Dokumentvorlage, Version vom 21.02.2019

Dossier zur Nutzenbewertung gemäß § 35a SGB V

Lenvatinib (Lenvima®)

Eisai GmbH

Modul 4 C – Anhang 4-G

In Kombination mit Pembrolizumab zur Behandlung des fortgeschrittenen oder rezidivierenden Endometriumkarzinoms bei Erwachsenen mit einem Fortschreiten der Erkrankung während oder nach vorheriger Platin-basierter Therapie in jedem Krankheitsstadium, wenn eine kurative chirurgische Behandlung oder Bestrahlung nicht in Frage kommt

Medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen

Stand: 07.12.2021

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Anhang 4-G1: Nachfolgende systemische Antikrebstherapie während des Überlebens Follow-up aus RCT (Studie 309) mit dem zu bewertenden Arzneimittel (Datenschnitt: 26.10.2020)

Participants whose First Subsequent Oncologic Therapy was Systemic (Incidence > 0% in One or More Treatment Groups)

Studie: KEYNOTE 775[a]	**Patienten mit Ereignis n (%)**	
Therapieklasse[c] **Therapiebegriff[d]**	**Pembrolizumab + Lenvatinib[b]** **(N[e]= 298)**	**Doxorubicin[b]** **(N[e]= 307)**
Patienten, die als erstes eine systemische Folgetherapie erhalten haben	72 (24,2)	134 (43,6)
PD1/PD-L1 checkpoint	1 (0,3)	22 (7,2)
Pembrolizumab	1 (0,3)	17 (5,5)
Durvalumab	0 (0,0)	2 (0,7)
Nivolumab	0 (0,0)	2 (0,7)
Atezolizumab	0 (0,0)	1 (0,3)
VEGF/VEGFR Inhibitor	2 (0,7)	19 (6,2)
Lenvatinib	1 (0,3)	11 (3,6)
Bevacizumab	1 (0,3)	8 (2,6)
Chemotherapie	61 (20,5)	75 (24,4)
Doxorubicin	37 (12,4)	7 (2,3)
Carboplatin	16 (5,4)	20 (6,5)
Paclitaxel	6 (2,0)	27 (8,8)
Gemcitabin	5 (1,7)	21 (6,8)
Cisplatin	6 (2,0)	5 (1,6)
Docetaxel	3 (1,0)	5 (1,6)
Cyclophosphamid	3 (1,0)	2 (0,7)
Epirubicin	3 (1,0)	0 (0,0)
Topotecan	0 (0,0)	3 (1,0)
Bortezomib	1 (0,3)	0 (0,0)
Capecitabin	1 (0,3)	0 (0,0)
Irinotecan	0 (0,0)	1 (0,3)
Melphalan	0 (0,0)	1 (0,3)
Oxaliplatin	0 (0,0)	1 (0,3)
Vinorelbin	0 (0,0)	1 (0,3)
Hormontherapie	10 (3,4)	31 (10,1)
Megestrol	2 (0,7)	14 (4,6)
Letrozol	4 (1,3)	5 (1,6)
Tamoxifen	1 (0,3)	8 (2,6)
Medroxyprogesteron	0 (0,0)	5 (1,6)
Anastrozol	2 (0,7)	1 (0,3)
Fulvestrant	0 (0,0)	2 (0,7)
Exemestan	1 (0,3)	0 (0,0)
Andere	0 (0,0)	5 (1,6)
Trastuzumab	0 (0,0)	2 (0,7)
Ly 3300054	0 (0,0)	1 (0,3)
Naptumomab Estafenatox	0 (0,0)	1 (0,3)
Pertuzumab	0 (0,0)	1 (0,3)
Unspezifiziert	0 (0,0)	1 (0,3)
Andere I-O	0 (0,0)	2 (0,7)
Ly 3321367	0 (0,0)	1 (0,3)
Tremelimumab	0 (0,0)	1 (0,3)
Zielgerichtete Therapie	2 (0,7)	5 (1,6)
Olaparib	0 (0,0)	3 (1,0)
Everolimus	1 (0,3)	1 (0,3)
Adavosertib	0 (0,0)	1 (0,3)
Mak 683	1 (0,3)	0 (0,0)

a: Datenschnitt: 26. Oktober 2020

b: Therapie mit Doxorubicin nach Maßgabe des Arztes; die Therapierationale wurde prospektiv mittels Prüfarztbefragung ermittelt. Die Population beinhaltet eine Doxorubicin-behandelte Patientin, die vor Randomisierung einer Therapie mit Paclitaxel zugewiesen wurde.

Studie: KEYNOTE 775[a]	**Patienten mit Ereignis n (%)**	
Therapieklasse[c] **Therapiebegriff[d]**	**Pembrolizumab + Lenvatinib[b]** **(N[e]= 298)**	**Doxorubicin[b]** **(N[e]= 307)**
c: Eine bestimmte Therapieklasse erscheint nur dann, wenn das Inzidenzkriterium > 0% (nach Rundung) in einer oder mehreren der Spalten erfüllt ist. Ein Patient mit mehreren verabreichten systemischen Therapien einer Therapieklasse wird ein einziges Mal zu dieser gerechnet. d: Jeder Patient wird nur einmal in der Kategorie der systemischen Therapien, in denen er ein Ereignis hatte, gewertet e: Anzahl der Patienten: Intention-To-Treat, nutzenbewertungsrelevante Population I-O: Immunonkologie; PD-1: Programmed Cell Death 1; PD-L1: Programmed Cell Death–Ligand 1; VEGF: Vascular Endothelial Growth Factor; VEGFR: Vascular Endothelial Growth Factor Receptor		

Anhang 4-G2: Ergänzende Analysen für den Endpunkt OS

Anhang 4-G2.1: Ergebnisse der Subgruppenanalysen mit p-Wert für Interaktionstests ≥ 0.05 für den Endpunkt OS aus RCT (Studie 309) mit dem zu bewertenden Arzneimittel (Datenschnitt: 26.10.2020)

Analysis of Overall Survival for Subgroups With P-value for Interaction test ≥ 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
Overall Survival	N[c]	Participants with Event n (%)	Median Time[d] in months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Age Group									
< 65	153	70 (45.8)	19.68 [13.90; -]	150	98 (65.3)	9.99 [7.29; 11.79]	0.51 [0.38; 0.70]	< 0.001	0.761
≥ 65	145	64 (44.1)	18.30 [14.92; -]	157	104 (66.2)	10.51 [8.02; 12.22]	0.46 [0.34; 0.63]	< 0.001	
Region									
Region 1	168	79 (47.0)	18.30 [14.85; 20.50]	179	121 (67.6)	9.50 [7.29; 12.45]	0.50 [0.37; 0.66]	< 0.001	0.638
Region 2	130	55 (42.3)	19.68 [13.47; -]	128	81 (63.3)	10.48 [8.08; 11.79]	0.47 [0.33; 0.67]	< 0.001	
ECOG Performance Status									
0	176	64 (36.4)	20.50 [18.30; -]	176	109 (61.9)	11.34 [9.99; 13.86]	0.42 [0.31; 0.57]	< 0.001	0.328
1	121	69 (57.0)	12.32 [9.99; 19.35]	131	93 (71.0)	7.29 [5.82; 9.79]	0.55 [0.40; 0.76]	< 0.001	
Race									
White	192	78 (40.6)	19.98 [17.22; -]	176	114 (64.8)	10.68 [7.59; 12.48]	0.42 [0.32; 0.57]	< 0.001	0.373
Asian	58	27 (46.6)	19.68 [11.53; -]	63	40 (63.5)	10.51 [8.08; 13.86]	0.55 [0.34; 0.91]	0.019	
Other	22	15 (68.2)	9.99 [5.26; 14.85]	27	21 (77.8)	7.89 [5.29; 10.88]	0.62 [0.31; 1.24]	0.175	
Prior History of Pelvic Radiation									
Yes	128	48 (37.5)	19.88 [18.23; -]	138	84 (60.9)	10.68 [8.48; 12.98]	0.44 [0.31; 0.63]	< 0.001	0.461
No	170	86 (50.6)	16.72 [13.47; 19.98]	169	118 (69.8)	9.36 [7.29; 11.79]	0.51 [0.39; 0.68]	< 0.001	
Histology									
Endometrioid	179	65 (36.3)	Not reached [18.30; -]	190	107 (56.3)	12.09 [9.99; 14.29]	0.47 [0.34; 0.64]	< 0.001	0.817
Non-endometrioid	119	69 (58.0)	12.52 [9.56; 17.22]	117	95 (81.2)	7.46 [6.08; 9.33]	0.47 [0.34; 0.65]	< 0.001	
Prior Lines of Therapy									
1	231	107 (46.3)	18.23 [13.90; -]	217	151 (69.6)	9.99 [7.69; 11.20]	0.47 [0.37; 0.60]	< 0.001	0.645
2	58	22 (37.9)	19.98 [17.22; -]	81	45 (55.6)	9.79 [8.28; 14.16]	0.46 [0.27; 0.77]	0.003	
≥3	9	5 (55.6)	11.43 [5.26; -]	9	6 (66.7)	14.39 [3.12; 17.18]	0.86 [0.26; 2.86]	0.807	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: intention-to-treat, population relevant for benefit assessment

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
Overall Survival	N[c]	Participants with Event n (%)	Median Time[d] in months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate

f: Two-sided p-value (Wald test)

g: Based on unstratified Cox regression model with treatment, subgroup as covariates and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Anhang 4-G3: Ergänzende Analysen für den Endpunkt PFS

Anhang 4-G3.1: Ergebnisse der Subgruppenanalysen mit p-Wert für Interaktionstests ≥ 0.05 für den Endpunkt PFS aus RCT (Studie 309) mit dem zu bewertenden Arzneimittel (Datenschnitt: 26.10.2020)

Analysis Progression-Free Survival Based on BICR Assessment per RECIST 1.1 for Subgroups With P-value for Interaction test ≥ 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		p-Value for Interaction Test[g]
Progression-Free Survival (BICR Primary Censoring Rule)	N[c]	Participants with Event n (%)	Median Time[d] in months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	
Age Group									
< 65	153	105 (68.6)	6.41 [5.32; 8.12]	150	110 (73.3)	3.48 [2.04; 3.84]	0.44 [0.33; 0.58]	< 0.001	0.506
≥ 65	145	97 (66.9)	7.26 [5.62; 8.12]	157	106 (67.5)	3.81 [3.45; 5.13]	0.46 [0.35; 0.62]	< 0.001	
Region									
Region 1	168	112 (66.7)	7.13 [5.59; 8.12]	179	130 (72.6)	3.71 [2.63; 3.91]	0.44 [0.34; 0.57]	< 0.001	0.764
Region 2	130	90 (69.2)	7.26 [5.55; 8.12]	128	86 (67.2)	3.68 [2.17; 5.55]	0.48 [0.35; 0.66]	< 0.001	
ECOG Performance Status									
0	176	119 (67.6)	7.43 [6.28; 9.04]	176	119 (67.6)	3.71 [3.45; 5.13]	0.46 [0.36; 0.60]	< 0.001	0.597
1	121	83 (68.6)	5.62 [3.94; 7.62]	131	97 (74.0)	3.48 [2.07; 3.88]	0.45 [0.33; 0.61]	< 0.001	
MMR Status									
pMMR	244	173 (70.9)	6.41 [5.55; 7.39]	255	178 (69.8)	3.65 [2.92; 3.94]	0.52 [0.41; 0.64]	< 0.001	0.064
dMMR	54	29 (53.7)	10.71 [5.68; -]	52	38 (73.1)	3.71 [2.04; 3.98]	0.30 [0.18; 0.51]	< 0.001	
Prior History of Pelvic Radiation									
Yes	128	79 (61.7)	8.81 [7.13; 10.71]	138	94 (68.1)	3.78 [3.12; 5.65]	0.36 [0.26; 0.50]	< 0.001	0.295
No	170	123 (72.4)	5.59 [4.40; 7.26]	169	122 (72.2)	3.48 [2.10; 3.84]	0.52 [0.40; 0.67]	< 0.001	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: intention-to-treat, population relevant for benefit assessment

d: From product-limit (Kaplan-Meier) method

e: Based on Cox regression model with treatment as a covariate stratified by ECOG performance status, geographic region, and prior history of pelvic radiation for pMMR subgroup category. Based on Cox regression model with treatment as a covariate for all other subgroup categories

f: Two-sided p-value (Wald test)

g: Based on unstratified Cox regression model with treatment, subgroup as covariates and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) for all subgroups with the exception of MMR status which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation, with treatment, subgroup as covariates and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

BICR: Blinded Independent Central Review; CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Anhang 4-G4: Ergänzende Analysen für den Endpunkt EORTC QLQ-C30 und EORTC QLQ-EN24 – Symptomatik

Anhang 4-G4.1: Ergebnisse der Analysen für den Endpunkt Zeit bis zur ersten Verschlechterung um mindestens 15 Punkte auf den Skalen des EORTC QLQ-C30 (Symptomskalen und Einzelfragen) und EORTC QLQ-EN24 (Symptomskalen) gegenüber Baseline aus RCT (Studie 309) mit dem zu bewertenden Arzneimittel (Datenschnitt: 26.10.2020)

Analysis of Time to First Deterioration for EORTC QLQ-C30 Symptom Scales and EORTC QLQ-EN24 Symptom Scales

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]	
	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]
EORTC QLQ-C30 Symptom Scales (15 points)								
Fatigue	282	181 (64.2)	2.17 [1.94; 3.12]	267	162 (60.7)	2.14 [1.61; 2.79]	0.92 [0.74; 1.14]	0.464
Nausea and Vomiting	282	201 (71.3)	2.10 [1.71; 2.79]	267	164 (61.4)	1.54 [1.41; 2.10]	0.82 [0.66; 1.01]	0.062
Pain	282	194 (68.8)	1.48 [1.41; 2.10]	267	162 (60.7)	2.10 [1.64; 2.53]	1.11 [0.90; 1.38]	0.320
Dyspnea	282	134 (47.5)	8.35 [5.65; 11.04]	267	121 (45.3)	3.78 [2.60; 4.93]	0.67 [0.52; 0.88]	0.003
Insomnia	282	163 (57.8)	3.52 [2.76; 4.86]	267	125 (46.8)	4.04 [2.46; 5.55]	0.97 [0.76; 1.24]	0.812
Appetite Loss	282	208 (73.8)	1.64 [1.41; 2.10]	267	157 (58.8)	2.10 [1.61; 2.76]	1.22 [0.99; 1.51]	0.068
Constipation	282	152 (53.9)	4.86 [3.48; 6.11]	267	139 (52.1)	2.23 [1.94; 3.06]	0.70 [0.55; 0.89]	0.003
Diarrhea	282	180 (63.8)	3.29 [2.76; 3.94]	267	100 (37.5)	5.03 [3.48; -]	1.46 [1.14; 1.87]	0.003
EORTC QLQ-EN24 Symptom Scales (15 points)								
Lymphoedema	240	135 (56.3)	4.11 [2.79; 5.82]	233	116 (49.8)	2.56 [2.04; 3.55]	0.77 [0.59; 1.00]	0.051
Urological symptoms	240	102 (42.5)	9.73 [5.55; -]	233	75 (32.2)	Not reached [3.98; -]	0.94 [0.69; 1.28]	0.703
Gastrointestinal symptoms	240	104 (43.3)	7.85 [4.96; 12.91]	233	65 (27.9)	Not reached [5.55; -]	1.06 [0.77; 1.47]	0.725
Poor body image	240	108 (45.0)	6.34 [4.21; -]	233	126 (54.1)	2.10 [1.48; 2.37]	0.54 [0.41; 0.70]	< 0.001
Sexual/vaginal problems	58	6 (10.3)	12.88 [2.79; -]	41	8 (19.5)	5.52 [2.10; -]	0.91 [0.26; 3.15]	0.877
Pain in back and pelvis	240	134 (55.8)	4.11 [2.99; 5.52]	233	91 (39.1)	4.60 [2.83; -]	1.07 [0.81; 1.41]	0.644
Tingling/numbness	240	102 (42.5)	11.27 [4.30; -]	233	84 (36.1)	6.11 [3.65; -]	0.89 [0.66; 1.19]	0.427
Muscular pain	240	150 (62.5)	2.10 [1.48; 2.76]	233	104 (44.6)	3.06 [2.33; 4.63]	1.33 [1.03; 1.72]	0.028
Hair loss	240	81 (33.8)	12.45 [8.25; -]	233	170 (73.0)	0.72 [0.72; 0.76]	0.12 [0.09; 0.17]	< 0.001
Taste change	240	162 (67.5)	1.61 [1.41; 2.10]	233	161 (69.1)	1.41 [0.95; 1.45]	0.73 [0.58; 0.91]	0.006

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]	
	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]

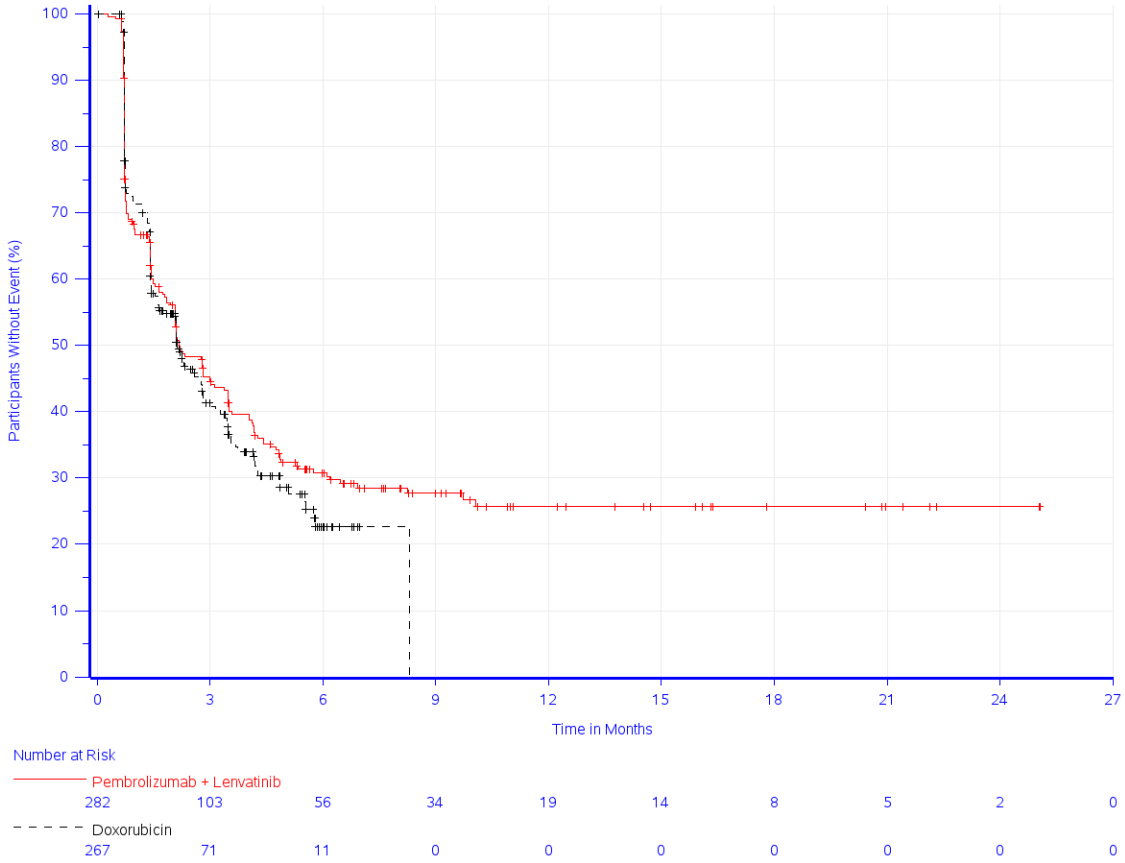
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 15 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

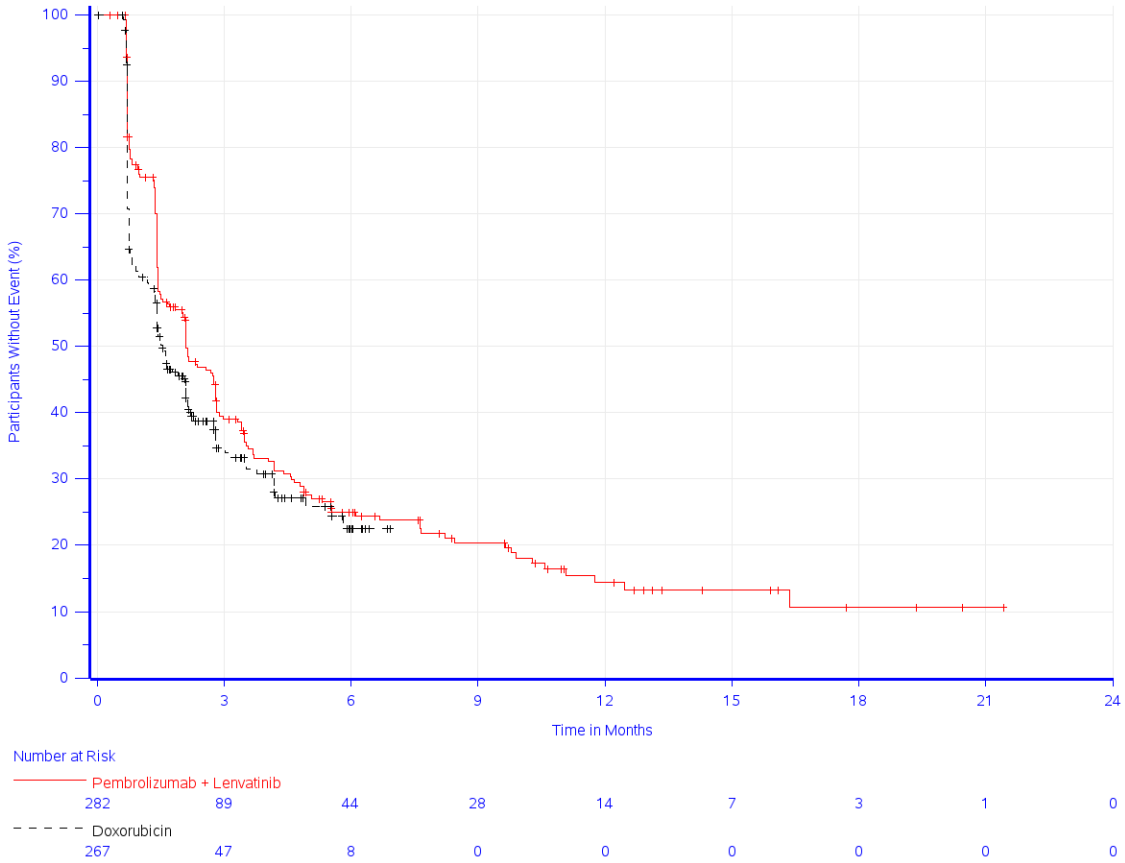
f: Based on Cox regression model with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items



Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-C30 Fatigue (15 points)



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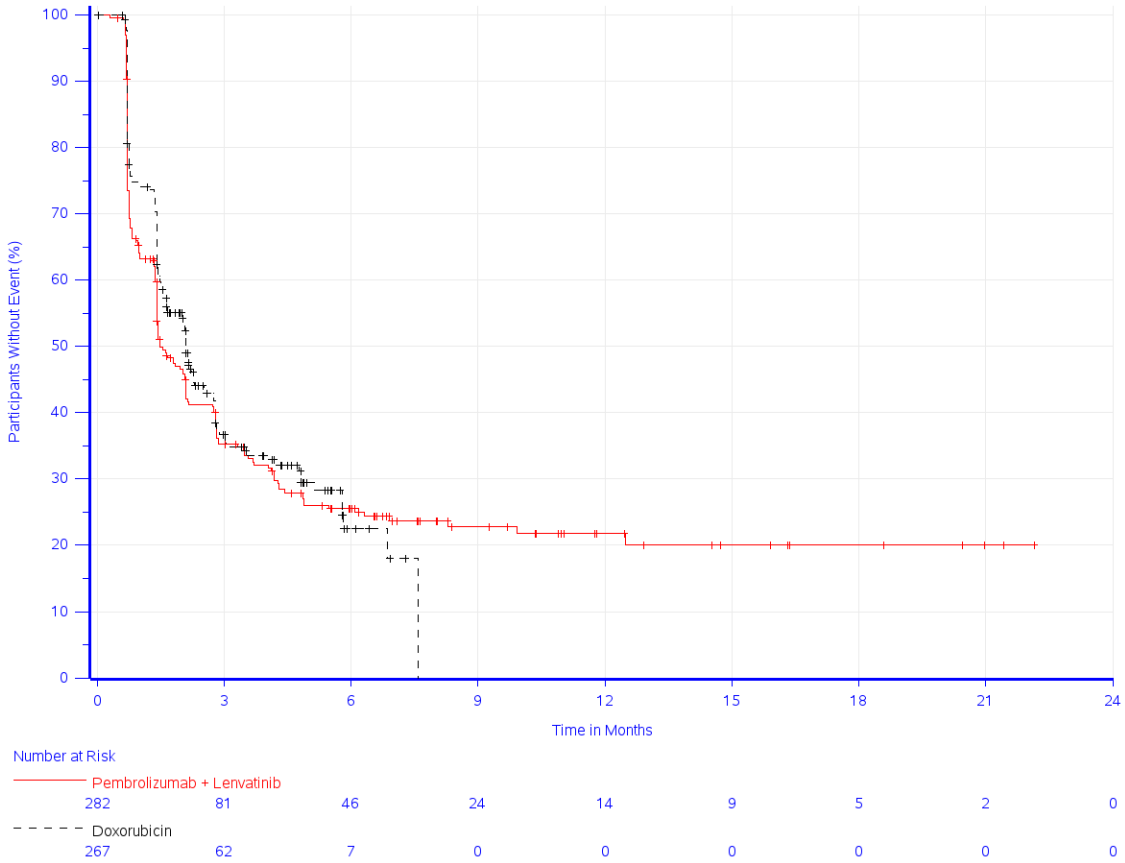

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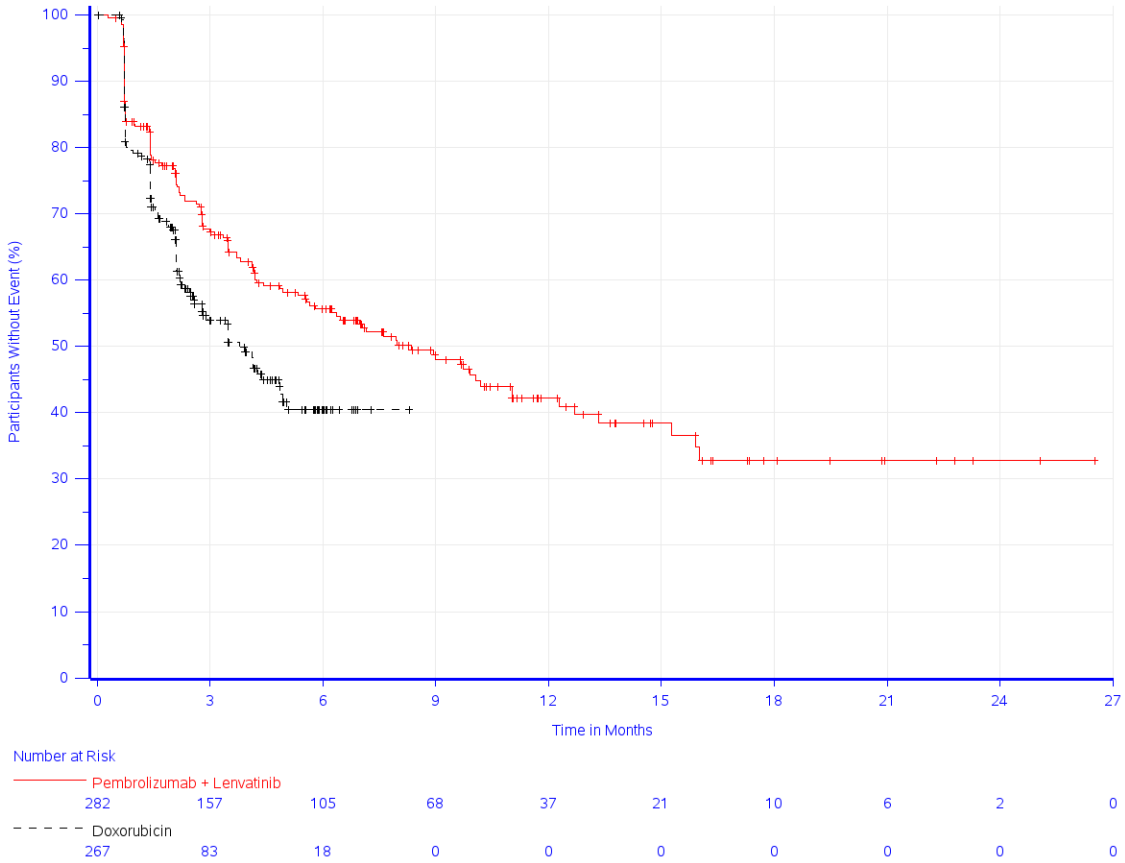

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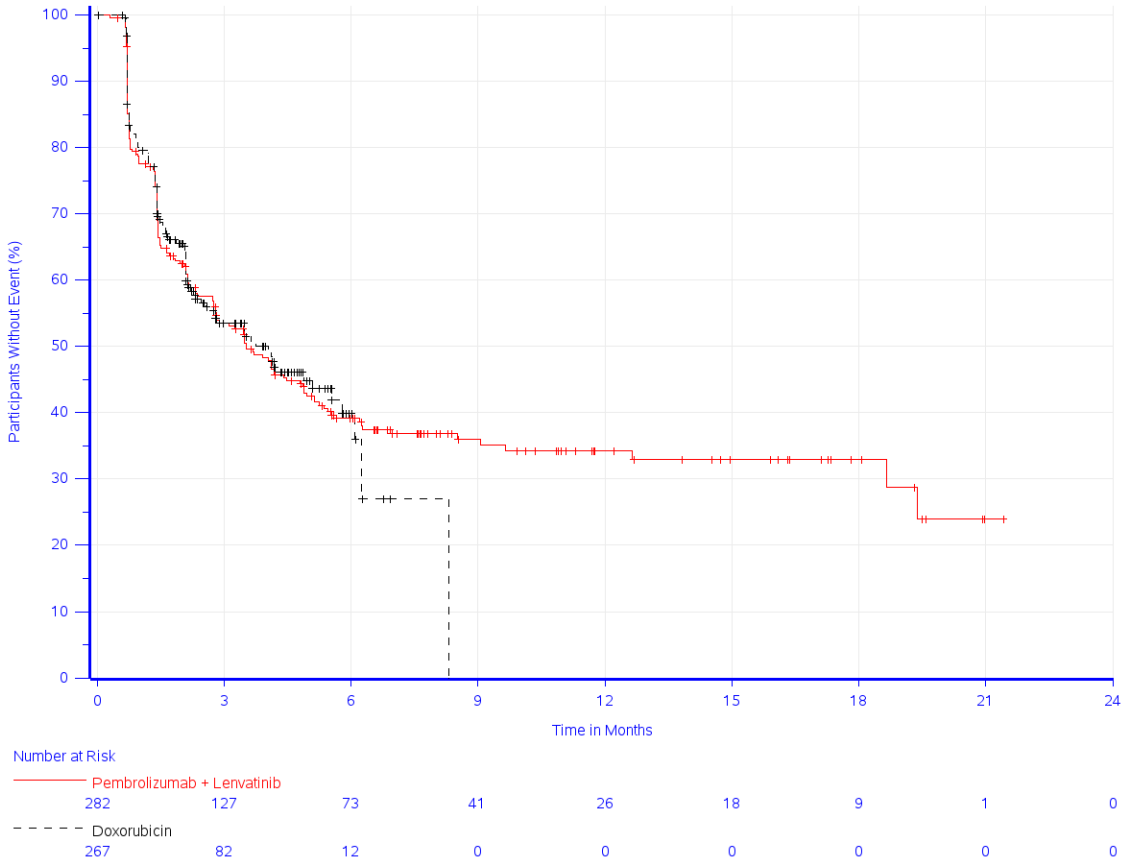

