43.63)	0.019 (-0.003, 0.041)	3.64 (0.42, 31.51)	
	T-DM1 (N=222)	1 (0.5)				0.2096	
LVEF decrease							
Yes	T-DXd (N=41)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.9995
	T-DM1 (N=39)	0				NE	
No	T-DXd (N=216)	1 (0.5)	NE (NE, NE)	NE (NE, NE)	0.005 (-0.004, 0.014)	NE (NE, NE)	
	T-DM1 (N=222)	0				0.4738	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 43 Serious Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=60)	2 (3.3)	NE (NE, NE)	NE (NE, NE)	0.033 (-0.012, 0.079)	NE (NE, NE)	0.9937
	T-DM1 (N=52)	0				0.3905	
No	T-DXd (N=197)	4 (2.0)	4.31 (0.48, 38.91)	4.24 (0.48, 37.64)	0.016 (-0.006, 0.037)	3.15 (0.35, 28.53)	
	T-DM1 (N=209)	1 (0.5)				0.2815	
LVEF decrease							
Yes	T-DXd (N=60)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.9994
	T-DM1 (N=52)	0				NE	
No	T-DXd (N=197)	1 (0.5)	NE (NE, NE)	NE (NE, NE)	0.005 (-0.005, 0.015)	NE (NE, NE)	
	T-DM1 (N=209)	0				0.4719	

Notes: Adverse events were coded using the MedDRA dictionary, Version 23.0 and graded according to NCI CTCAE v5.0. ILD includes all events that were submitted to the ILD Adjudication Committee for adjudication and adjudicated as drug-related ILD.

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model

[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.

NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
<65	T-DXd (N=209)	1 (0.5)	NE (NE, NE)	NE (NE, NE)	0.005 (-0.005, 0.014)	NE (NE, NE)	0.9999
	T-DM1 (N=204)	0				0.5637	
>=65	T-DXd (N=48)	1 (2.1)	NE (NE, NE)	NE (NE, NE)	0.021 (-0.020, 0.061)	NE (NE, NE)	
	T-DM1 (N=57)	0				0.2976	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Age