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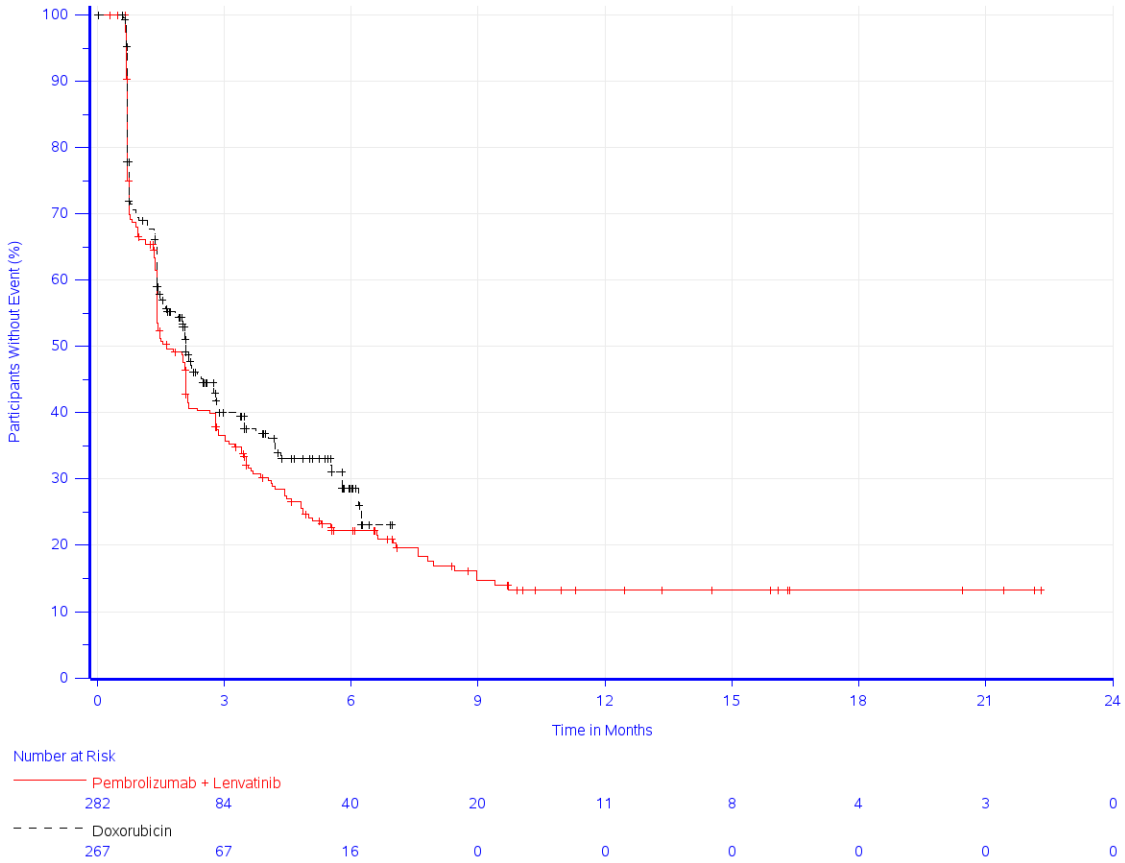
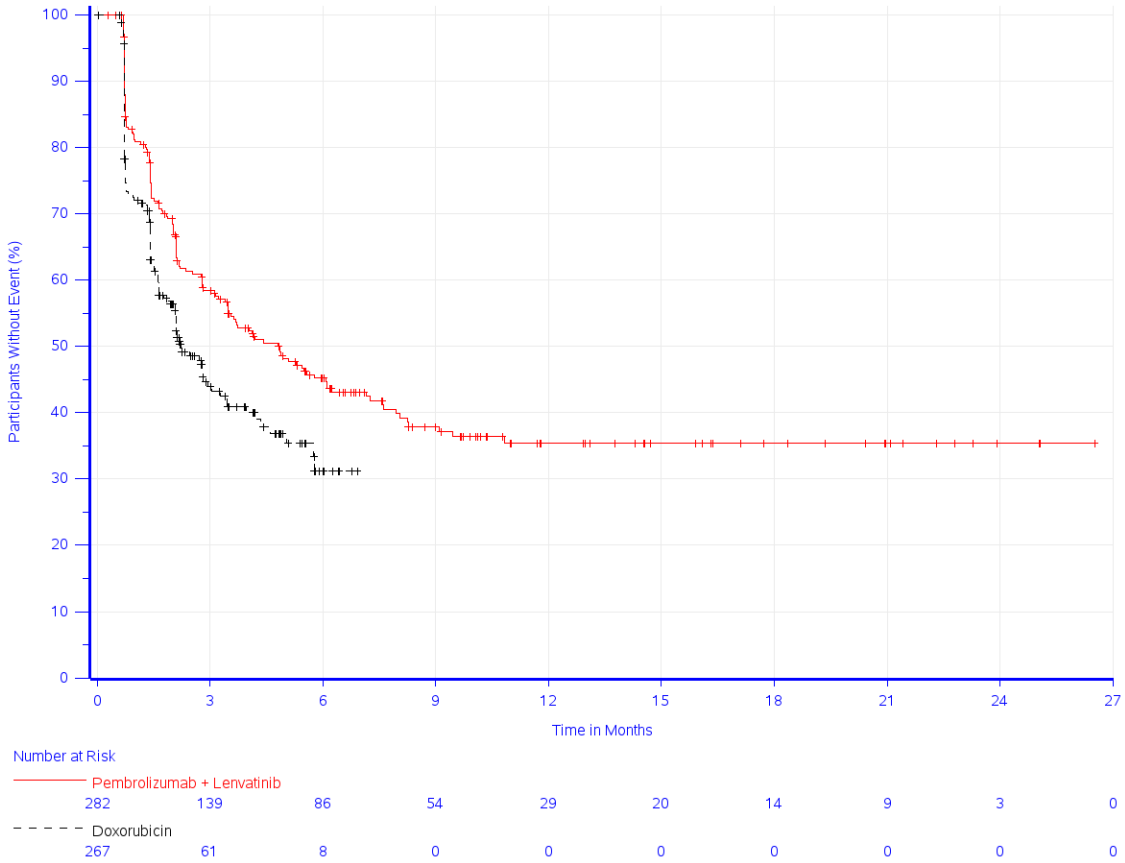
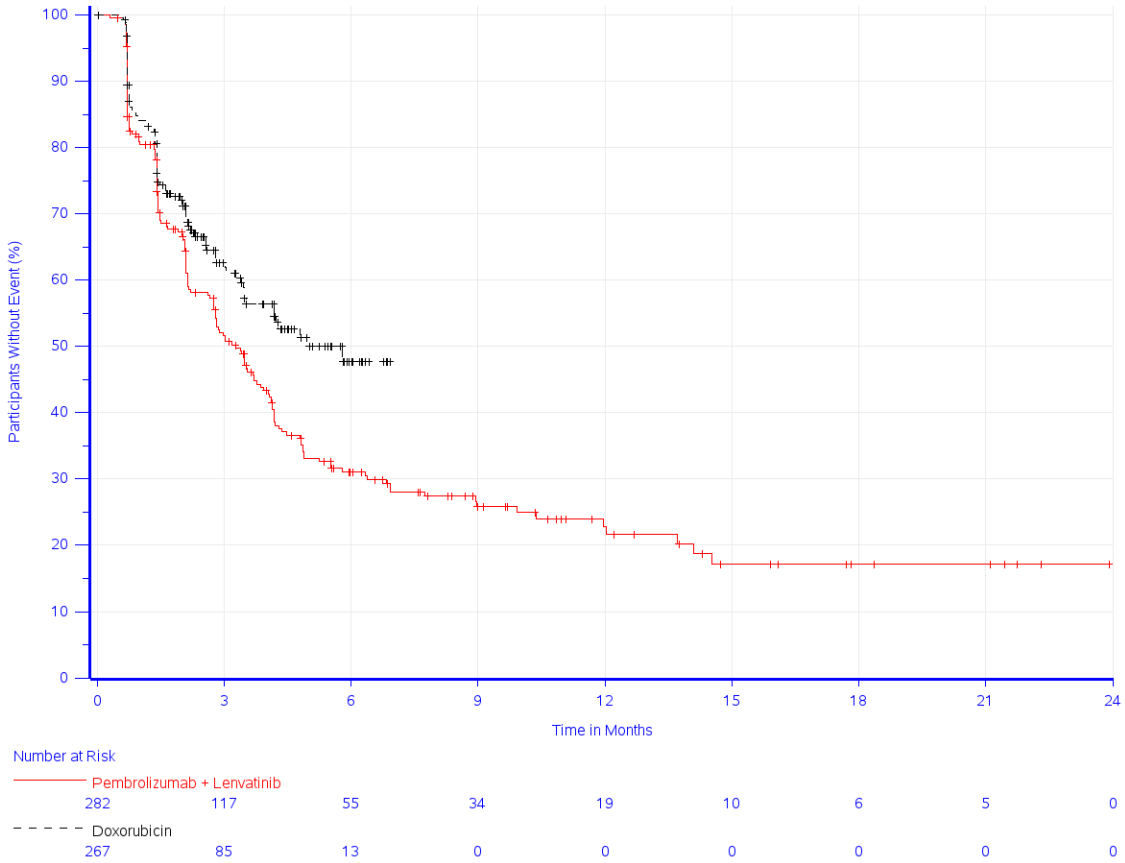


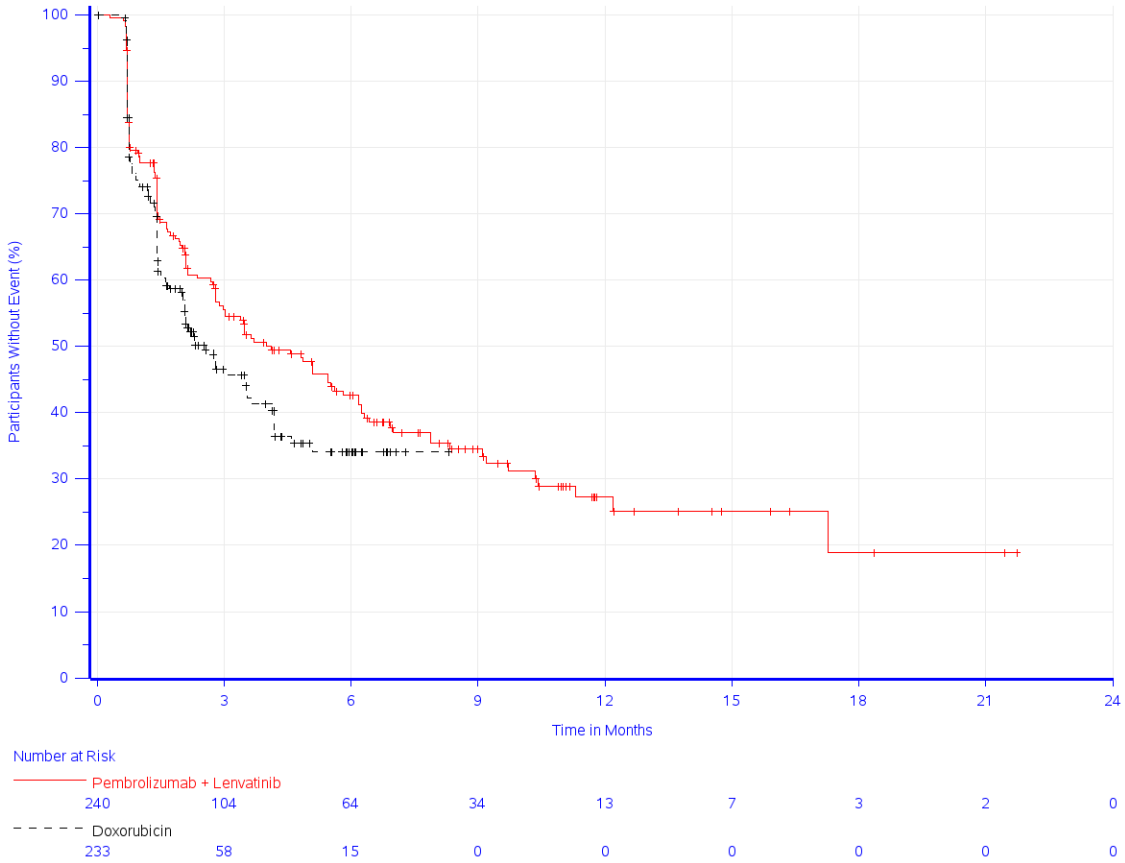
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-C30 Appetite Loss (15 points)



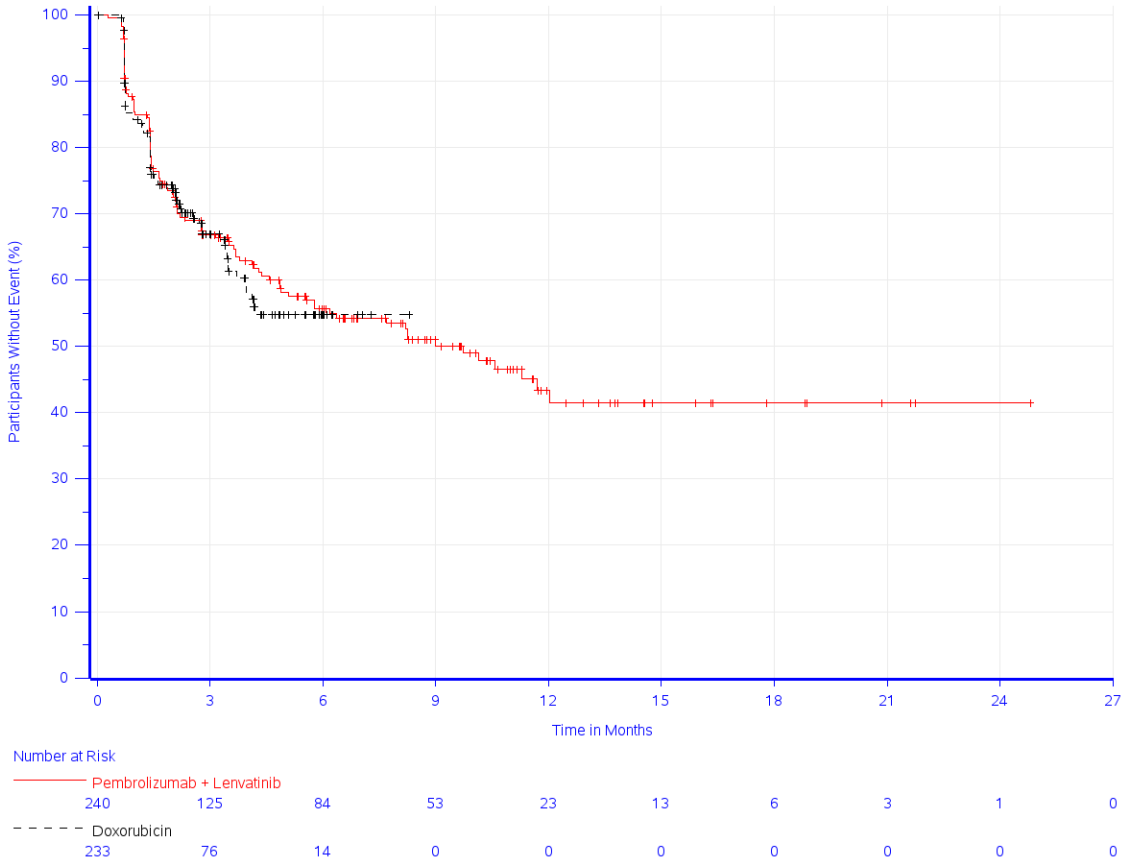
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-C30 Constipation (15 points)



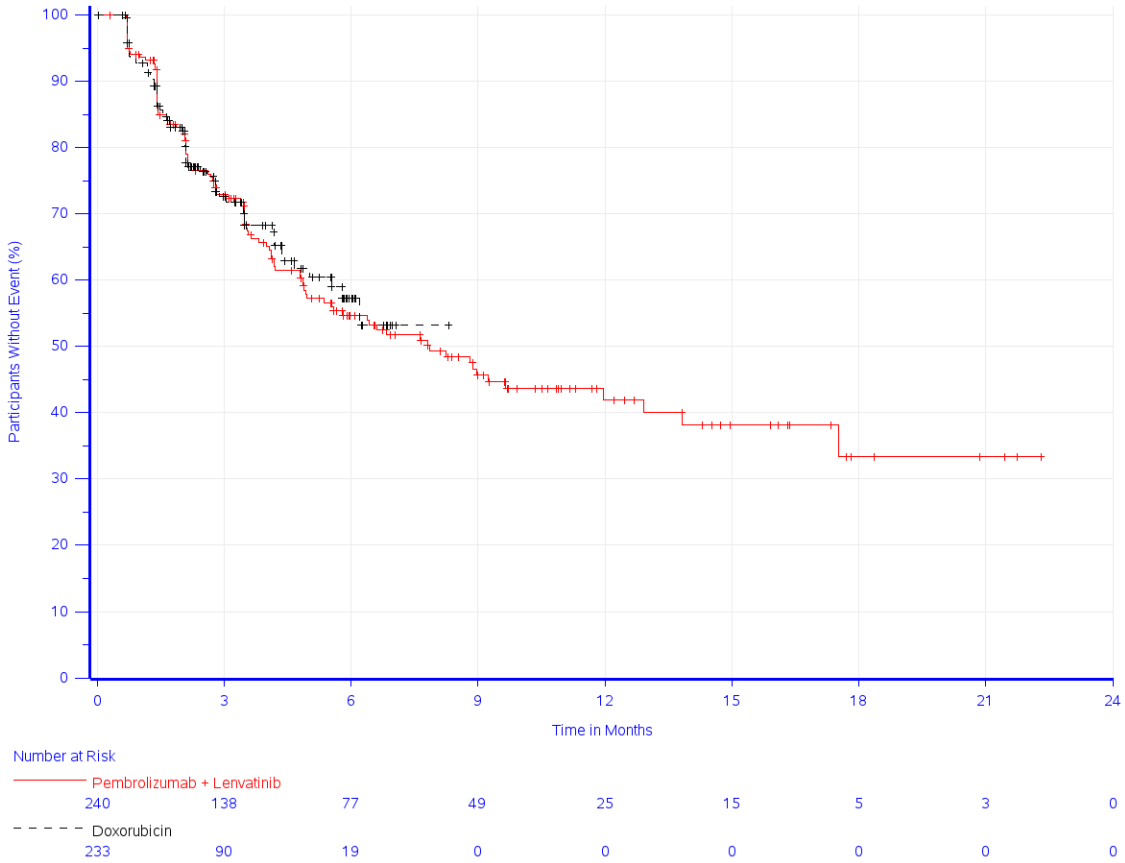
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-C30 Diarrhea (15 points)



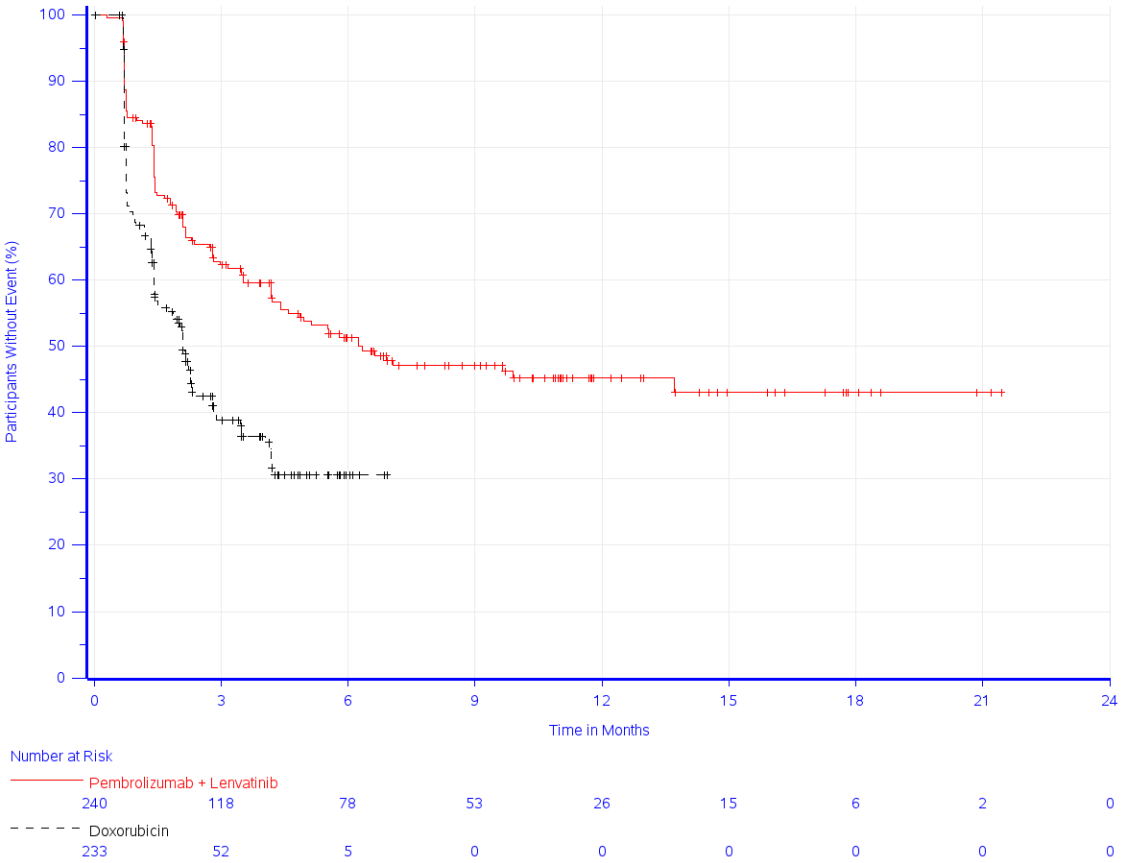
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-EN24 Lymphoedema (15 points)



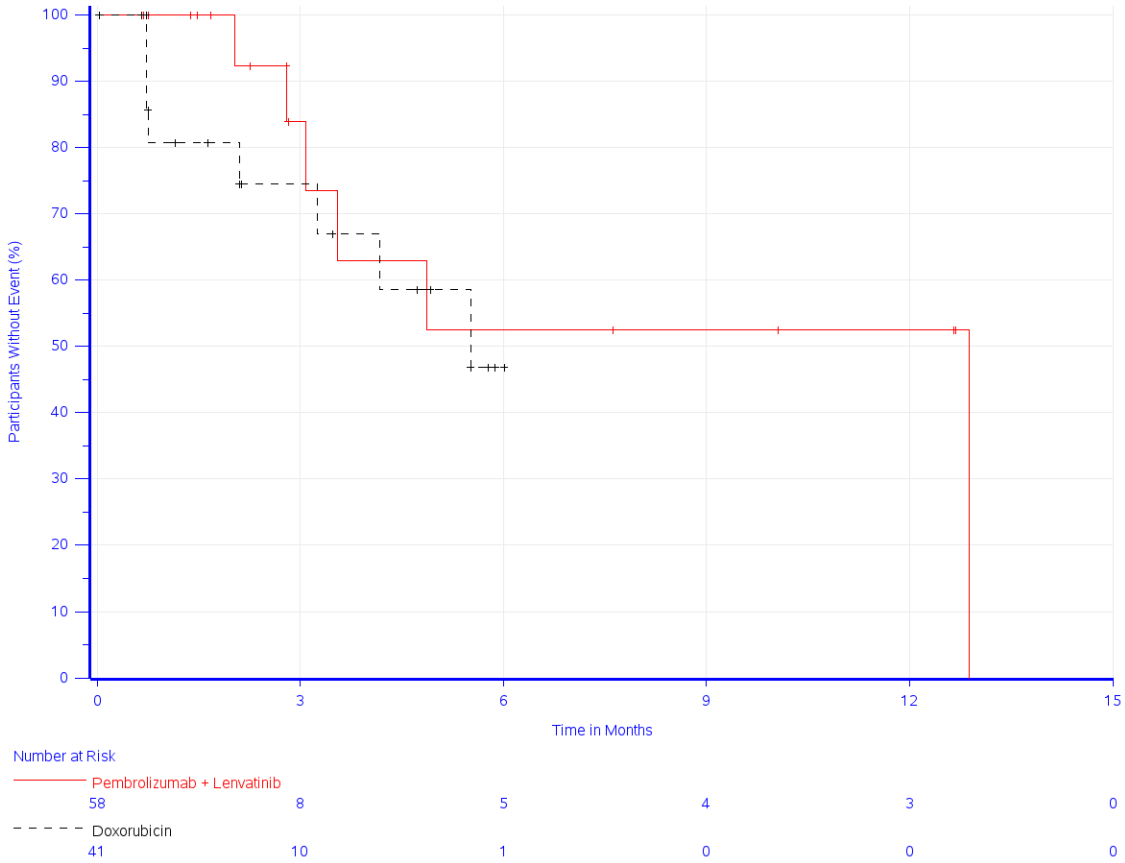
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-EN24 Urological Symptoms (15 points)



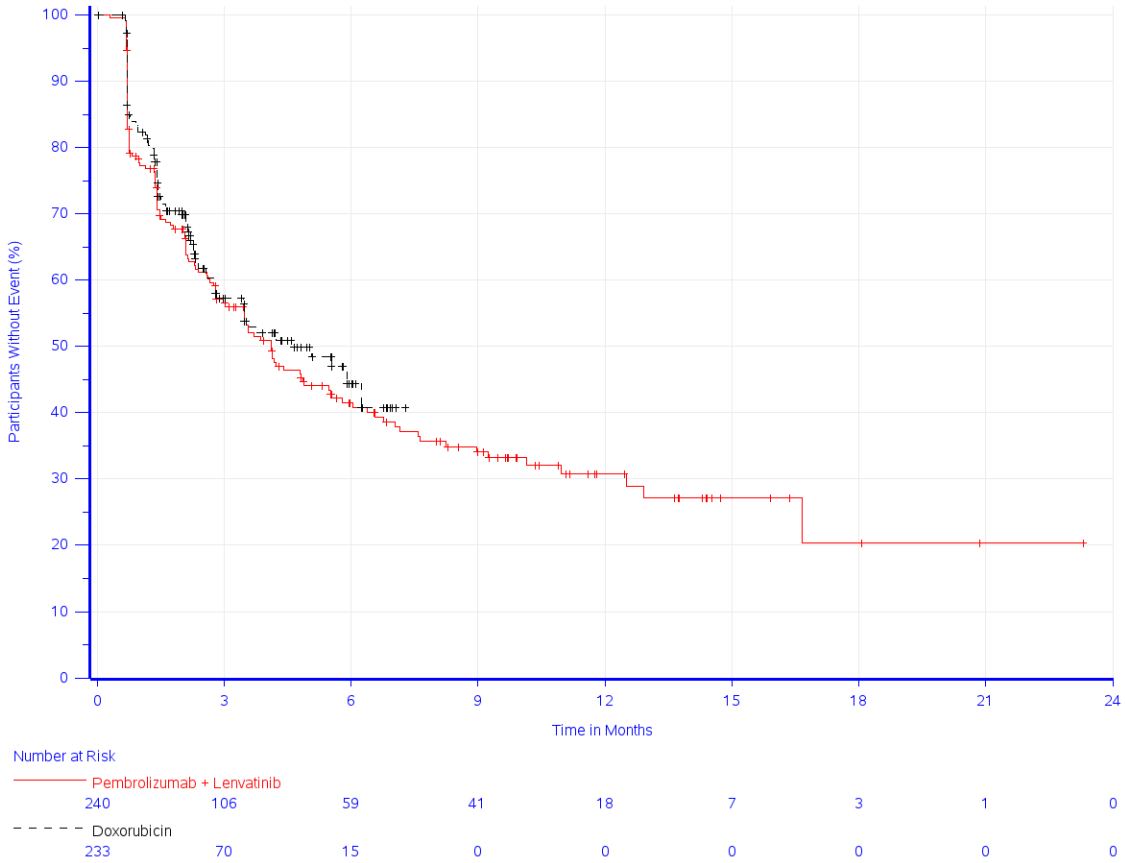
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-EN24 Gastrointestinal Symptoms (15 points)



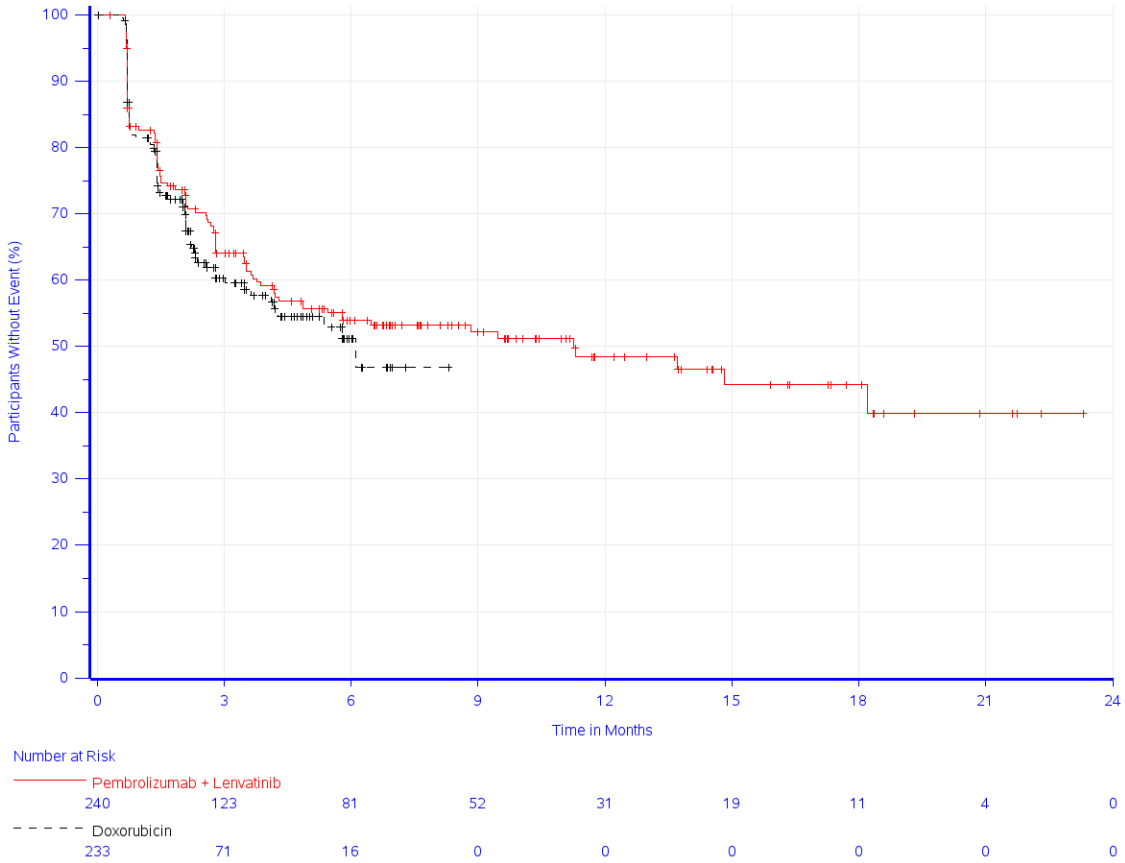
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-EN24 Poor Body Image (15 points)



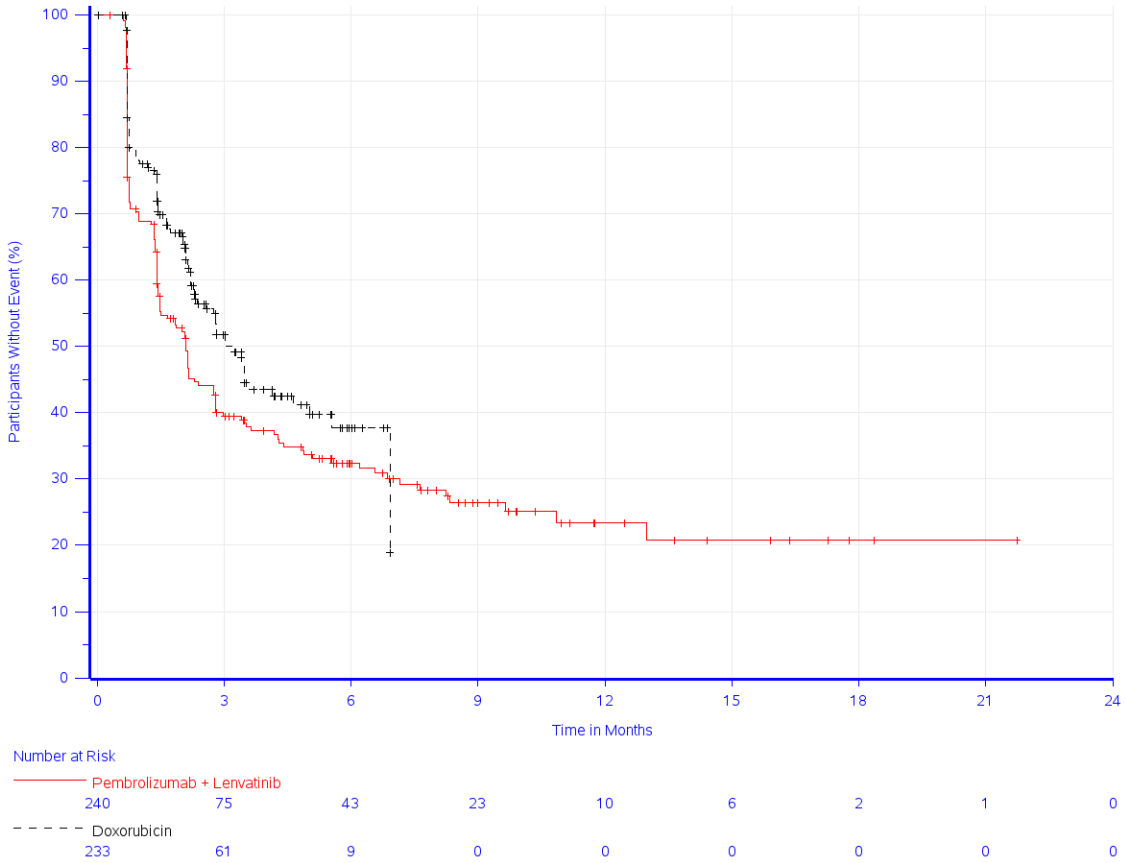
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-EN24 Sexual/Vaginal Problems (15 points)



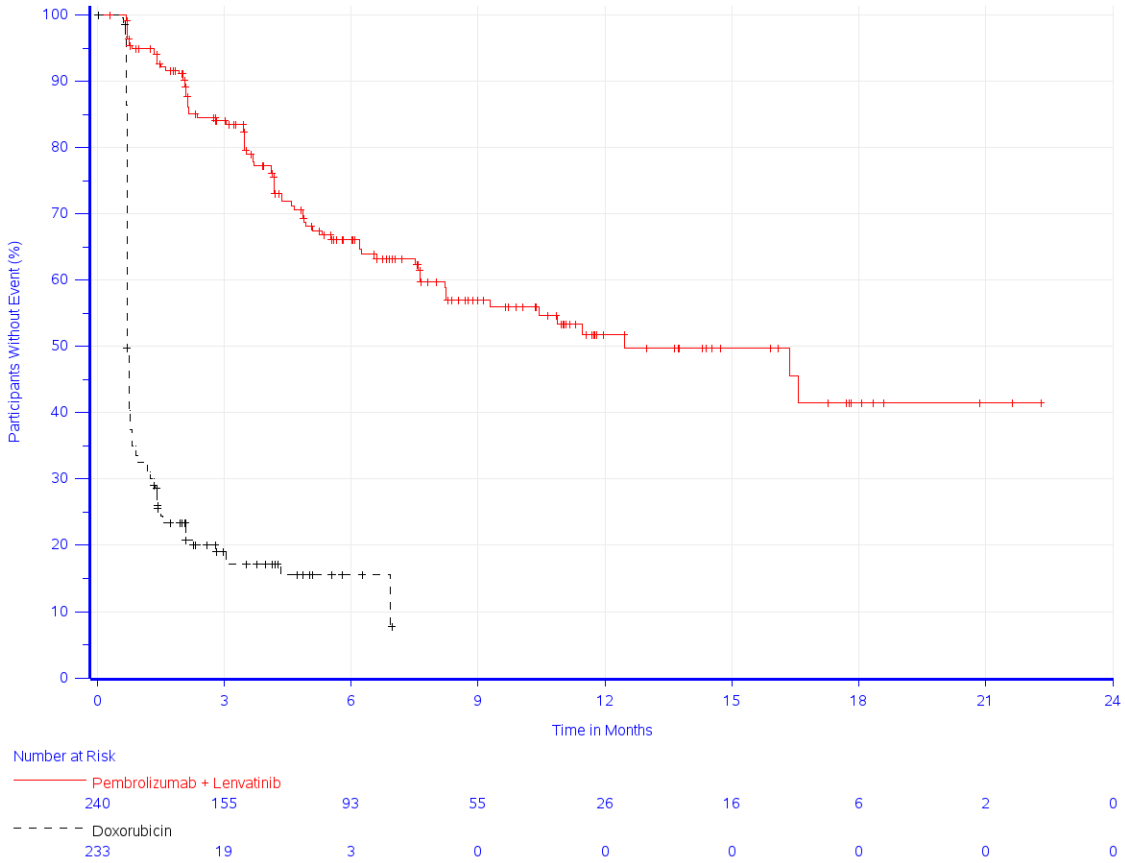
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-EN24 Pain in Back and Pelvis (15 points)



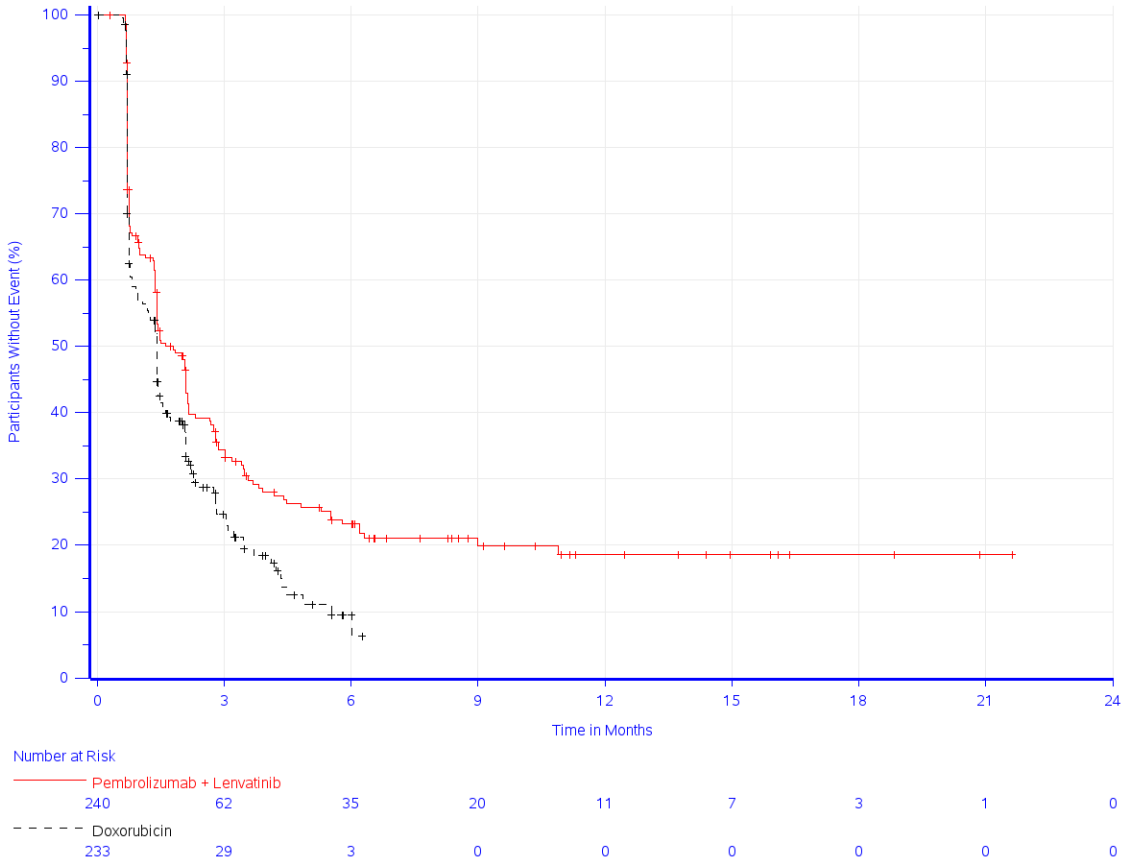
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-EN24 Tingling/Numbness (15 points)



Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-EN24 Muscular Pain (15 points)



Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-EN24 Hair Loss (15 points)



Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-EN24 Taste Change (15 points)

Anhang 4-G4.2: Ergebnisse der Subgruppenanalysen mit p-Wert für Interaktionstests ≥ 0.05 für den Endpunkt Zeit bis zur ersten Verschlechterung um mindestens 10 Punkte auf den Skalen des EORTC QLQ-C30 (Symptomskalen und Einzelfragen) und EORTC QLQ-EN24 (Symptomskalen) gegenüber Baseline aus RCT (Studie 309) mit dem zu bewertenden Arzneimittel (Datenschnitt: 26.10.2020)

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-C30 Fatigue (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
EORTC QLQ-C30 Fatigue	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age Group									
< 65	146	114 (78.1)	1.41 [0.82; 2.07]	135	99 (73.3)	1.22 [0.76; 1.41]	0.86 [0.66; 1.13]	0.285	0.154
≥ 65	136	118 (86.8)	0.92 [0.76; 1.38]	132	103 (78.0)	0.95 [0.76; 1.41]	1.15 [0.88; 1.49]	0.310	
Region									
Region 1	152	126 (82.9)	0.82 [0.72; 1.38]	152	116 (76.3)	0.95 [0.76; 1.38]	1.07 [0.83; 1.37]	0.622	0.470
Region 2	130	106 (81.5)	1.41 [0.95; 2.07]	115	86 (74.8)	1.35 [0.76; 1.54]	0.92 [0.69; 1.22]	0.555	
MMR Status									
pMMR	233	198 (85.0)	1.02 [0.76; 1.41]	226	173 (76.5)	1.22 [0.76; 1.41]	1.04 [0.84; 1.28]	0.730	0.429
dMMR	49	34 (69.4)	1.91 [0.79; 2.79]	41	29 (70.7)	0.79 [0.72; 2.76]	0.83 [0.50; 1.37]	0.474	
ECOG Performance Status									
0	171	142 (83.0)	1.35 [0.76; 1.41]	156	120 (76.9)	0.79 [0.72; 1.38]	0.89 [0.70; 1.14]	0.367	0.231
1	111	90 (81.1)	1.35 [0.76; 1.45]	111	82 (73.9)	1.38 [0.79; 1.45]	1.11 [0.83; 1.51]	0.479	
Prior History of Pelvic Radiation									
Yes	122	98 (80.3)	0.76 [0.72; 1.38]	118	86 (72.9)	1.02 [0.76; 1.41]	1.15 [0.86; 1.53]	0.355	0.222
No	160	134 (83.8)	1.41 [0.99; 1.81]	149	116 (77.9)	1.18 [0.76; 1.41]	0.87 [0.67; 1.11]	0.258	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-C30 Nausea and Vomiting (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
EORTC QLQ-C30 Nausea and Vomiting	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age Group									
< 65	146	100 (68.5)	2.14 [1.45; 2.83]	135	83 (61.5)	1.45 [1.18; 2.14]	0.78 [0.58; 1.05]	0.105	0.518
≥ 65	136	101 (74.3)	2.10 [1.51; 2.79]	132	81 (61.4)	1.61 [1.38; 2.14]	0.87 [0.65; 1.17]	0.361	
Region									
Region 1	152	108 (71.1)	2.10 [1.45; 2.33]	152	90 (59.2)	1.54 [1.18; 2.27]	0.92 [0.69; 1.22]	0.542	0.422
Region 2	130	93 (71.5)	2.79 [1.51; 3.45]	115	74 (64.3)	1.61 [1.38; 2.10]	0.73 [0.53; 1.00]	0.049	
MMR Status									
pMMR	233	164 (70.4)	2.10 [1.54; 2.79]	226	139 (61.5)	1.54 [1.38; 2.10]	0.83 [0.66; 1.04]	0.111	0.750
dMMR	49	37 (75.5)	2.14 [1.41; 3.52]	41	25 (61.0)	1.45 [0.76; 2.76]	0.75 [0.44; 1.28]	0.294	
ECOG Performance Status									
0	171	121 (70.8)	2.14 [1.71; 2.99]	156	99 (63.5)	1.58 [1.38; 2.10]	0.74 [0.56; 0.97]	0.032	0.217
1	111	80 (72.1)	2.10 [1.41; 2.79]	111	65 (58.6)	1.45 [0.99; 2.79]	0.97 [0.69; 1.35]	0.848	
Prior History of Pelvic Radiation									
Yes	122	90 (73.8)	2.14 [1.45; 2.83]	118	73 (61.9)	1.41 [0.99; 2.10]	0.84 [0.61; 1.15]	0.283	0.658
No	160	111 (69.4)	2.10 [1.45; 2.79]	149	91 (61.1)	1.61 [1.38; 2.20]	0.81 [0.61; 1.07]	0.140	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-C30 Pain (10 points)
With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
EORTC QLQ-C30 Pain	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age Group									
< 65	146	91 (62.3)	2.10 [1.48; 2.83]	135	79 (58.5)	2.10 [1.45; 2.76]	0.95 [0.70; 1.29]	0.752	0.093
≥ 65	136	103 (75.7)	1.41 [0.95; 1.48]	132	83 (62.9)	2.14 [1.61; 2.79]	1.31 [0.98; 1.76]	0.070	
Region									
Region 1	152	99 (65.1)	1.48 [1.41; 2.17]	152	89 (58.6)	2.10 [1.54; 2.76]	1.05 [0.79; 1.41]	0.730	0.544
Region 2	130	95 (73.1)	1.64 [1.35; 2.10]	115	73 (63.5)	2.14 [1.51; 2.79]	1.18 [0.87; 1.61]	0.285	
MMR Status									
pMMR	233	165 (70.8)	1.45 [1.41; 1.97]	226	140 (61.9)	2.07 [1.48; 2.27]	1.13 [0.90; 1.42]	0.298	0.769
dMMR	49	29 (59.2)	2.86 [1.45; 6.90]	41	22 (53.7)	3.06 [2.10; 5.13]	1.03 [0.59; 1.81]	0.915	
ECOG Performance Status									
0	171	122 (71.3)	1.48 [1.41; 2.10]	156	92 (59.0)	2.17 [1.54; 2.79]	1.22 [0.93; 1.61]	0.146	0.306
1	111	72 (64.9)	1.81 [1.41; 2.86]	111	70 (63.1)	2.10 [1.45; 2.60]	0.96 [0.69; 1.35]	0.825	
Prior History of Pelvic Radiation									
Yes	122	77 (63.1)	2.07 [1.41; 3.32]	118	66 (55.9)	2.53 [2.04; 3.48]	1.13 [0.81; 1.58]	0.462	0.822
No	160	117 (73.1)	1.45 [1.41; 2.10]	149	96 (64.4)	1.68 [1.45; 2.17]	1.09 [0.83; 1.43]	0.555	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-C30 Dyspnea (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
EORTC QLQ-C30 Dyspnea	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Age Group									
< 65	146	73 (50.0)	8.94 [4.44; 11.04]	135	62 (45.9)	3.48 [2.10; -]	0.65 [0.45; 0.93]	0.017	0.719
≥ 65	136	61 (44.9)	7.98 [5.52; 15.90]	132	59 (44.7)	4.14 [2.60; -]	0.69 [0.47; 1.00]	0.052	
Region									
Region 1	152	66 (43.4)	9.66 [6.24; 15.90]	152	70 (46.1)	3.42 [2.17; 4.90]	0.54 [0.37; 0.77]	< 0.001	0.149
Region 2	130	68 (52.3)	6.97 [3.81; 11.04]	115	51 (44.3)	4.86 [2.83; -]	0.85 [0.58; 1.25]	0.413	
MMR Status									
pMMR	233	109 (46.8)	7.98 [4.86; 12.29]	226	103 (45.6)	3.78 [2.56; 4.93]	0.69 [0.52; 0.92]	0.011	0.643
dMMR	49	25 (51.0)	9.73 [4.21; -]	41	18 (43.9)	4.14 [1.41; -]	0.58 [0.30; 1.14]	0.117	
ECOG Performance Status									
0	171	76 (44.4)	10.05 [7.16; 13.34]	156	70 (44.9)	3.78 [2.46; -]	0.53 [0.37; 0.76]	< 0.001	0.131
1	111	58 (52.3)	3.71 [2.76; 9.73]	111	51 (45.9)	4.14 [2.10; -]	0.91 [0.62; 1.34]	0.642	
Prior History of Pelvic Radiation									
Yes	122	59 (48.4)	9.00 [4.86; 11.04]	118	45 (38.1)	Not reached [3.48; -]	0.75 [0.50; 1.14]	0.184	0.133
No	160	75 (46.9)	7.16 [4.44; 16.00]	149	76 (51.0)	2.83 [2.10; 4.11]	0.61 [0.44; 0.86]	0.004	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-C30 Insomnia (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
EORTC QLQ-C30 Insomnia	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age Group									
< 65	146	78 (53.4)	4.11 [2.83; 9.66]	135	55 (40.7)	5.55 [2.56; -]	1.11 [0.78; 1.58]	0.555	0.663
≥ 65	136	85 (62.5)	2.79 [2.10; 4.40]	132	70 (53.0)	3.48 [2.10; 4.24]	0.90 [0.65; 1.24]	0.507	
Region									
Region 1	152	85 (55.9)	3.91 [2.73; 5.52]	152	73 (48.0)	3.48 [2.17; 5.09]	0.86 [0.62; 1.18]	0.350	0.331
Region 2	130	78 (60.0)	3.48 [2.10; 4.96]	115	52 (45.2)	4.90 [2.10; -]	1.17 [0.82; 1.68]	0.380	
MMR Status									
pMMR	233	135 (57.9)	3.48 [2.37; 4.90]	226	109 (48.2)	3.65 [2.10; 5.55]	0.95 [0.73; 1.23]	0.706	0.695
dMMR	49	28 (57.1)	4.11 [2.14; 19.38]	41	16 (39.0)	5.09 [3.48; -]	1.09 [0.58; 2.04]	0.790	
ECOG Performance Status									
0	171	96 (56.1)	4.40 [2.79; 6.21]	156	74 (47.4)	4.04 [2.30; 6.24]	0.90 [0.66; 1.24]	0.530	0.401
1	111	67 (60.4)	2.83 [2.14; 4.17]	111	51 (45.9)	3.75 [2.10; -]	1.14 [0.79; 1.65]	0.482	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-C30 Appetite loss (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
EORTC QLQ-C30 Appetite loss	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age Group									
< 65	146	99 (67.8)	2.10 [1.45; 2.83]	135	73 (54.1)	2.10 [1.61; 3.48]	1.14 [0.84; 1.54]	0.417	0.511
≥ 65	136	109 (80.1)	1.41 [0.95; 2.04]	132	84 (63.6)	2.07 [1.41; 2.76]	1.21 [0.90; 1.62]	0.200	
Region									
Region 1	152	107 (70.4)	2.04 [1.41; 2.17]	152	88 (57.9)	2.17 [1.48; 2.79]	1.07 [0.80; 1.43]	0.631	0.579
Region 2	130	101 (77.7)	1.54 [1.35; 2.14]	115	69 (60.0)	2.04 [1.41; 3.48]	1.28 [0.94; 1.74]	0.116	
MMR Status									
pMMR	233	178 (76.4)	1.48 [1.41; 2.10]	226	133 (58.8)	2.10 [1.61; 2.76]	1.31 [1.04; 1.65]	0.020	0.084
dMMR	49	30 (61.2)	4.60 [1.41; 8.97]	41	24 (58.5)	1.84 [0.79; -]	0.76 [0.43; 1.35]	0.352	
ECOG Performance Status									
0	171	131 (76.6)	1.45 [1.41; 2.10]	156	90 (57.7)	2.37 [1.61; 3.35]	1.28 [0.97; 1.68]	0.076	0.291
1	111	77 (69.4)	2.10 [1.41; 2.86]	111	67 (60.4)	2.00 [1.41; 2.23]	1.02 [0.73; 1.42]	0.918	
Prior History of Pelvic Radiation									
Yes	122	89 (73.0)	1.64 [1.41; 2.79]	118	67 (56.8)	2.17 [1.41; 3.48]	1.19 [0.86; 1.65]	0.284	0.740
No	160	119 (74.4)	1.81 [1.41; 2.10]	149	90 (60.4)	2.04 [1.45; 2.76]	1.15 [0.87; 1.51]	0.334	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-C30 Constipation (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
EORTC QLQ-C30 Constipation	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Age Group									
< 65	146	78 (53.4)	5.09 [3.48; 7.59]	135	69 (51.1)	2.46 [1.64; 3.29]	0.62 [0.44; 0.87]	0.006	0.590
≥ 65	136	74 (54.4)	4.11 [2.04; 7.95]	132	70 (53.0)	2.20 [1.61; 4.34]	0.75 [0.53; 1.05]	0.092	
Region									
Region 1	152	79 (52.0)	4.93 [2.53; 8.25]	152	82 (53.9)	2.07 [1.51; 2.89]	0.63 [0.46; 0.87]	0.005	0.252
Region 2	130	73 (56.2)	4.80 [3.48; 6.11]	115	57 (49.6)	2.83 [2.10; -]	0.77 [0.54; 1.10]	0.156	
MMR Status									
pMMR	233	131 (56.2)	4.11 [2.83; 5.59]	226	120 (53.1)	2.10 [1.64; 2.89]	0.72 [0.56; 0.93]	0.012	0.551
dMMR	49	21 (42.9)	Not reached [3.42; -]	41	19 (46.3)	3.06 [2.10; 5.78]	0.58 [0.30; 1.12]	0.104	
ECOG Performance Status									
0	171	91 (53.2)	4.93 [3.48; 7.95]	156	89 (57.1)	2.14 [1.61; 2.89]	0.58 [0.43; 0.78]	< 0.001	0.073
1	111	61 (55.0)	3.55 [2.17; 6.24]	111	50 (45.0)	2.96 [1.64; -]	0.89 [0.60; 1.31]	0.542	
Prior History of Pelvic Radiation									
Yes	122	72 (59.0)	3.22 [2.04; 5.49]	118	59 (50.0)	2.79 [1.51; 4.60]	0.89 [0.63; 1.27]	0.519	0.114
No	160	80 (50.0)	5.59 [4.04; 9.10]	149	80 (53.7)	2.14 [1.64; 3.06]	0.55 [0.40; 0.76]	< 0.001	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-C30 Diarrhea (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
EORTC QLQ-C30 Diarrhea	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age Group									
< 65	146	94 (64.4)	3.02 [2.14; 4.14]	135	43 (31.9)	Not reached [4.17; -]	1.73 [1.20; 2.50]	0.003	0.177
≥ 65	136	86 (63.2)	3.55 [2.76; 4.17]	132	57 (43.2)	4.24 [2.79; -]	1.24 [0.88; 1.74]	0.210	
Region									
Region 1	152	97 (63.8)	2.83 [2.10; 3.68]	152	55 (36.2)	4.27 [3.42; -]	1.66 [1.18; 2.31]	0.003	0.320
Region 2	130	83 (63.8)	3.71 [2.79; 4.80]	115	45 (39.1)	Not reached [3.06; -]	1.26 [0.87; 1.83]	0.217	
MMR Status									
pMMR	233	142 (60.9)	3.48 [2.76; 3.94]	226	77 (34.1)	Not reached [4.17; -]	1.62 [1.22; 2.15]	< 0.001	0.090
dMMR	49	38 (77.6)	2.79 [1.41; 6.34]	41	23 (56.1)	2.56 [1.41; 5.78]	0.95 [0.54; 1.64]	0.842	
ECOG Performance Status									
0	171	114 (66.7)	3.48 [2.79; 4.14]	156	61 (39.1)	4.80 [3.42; -]	1.36 [0.99; 1.87]	0.057	0.764
1	111	66 (59.5)	2.79 [2.10; 4.14]	111	39 (35.1)	Not reached [2.83; -]	1.59 [1.07; 2.38]	0.023	
Prior History of Pelvic Radiation									
Yes	122	84 (68.9)	2.63 [1.64; 3.02]	118	47 (39.8)	4.17 [2.56; -]	1.59 [1.10; 2.29]	0.012	0.507
No	160	96 (60.0)	3.88 [3.29; 4.21]	149	53 (35.6)	5.78 [4.17; -]	1.35 [0.96; 1.91]	0.082	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-EN24 Lymphoedema (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		p-Value for Interaction Test[h]
EORTC QLQ-EN24 Lymphoedema	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	
Age Group									
< 65	121	67 (55.4)	3.65 [2.10; 6.93]	114	55 (48.2)	2.79 [2.04; 4.17]	0.78 [0.54; 1.13]	0.190	0.885
≥ 65	119	68 (57.1)	4.11 [2.79; 6.18]	119	61 (51.3)	2.27 [1.54; 3.65]	0.82 [0.57; 1.17]	0.267	
Region									
Region 1	143	77 (53.8)	5.09 [3.02; 7.00]	143	71 (49.7)	2.56 [1.45; 4.14]	0.68 [0.49; 0.96]	0.029	0.342
Region 2	97	58 (59.8)	2.89 [2.07; 5.45]	90	45 (50.0)	2.79 [1.61; 5.09]	0.98 [0.66; 1.46]	0.934	
MMR Status									
pMMR	202	113 (55.9)	4.01 [2.79; 6.18]	193	97 (50.3)	2.56 [2.04; 3.55]	0.77 [0.58; 1.02]	0.069	0.939
dMMR	38	22 (57.9)	5.09 [2.07; 12.19]	40	19 (47.5)	3.48 [1.38; -]	0.79 [0.42; 1.49]	0.463	
ECOG Performance Status									
0	143	85 (59.4)	4.01 [2.10; 6.24]	133	65 (48.9)	2.79 [2.04; 4.60]	0.87 [0.62; 1.22]	0.426	0.464
1	97	50 (51.5)	3.65 [2.79; 6.31]	100	51 (51.0)	2.33 [1.45; 3.48]	0.71 [0.47; 1.06]	0.091	
Prior History of Pelvic Radiation									
Yes	107	60 (56.1)	5.09 [2.69; 6.24]	106	51 (48.1)	3.48 [2.04; 4.21]	0.80 [0.54; 1.19]	0.272	0.814
No	133	75 (56.4)	3.65 [2.73; 6.31]	127	65 (51.2)	2.20 [1.51; 3.55]	0.78 [0.55; 1.10]	0.151	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

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Subgroup Analysis of Time to First Deterioration for EORTC QLQ-EN24 Urological symptoms (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		p-Value for Interaction Test[h]
EORTC QLQ-EN24 Urological symptoms	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	
Age Group									
< 65	121	51 (42.1)	9.73 [4.86; -]	114	37 (32.5)	Not reached [3.45; -]	0.88 [0.56; 1.37]	0.563	0.680
≥ 65	119	51 (42.9)	8.25 [4.30; -]	119	38 (31.9)	Not reached [3.98; -]	1.03 [0.67; 1.59]	0.902	
Region									
Region 1	143	56 (39.2)	10.58 [5.55; -]	143	43 (30.1)	Not reached [3.98; -]	0.92 [0.61; 1.40]	0.703	0.955
Region 2	97	46 (47.4)	8.25 [3.65; -]	90	32 (35.6)	Not reached [2.79; -]	0.98 [0.62; 1.56]	0.935	
MMR Status									
pMMR	202	88 (43.6)	8.25 [4.57; 11.70]	193	58 (30.1)	Not reached [4.17; -]	1.07 [0.76; 1.51]	0.694	0.080
dMMR	38	14 (36.8)	Not reached [5.09; -]	40	17 (42.5)	3.48 [1.45; -]	0.52 [0.24; 1.09]	0.084	
ECOG Performance Status									
0	143	61 (42.7)	10.15 [5.09; -]	133	45 (33.8)	Not reached [3.48; -]	0.92 [0.62; 1.38]	0.690	0.734
1	97	41 (42.3)	8.25 [4.17; -]	100	30 (30.0)	Not reached [3.71; -]	1.00 [0.62; 1.63]	0.996	
Prior History of Pelvic Radiation									
Yes	107	49 (45.8)	5.78 [3.15; -]	106	31 (29.2)	Not reached [3.98; -]	1.30 [0.82; 2.05]	0.268	0.142
No	133	53 (39.8)	10.15 [6.18; -]	127	44 (34.6)	4.24 [3.45; -]	0.73 [0.48; 1.12]	0.146	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

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Subgroup Analysis of Time to First Deterioration for EORTC QLQ-EN24 Gastrointestinal symptoms (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
EORTC QLQ-EN24 Gastrointestinal symptoms	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Age Group									
< 65	121	69 (57.0)	3.68 [2.76; 5.82]	114	45 (39.5)	4.37 [2.76; -]	1.02 [0.69; 1.51]	0.920	0.453
≥ 65	119	69 (58.0)	4.17 [2.83; 5.78]	119	55 (46.2)	4.14 [2.76; 5.29]	0.86 [0.60; 1.24]	0.421	
Region									
Region 1	143	79 (55.2)	3.15 [2.17; 5.09]	143	62 (43.4)	4.17 [2.60; 5.78]	0.94 [0.67; 1.32]	0.714	0.767
Region 2	97	59 (60.8)	4.83 [3.32; 6.47]	90	38 (42.2)	4.21 [2.89; -]	0.94 [0.61; 1.43]	0.763	
MMR Status									
pMMR	202	113 (55.9)	4.11 [2.83; 4.93]	193	79 (40.9)	4.21 [3.02; 6.14]	1.00 [0.74; 1.35]	0.991	0.445
dMMR	38	25 (65.8)	4.24 [2.14; 8.35]	40	21 (52.5)	2.89 [2.04; 5.78]	0.76 [0.41; 1.43]	0.395	
Prior History of Pelvic Radiation									
Yes	107	68 (63.6)	2.83 [2.14; 3.55]	106	48 (45.3)	4.17 [2.60; 5.55]	1.23 [0.84; 1.79]	0.288	0.131
No	133	70 (52.6)	5.82 [4.17; 8.35]	127	52 (40.9)	4.83 [2.76; 6.24]	0.75 [0.51; 1.10]	0.136	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-EN24 Poor body image (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		p-Value for Interaction Test[h]
EORTC QLQ-EN24 Poor body image	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	
Age Group									
< 65	121	52 (43.0)	9.89 [3.48; -]	114	52 (45.6)	2.17 [1.41; -]	0.64 [0.43; 0.95]	0.026	0.367
≥ 65	119	56 (47.1)	5.52 [3.52; -]	119	74 (62.2)	2.00 [1.41; 2.30]	0.46 [0.32; 0.65]	< 0.001	
Region									
Region 1	143	62 (43.4)	6.24 [4.17; -]	143	80 (55.9)	2.10 [1.41; 2.33]	0.47 [0.34; 0.67]	< 0.001	0.383
Region 2	97	46 (47.4)	6.90 [3.48; -]	90	46 (51.1)	2.10 [1.48; 4.21]	0.62 [0.41; 0.95]	0.028	
MMR Status									
pMMR	202	89 (44.1)	6.24 [4.17; -]	193	103 (53.4)	2.14 [1.48; 2.79]	0.54 [0.40; 0.72]	< 0.001	0.867
dMMR	38	19 (50.0)	9.66 [2.17; -]	40	23 (57.5)	2.10 [1.35; 4.21]	0.51 [0.27; 0.97]	0.040	
ECOG Performance Status									
0	143	64 (44.8)	6.90 [4.21; -]	133	75 (56.4)	2.14 [1.41; 2.33]	0.48 [0.34; 0.68]	< 0.001	0.349
1	97	44 (45.4)	4.86 [2.79; -]	100	51 (51.0)	2.10 [1.41; 4.14]	0.62 [0.41; 0.94]	0.025	
Prior History of Pelvic Radiation									
Yes	107	53 (49.5)	4.60 [2.99; 13.70]	106	60 (56.6)	2.07 [1.41; 2.37]	0.58 [0.40; 0.85]	0.005	0.538
No	133	55 (41.4)	9.89 [4.96; -]	127	66 (52.0)	2.23 [1.41; 3.48]	0.49 [0.34; 0.71]	< 0.001	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-EN24 Sexual/vaginal problems (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		p-Value for Interaction Test[h]
EORTC QLQ-EN24 Sexual/vaginal problems	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	
Age Group									
< 65	42	6 (14.3)	2.79 [1.38; -]	21	6 (28.6)	5.88 [0.72; -]	0.80 [0.24; 2.63]	0.714	0.932
≥ 65	16	4 (25.0)	3.55 [0.69; -]	20	5 (25.0)	4.83 [0.76; -]	0.80 [0.21; 3.05]	0.746	
Region									
Region 1	43	9 (20.9)	3.55 [1.48; -]	31	8 (25.8)	4.83 [1.15; 5.88]	0.92 [0.34; 2.45]	0.864	0.751
Region 2	15	1 (6.7)	Not reached [0.72; -]	10	3 (30.0)	Not reached [0.72; -]	0.89 [0.09; 8.65]	0.921	
MMR Status									
pMMR	50	10 (20.0)	3.55 [1.48; -]	37	10 (27.0)	4.83 [2.10; 5.88]	1.23 [0.43; 3.55]	0.701	n.a.
dMMR	8	0 (0.0)	Not reached [-; -]	4	1 (25.0)	Not reached [1.15; -]	n.a. [n.a.; n.a.]	n.a.	
ECOG Performance Status									
0	45	8 (17.8)	3.55 [1.48; -]	29	8 (27.6)	4.83 [1.15; -]	0.96 [0.35; 2.65]	0.931	0.573
1	13	2 (15.4)	2.09 [1.38; -]	12	3 (25.0)	4.16 [0.72; -]	2.33 [0.31; 17.74]	0.414	
Prior History of Pelvic Radiation									
Yes	25	4 (16.0)	1.05 [0.69; -]	20	5 (25.0)	3.25 [0.72; -]	1.79 [0.47; 6.77]	0.391	0.271
No	33	6 (18.2)	3.55 [1.48; -]	21	6 (28.6)	4.83 [0.76; -]	0.66 [0.20; 2.18]	0.498	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items; MMR: Mismatch Repair; n.a.: not applicable (when estimation not possible); pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-EN24 Pain in back and pelvis (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
EORTC QLQ-EN24 Pain in back and pelvis	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Region									
Region 1	143	77 (53.8)	3.48 [2.14; 5.49]	143	61 (42.7)	3.48 [2.37; 5.55]	1.05 [0.75; 1.49]	0.769	0.368
Region 2	97	57 (58.8)	4.86 [3.48; 7.03]	90	30 (33.3)	6.24 [3.55; -]	1.25 [0.79; 1.98]	0.332	
MMR Status									
pMMR	202	117 (57.9)	3.58 [2.76; 4.80]	193	75 (38.9)	5.06 [2.60; -]	1.15 [0.85; 1.56]	0.349	0.178
dMMR	38	17 (44.7)	10.97 [3.48; -]	40	16 (40.0)	3.75 [1.45; -]	0.67 [0.32; 1.39]	0.285	
ECOG Performance Status									
0	143	82 (57.3)	4.11 [2.79; 6.57]	133	57 (42.9)	3.55 [2.33; 6.24]	1.00 [0.71; 1.42]	0.990	0.416
1	97	52 (53.6)	4.14 [2.14; 5.55]	100	34 (34.0)	Not reached [2.83; -]	1.29 [0.83; 2.00]	0.258	
Prior History of Pelvic Radiation									
Yes	107	52 (48.6)	4.80 [2.79; 12.91]	106	40 (37.7)	6.24 [3.45; -]	1.07 [0.70; 1.64]	0.741	0.583
No	133	82 (61.7)	3.71 [2.66; 5.49]	127	51 (40.2)	5.06 [2.23; -]	1.13 [0.79; 1.62]	0.510	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-EN24 Tingling/numbness (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
EORTC QLQ-EN24 Tingling/numbness	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age Group									
< 65	121	47 (38.8)	13.70 [4.86; -]	114	31 (27.2)	Not reached [6.11; -]	1.06 [0.66; 1.68]	0.814	0.316
≥ 65	119	55 (46.2)	9.46 [2.79; 18.20]	119	53 (44.5)	4.11 [2.20; -]	0.80 [0.55; 1.18]	0.269	
Region									
Region 1	143	58 (40.6)	13.70 [4.21; -]	143	56 (39.2)	5.36 [2.30; -]	0.76 [0.52; 1.11]	0.161	0.173
Region 2	97	44 (45.4)	9.46 [3.52; -]	90	28 (31.1)	Not reached [3.48; -]	1.15 [0.71; 1.86]	0.572	
MMR Status									
pMMR	202	88 (43.6)	6.47 [3.78; -]	193	66 (34.2)	6.11 [3.65; -]	0.99 [0.72; 1.37]	0.959	0.093
dMMR	38	14 (36.8)	Not reached [8.84; -]	40	18 (45.0)	5.36 [2.04; -]	0.49 [0.23; 1.06]	0.069	
ECOG Performance Status									
0	143	60 (42.0)	13.70 [3.78; -]	133	44 (33.1)	Not reached [4.11; -]	0.99 [0.67; 1.48]	0.968	0.552
1	97	42 (43.3)	8.84 [3.65; -]	100	40 (40.0)	5.36 [2.20; -]	0.80 [0.51; 1.25]	0.325	
Prior History of Pelvic Radiation									
Yes	107	49 (45.8)	11.30 [2.79; -]	106	41 (38.7)	6.11 [2.30; -]	0.89 [0.58; 1.36]	0.583	0.892
No	133	53 (39.8)	11.27 [4.14; -]	127	43 (33.9)	Not reached [3.48; -]	0.90 [0.60; 1.36]	0.614	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-EN24 Muscular pain (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		p-Value for Interaction Test[h]
EORTC QLQ-EN24 Muscular pain	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	
Age Group									
< 65	121	76 (62.8)	1.84 [1.41; 2.17]	114	51 (44.7)	2.76 [2.14; 4.63]	1.37 [0.95; 1.96]	0.088	0.988
≥ 65	119	74 (62.2)	2.40 [1.48; 4.30]	119	53 (44.5)	3.48 [2.37; -]	1.27 [0.89; 1.83]	0.189	
Region									
Region 1	143	88 (61.5)	2.00 [1.41; 2.17]	143	65 (45.5)	3.02 [2.20; 4.14]	1.37 [0.99; 1.90]	0.056	0.962
Region 2	97	62 (63.9)	2.30 [1.41; 4.30]	90	39 (43.3)	3.48 [2.14; -]	1.29 [0.86; 1.94]	0.223	
MMR Status									
pMMR	202	123 (60.9)	2.10 [1.45; 2.79]	193	85 (44.0)	3.22 [2.30; 5.03]	1.32 [0.99; 1.75]	0.058	0.850
dMMR	38	27 (71.1)	2.14 [1.41; 4.30]	40	19 (47.5)	3.06 [2.04; -]	1.40 [0.77; 2.56]	0.271	
ECOG Performance Status									
0	143	94 (65.7)	2.00 [1.41; 2.76]	133	67 (50.4)	2.37 [2.14; 3.48]	1.22 [0.88; 1.68]	0.228	0.460
1	97	56 (57.7)	2.14 [1.45; 3.65]	100	37 (37.0)	4.14 [2.83; -]	1.54 [1.01; 2.35]	0.044	
Prior History of Pelvic Radiation									
Yes	107	66 (61.7)	1.51 [1.41; 2.30]	106	47 (44.3)	3.48 [2.33; -]	1.50 [1.02; 2.19]	0.037	0.531
No	133	84 (63.2)	2.17 [1.48; 3.42]	127	57 (44.9)	3.02 [2.10; 5.55]	1.21 [0.86; 1.70]	0.279	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-EN24 Hair loss (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		p-Value for Interaction Test[h]
EORTC QLQ-EN24 Hair loss	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	
Age Group									
< 65	121	40 (33.1)	16.56 [7.62; -]	114	80 (70.2)	0.76 [0.72; 0.82]	0.15 [0.10; 0.23]	< 0.001	0.679
≥ 65	119	41 (34.5)	11.47 [7.59; -]	119	90 (75.6)	0.72 [0.72; 0.76]	0.11 [0.07; 0.18]	< 0.001	
Region									
Region 1	143	47 (32.9)	11.47 [7.62; -]	143	104 (72.7)	0.72 [0.72; 0.76]	0.10 [0.07; 0.16]	< 0.001	0.380
Region 2	97	34 (35.1)	16.36 [6.21; -]	90	66 (73.3)	0.76 [0.72; 0.82]	0.17 [0.11; 0.27]	< 0.001	
MMR Status									
pMMR	202	68 (33.7)	10.88 [7.62; -]	193	138 (71.5)	0.72 [0.72; 0.76]	0.13 [0.09; 0.18]	< 0.001	0.638
dMMR	38	13 (34.2)	16.36 [7.62; -]	40	32 (80.0)	0.76 [0.72; 0.82]	0.10 [0.05; 0.23]	< 0.001	
ECOG Performance Status									
0	143	47 (32.9)	16.36 [9.30; -]	133	98 (73.7)	0.72 [0.72; 0.76]	0.12 [0.08; 0.18]	< 0.001	0.282
1	97	34 (35.1)	7.62 [6.21; -]	100	72 (72.0)	0.76 [0.72; 0.82]	0.15 [0.09; 0.24]	< 0.001	
Prior History of Pelvic Radiation									
Yes	107	44 (41.1)	9.30 [6.21; 16.56]	106	82 (77.4)	0.72 [0.72; 0.76]	0.15 [0.10; 0.22]	< 0.001	0.479
No	133	37 (27.8)	Not reached [10.45; -]	127	88 (69.3)	0.76 [0.72; 0.82]	0.12 [0.08; 0.18]	< 0.001	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-EN24 Taste change (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		p-Value for Interaction Test[h]
EORTC QLQ-EN24 Taste change	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	
Age Group									
< 65	121	83 (68.6)	1.81 [1.38; 2.17]	114	73 (64.0)	1.41 [0.95; 1.61]	0.76 [0.55; 1.05]	0.102	0.571
≥ 65	119	79 (66.4)	1.61 [1.35; 2.14]	119	88 (73.9)	1.41 [0.76; 1.54]	0.70 [0.51; 0.95]	0.022	
Region									
Region 1	143	89 (62.2)	1.61 [1.38; 2.14]	143	99 (69.2)	1.41 [1.08; 1.71]	0.71 [0.53; 0.94]	0.019	0.557
Region 2	97	73 (75.3)	1.81 [0.95; 2.17]	90	62 (68.9)	1.41 [0.76; 1.48]	0.77 [0.54; 1.09]	0.135	
MMR Status									
pMMR	202	138 (68.3)	1.48 [1.38; 2.10]	193	133 (68.9)	1.41 [0.95; 1.51]	0.77 [0.60; 0.98]	0.036	0.227
dMMR	38	24 (63.2)	2.17 [1.41; 3.91]	40	28 (70.0)	1.41 [0.76; 2.10]	0.52 [0.29; 0.93]	0.028	
ECOG Performance Status									
0	143	99 (69.2)	2.07 [1.41; 2.14]	133	99 (74.4)	1.38 [0.76; 1.45]	0.63 [0.47; 0.84]	0.001	0.138
1	97	63 (64.9)	1.45 [1.35; 2.66]	100	62 (62.0)	1.41 [0.95; 2.04]	0.89 [0.62; 1.27]	0.525	
Prior History of Pelvic Radiation									
Yes	107	77 (72.0)	1.61 [1.38; 2.14]	106	74 (69.8)	1.41 [0.82; 2.04]	0.78 [0.57; 1.09]	0.143	0.431
No	133	85 (63.9)	1.81 [1.41; 2.17]	127	87 (68.5)	1.38 [0.79; 1.54]	0.69 [0.50; 0.93]	0.016	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Anhang 4-G5: Ergänzende Analysen für den Endpunkt EQ-5D VAS