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
<75	T-DXd (N=250)	2 (0.8)	NE (NE, NE)	NE (NE, NE)	0.008 (-0.003, 0.019)	NE (NE, NE)	0.9996
	T-DM1 (N=253)	0				0.2657	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Region	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Asia	T-DXd (N=147)	1 (0.7)	NE (NE, NE)	NE (NE, NE)	0.007 (-0.006, 0.020)	NE (NE, NE)	1.0000
	T-DM1 (N=159)	0				0.5403	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	1 (1.9)	NE (NE, NE)	NE (NE, NE)	0.019 (-0.018, 0.057)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.3576	
Rest of World	T-DXd (N=41)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=36)	0				NE	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
White	T-DXd (N=71)	1 (1.4)	NE (NE, NE)	NE (NE, NE)	0.014 (-0.013, 0.041)	NE (NE, NE)	1.0000
	T-DM1 (N=71)	0				0.3627	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	1 (0.7)	NE (NE, NE)	NE (NE, NE)	0.007 (-0.006, 0.020)	NE (NE, NE)	
	T-DM1 (N=161)	0				0.5453	
Other	T-DXd (N=27)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=20)	0				NE	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
0	T-DXd (N=152)	2 (1.3)	NE (NE, NE)	NE (NE, NE)	0.013 (-0.005, 0.031)	NE (NE, NE)	0.9989
	T-DM1 (N=174)	0				0.2280	
1	T-DXd (N=105)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=87)	0				NE	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Positive	T-DXd (N=133)	1 (0.8)	NE (NE, NE)	NE (NE, NE)	0.008 (-0.007, 0.022)	NE (NE, NE)	1.0000
	T-DM1 (N=139)	0				0.5145	
Negative	T-DXd (N=123)	1 (0.8)	NE (NE, NE)	NE (NE, NE)	0.008 (-0.008, 0.024)	NE (NE, NE)	
	T-DM1 (N=121)	0				0.3569	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Positive	T-DXd (N=129)	1 (0.8)	NE (NE, NE)	NE (NE, NE)	0.008 (-0.007, 0.023)	NE (NE, NE)	1.0000
	T-DM1 (N=132)	0				0.5351	
Negative	T-DXd (N=127)	1 (0.8)	NE (NE, NE)	NE (NE, NE)	0.008 (-0.007, 0.023)	NE (NE, NE)	
	T-DM1 (N=127)	0				0.3578	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Positive	T-DXd (N=81)	1 (1.2)	NE (NE, NE)	NE (NE, NE)	0.012 (-0.012, 0.036)	NE (NE, NE)	0.9999
	T-DM1 (N=92)	0				0.4682	
Negative	T-DXd (N=174)	1 (0.6)	NE (NE, NE)	NE (NE, NE)	0.006 (-0.005, 0.017)	NE (NE, NE)	
	T-DM1 (N=167)	0				0.3607	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=160)	1 (0.6)	NE (NE, NE)	NE (NE, NE)	0.006 (-0.006, 0.018)	NE (NE, NE)	0.9999
	T-DM1 (N=157)	0				0.6038	
No	T-DXd (N=97)	1 (1.0)	NE (NE, NE)	NE (NE, NE)	0.010 (-0.010, 0.030)	NE (NE, NE)	
	T-DM1 (N=104)	0				0.3416	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
< 3 lines	T-DXd (N=186)	2 (1.1)	NE (NE, NE)	NE (NE, NE)	0.011 (-0.004, 0.026)	NE (NE, NE)	0.9989
	T-DM1 (N=189)	0				0.2645	
>= 3 lines	T-DXd (N=71)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=72)	0				NE	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
< 3 lines	T-DXd (N=154)	1 (0.6)	NE (NE, NE)	NE (NE, NE)	0.006 (-0.006, 0.019)	NE (NE, NE)	0.9996
	T-DM1 (N=151)	0				0.6065	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Within Normal Range	T-DXd (N=130)	1 (0.8)	NE (NE, NE)	NE (NE, NE)	0.008 (-0.007, 0.023)	NE (NE, NE)	1.0000
	T-DM1 (N=130)	0				0.6285	
Mild Impairment	T-DXd (N=92)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=104)	0				NE	
Moderate Impairment	T-DXd (N=30)	1 (3.3)	NE (NE, NE)	NE (NE, NE)	0.033 (-0.031, 0.098)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.4386	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Within Normal Range	T-DXd (N=208)	2 (1.0)	NE (NE, NE)	NE (NE, NE)	0.010 (-0.004, 0.023)	NE (NE, NE)	0.9991
	T-DM1 (N=212)	0				0.2682	
Mild Impairment	T-DXd (N=49)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=49)	0				NE	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=192)	1 (0.5)	NE (NE, NE)	NE (NE, NE)	0.005 (-0.005, 0.015)	NE (NE, NE)	0.9999
	T-DM1 (N=188)	0				0.5637	
No	T-DXd (N=65)	1 (1.5)	NE (NE, NE)	NE (NE, NE)	0.015 (-0.015, 0.045)	NE (NE, NE)	
	T-DM1 (N=73)	0				0.3367	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=41)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.9992
	T-DM1 (N=39)	0				NE	
No	T-DXd (N=216)	2 (0.9)	NE (NE, NE)	NE (NE, NE)	0.009 (-0.004, 0.022)	NE (NE, NE)	
	T-DM1 (N=222)	0				0.2568	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 45 Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=60)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.9991
	T-DM1 (N=52)	0				NE	
No	T-DXd (N=197)	2 (1.0)	NE (NE, NE)	NE (NE, NE)	0.010 (-0.004, 0.024)	NE (NE, NE)	
	T-DM1 (N=209)	0				0.2504	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Age	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
<65	T-DXd (N=209)	17 (8.1)	4.43 (1.46, 13.39)	4.15 (1.42, 12.12)	0.062 (0.020, 0.103)	2.51 (0.84, 7.53)	0.3561
	T-DM1 (N=204)	4 (2.0)				0.0881	
>=65	T-DXd (N=48)	8 (16.7)	11.20 (1.35, 93.08)	9.50 (1.23, 73.29)	0.149 (0.038, 0.260)	7.94 (0.99, 63.52)	
	T-DM1 (N=57)	1 (1.8)				0.0203	
LVEF decrease							
<65	T-DXd (N=209)	7 (3.3)	7.03 (0.86, 57.69)	6.83 (0.85, 55.04)	0.029 (0.002, 0.055)	5.00 (0.61, 40.81)	0.9996
	T-DM1 (N=204)	1 (0.5)				0.0955	
>=65	T-DXd (N=48)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=57)	0				NE	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Age							
Adjudicated drug-related ILD/Pneumonitis							
<75	T-DXd (N=250)	24 (9.6)	5.27 (1.98, 14.04)	4.86 (1.88, 12.53)	0.076 (0.036, 0.117)	3.11 (1.18, 8.20)	0.9910
	T-DM1 (N=253)	5 (2.0)				0.0153	
>=75	T-DXd (N=7)	1 (14.3)	NE (NE, NE)	NE (NE, NE)	0.143 (-0.116, 0.402)	NE (NE, NE)	
	T-DM1 (N=8)	0				0.2850	
LVEF decrease							
<75	T-DXd (N=250)	7 (2.8)	7.26 (0.89, 59.43)	7.08 (0.88, 57.16)	0.024 (0.002, 0.046)	5.33 (0.65, 43.51)	0.9996
	T-DM1 (N=253)	1 (0.4)				0.0803	
>=75	T-DXd (N=7)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=8)	0				NE	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Region