Anhang 4-G5.1: Ergebnisse der Subgruppenanalysen mit p-Wert für Interaktionstests ≥ 0.05 für den Endpunkt Zeit bis zur ersten Verschlechterung um mindestens 15 mm auf den Skalen der EQ-5D VAS gegenüber Baseline aus RCT (Studie 309) mit dem zu bewertenden Arzneimittel (Datenschnitt: 26.10.2020)

Analysis of Time to First Deterioration for EQ-5D VAS (15 points)

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
EQ-5D VAS	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age Group									
< 65	146	81 (55.5)	4.47 [2.79; 7.49]	135	72 (53.3)	3.48 [2.00; 4.37]	0.72 [0.51; 0.99]	0.046	0.354
≥ 65	136	82 (60.3)	3.91 [2.10; 4.80]	132	72 (54.5)	2.83 [2.14; 4.47]	0.95 [0.69; 1.32]	0.763	
Region									
Region 1	152	82 (53.9)	4.40 [2.79; 7.49]	152	82 (53.9)	2.73 [2.07; 4.17]	0.76 [0.55; 1.04]	0.085	0.456
Region 2	130	81 (62.3)	4.14 [2.10; 5.36]	115	62 (53.9)	3.48 [2.10; 5.55]	0.91 [0.65; 1.28]	0.583	
MMR Status									
pMMR	233	137 (58.8)	3.91 [2.76; 4.60]	226	122 (54.0)	2.83 [2.10; 4.17]	0.88 [0.69; 1.14]	0.332	0.136
dMMR	49	26 (53.1)	6.74 [2.79; -]	41	22 (53.7)	3.48 [1.45; 5.78]	0.54 [0.29; 0.98]	0.044	
ECOG Performance Status									
0	171	99 (57.9)	4.40 [2.79; 6.24]	156	82 (52.6)	3.52 [2.27; 5.55]	0.87 [0.64; 1.17]	0.348	0.611
1	111	64 (57.7)	4.14 [2.33; 5.52]	111	62 (55.9)	2.60 [1.54; 4.14]	0.78 [0.54; 1.11]	0.169	
Prior History of Pelvic Radiation									
Yes	122	70 (57.4)	4.40 [2.79; 7.49]	118	59 (50.0)	3.48 [2.14; -]	0.88 [0.62; 1.26]	0.500	0.753
No	160	93 (58.1)	4.17 [2.27; 5.52]	149	85 (57.0)	2.79 [2.00; 4.17]	0.79 [0.58; 1.07]	0.123	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 15 points or more decrease from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EQ-5D VAS: European Quality of Life 5 Dimensions Visual Analog Scale; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Anhang 4-G6: Ergänzende Analysen für den Endpunkt EORTC QLQ-C30 und EORTC QLQ-EN24 – Funktion

Anhang 4-G6.1: Ergebnisse der Analysen für den Endpunkt Zeit bis zur ersten Verschlechterung um mindestens 15 Punkte auf den Skalen des EORTC QLQ-C30 (Globaler Gesundheitsstatus und Funktionsskalen) und EORTC QLQ-EN24 (Funktionsskalen) gegenüber Baseline aus RCT (Studie 309) mit dem zu bewertenden Arzneimittel (Datenschnitt: 26.10.2020)

Analysis of Time to First Deterioration for EORTC QLQ-C30 Global Health Status/QoL, EORTC QLQ-C30 Functional Scales and EORTC QLQ-EN24 Functional Scales

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]	
	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]
EORTC QLQ-C30 Global Health Status/QoL (15 points)								
Global Health Status/QoL	282	200 (70.9)	2.07 [1.45; 2.10]	267	162 (60.7)	2.17 [2.04; 2.79]	1.02 [0.82; 1.26]	0.870
EORTC QLQ-C30 Functional Scales (15 points)								
Physical Functioning	282	177 (62.8)	2.86 [2.33; 4.11]	267	123 (46.1)	3.98 [2.79; 5.78]	1.14 [0.90; 1.44]	0.293
Role Functioning	282	202 (71.6)	1.45 [1.41; 2.10]	267	177 (66.3)	1.41 [1.41; 2.07]	0.95 [0.77; 1.17]	0.642
Emotional Functioning	282	146 (51.8)	5.52 [4.17; 8.08]	267	112 (41.9)	4.14 [2.79; -]	0.82 [0.63; 1.06]	0.135
Cognitive Functioning	282	183 (64.9)	3.32 [2.63; 4.17]	267	143 (53.6)	2.27 [2.10; 2.96]	0.93 [0.74; 1.16]	0.514
Social Functioning	282	194 (68.8)	2.07 [1.45; 2.33]	267	172 (64.4)	1.77 [1.41; 2.23]	0.89 [0.72; 1.10]	0.289
EORTC QLQ-EN24 Functional Scales (15 points)								
Sexual interest	239	42 (17.6)	Not reached [-; -]	229	31 (13.5)	Not reached [-; -]	1.00 [0.62; 1.62]	0.995
Sexual activity	239	40 (16.7)	Not reached [-; -]	229	28 (12.2)	Not reached [-; -]	1.10 [0.67; 1.80]	0.714
Sexual enjoyment	58	9 (15.5)	12.88 [0.76; -]	41	7 (17.1)	5.52 [2.10; -]	1.67 [0.44; 6.29]	0.447

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

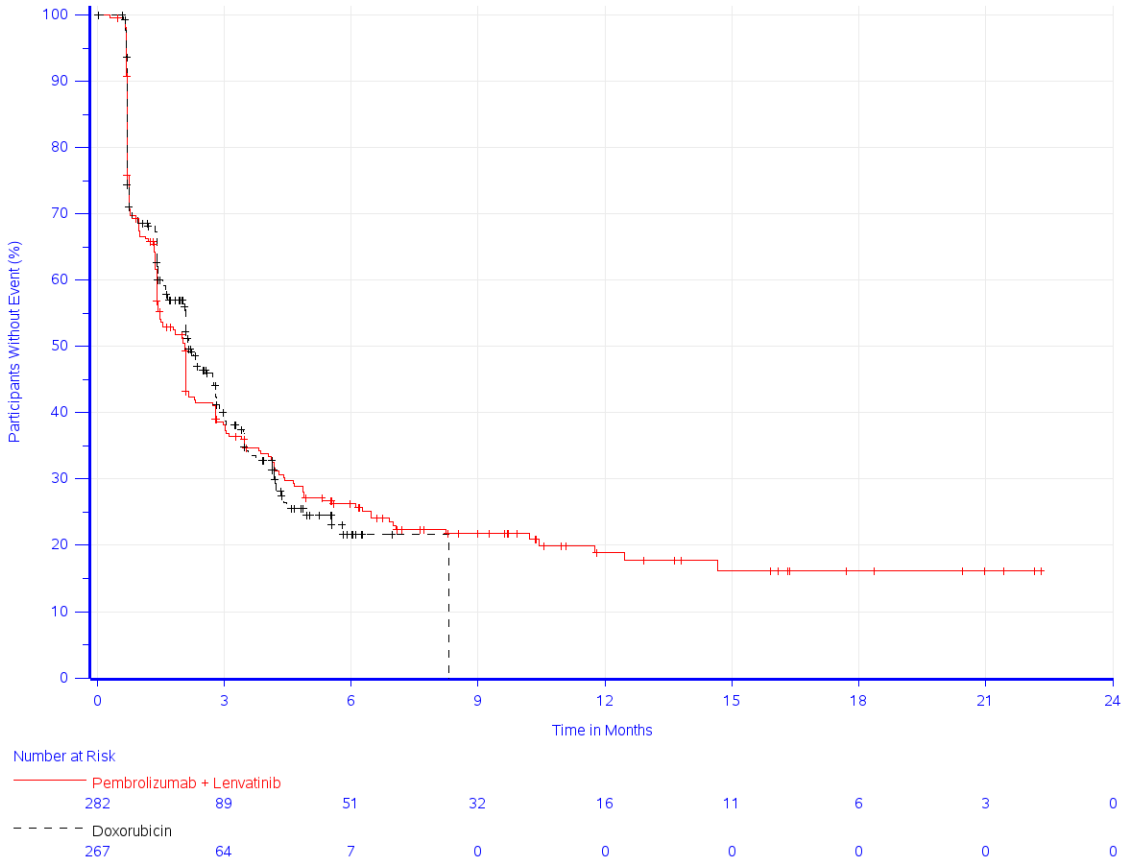
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 15 points or more decrease from baseline

e: From product-limit (Kaplan-Meier) method for censored data

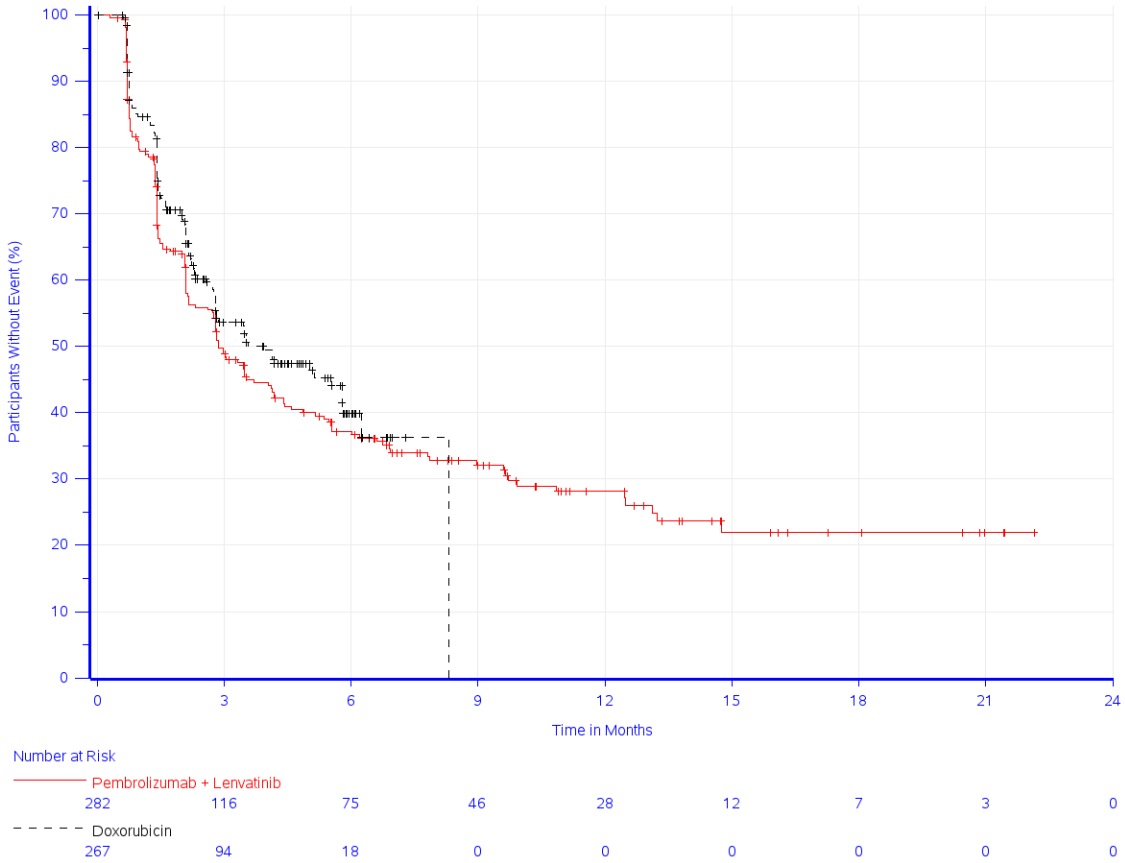
f: Based on Cox regression model with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

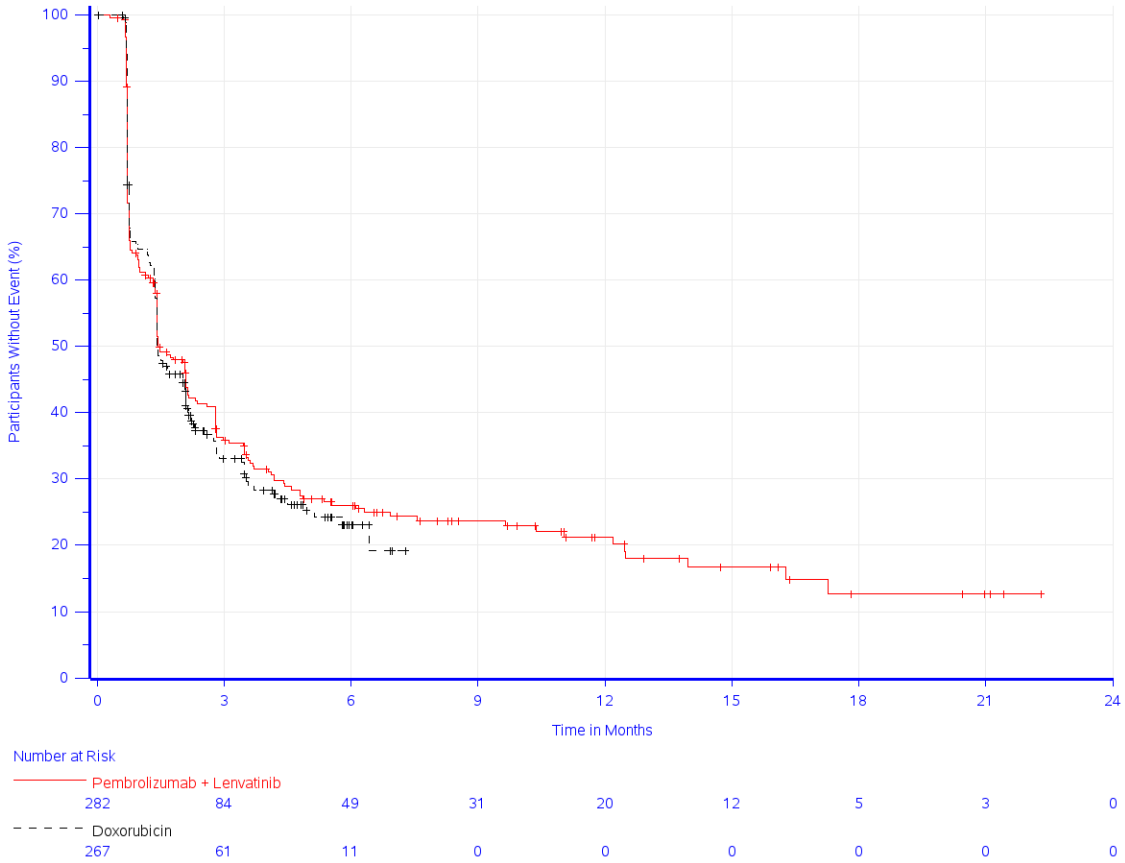
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items; QoL: Quality of Life



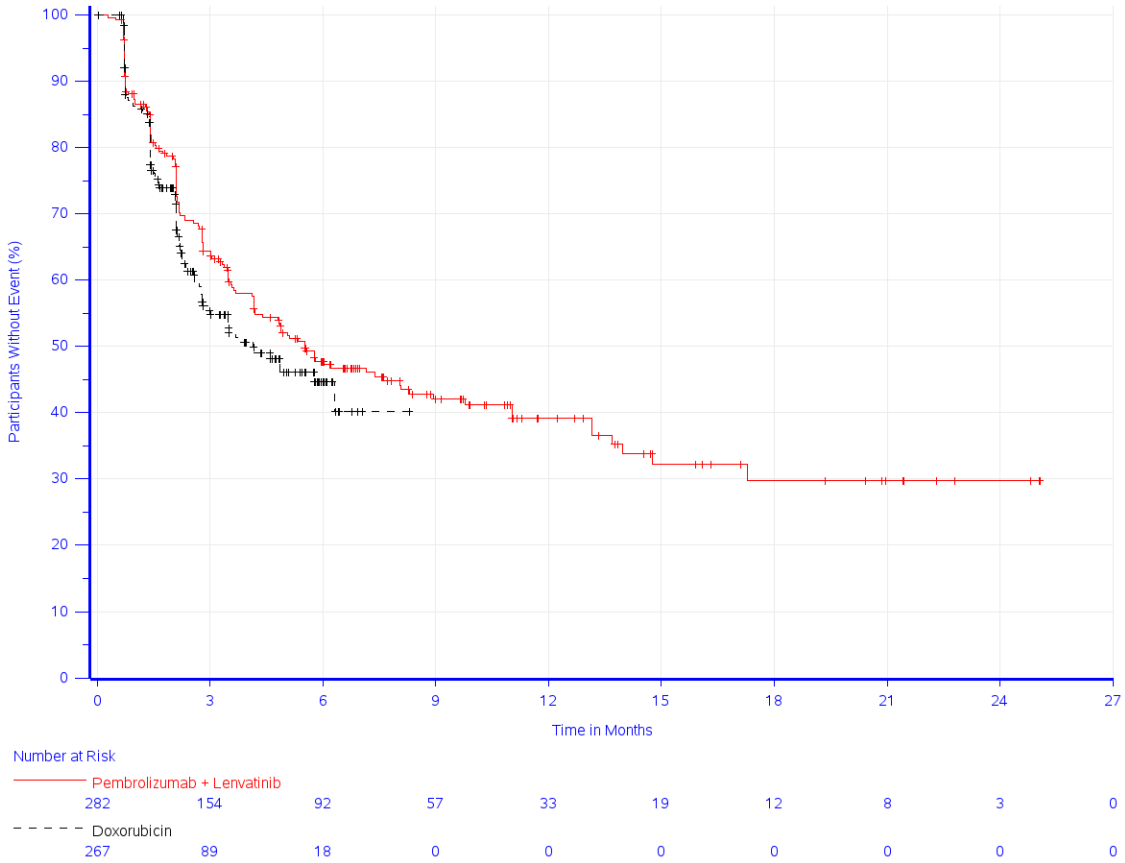
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-C30 Global Health Status/QoL (15 points)



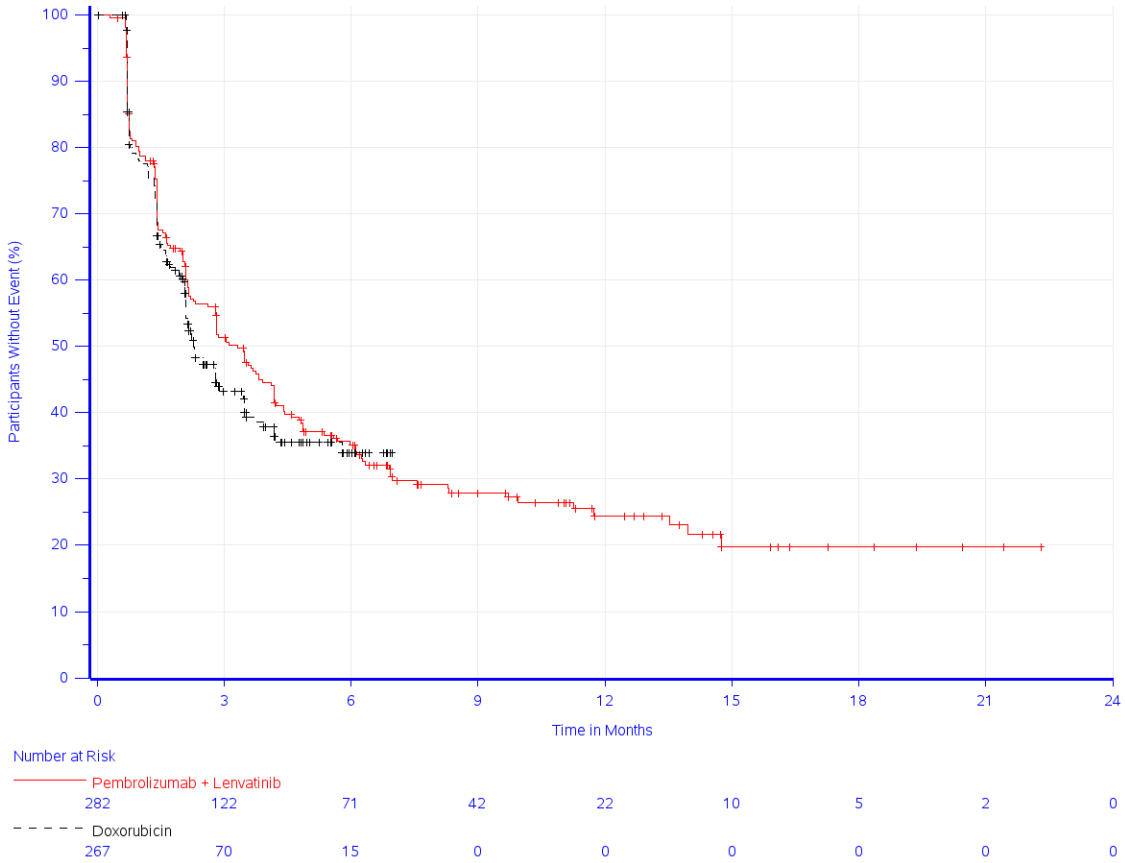
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-C30 Physical Functioning (15 points)



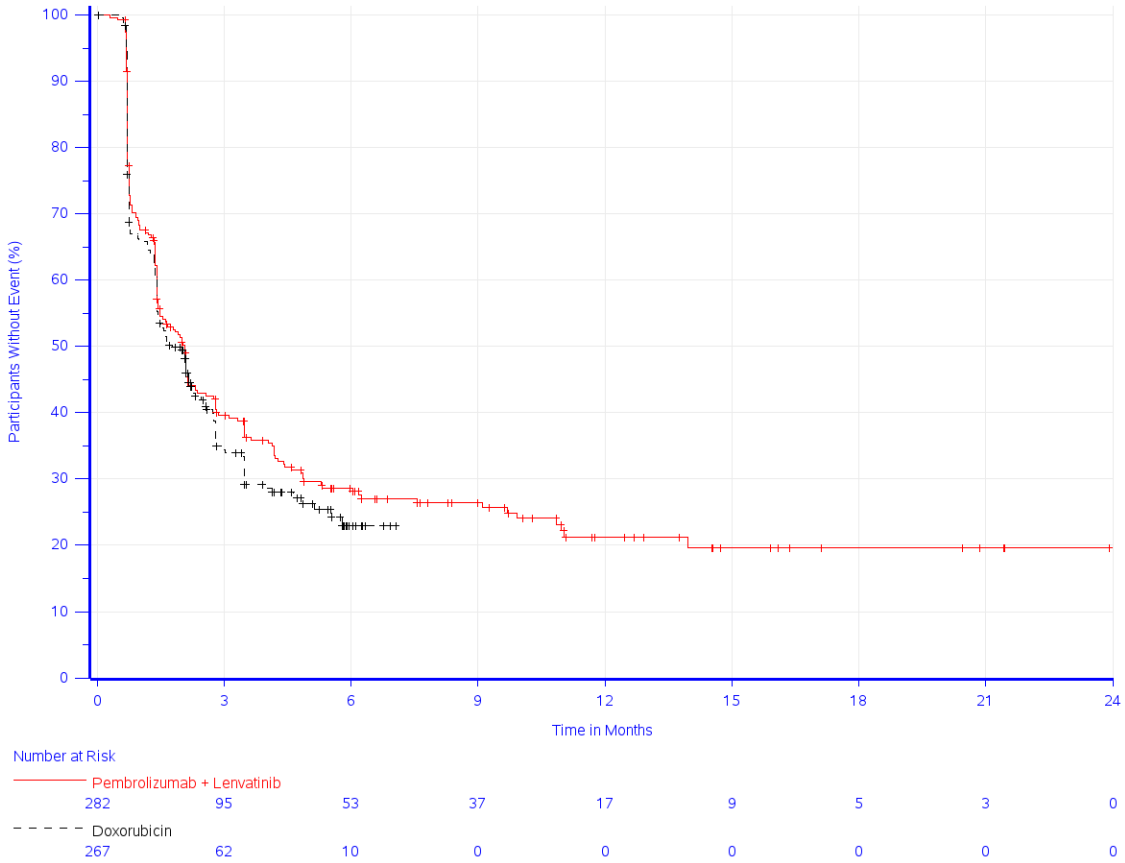
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-C30 Role Functioning (15 points)



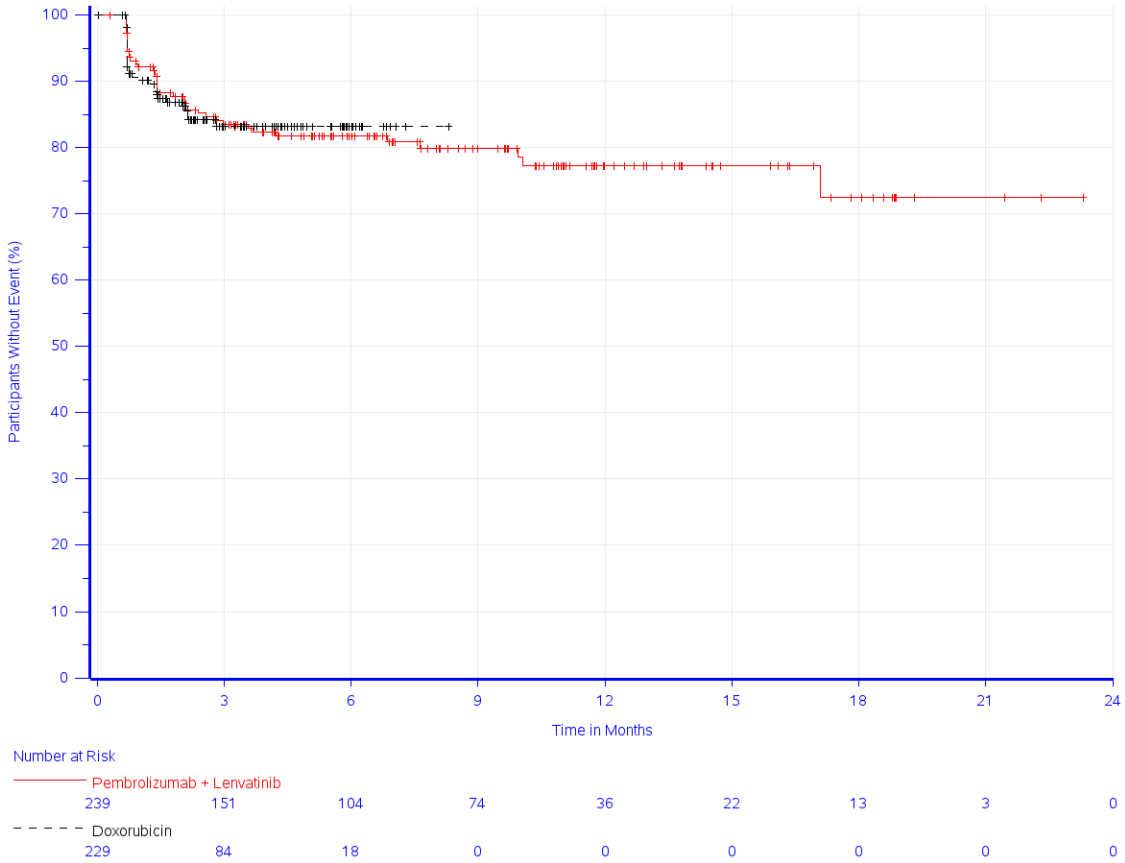
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-C30 Emotional Functioning (15 points)



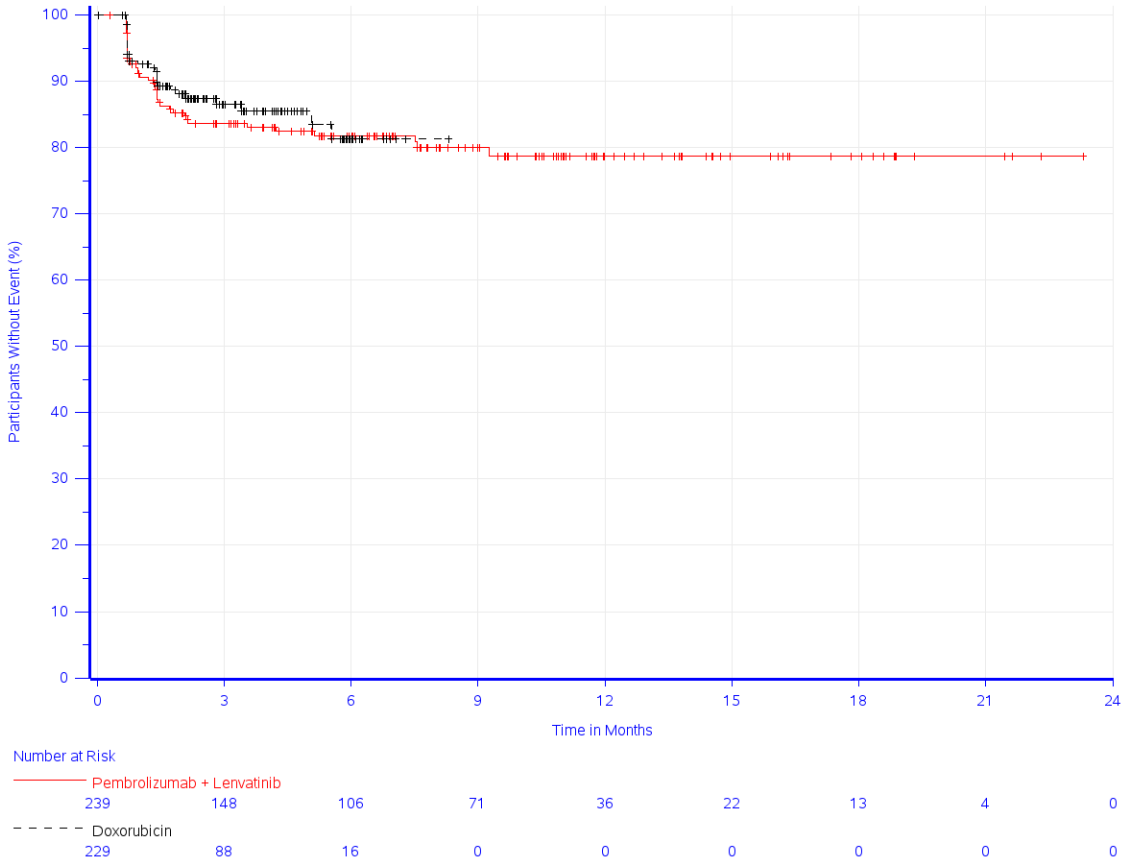
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-C30 Cognitive Functioning (15 points)



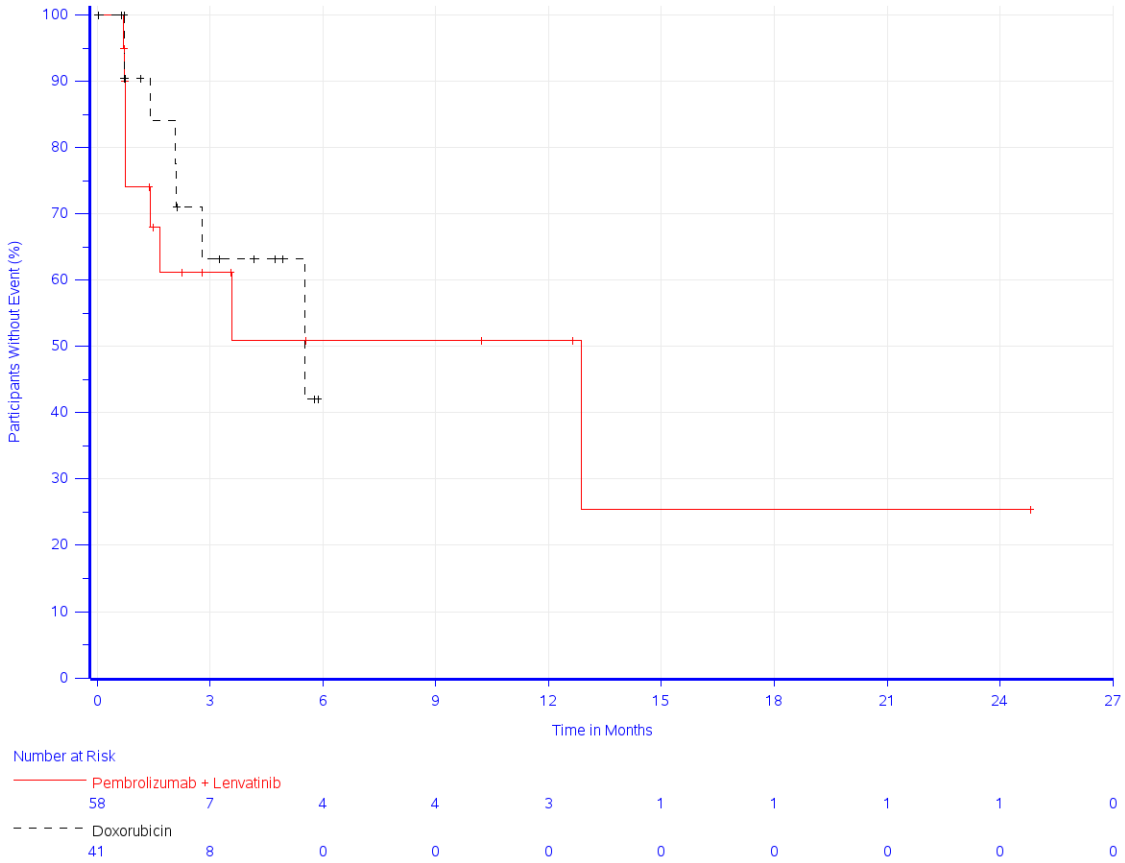
Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-C30 Social Functioning (15 points)



Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-EN24 Sexual interest (15 points)



Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-EN24 Sexual activity (15 points)



Kaplan Meier Curves of Time to First Deterioration for EORTC QLQ-EN24 Sexual enjoyment (15 points)

Anhang 4-G6.2: Ergebnisse der Subgruppenanalysen mit p-Wert für Interaktionstests ≥ 0.05 für den Endpunkt Zeit bis zur ersten Verschlechterung um mindestens 10 Punkte auf den Skalen des EORTC QLQ-C30 (Funktionsskalen) und EORTC QLQ-EN24 (Funktionsskalen) gegenüber Baseline aus RCT (Studie 309) mit dem zu bewertenden Arzneimittel (Datenschnitt: 26.10.2020)

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-C30 Global Health Status/QoL (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
EORTC QLQ-C30 Global Health Status/QoL	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age Group									
< 65	146	99 (67.8)	2.10 [2.07; 2.83]	135	78 (57.8)	2.17 [1.45; 2.79]	0.88 [0.65; 1.19]	0.407	0.149
≥ 65	136	101 (74.3)	1.41 [1.15; 2.04]	132	84 (63.6)	2.33 [1.58; 3.06]	1.17 [0.87; 1.57]	0.289	
Region									
Region 1	152	101 (66.4)	2.07 [1.45; 2.33]	152	86 (56.6)	2.33 [2.10; 3.48]	1.02 [0.76; 1.37]	0.904	0.895
Region 2	130	99 (76.2)	1.81 [1.41; 2.17]	115	76 (66.1)	2.10 [1.41; 2.79]	1.00 [0.74; 1.35]	0.985	
MMR Status									
pMMR	233	170 (73.0)	1.84 [1.41; 2.10]	226	138 (61.1)	2.17 [1.61; 2.79]	1.08 [0.86; 1.36]	0.506	0.163
dMMR	49	30 (61.2)	3.48 [1.41; 10.22]	41	24 (58.5)	2.20 [1.41; 4.37]	0.70 [0.40; 1.23]	0.214	
ECOG Performance Status									
0	171	128 (74.9)	1.54 [1.41; 2.10]	156	99 (63.5)	2.10 [1.45; 2.43]	1.04 [0.80; 1.36]	0.751	0.677
1	111	72 (64.9)	2.10 [1.45; 3.06]	111	63 (56.8)	2.73 [2.07; 3.45]	0.95 [0.68; 1.35]	0.792	
Prior History of Pelvic Radiation									
Yes	122	89 (73.0)	2.07 [1.41; 2.33]	118	65 (55.1)	2.73 [2.10; 3.52]	1.27 [0.92; 1.76]	0.143	0.059
No	160	111 (69.4)	2.07 [1.41; 2.17]	149	97 (65.1)	2.07 [1.41; 2.76]	0.85 [0.64; 1.13]	0.258	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; QoL: Quality of Life; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-C30 Physical Functioning (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
EORTC QLQ-C30 Physical Functioning	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Age Group									
< 65	146	101 (69.2)	1.45 [1.41; 2.10]	135	79 (58.5)	2.17 [2.04; 3.45]	1.15 [0.85; 1.55]	0.358	0.760
≥ 65	136	107 (78.7)	1.41 [1.38; 2.10]	132	83 (62.9)	2.00 [1.41; 2.30]	1.18 [0.88; 1.58]	0.274	
MMR Status									
pMMR	233	178 (76.4)	1.41 [1.41; 1.48]	226	138 (61.1)	2.10 [1.61; 2.56]	1.24 [0.99; 1.56]	0.060	0.223
dMMR	49	30 (61.2)	2.99 [1.38; 8.97]	41	24 (58.5)	2.33 [1.25; 3.48]	0.86 [0.50; 1.49]	0.585	
Prior History of Pelvic Radiation									
Yes	122	91 (74.6)	1.45 [1.38; 1.61]	118	66 (55.9)	2.73 [2.04; 3.48]	1.41 [1.02; 1.94]	0.037	0.107
No	160	117 (73.1)	1.45 [1.41; 2.10]	149	96 (64.4)	2.04 [1.41; 2.20]	1.02 [0.77; 1.34]	0.913	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-C30 Role Functioning (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
EORTC QLQ-C30 Role Functioning	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age Group									
< 65	146	96 (65.8)	2.17 [1.41; 3.58]	135	88 (65.2)	1.41 [1.38; 2.10]	0.82 [0.61; 1.10]	0.188	0.124
≥ 65	136	106 (77.9)	1.41 [0.95; 1.64]	132	89 (67.4)	1.41 [1.35; 2.14]	1.12 [0.85; 1.50]	0.418	
MMR Status									
pMMR	233	172 (73.8)	1.41 [1.31; 2.07]	226	150 (66.4)	1.41 [1.38; 2.04]	1.00 [0.80; 1.26]	0.984	0.251
dMMR	49	30 (61.2)	3.45 [2.07; 9.66]	41	27 (65.9)	2.10 [1.41; 3.48]	0.71 [0.42; 1.22]	0.216	
ECOG Performance Status									
0	171	128 (74.9)	1.45 [1.35; 2.07]	156	104 (66.7)	1.48 [1.38; 2.10]	1.03 [0.79; 1.34]	0.832	0.325
1	111	74 (66.7)	2.10 [1.41; 3.48]	111	73 (65.8)	1.41 [1.38; 2.10]	0.85 [0.61; 1.18]	0.326	
Prior History of Pelvic Radiation									
Yes	122	86 (70.5)	1.48 [1.31; 2.79]	118	71 (60.2)	2.04 [1.41; 2.76]	1.01 [0.73; 1.40]	0.945	0.438
No	160	116 (72.5)	1.45 [1.41; 2.10]	149	106 (71.1)	1.41 [1.35; 2.04]	0.91 [0.70; 1.19]	0.498	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-C30 Emotional Functioning (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
EORTC QLQ-C30 Emotional Functioning	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Age Group									
< 65	146	72 (49.3)	7.62 [4.90; 13.14]	135	52 (38.5)	6.31 [2.56; -]	0.76 [0.52; 1.10]	0.142	0.556
≥ 65	136	74 (54.4)	4.17 [3.06; 7.39]	132	60 (45.5)	3.75 [2.73; 5.78]	0.95 [0.67; 1.35]	0.789	
Region									
Region 1	152	78 (51.3)	4.90 [3.48; 11.04]	152	66 (43.4)	3.68 [2.27; -]	0.85 [0.60; 1.19]	0.331	0.716
Region 2	130	68 (52.3)	6.05 [4.11; 8.94]	115	46 (40.0)	4.86 [2.96; -]	0.87 [0.59; 1.28]	0.469	
MMR Status									
pMMR	233	116 (49.8)	5.52 [4.17; 8.94]	226	99 (43.8)	3.68 [2.76; 6.31]	0.74 [0.56; 0.98]	0.039	0.080
dMMR	49	30 (61.2)	4.83 [2.14; 11.04]	41	13 (31.7)	Not reached [2.73; -]	1.42 [0.72; 2.81]	0.313	
ECOG Performance Status									
0	171	86 (50.3)	5.78 [4.40; 11.04]	156	66 (42.3)	4.17 [2.60; -]	0.79 [0.57; 1.10]	0.162	0.473
1	111	60 (54.1)	4.17 [2.79; 9.79]	111	46 (41.4)	4.14 [2.73; -]	0.96 [0.65; 1.43]	0.851	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-C30 Cognitive Functioning (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
EORTC QLQ-C30 Cognitive Functioning	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Age Group									
< 65	146	88 (60.3)	3.91 [2.79; 4.86]	135	69 (51.1)	2.79 [2.10; 3.94]	0.88 [0.64; 1.22]	0.456	0.840
≥ 65	136	95 (69.9)	2.83 [2.04; 3.48]	132	74 (56.1)	2.17 [1.68; 2.96]	0.94 [0.69; 1.29]	0.706	
Region									
Region 1	152	88 (57.9)	3.58 [2.63; 4.86]	152	83 (54.6)	2.27 [1.94; 2.79]	0.76 [0.56; 1.04]	0.084	0.059
Region 2	130	95 (73.1)	2.83 [2.10; 3.91]	115	60 (52.2)	2.50 [2.10; 4.24]	1.11 [0.80; 1.55]	0.524	
MMR Status									
pMMR	233	151 (64.8)	2.86 [2.17; 3.91]	226	126 (55.8)	2.23 [2.07; 2.79]	0.90 [0.70; 1.14]	0.382	0.466
dMMR	49	32 (65.3)	4.11 [2.33; 6.34]	41	17 (41.5)	Not reached [2.14; -]	1.14 [0.62; 2.10]	0.666	
ECOG Performance Status									
0	171	106 (62.0)	4.11 [2.83; 5.59]	156	83 (53.2)	2.30 [2.10; 3.48]	0.79 [0.58; 1.06]	0.114	0.147
1	111	77 (69.4)	2.17 [1.64; 3.48]	111	60 (54.1)	2.23 [1.68; 3.71]	1.15 [0.81; 1.61]	0.437	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-C30 Social Functioning (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
EORTC QLQ-C30 Social Functioning	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age Group									
< 65	146	99 (67.8)	2.07 [1.41; 2.79]	135	82 (60.7)	1.64 [1.38; 2.46]	0.94 [0.70; 1.27]	0.703	0.827
≥ 65	136	95 (69.9)	2.00 [1.41; 2.79]	132	90 (68.2)	2.07 [1.41; 2.60]	0.88 [0.65; 1.17]	0.373	
Region									
Region 1	152	104 (68.4)	2.10 [1.48; 2.56]	152	97 (63.8)	1.68 [1.41; 2.53]	0.88 [0.66; 1.16]	0.353	0.874
Region 2	130	90 (69.2)	1.91 [1.41; 2.83]	115	75 (65.2)	2.00 [1.41; 2.60]	0.96 [0.70; 1.31]	0.776	
MMR Status									
pMMR	233	163 (70.0)	2.00 [1.41; 2.14]	226	148 (65.5)	1.64 [1.41; 2.20]	0.89 [0.71; 1.11]	0.303	0.905
dMMR	49	31 (63.3)	2.10 [1.45; 9.69]	41	24 (58.5)	2.17 [1.41; 5.13]	0.92 [0.53; 1.59]	0.764	
ECOG Performance Status									
0	171	117 (68.4)	2.00 [1.41; 2.14]	156	99 (63.5)	1.61 [1.41; 2.27]	0.95 [0.72; 1.24]	0.694	0.957
1	111	77 (69.4)	2.10 [1.41; 3.48]	111	73 (65.8)	2.07 [1.41; 2.79]	0.84 [0.61; 1.17]	0.315	
Prior History of Pelvic Radiation									
Yes	122	81 (66.4)	2.00 [1.41; 3.48]	118	74 (62.7)	1.54 [1.35; 2.53]	0.82 [0.59; 1.13]	0.223	0.430
No	160	113 (70.6)	2.07 [1.41; 2.33]	149	98 (65.8)	2.07 [1.41; 2.56]	0.98 [0.75; 1.29]	0.910	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-EN24 Sexual interest (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
EORTC QLQ-EN24 Sexual interest	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age Group									
< 65	121	25 (20.7)	Not reached [-; -]	111	15 (13.5)	Not reached [-; -]	1.13 [0.58; 2.20]	0.709	0.385
≥ 65	118	17 (14.4)	Not reached [-; -]	118	16 (13.6)	Not reached [-; -]	0.89 [0.44; 1.77]	0.731	
Region									
Region 1	143	32 (22.4)	Not reached [17.08; -]	142	23 (16.2)	Not reached [-; -]	1.08 [0.62; 1.88]	0.777	0.660
Region 2	96	10 (10.4)	Not reached [-; -]	87	8 (9.2)	Not reached [-; -]	0.89 [0.34; 2.31]	0.804	
MMR Status									
pMMR	201	40 (19.9)	Not reached [-; -]	189	26 (13.8)	Not reached [-; -]	1.11 [0.67; 1.86]	0.678	0.206
dMMR	38	2 (5.3)	Not reached [-; -]	40	5 (12.5)	Not reached [-; -]	0.39 [0.07; 2.00]	0.257	
ECOG Performance Status									
0	143	30 (21.0)	Not reached [-; -]	131	24 (18.3)	Not reached [-; -]	0.94 [0.54; 1.62]	0.819	0.396
1	96	12 (12.5)	Not reached [17.08; -]	98	7 (7.1)	Not reached [-; -]	1.17 [0.44; 3.14]	0.754	
Prior History of Pelvic Radiation									
Yes	107	18 (16.8)	Not reached [-; -]	105	15 (14.3)	Not reached [-; -]	0.90 [0.44; 1.83]	0.769	0.716
No	132	24 (18.2)	Not reached [17.08; -]	124	16 (12.9)	Not reached [-; -]	1.11 [0.58; 2.12]	0.747	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-EN24 Sexual activity (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
EORTC QLQ-EN24 Sexual activity	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age Group									
< 65	121	23 (19.0)	Not reached [-; -]	111	16 (14.4)	Not reached [-; -]	1.08 [0.56; 2.09]	0.816	0.993
≥ 65	118	17 (14.4)	Not reached [-; -]	118	12 (10.2)	Not reached [-; -]	1.21 [0.57; 2.54]	0.618	
Region									
Region 1	143	27 (18.9)	Not reached [-; -]	142	20 (14.1)	Not reached [-; -]	1.16 [0.64; 2.09]	0.630	0.957
Region 2	96	13 (13.5)	Not reached [-; -]	87	8 (9.2)	Not reached [-; -]	1.17 [0.48; 2.89]	0.727	
MMR Status									
pMMR	201	38 (18.9)	Not reached [-; -]	189	24 (12.7)	Not reached [-; -]	1.22 [0.72; 2.05]	0.465	0.201
dMMR	38	2 (5.3)	Not reached [-; -]	40	4 (10.0)	Not reached [5.55; -]	0.39 [0.07; 2.20]	0.285	
ECOG Performance Status									
0	143	29 (20.3)	Not reached [-; -]	131	20 (15.3)	Not reached [-; -]	1.09 [0.61; 1.96]	0.761	0.937
1	96	11 (11.5)	Not reached [-; -]	98	8 (8.2)	Not reached [-; -]	1.21 [0.48; 3.08]	0.684	
Prior History of Pelvic Radiation									
Yes	107	17 (15.9)	Not reached [-; -]	105	16 (15.2)	Not reached [-; -]	0.80 [0.39; 1.62]	0.531	0.257
No	132	23 (17.4)	Not reached [-; -]	124	12 (9.7)	Not reached [-; -]	1.59 [0.79; 3.22]	0.197	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Subgroup Analysis of Time to First Deterioration for EORTC QLQ-EN24 Sexual enjoyment (10 points) With P-value for Interaction test >= 0.05

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		p-Value for Interaction Test[h]
EORTC QLQ-EN24 Sexual enjoyment	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	
Age Group									
< 65	42	7 (16.7)	n.c.	21	2 (9.5)	n.c.	n.c.	n.c.	n.c.
≥ 65	16	2 (12.5)	n.c.	20	5 (25.0)	n.c.	n.c.	n.c.	
Region									
Region 1	43	7 (16.3)	12.88 [0.76; -]	31	5 (16.1)	5.52 [1.41; -]	1.05 [0.32; 3.46]	0.941	0.471
Region 2	15	2 (13.3)	1.68 [1.41; -]	10	2 (20.0)	Not reached [0.72; -]	3.71 [0.33; 41.55]	0.287	
MMR Status									
pMMR	50	9 (18.0)	12.88 [0.76; -]	37	7 (18.9)	5.52 [2.07; -]	1.67 [0.44; 6.29]	0.447	n.a.
dMMR	8	0 (0.0)	Not reached [-; -]	4	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
ECOG Performance Status									
0	45	7 (15.6)	12.88 [0.76; -]	29	5 (17.2)	Not reached [1.41; -]	1.36 [0.42; 4.47]	0.610	0.641
1	13	2 (15.4)	3.58 [0.76; -]	12	2 (16.7)	5.52 [2.07; -]	1.03 [0.14; 7.42]	0.977	
Prior History of Pelvic Radiation									
Yes	25	4 (16.0)	n.c.	20	3 (15.0)	n.c.	n.c.	n.c.	n.c.
No	33	5 (15.2)	n.c.	21	4 (19.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: full-analysis-set, population relevant for benefit assessment

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline

e: From product-limit (Kaplan-Meier) method for censored data

f: Based on unstratified Cox regression model with treatment as a covariate for all subgroups with the exception of pMMR subgroup category, which utilized the Cox regression model stratified by ECOG performance status, geographic region, and prior history of pelvic radiation

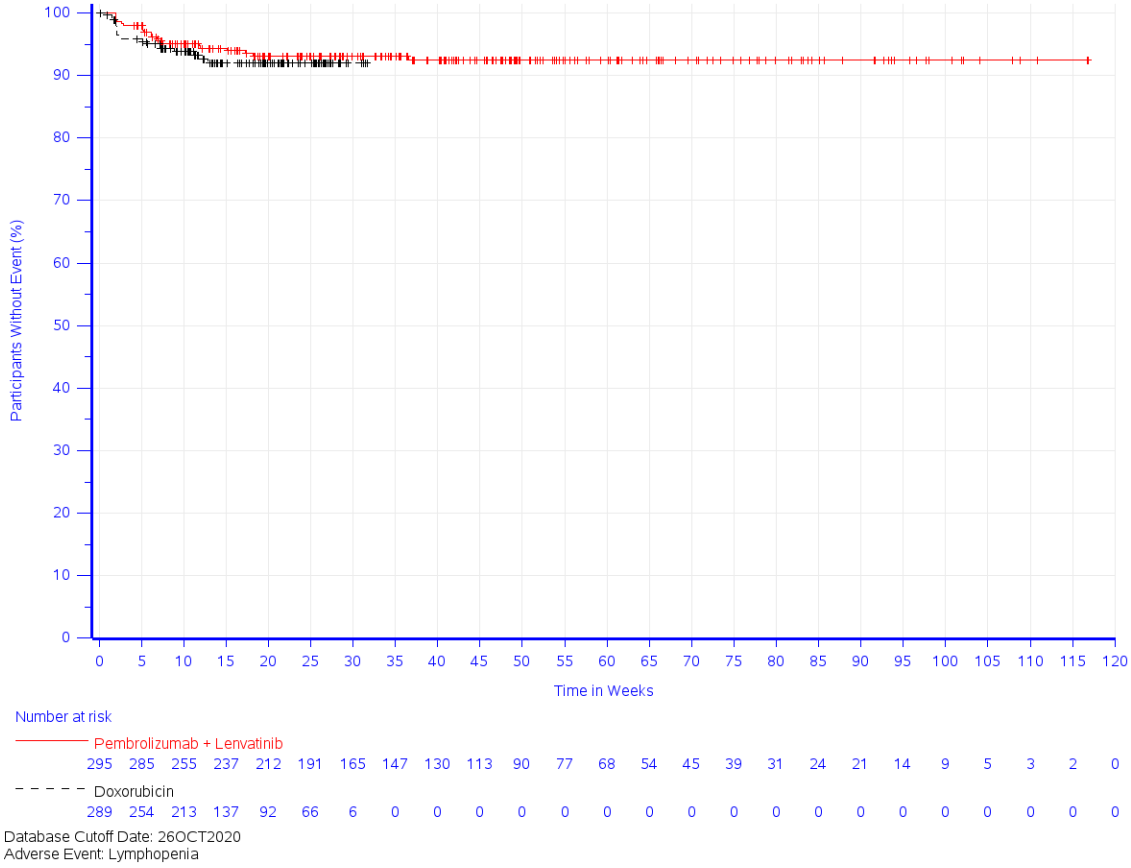
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

h: Based on unstratified Cox regression model with treatment, subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term) with the exception of MMR status subgroup, which utilized the Cox regression model stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

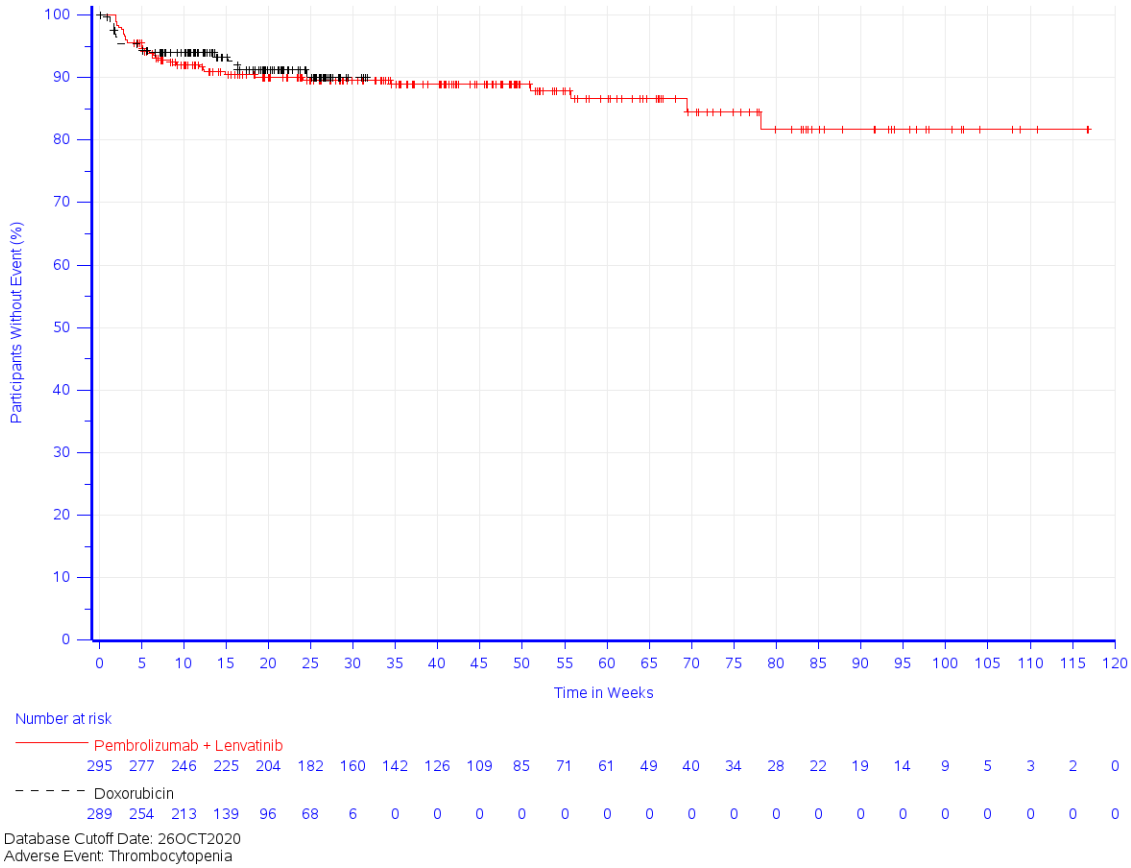
CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items; MMR: Mismatch Repair; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 participants per subgroup and at least 10 events in one of the subgroups necessary; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Anhang 4-G7: Ergänzende Analysen für den Endpunkt Verträglichkeit

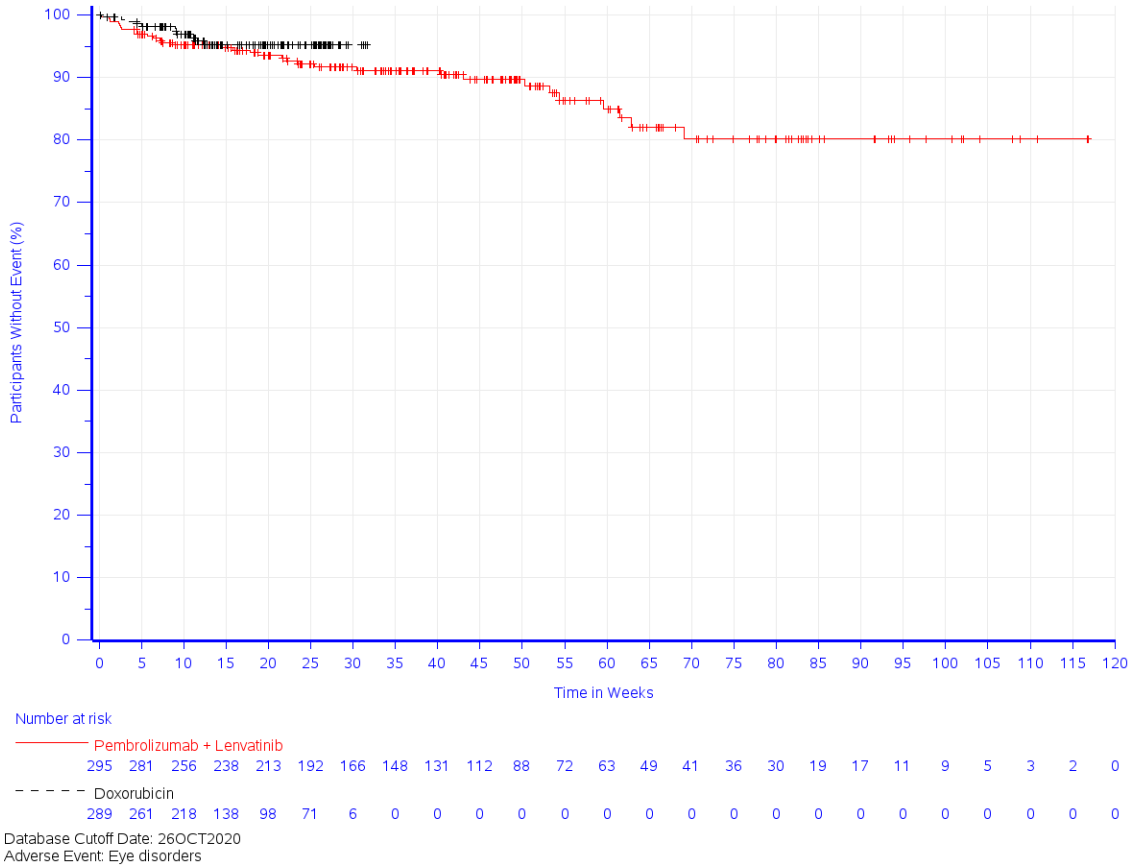
Anhang 4-G7.1: Kaplan-Meier-Kurven für die Analysen der Verträglichkeitsendpunkte mit statistisch nicht signifikanten Unterschieden zwischen den Studienarmen



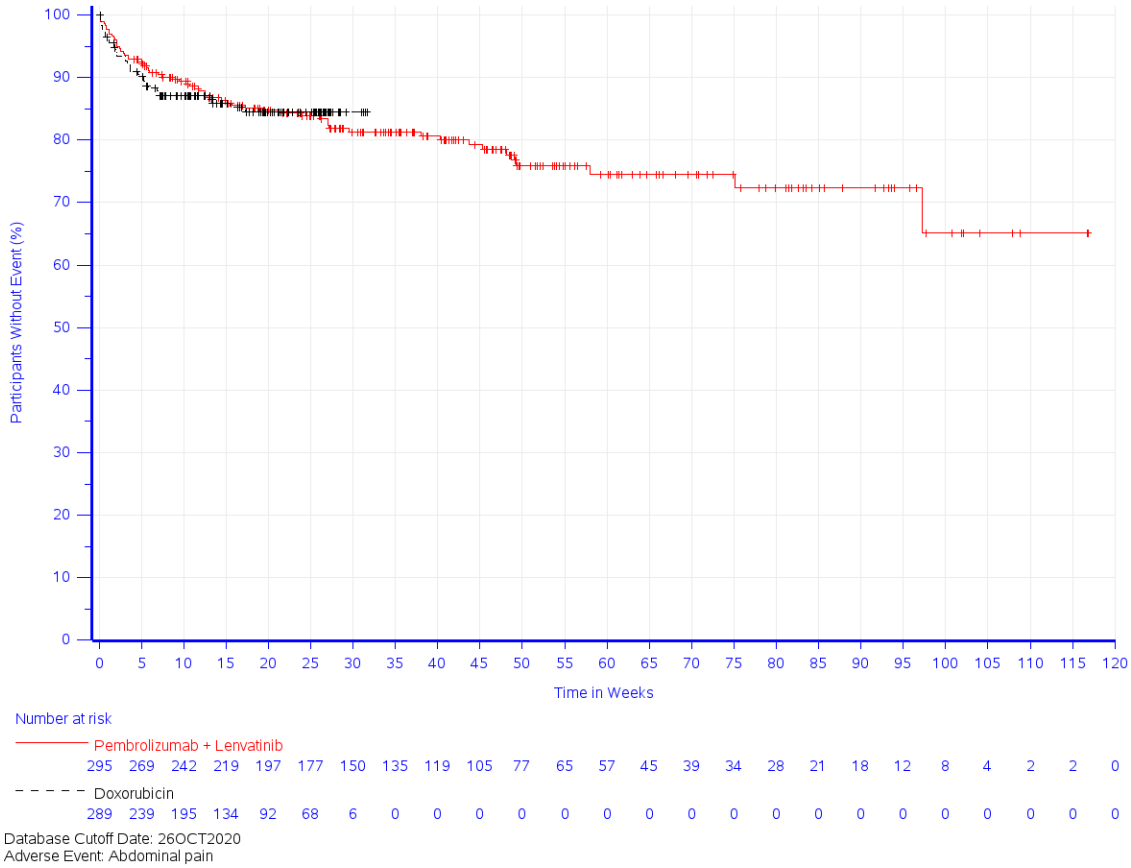
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Lymphopenia