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Asia	T-DXd (N=147)	15 (10.2)	4.40 (1.43, 13.59)	4.06 (1.38, 11.94)	0.077 (0.022, 0.132)	2.23 (0.73, 6.77)	0.9971
	T-DM1 (N=159)	4 (2.5)				0.1468	
North America	T-DXd (N=17)	1 (5.9)	NE (NE, NE)	NE (NE, NE)	0.059 (-0.053, 0.171)	NE (NE, NE)	
	T-DM1 (N=17)	0				0.4054	
Europe	T-DXd (N=52)	4 (7.7)	NE (NE, NE)	NE (NE, NE)	0.077 (0.004, 0.149)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.0950	
Rest of World	T-DXd (N=41)	5 (12.2)	4.86 (0.54, 43.73)	4.39 (0.54, 35.85)	0.094 (-0.019, 0.208)	3.81 (0.45, 32.62)	
	T-DM1 (N=36)	1 (2.8)				0.1888	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Region	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
LVEF decrease							
Asia	T-DXd (N=147)	6 (4.1)	NE (NE, NE)	NE (NE, NE)	0.041 (0.009, 0.073)	NE (NE, NE)	1.0000
	T-DM1 (N=159)	0				0.0361	
North America	T-DXd (N=17)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=17)	0				NE	
Europe	T-DXd (N=52)	0	NE (NE, NE)	NE (NE, NE)	-0.020 (-0.060, 0.019)	NE (NE, NE)	
	T-DM1 (N=49)	1 (2.0)				0.2770	
Rest of World	T-DXd (N=41)	1 (2.4)	NE (NE, NE)	NE (NE, NE)	0.024 (-0.023, 0.072)	NE (NE, NE)	
	T-DM1 (N=36)	0				0.3625	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
White	T-DXd (N=71)	5 (7.0)	5.30 (0.60, 46.59)	5.00 (0.60, 41.73)	0.056 (-0.009, 0.122)	3.61 (0.42, 31.02)	0.9941
	T-DM1 (N=71)	1 (1.4)				0.2100	
Black or African American	T-DXd (N=10)	1 (10.0)	NE (NE, NE)	NE (NE, NE)	0.100 (-0.086, 0.286)	NE (NE, NE)	
	T-DM1 (N=9)	0				0.3711	
Asian	T-DXd (N=149)	15 (10.1)	4.39 (1.42, 13.56)	4.05 (1.38, 11.93)	0.076 (0.022, 0.130)	2.25 (0.74, 6.84)	
	T-DM1 (N=161)	4 (2.5)				0.1418	
Other	T-DXd (N=27)	4 (14.8)	NE (NE, NE)	NE (NE, NE)	0.148 (0.014, 0.282)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.1140	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Race