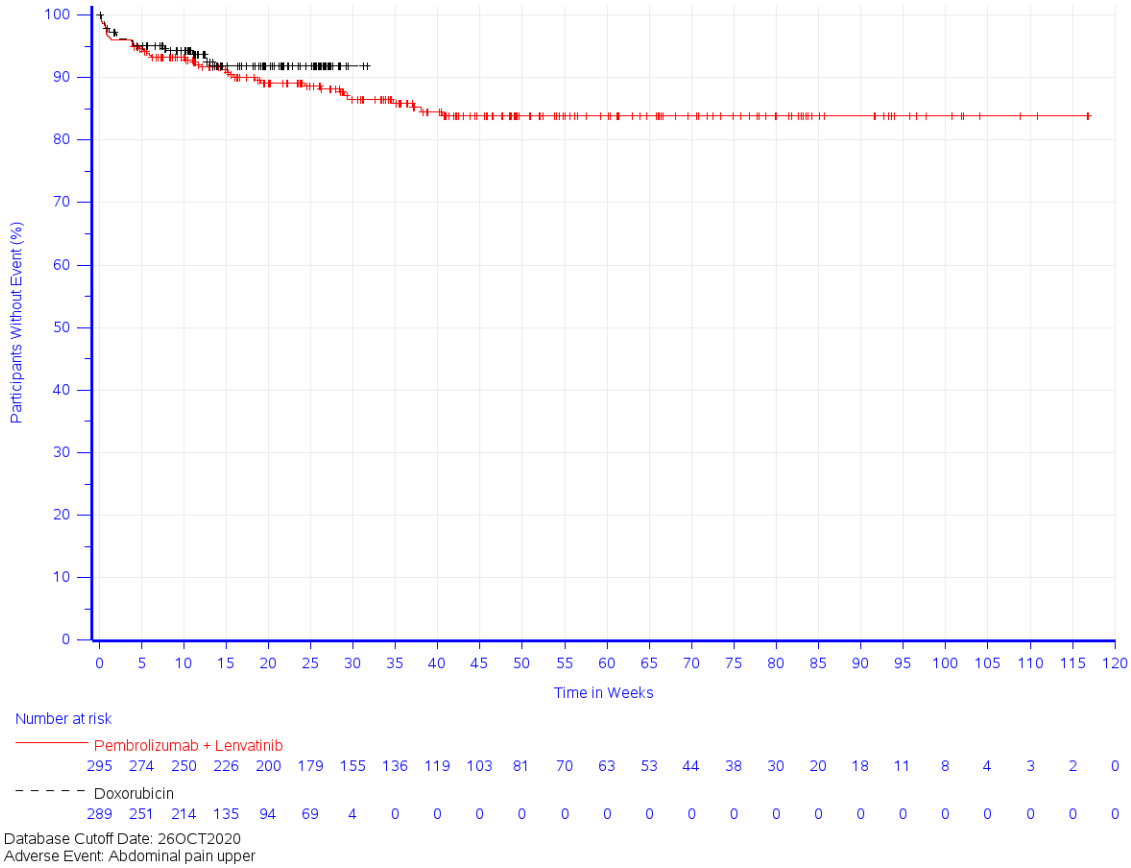
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Thrombocytopenia



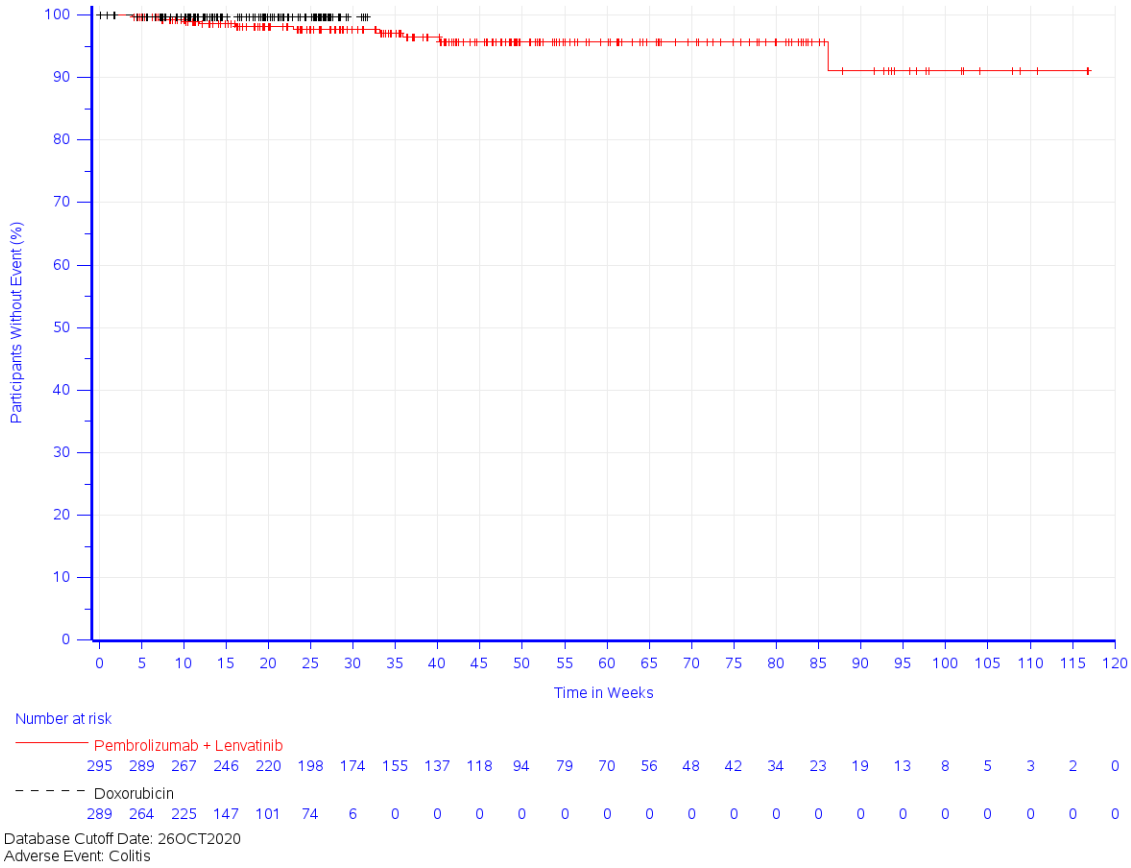
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Eye disorders



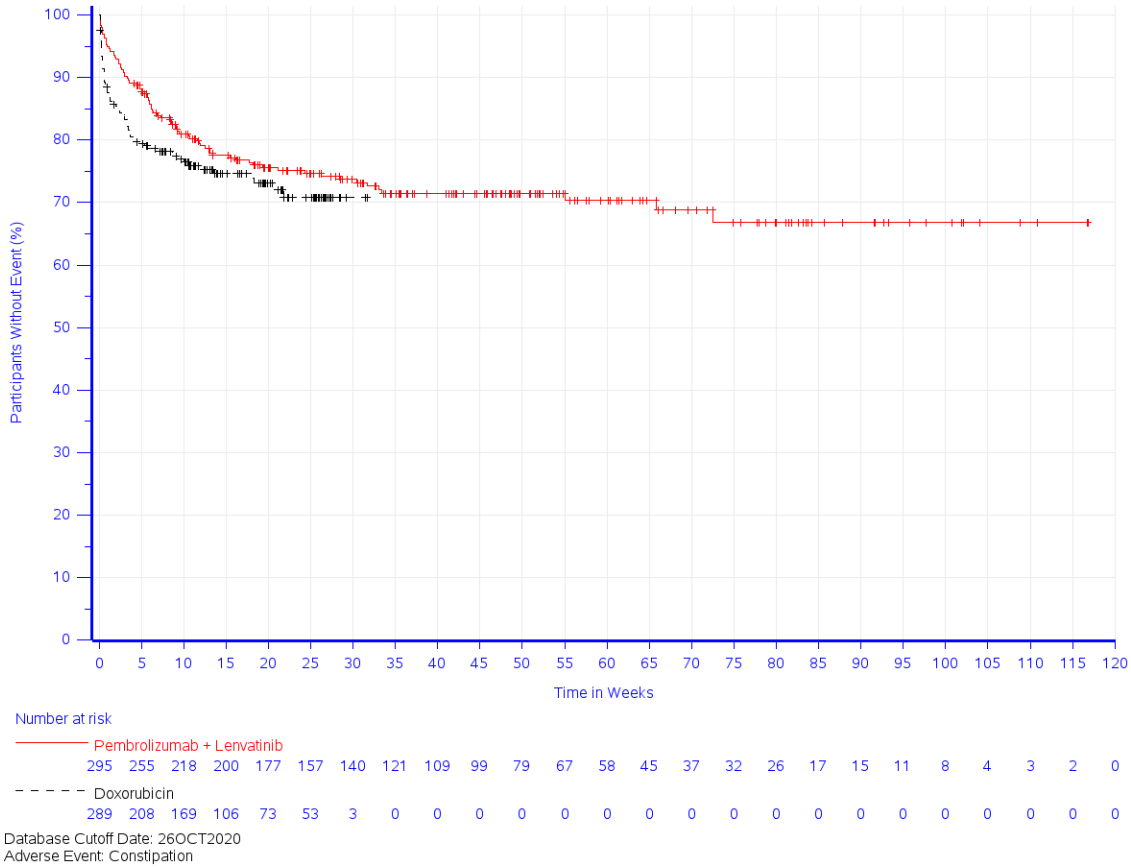
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Abdominal pain



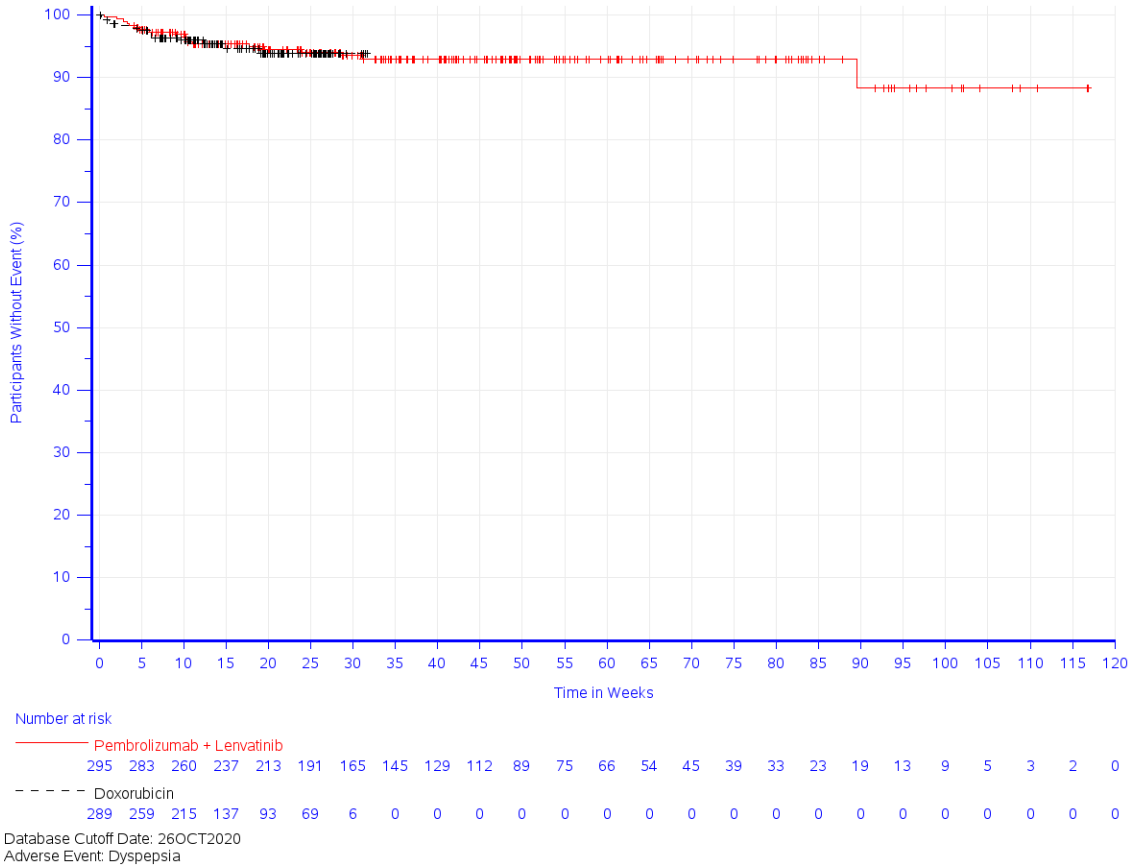
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Abdominal pain upper



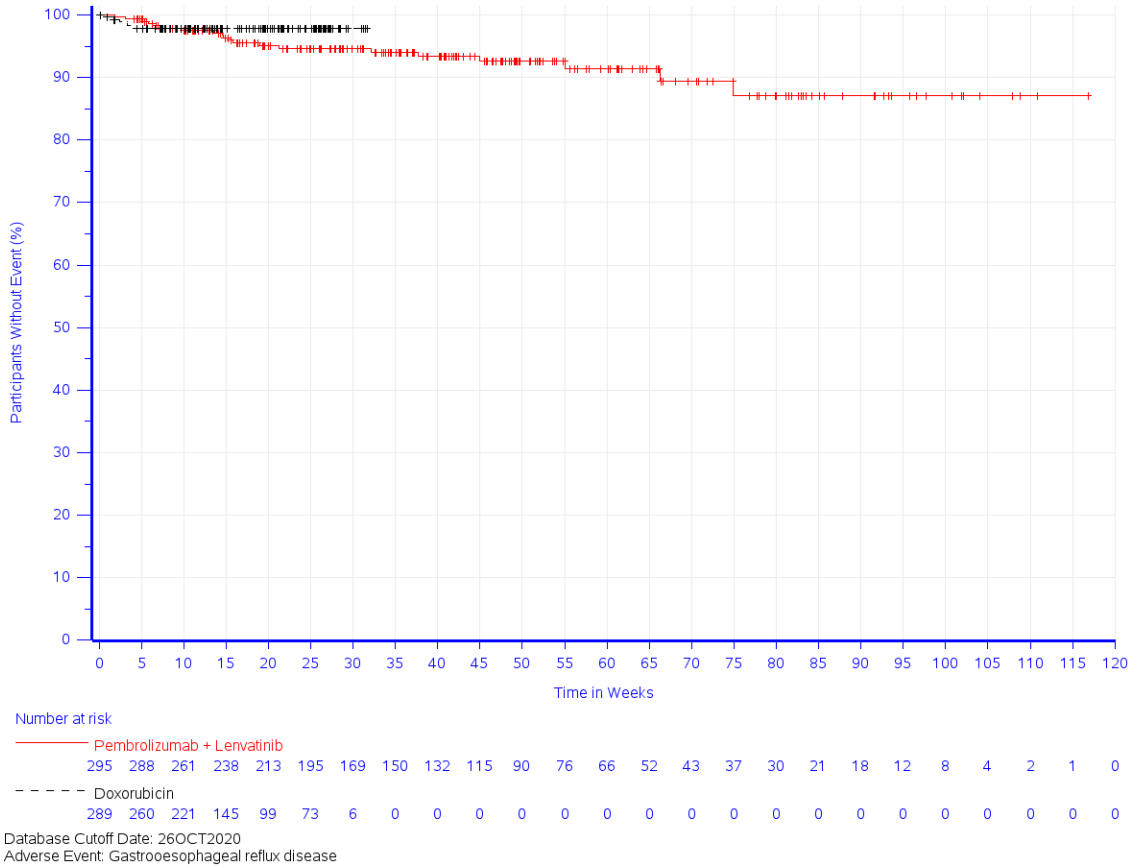
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Colitis



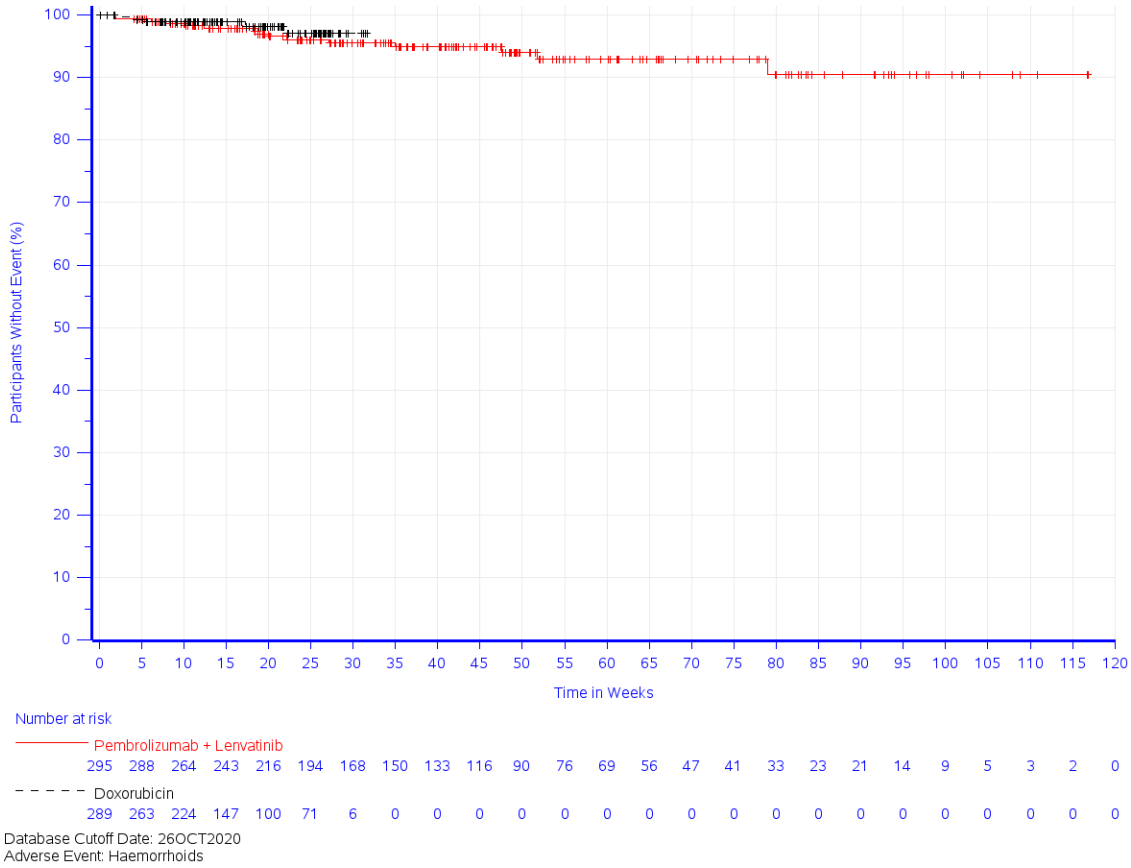
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Constipation



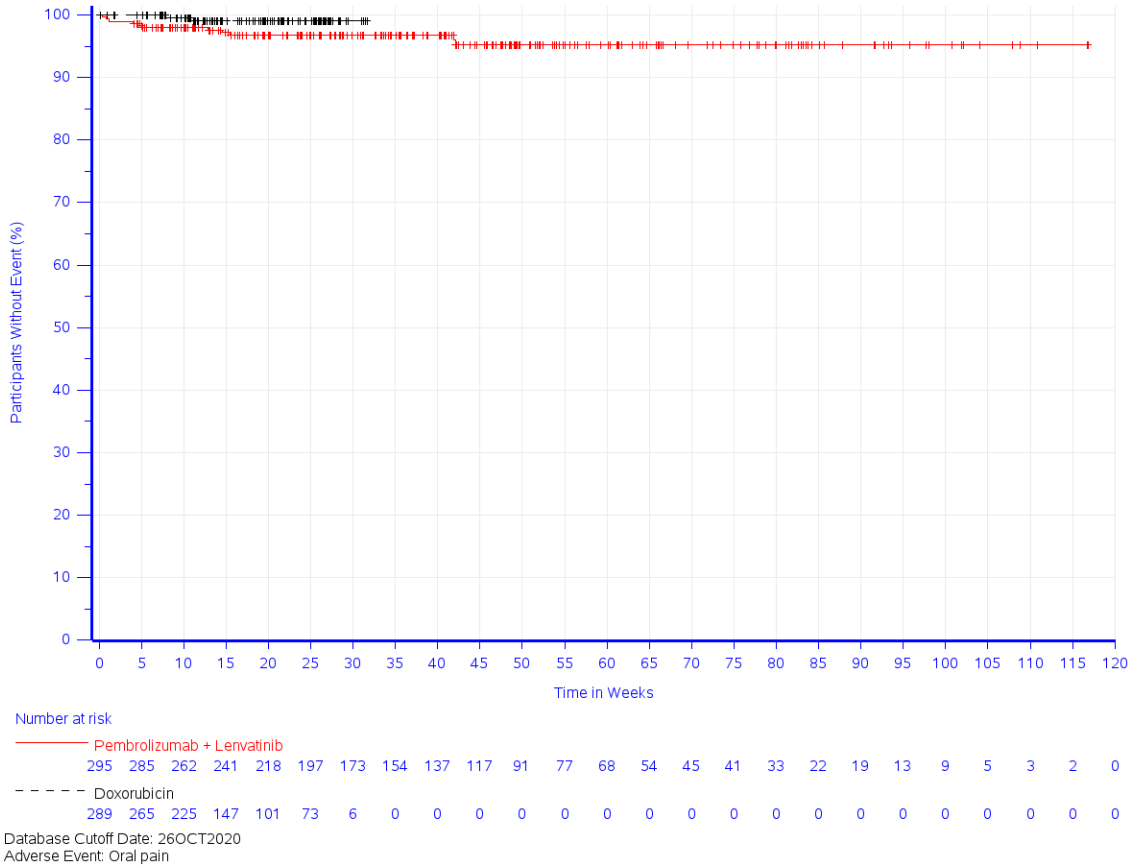
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Dyspepsia



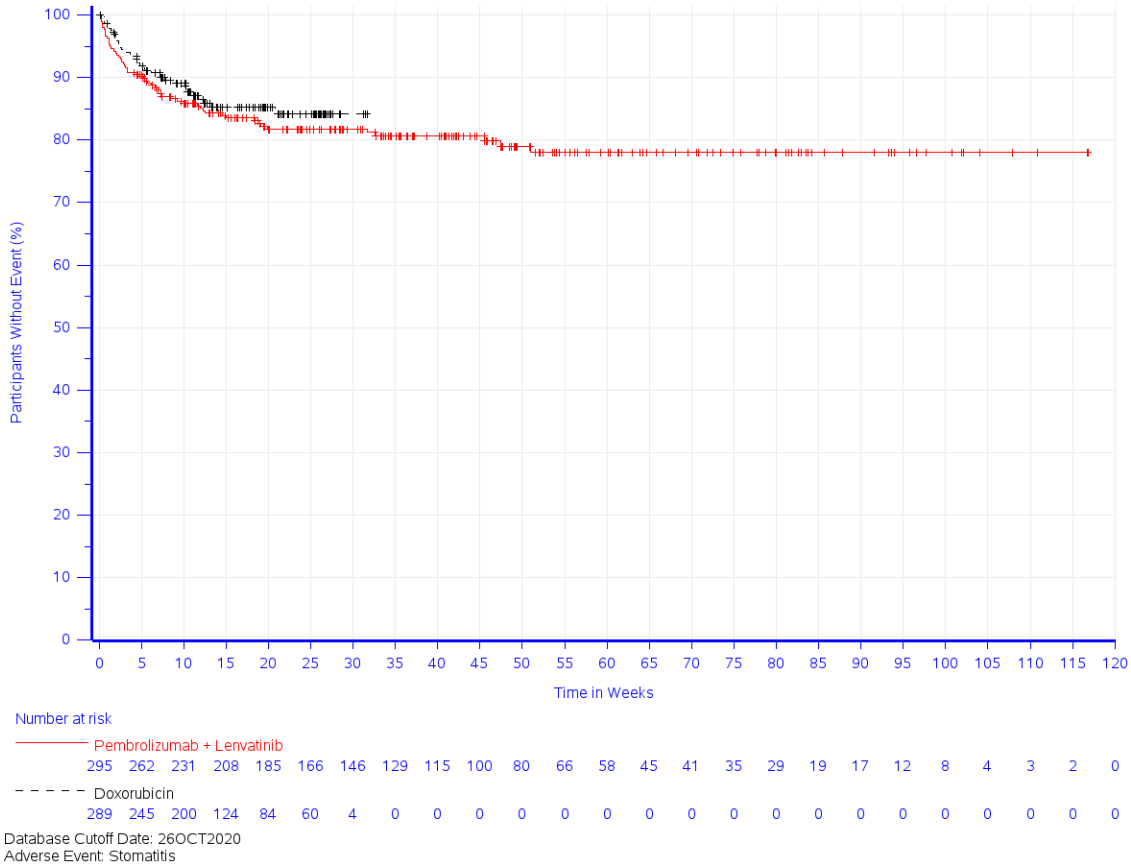
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Gastrooesophageal reflux disease



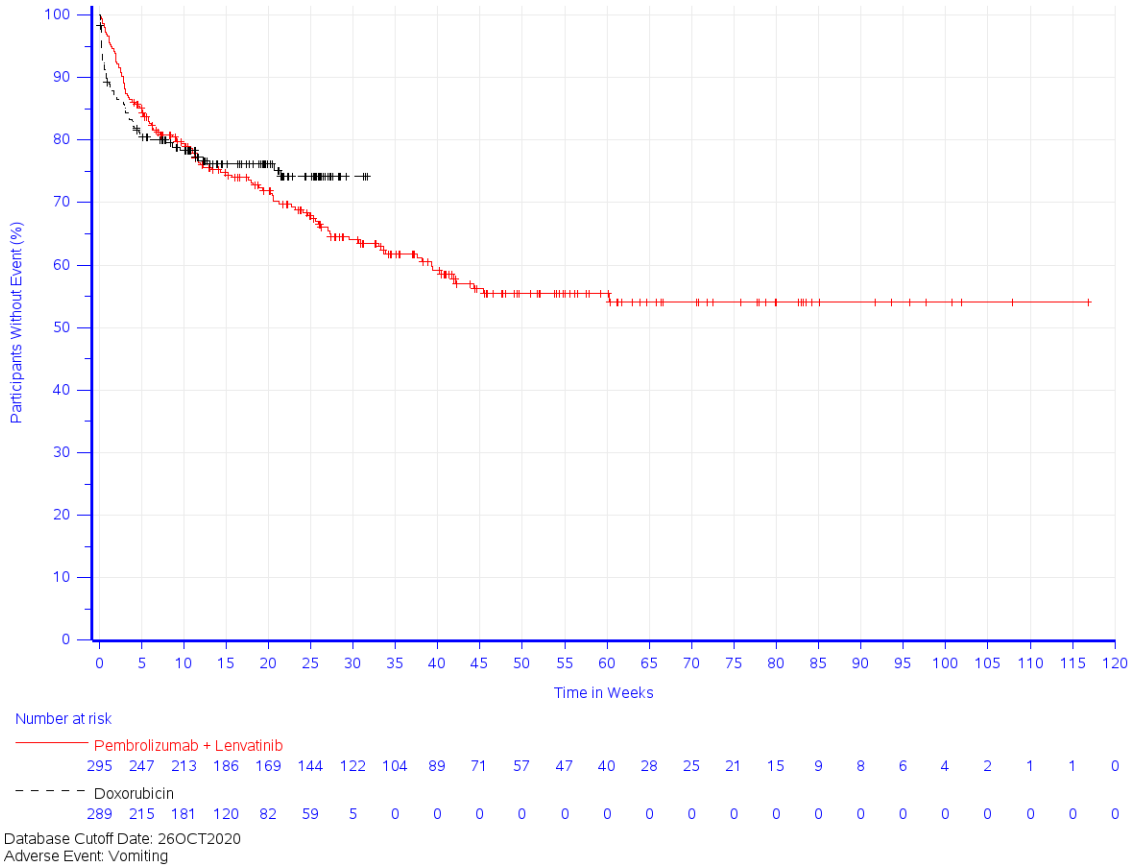
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Haemorrhoids



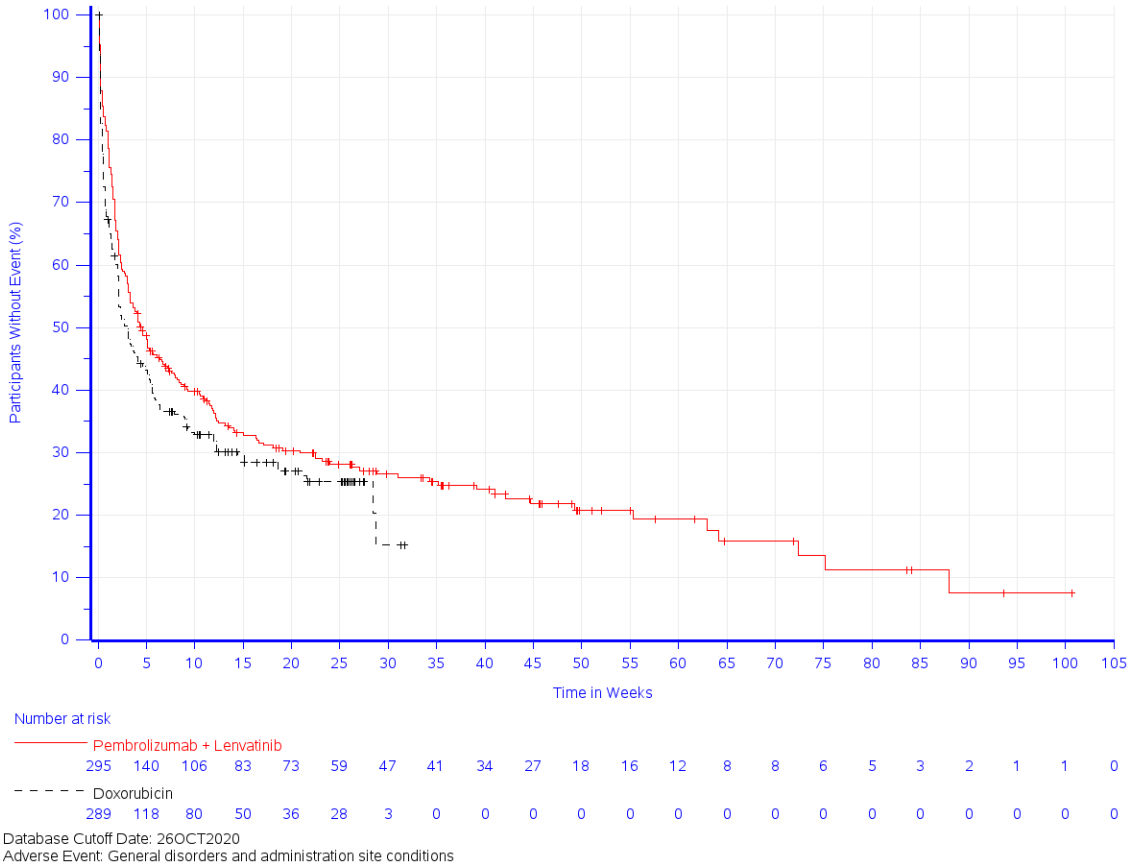
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Oral pain



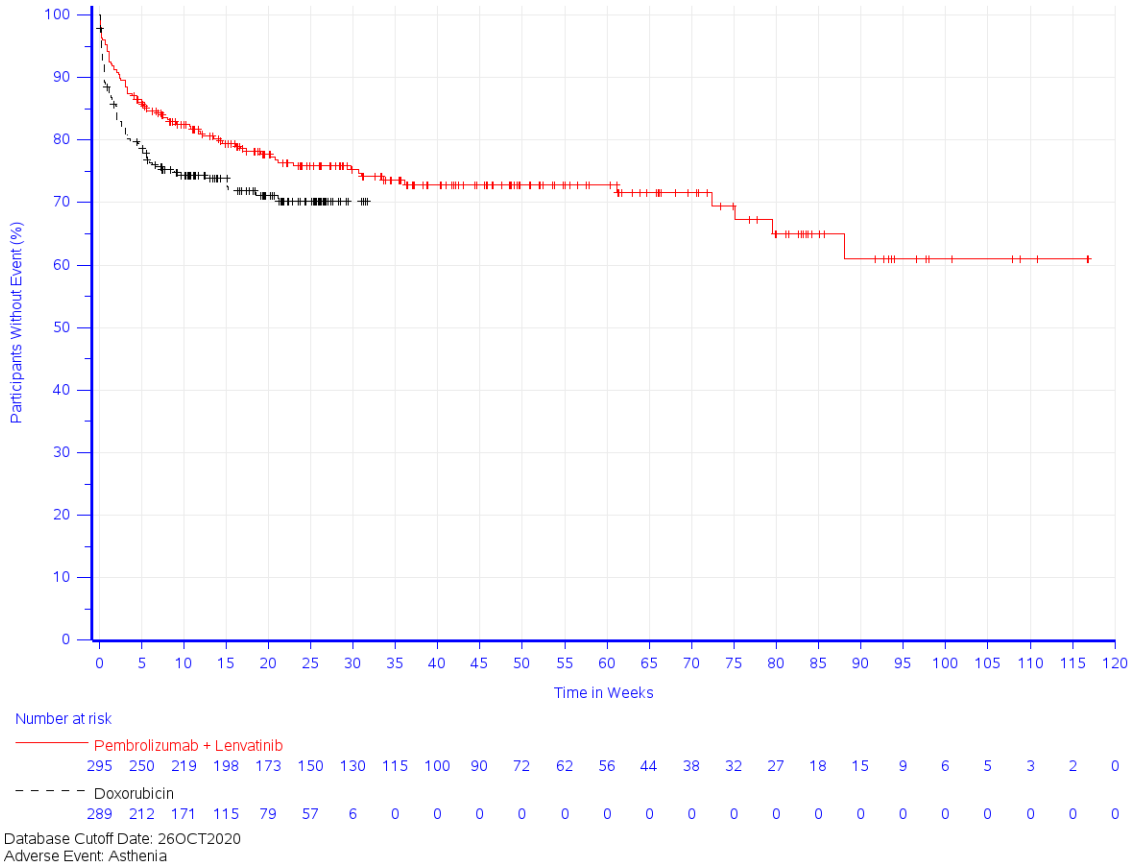
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Stomatitis



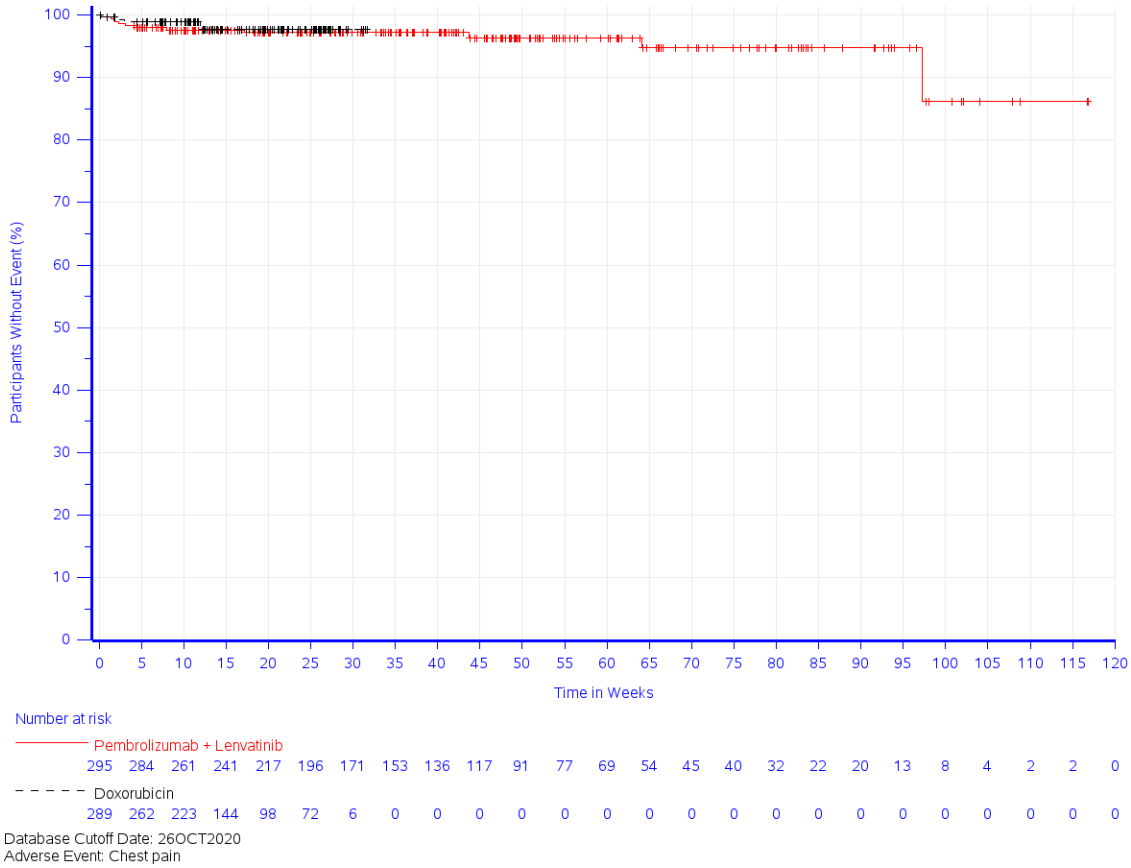
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Vomiting



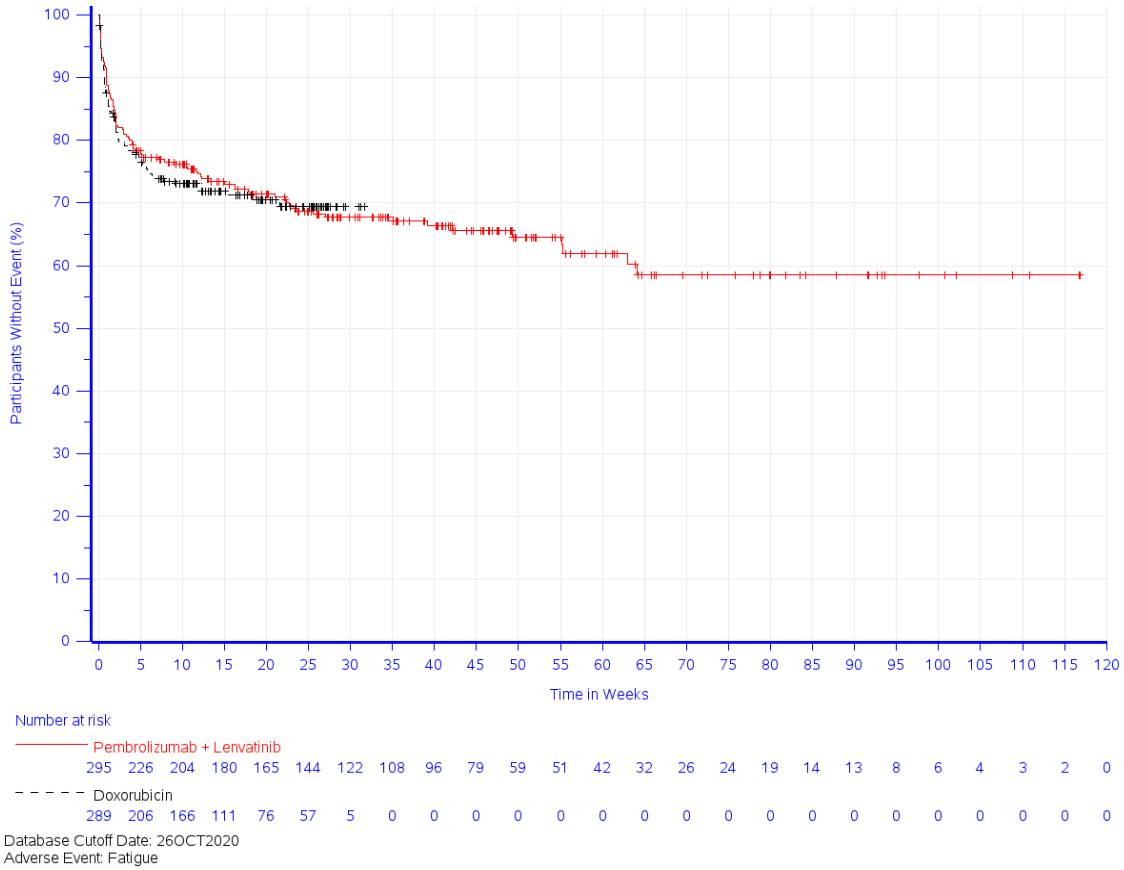
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: General disorders and administration site conditions



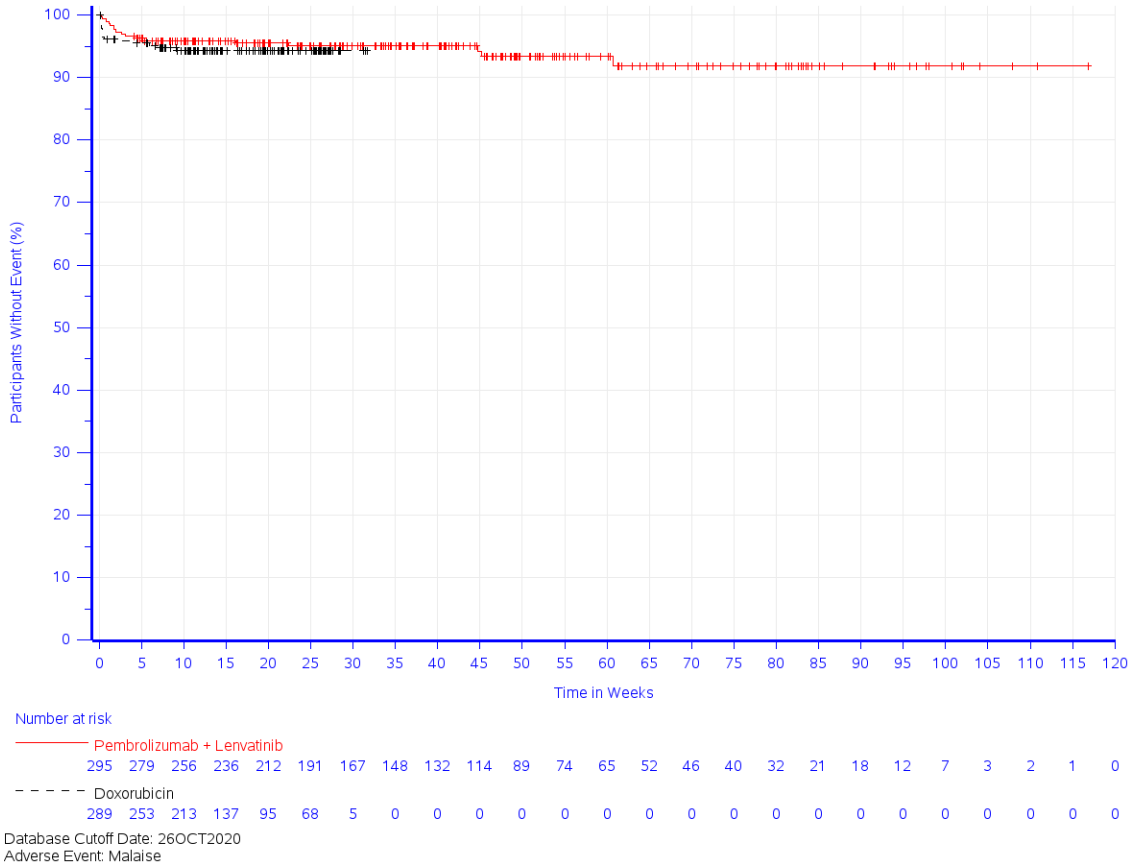
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Asthenia



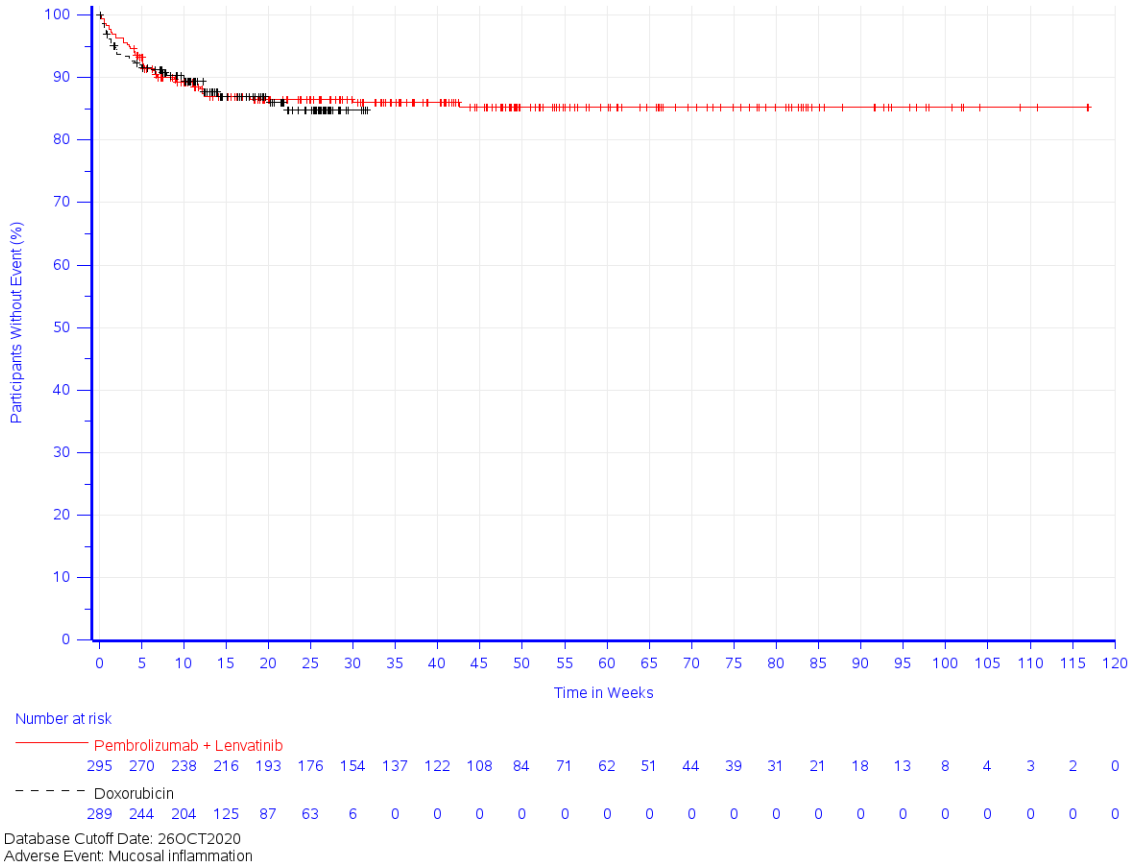
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Chest pain



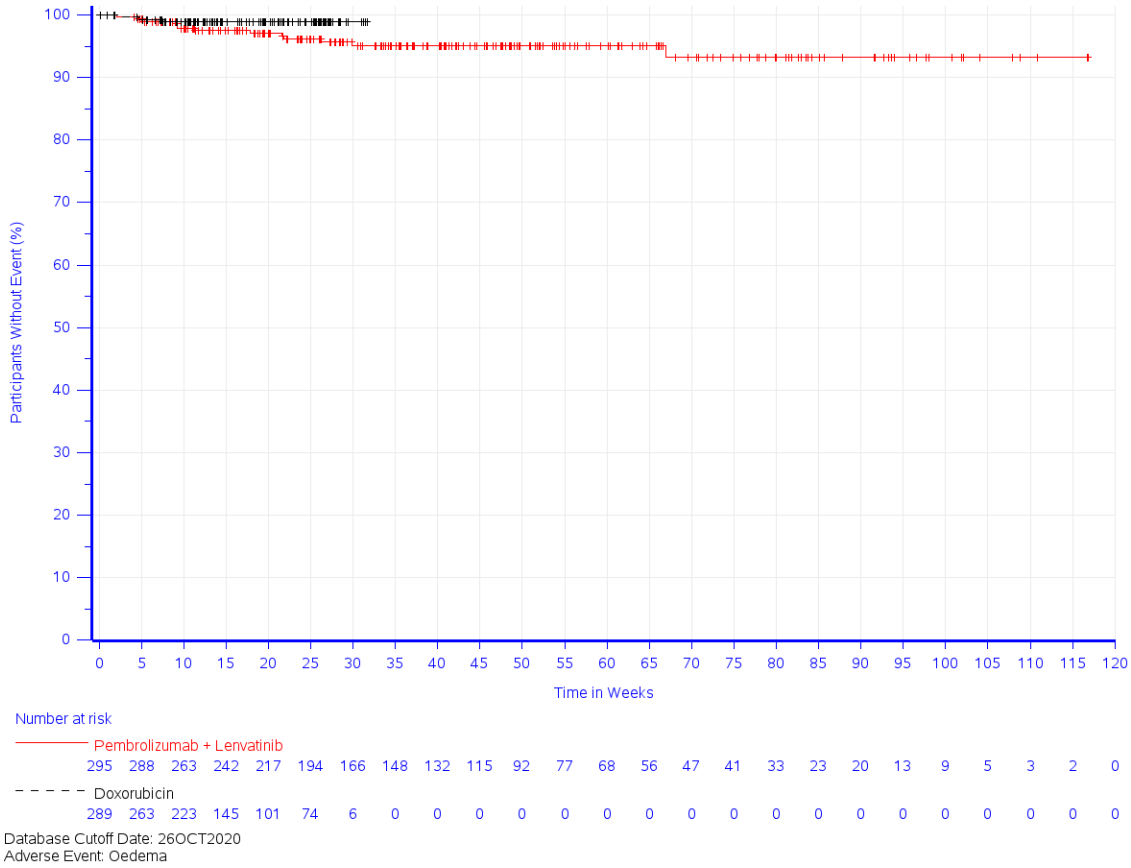
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Fatigue



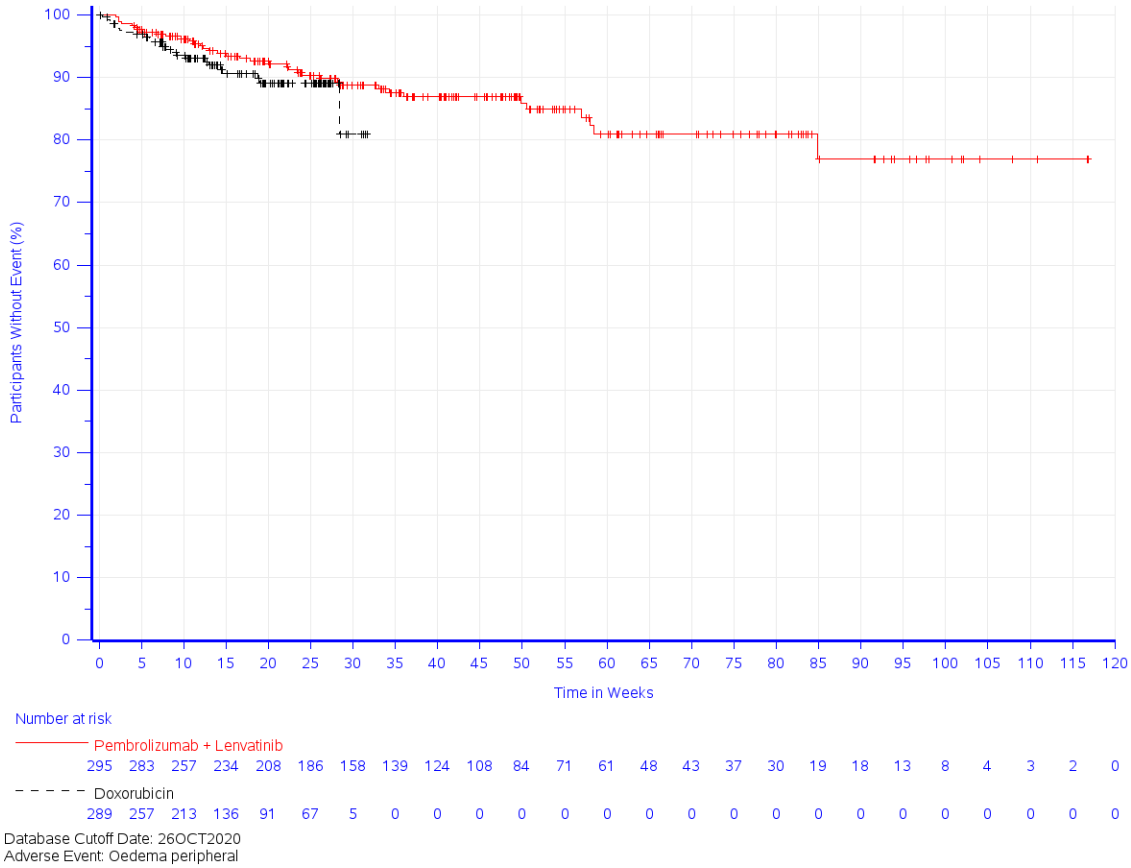
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Malaise



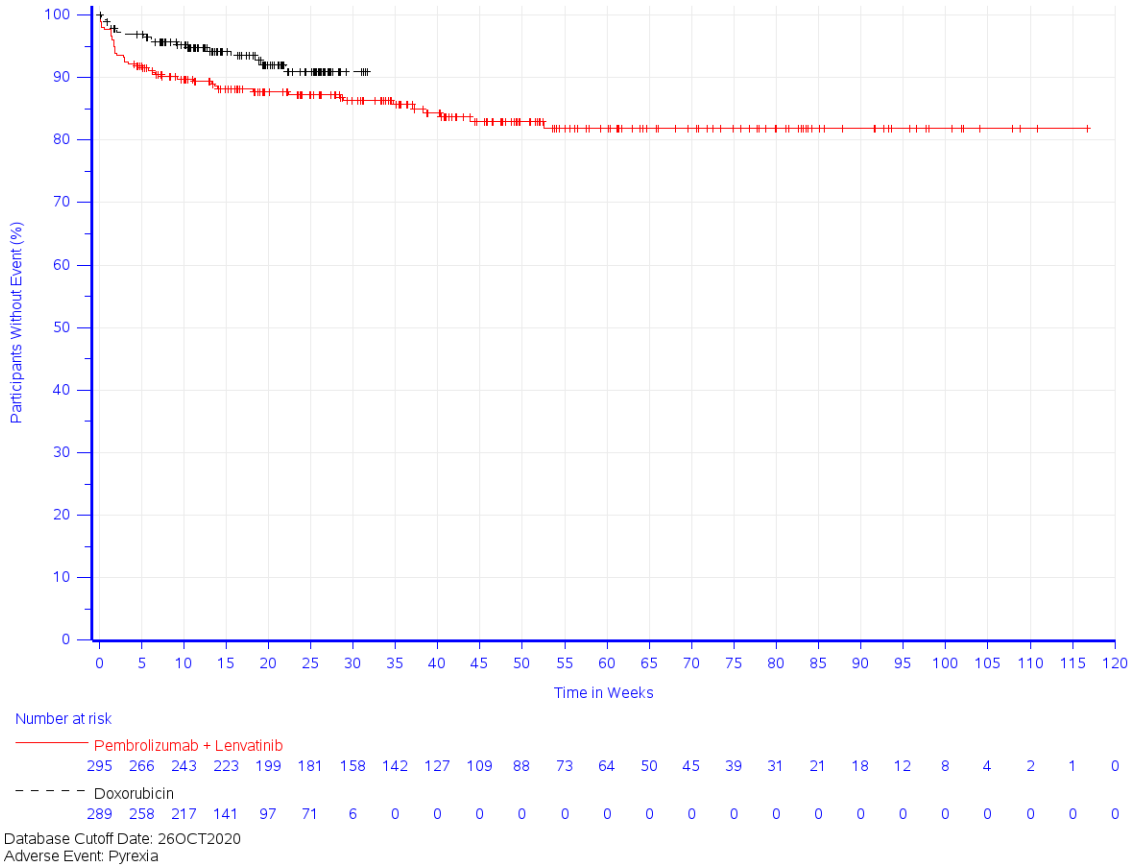
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Mucosal inflammation



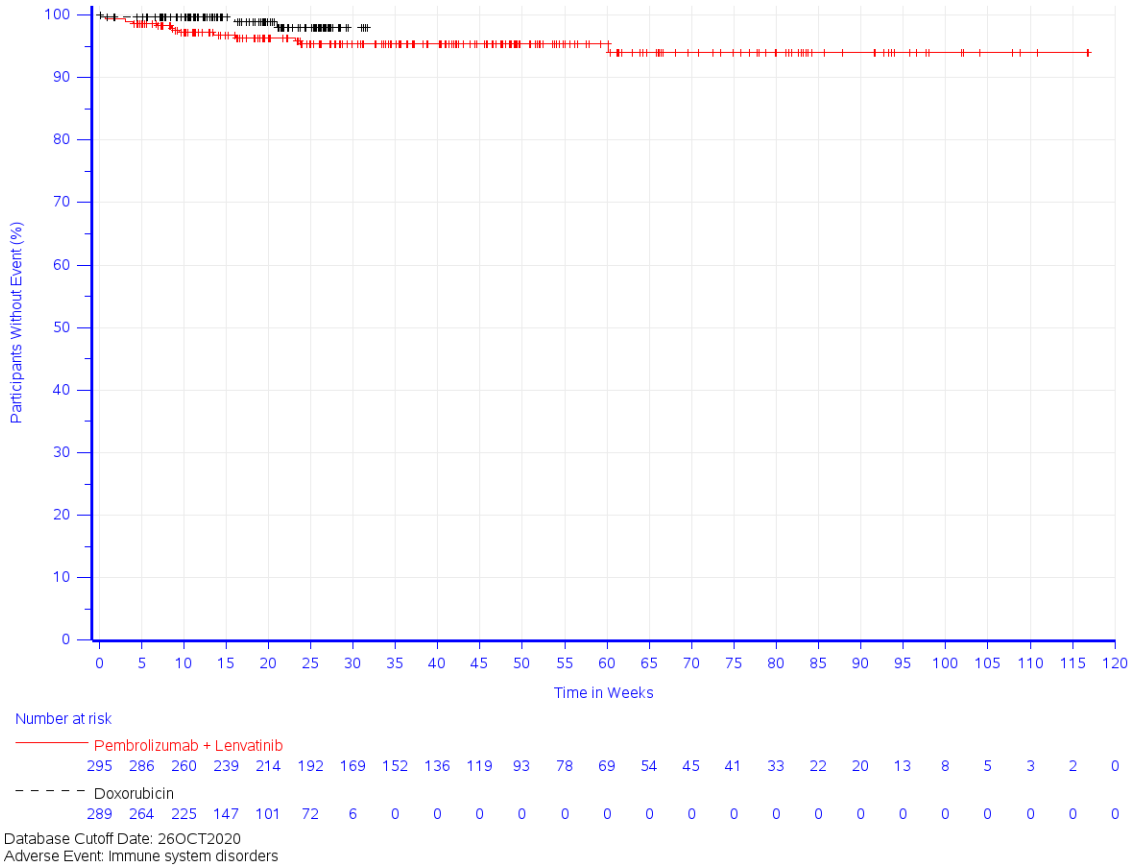
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Oedema



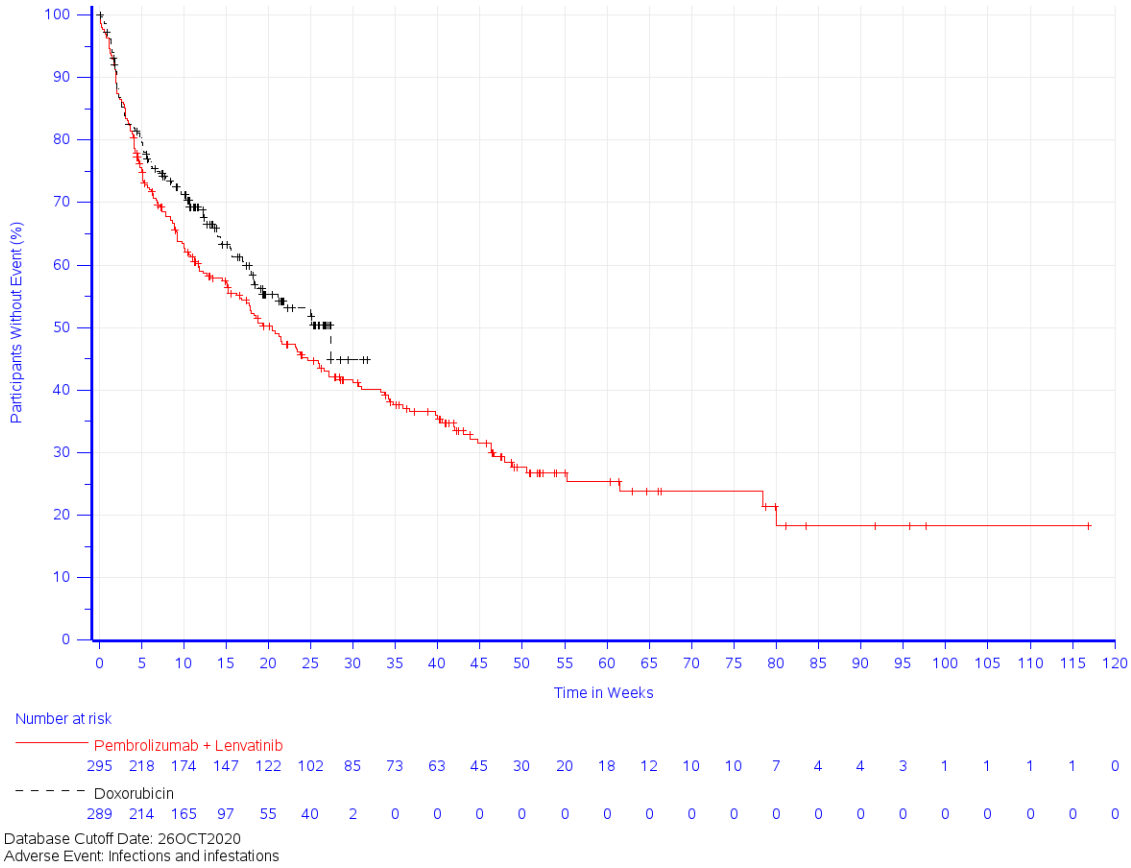
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Oedema peripheral



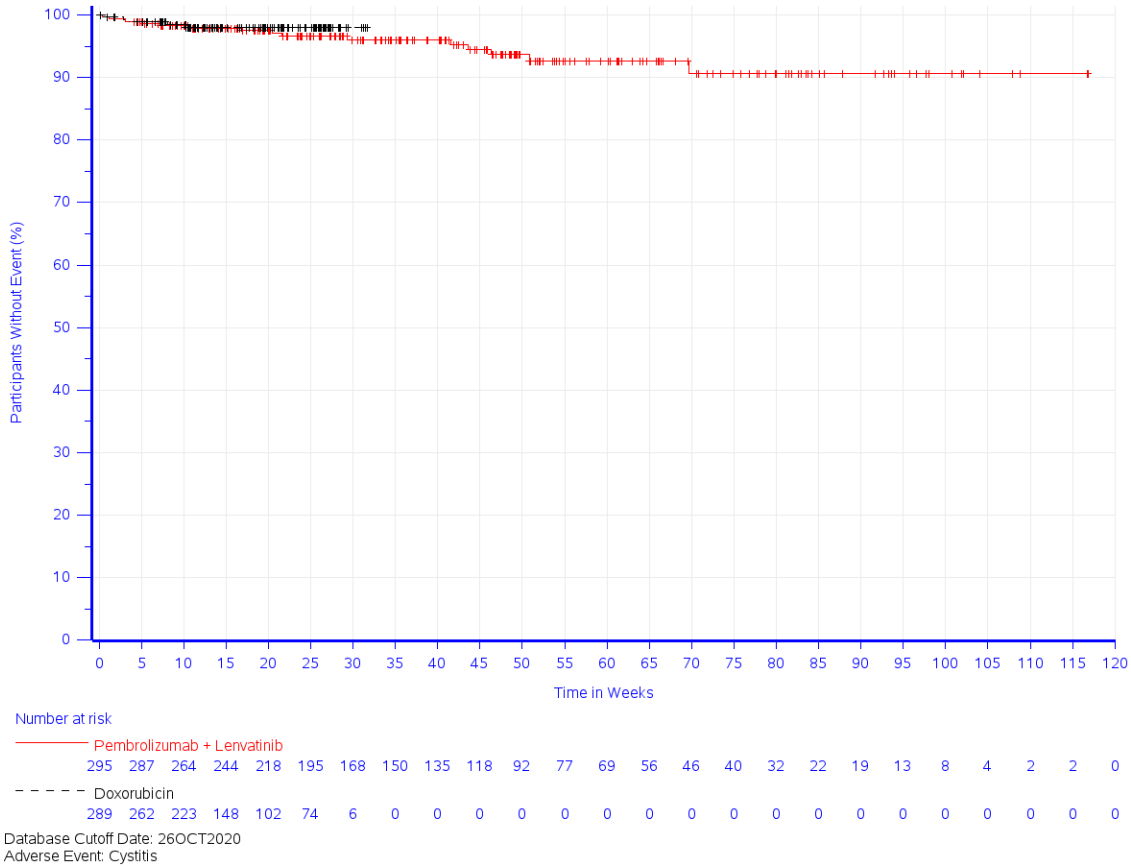
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Pyrexia



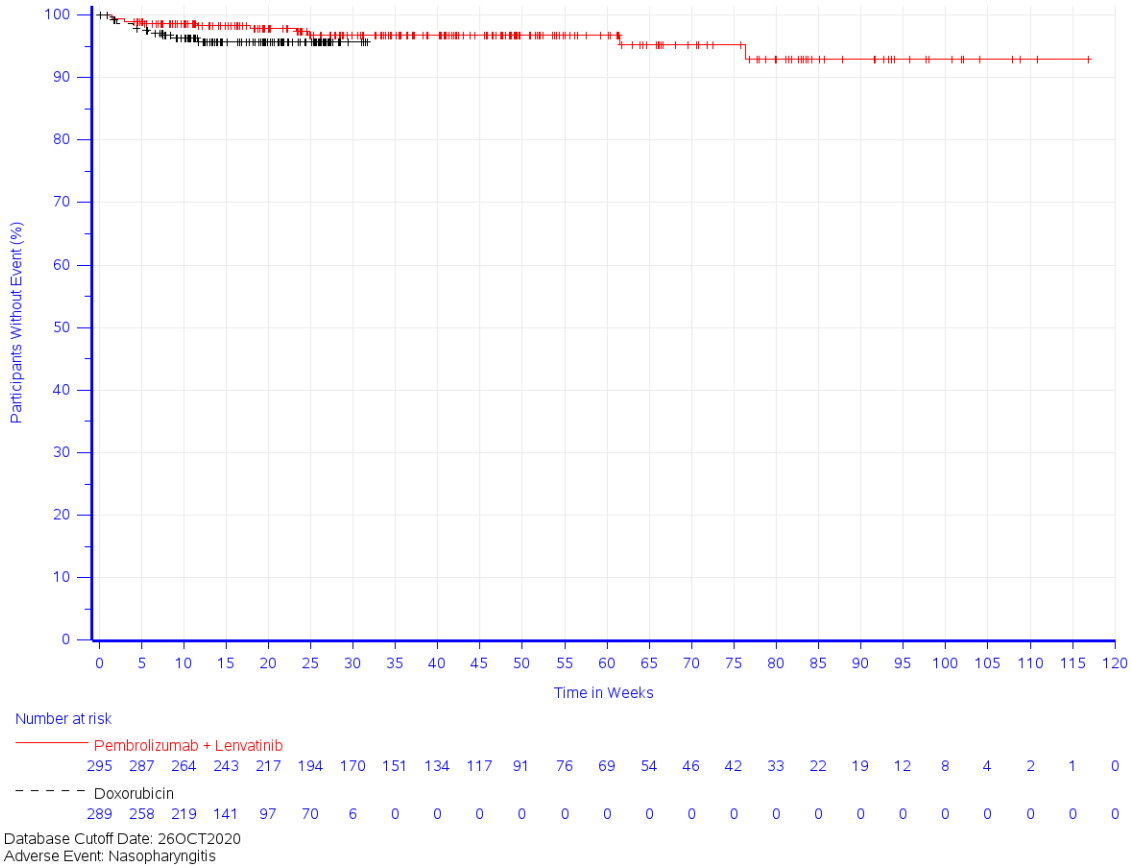
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Immune system disorders