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
LVEF decrease							
White	T-DXd (N=71)	0	NE (NE, NE)	NE (NE, NE)	-0.014 (-0.041, 0.013)	NE (NE, NE)	1.0000
	T-DM1 (N=71)	1 (1.4)				0.2760	
Black or African American	T-DXd (N=10)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=9)	0				NE	
Asian	T-DXd (N=149)	6 (4.0)	NE (NE, NE)	NE (NE, NE)	0.040 (0.009, 0.072)	NE (NE, NE)	
	T-DM1 (N=161)	0				0.0355	
Other	T-DXd (N=27)	1 (3.7)	NE (NE, NE)	NE (NE, NE)	0.037 (-0.034, 0.108)	NE (NE, NE)	
	T-DM1 (N=20)	0				0.4015	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

ECOG PS

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
0	T-DXd (N=152)	16 (10.5)	5.00 (1.63, 15.30)	4.58 (1.56, 13.40)	0.082 (0.029, 0.136)	2.69 (0.90, 8.09)	0.6608
	T-DM1 (N=174)	4 (2.3)				0.0663	
1	T-DXd (N=105)	9 (8.6)	8.06 (1.00, 64.93)	7.46 (0.96, 57.72)	0.074 (0.016, 0.132)	5.71 (0.72, 45.22)	
	T-DM1 (N=87)	1 (1.1)				0.0626	
LVEF decrease							
0	T-DXd (N=152)	3 (2.0)	3.48 (0.36, 33.83)	3.43 (0.36, 32.67)	0.014 (-0.011, 0.039)	2.59 (0.26, 25.35)	0.9941
	T-DM1 (N=174)	1 (0.6)				0.3967	
1	T-DXd (N=105)	4 (3.8)	NE (NE, NE)	NE (NE, NE)	0.038 (0.001, 0.075)	NE (NE, NE)	
	T-DM1 (N=87)	0				0.1199	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Hormone Receptor Status

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Positive	T-DXd (N=133)	13 (9.8)	7.42 (1.64, 33.55)	6.79 (1.56, 29.53)	0.083 (0.029, 0.138)	4.56 (1.02, 20.30)	0.6076
	T-DM1 (N=139)	2 (1.4)				0.0289	
Negative	T-DXd (N=123)	12 (9.8)	4.25 (1.17, 15.47)	3.93 (1.14, 13.60)	0.073 (0.013, 0.132)	2.53 (0.71, 9.02)	
	T-DM1 (N=121)	3 (2.5)				0.1394	
LVEF decrease							
Positive	T-DXd (N=133)	3 (2.3)	3.18 (0.33, 30.99)	3.14 (0.33, 29.77)	0.015 (-0.014, 0.044)	2.40 (0.25, 23.11)	0.9926
	T-DM1 (N=139)	1 (0.7)				0.4341	
Negative	T-DXd (N=123)	4 (3.3)	NE (NE, NE)	NE (NE, NE)	0.033 (0.001, 0.064)	NE (NE, NE)	
	T-DM1 (N=121)	0				0.0912	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Estrogen Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Positive	T-DXd (N=129)	13 (10.1)	7.28 (1.61, 32.96)	6.65 (1.53, 28.89)	0.086 (0.030, 0.142)	4.50 (1.01, 20.03)	0.6192
	T-DM1 (N=132)	2 (1.5)				0.0308	
Negative	T-DXd (N=127)	12 (9.4)	4.31 (1.19, 15.67)	4.00 (1.16, 13.84)	0.071 (0.014, 0.128)	2.53 (0.71, 9.01)	
	T-DM1 (N=127)	3 (2.4)				0.1394	
LVEF decrease							
Positive	T-DXd (N=129)	3 (2.3)	3.12 (0.32, 30.37)	3.07 (0.32, 29.13)	0.016 (-0.014, 0.046)	2.39 (0.25, 22.98)	0.9925
	T-DM1 (N=132)	1 (0.8)				0.4370	
Negative	T-DXd (N=127)	4 (3.1)	NE (NE, NE)	NE (NE, NE)	0.031 (0.001, 0.062)	NE (NE, NE)	
	T-DM1 (N=127)	0				0.0912	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Progesterone Receptors

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Positive	T-DXd (N=81)	7 (8.6)	8.61 (1.04, 71.53)	7.95 (1.00, 63.25)	0.076 (0.011, 0.140)	4.94 (0.61, 40.19)	0.6679
	T-DM1 (N=92)	1 (1.1)				0.0980	
Negative	T-DXd (N=174)	18 (10.3)	4.70 (1.56, 14.20)	4.32 (1.49, 12.50)	0.079 (0.029, 0.130)	2.86 (0.96, 8.51)	
	T-DM1 (N=167)	4 (2.4)				0.0484	
LVEF decrease							
Positive	T-DXd (N=81)	2 (2.5)	2.30 (0.21, 25.89)	2.27 (0.21, 24.59)	0.014 (-0.026, 0.054)	1.62 (0.15, 17.87)	0.9942
	T-DM1 (N=92)	1 (1.1)				0.6925	
Negative	T-DXd (N=174)	5 (2.9)	NE (NE, NE)	NE (NE, NE)	0.029 (0.004, 0.054)	NE (NE, NE)	
	T-DM1 (N=167)	0				0.0550	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Prior Treatment with Pertuzumab

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=160)	15 (9.4)	3.14 (1.11, 8.87)	2.94 (1.10, 7.91)	0.062 (0.009, 0.115)	1.84 (0.66, 5.11)	0.9867
	T-DM1 (N=157)	5 (3.2)				0.2337	
No	T-DXd (N=97)	10 (10.3)	NE (NE, NE)	NE (NE, NE)	0.103 (0.043, 0.164)	NE (NE, NE)	
	T-DM1 (N=104)	0				0.0065	
LVEF decrease							
Yes	T-DXd (N=160)	1 (0.6)	NE (NE, NE)	NE (NE, NE)	0.006 (-0.006, 0.018)	NE (NE, NE)	0.9935
	T-DM1 (N=157)	0				0.3977	
No	T-DXd (N=97)	6 (6.2)	6.79 (0.80, 57.47)	6.43 (0.79, 52.47)	0.052 (0.001, 0.104)	4.90 (0.59, 40.86)	
	T-DM1 (N=104)	1 (1.0)				0.1042	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Lines of Prior Systemic Therapy Not Including Hormone Therapy

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
< 3 lines	T-DXd (N=186)	18 (9.7)	4.96 (1.64, 14.94)	4.57 (1.58, 13.26)	0.076 (0.028, 0.123)	3.06 (1.03, 9.06)	0.8007
	T-DM1 (N=189)	4 (2.1)				0.0342	
>= 3 lines	T-DXd (N=71)	7 (9.9)	7.77 (0.93, 64.84)	7.10 (0.90, 56.23)	0.085 (0.010, 0.159)	4.29 (0.52, 35.50)	
	T-DM1 (N=72)	1 (1.4)				0.1417	
LVEF decrease							
< 3 lines	T-DXd (N=186)	3 (1.6)	NE (NE, NE)	NE (NE, NE)	0.016 (-0.002, 0.034)	NE (NE, NE)	0.9936
	T-DM1 (N=189)	0				0.1109	
>= 3 lines	T-DXd (N=71)	4 (5.6)	4.24 (0.46, 38.90)	4.06 (0.46, 35.41)	0.042 (-0.018, 0.103)	2.66 (0.29, 24.35)	
	T-DM1 (N=72)	1 (1.4)				0.3672	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Lines of Systemic Therapy Prior to Pertuzumab Treatment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
< 3 lines	T-DXd (N=154)	15 (9.7)	3.15 (1.12, 8.90)	2.94 (1.10, 7.89)	0.064 (0.009, 0.119)	1.85 (0.67, 5.14)	0.9998
	T-DM1 (N=151)	5 (3.3)				0.2306	
>= 3 lines	T-DXd (N=6)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=6)	0				NE	
LVEF decrease							
< 3 lines	T-DXd (N=154)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE
	T-DM1 (N=151)	0				NE	
>= 3 lines	T-DXd (N=6)	1 (16.7)	NE (NE, NE)	NE (NE, NE)	0.167 (-0.132, 0.465)	NE (NE, NE)	
	T-DM1 (N=6)	0				0.4142	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Within Normal Range	T-DXd (N=130)	11 (8.5)	11.92 (1.52, 93.77)	11.00 (1.44, 83.98)	0.077 (0.027, 0.127)	5.78 (0.74, 45.03)	0.3962
	T-DM1 (N=130)	1 (0.8)				0.0586	
Mild Impairment	T-DXd (N=92)	6 (6.5)	1.74 (0.48, 6.38)	1.70 (0.49, 5.82)	0.027 (-0.036, 0.089)	1.19 (0.34, 4.24)	
	T-DM1 (N=104)	4 (3.8)				0.7850	
Moderate Impairment	T-DXd (N=30)	8 (26.7)	NE (NE, NE)	NE (NE, NE)	0.267 (0.108, 0.425)	NE (NE, NE)	
	T-DM1 (N=22)	0				0.0284	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Renal Impairment at Baseline

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
LVEF decrease							
Within Normal Range	T-DXd (N=130)	6 (4.6)	NE (NE, NE)	NE (NE, NE)	0.046 (0.010, 0.082)	NE (NE, NE)	1.0000
	T-DM1 (N=130)	0				0.0393	
Mild Impairment	T-DXd (N=92)	1 (1.1)	1.13 (0.07, 18.36)	1.13 (0.07, 17.82)	0.001 (-0.027, 0.030)	0.93 (0.06, 14.94)	
	T-DM1 (N=104)	1 (1.0)				0.9609	
Moderate Impairment	T-DXd (N=30)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	
	T-DM1 (N=22)	0				NE	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Hepatic Impairment

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Within Normal Range	T-DXd (N=208)	19 (9.1)	5.23 (1.75, 15.64)	4.84 (1.68, 13.99)	0.072 (0.029, 0.116)	3.32 (1.12, 9.83)	0.9940
	T-DM1 (N=212)	4 (1.9)				0.0215	
Mild Impairment	T-DXd (N=49)	6 (12.2)	6.70 (0.78, 57.88)	6.00 (0.75, 48.01)	0.102 (0.002, 0.202)	2.95 (0.36, 24.54)	
	T-DM1 (N=49)	1 (2.0)				0.2929	
LVEF decrease							
Within Normal Range	T-DXd (N=208)	5 (2.4)	5.20 (0.60, 44.87)	5.10 (0.60, 43.25)	0.019 (-0.003, 0.042)	4.28 (0.50, 36.66)	0.9940
	T-DM1 (N=212)	1 (0.5)				0.1485	
Mild Impairment	T-DXd (N=49)	2 (4.1)	NE (NE, NE)	NE (NE, NE)	0.041 (-0.015, 0.096)	NE (NE, NE)	
	T-DM1 (N=49)	0				0.3345	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Baseline Visceral Disease

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=192)	19 (9.9)	20.54 (2.72, 155.03)	18.60 (2.52, 137.58)	0.094 (0.050, 0.137)	11.91 (1.59, 89.08)	0.0560
	T-DM1 (N=188)	1 (0.5)				0.0021	
No	T-DXd (N=65)	6 (9.2)	1.75 (0.47, 6.51)	1.68 (0.50, 5.71)	0.038 (-0.050, 0.125)	1.14 (0.32, 4.10)	
	T-DM1 (N=73)	4 (5.5)				0.8386	
LVEF decrease							
Yes	T-DXd (N=192)	5 (2.6)	5.00 (0.58, 43.21)	4.90 (0.58, 41.51)	0.021 (-0.004, 0.046)	3.67 (0.42, 31.64)	0.9942
	T-DM1 (N=188)	1 (0.5)				0.2061	
No	T-DXd (N=65)	2 (3.1)	NE (NE, NE)	NE (NE, NE)	0.031 (-0.011, 0.073)	NE (NE, NE)	
	T-DM1 (N=73)	0				0.1943	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

Baseline CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=41)	7 (17.1)	NE (NE, NE)	NE (NE, NE)	0.171 (0.056, 0.286)	NE (NE, NE)	0.9892
	T-DM1 (N=39)	0				0.0924	
No	T-DXd (N=216)	18 (8.3)	3.95 (1.44, 10.83)	3.70 (1.40, 9.79)	0.061 (0.019, 0.103)	2.57 (0.95, 6.96)	
	T-DM1 (N=222)	5 (2.3)				0.0538	
LVEF decrease							
Yes	T-DXd (N=41)	0	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.9997
	T-DM1 (N=39)	0				NE	
No	T-DXd (N=216)	7 (3.2)	7.40 (0.90, 60.67)	7.19 (0.89, 57.99)	0.028 (0.003, 0.053)	5.56 (0.68, 45.29)	
	T-DM1 (N=222)	1 (0.5)				0.0713	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable

Table 47 Non-Severe Treatment-Emergent Adverse Events of Special Interest by AESI Category by pre-specified subgroup – Safety Analysis Set

History of CNS Metastases

	Treatment arm	n (%)	OR[b] (95% CI)	RR[c] (95% CI)	ARR[d] (95% CI)	HR[e] (95% CI) p-value	Interaction p-value[f]
Adjudicated drug-related ILD/Pneumonitis							
Yes	T-DXd (N=60)	9 (15.0)	NE (NE, NE)	NE (NE, NE)	0.150 (0.060, 0.240)	NE (NE, NE)	0.9869
	T-DM1 (N=52)	0				0.0383	
No	T-DXd (N=197)	16 (8.1)	3.61 (1.30, 10.04)	3.39 (1.27, 9.09)	0.057 (0.014, 0.101)	2.29 (0.84, 6.28)	
	T-DM1 (N=209)	5 (2.4)				0.0978	
LVEF decrease							
Yes	T-DXd (N=60)	1 (1.7)	0.86 (0.05, 14.17)	0.87 (0.06, 13.51)	-0.003 (-0.052, 0.047)	0.75 (0.05, 11.92)	0.9934
	T-DM1 (N=52)	1 (1.9)				0.8350	
No	T-DXd (N=197)	6 (3.0)	NE (NE, NE)	NE (NE, NE)	0.030 (0.006, 0.054)	NE (NE, NE)	
	T-DM1 (N=209)	0				0.0298	

[a] IR: Incidence rate per person-years. [b] OR: odds-ratio; obtained via a logistic regression model
[c] RR: Relative risk; derived using the Cochran-Mantel-Haenszel method. [d] ARR: Absolute Risk Reduction; derived using the Cochran-Mantel-Haenszel method and presented on the risk scale. [e] HR: Hazard ratio obtained from a Cox proportional hazards model, p-value from log-rank test

[f] P-value for interaction obtained with a Cox proportional hazards model including treatment times subgroup interaction term. Due to the high number of endpoints, subgroups, and tests performed, a p-value smaller than 5% should be interpreted as an exploratory signal only and not as a statistically significant difference.
NE - Not Evaluable