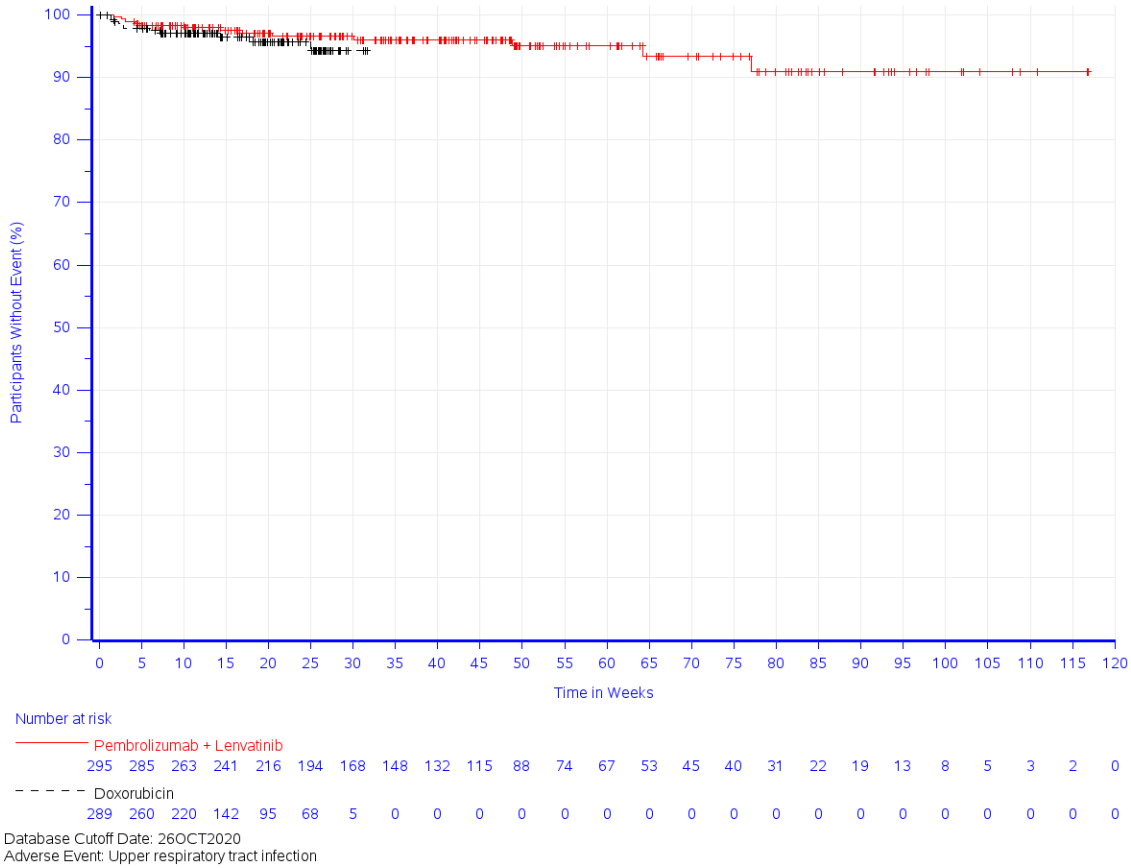
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Infections and infestations



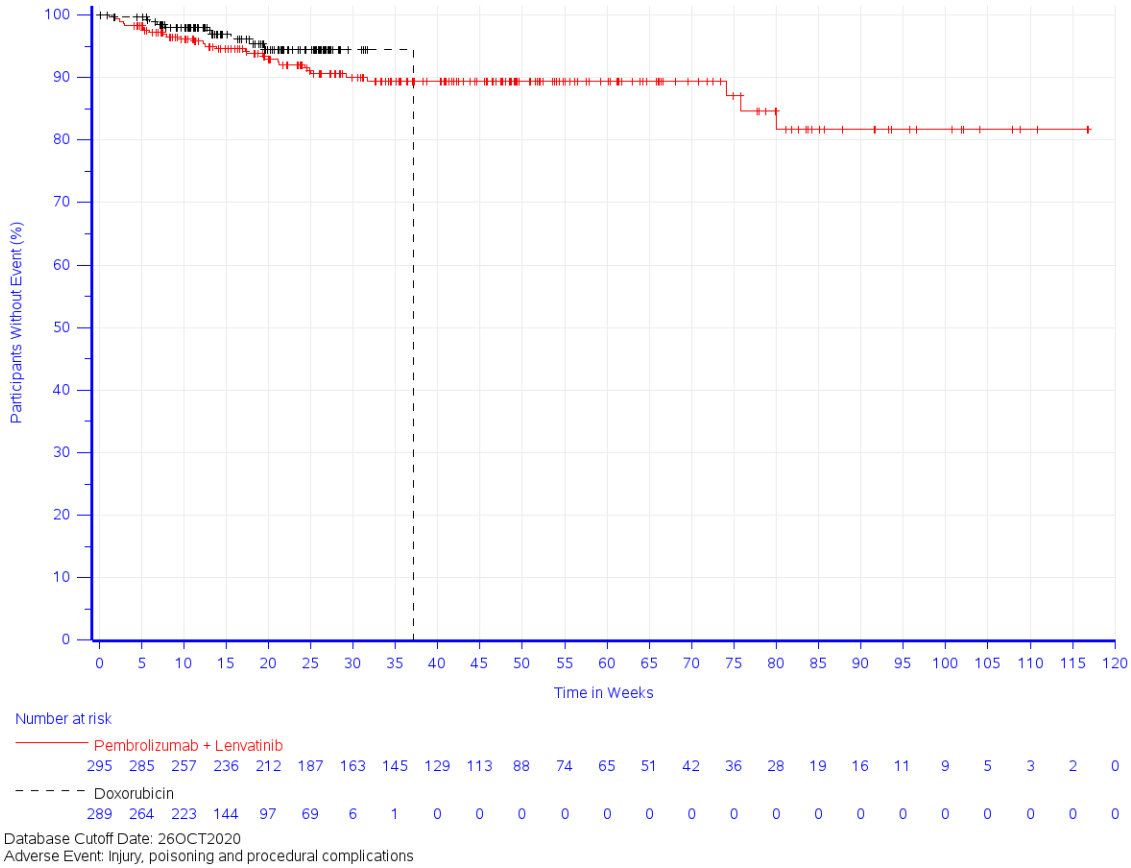
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Cystitis



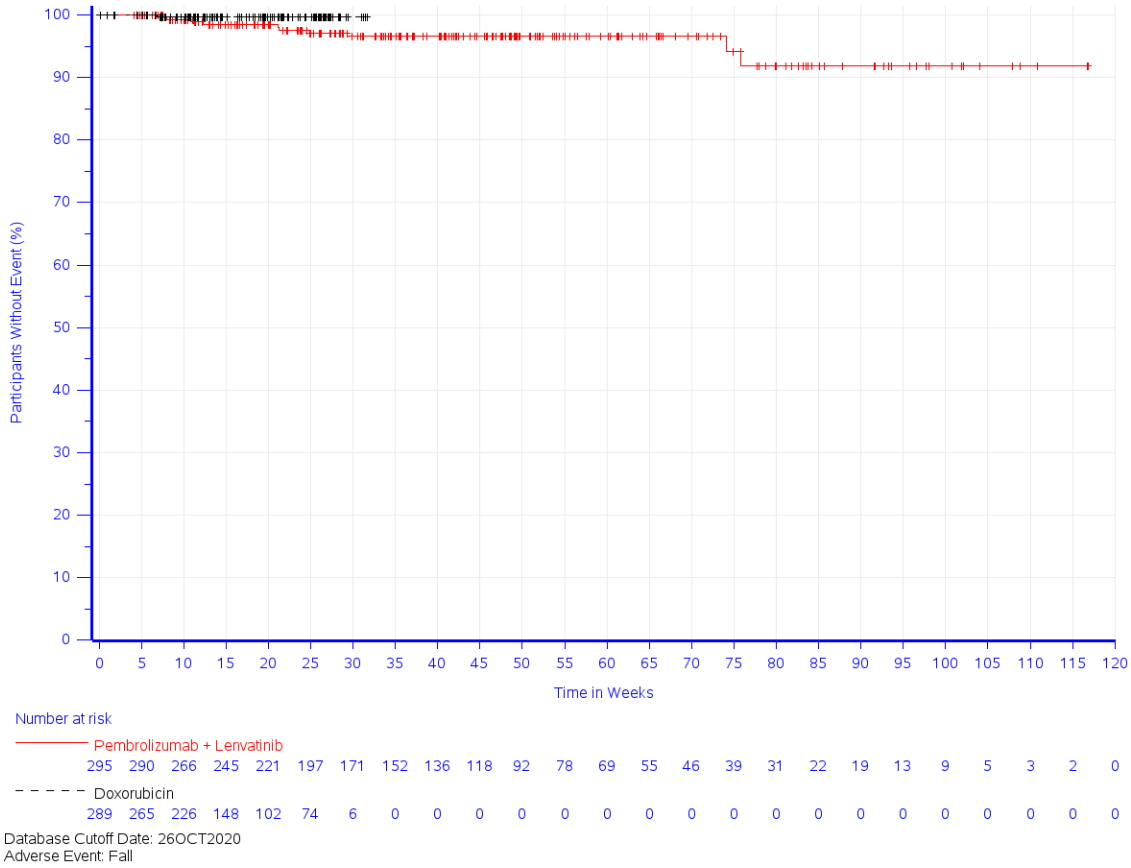
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Nasopharyngitis



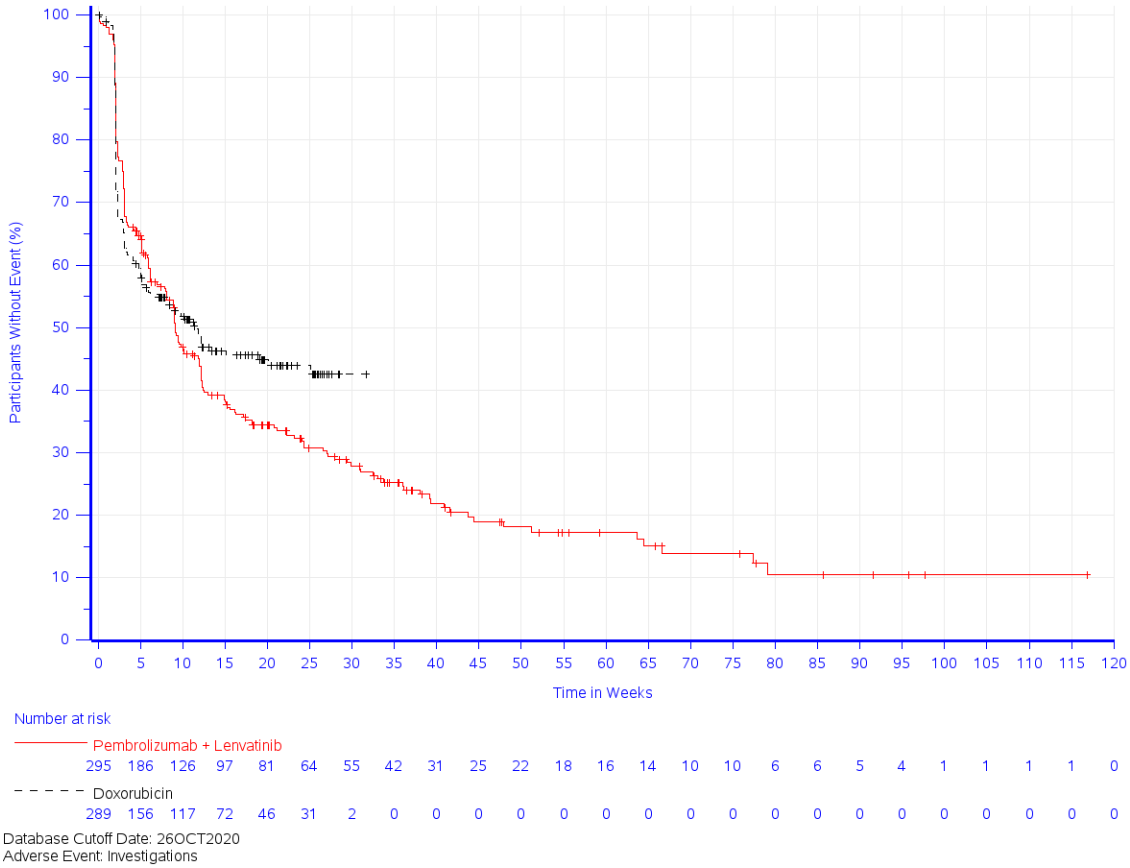
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Upper respiratory tract infection



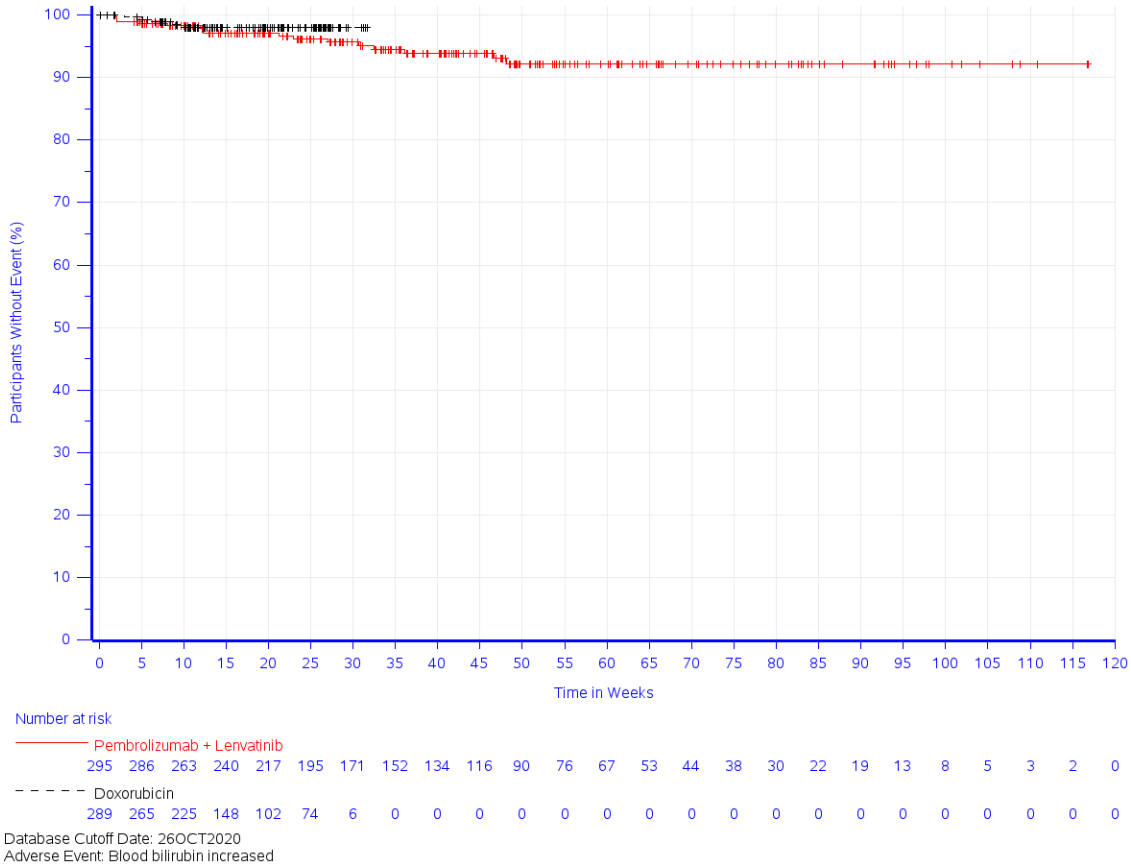
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Injury, poisoning and procedural complications



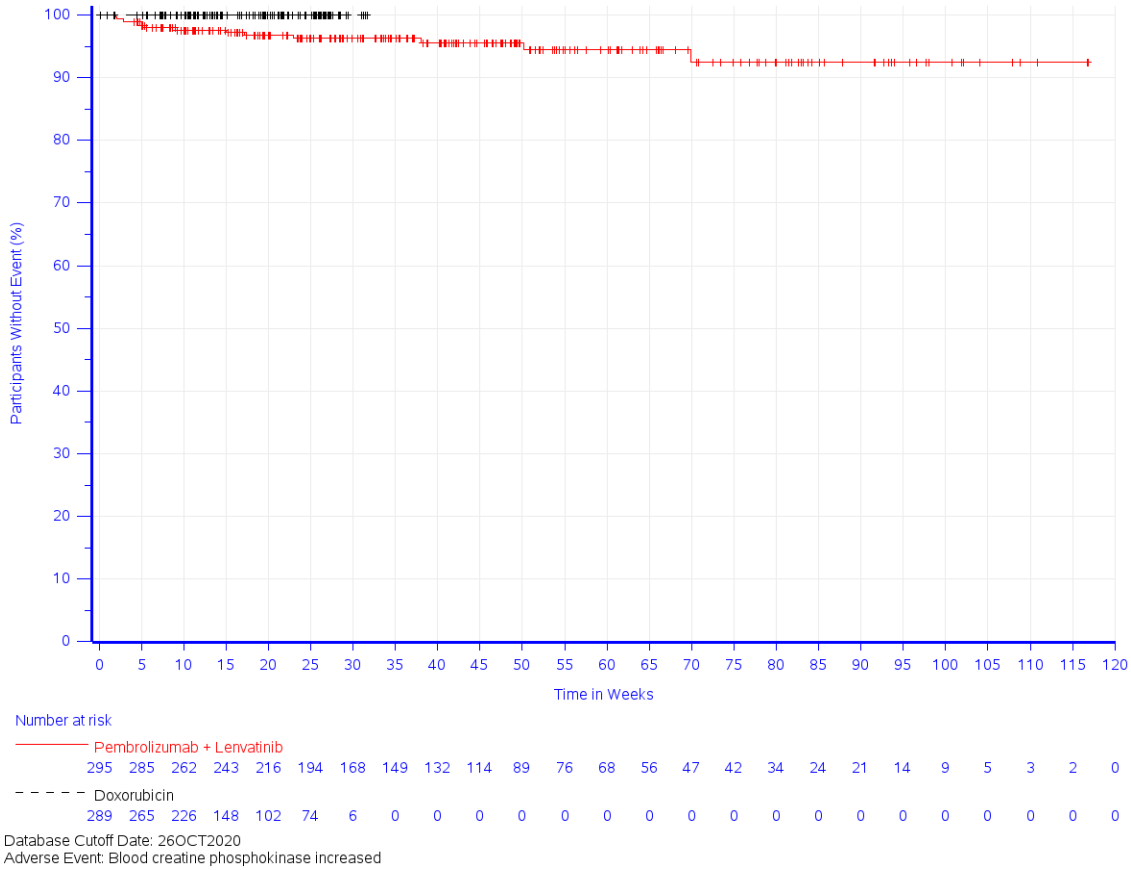
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Fall



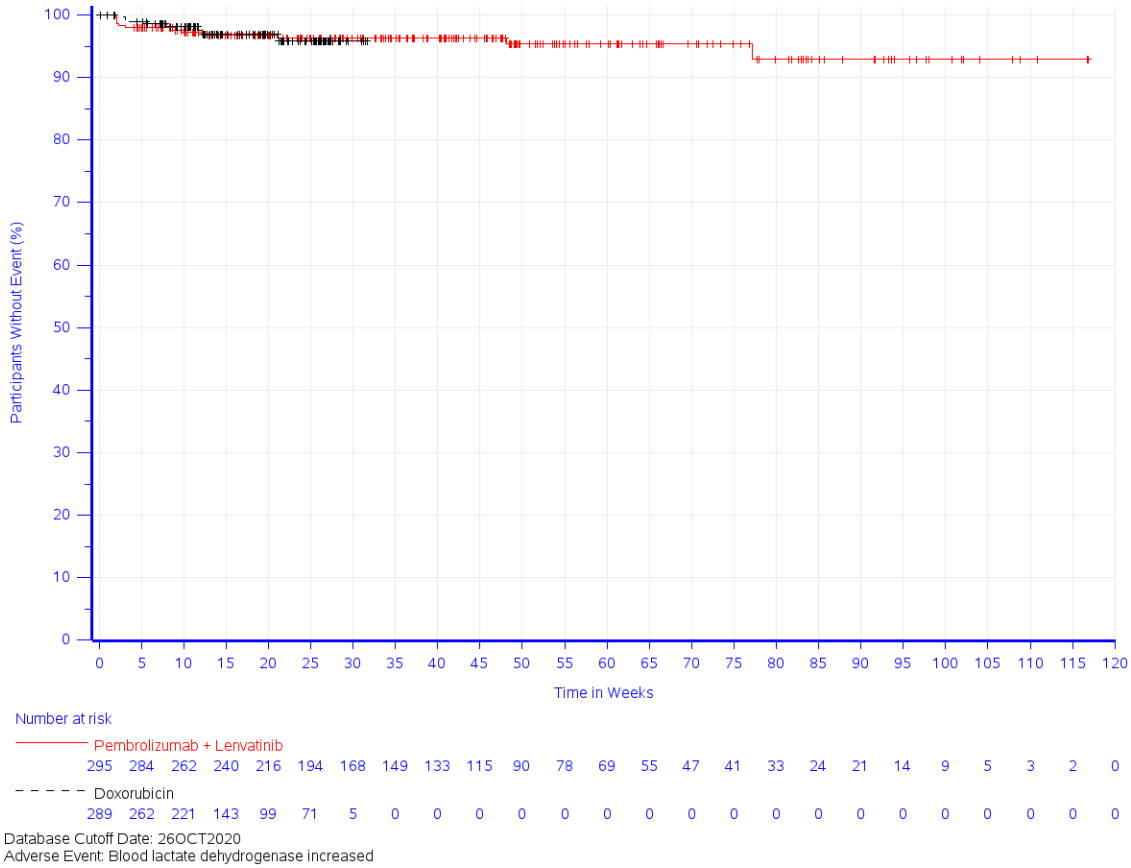
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Investigations



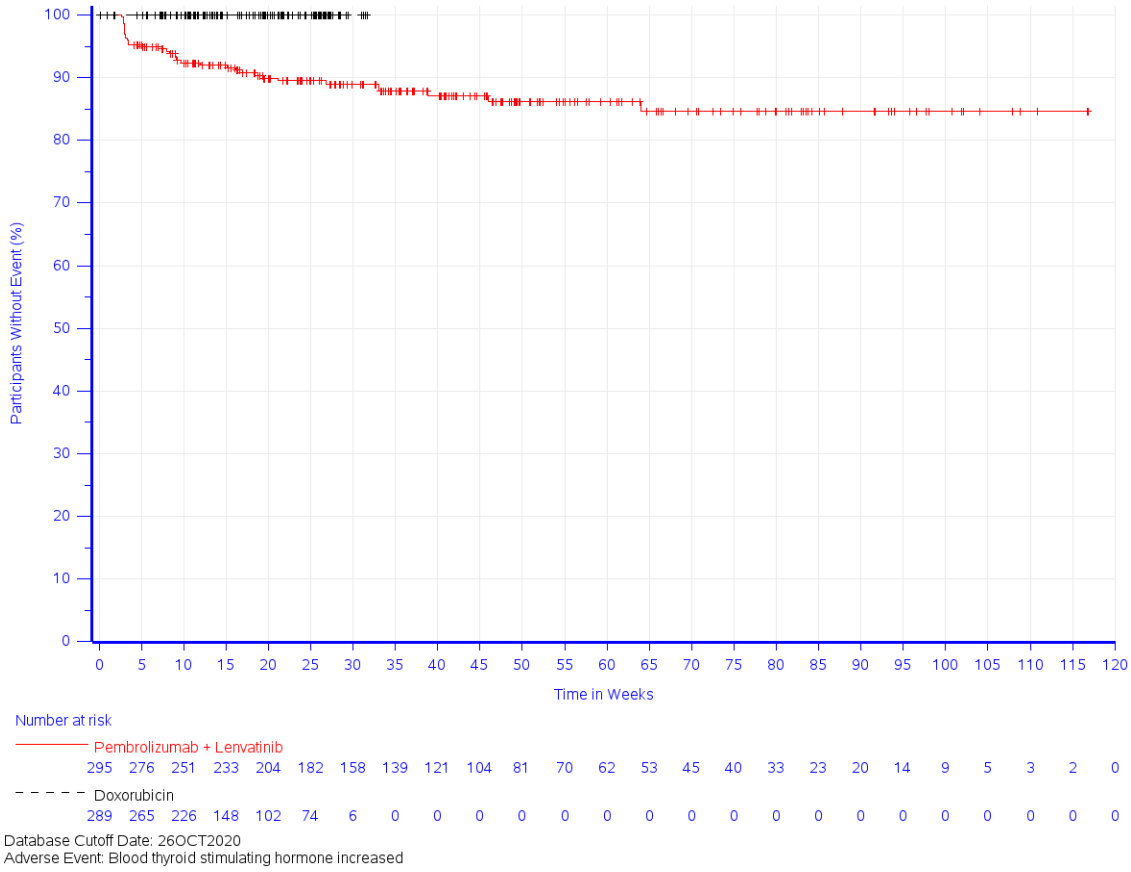
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Blood bilirubin increased



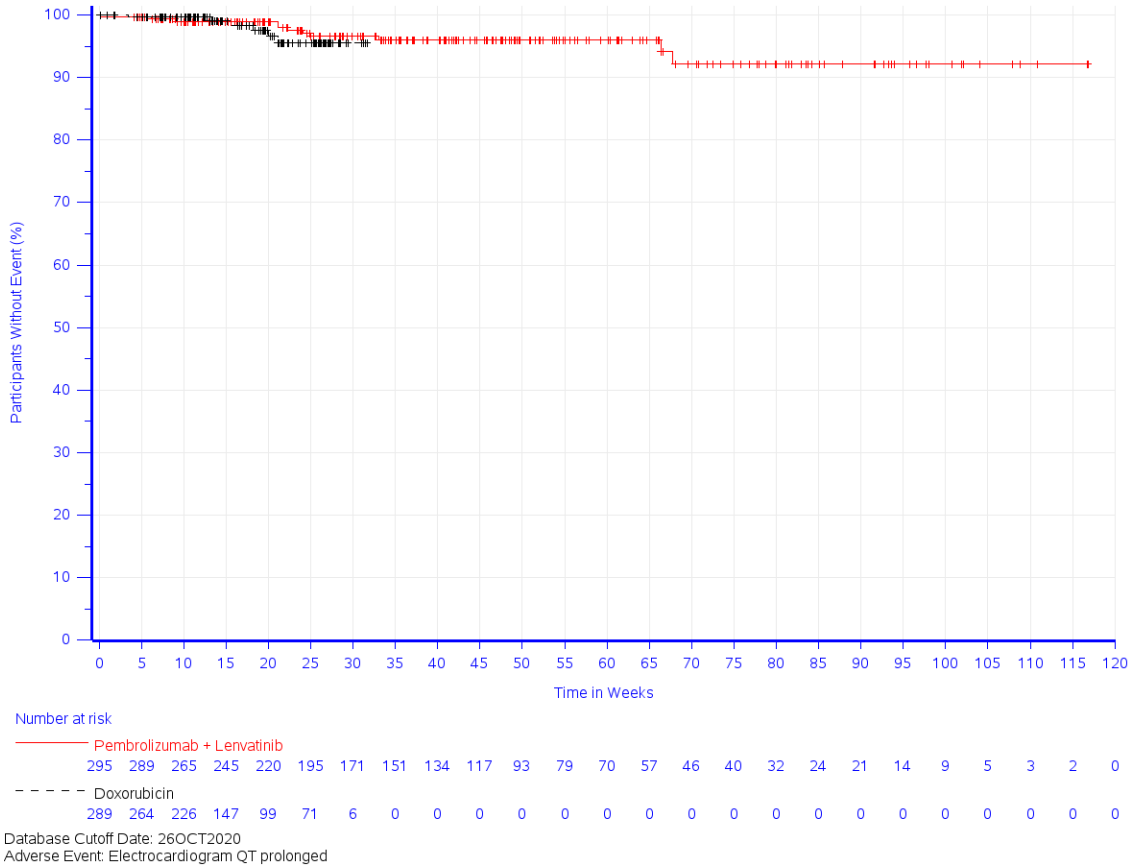
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Blood creatine phosphokinase increased



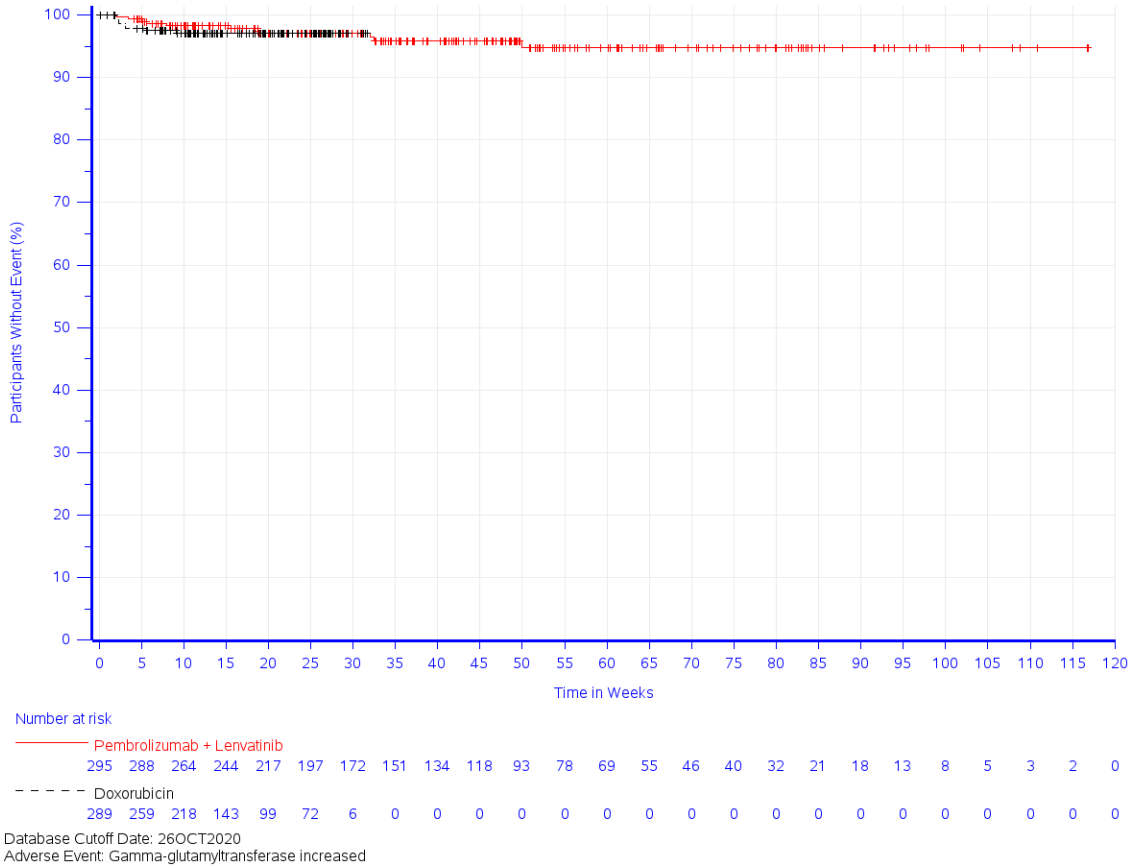
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Blood lactate dehydrogenase increased



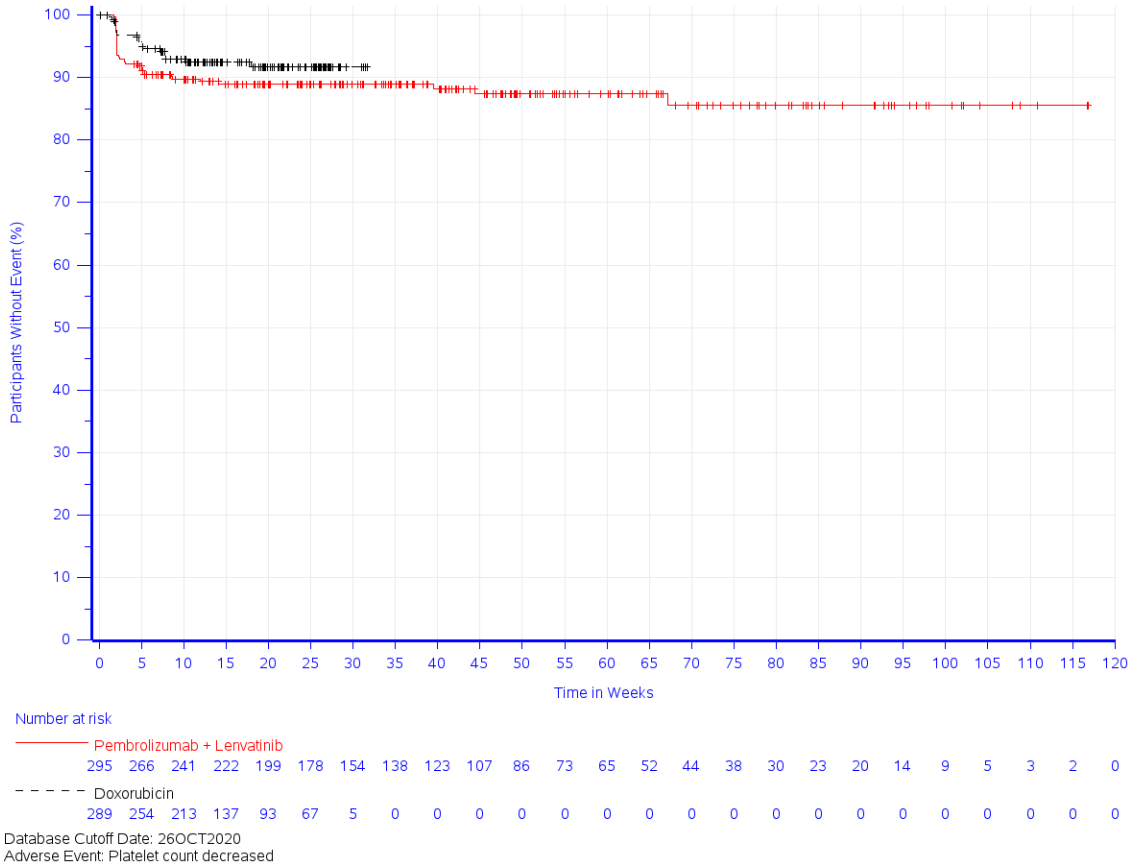
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Blood thyroid stimulating hormone increased



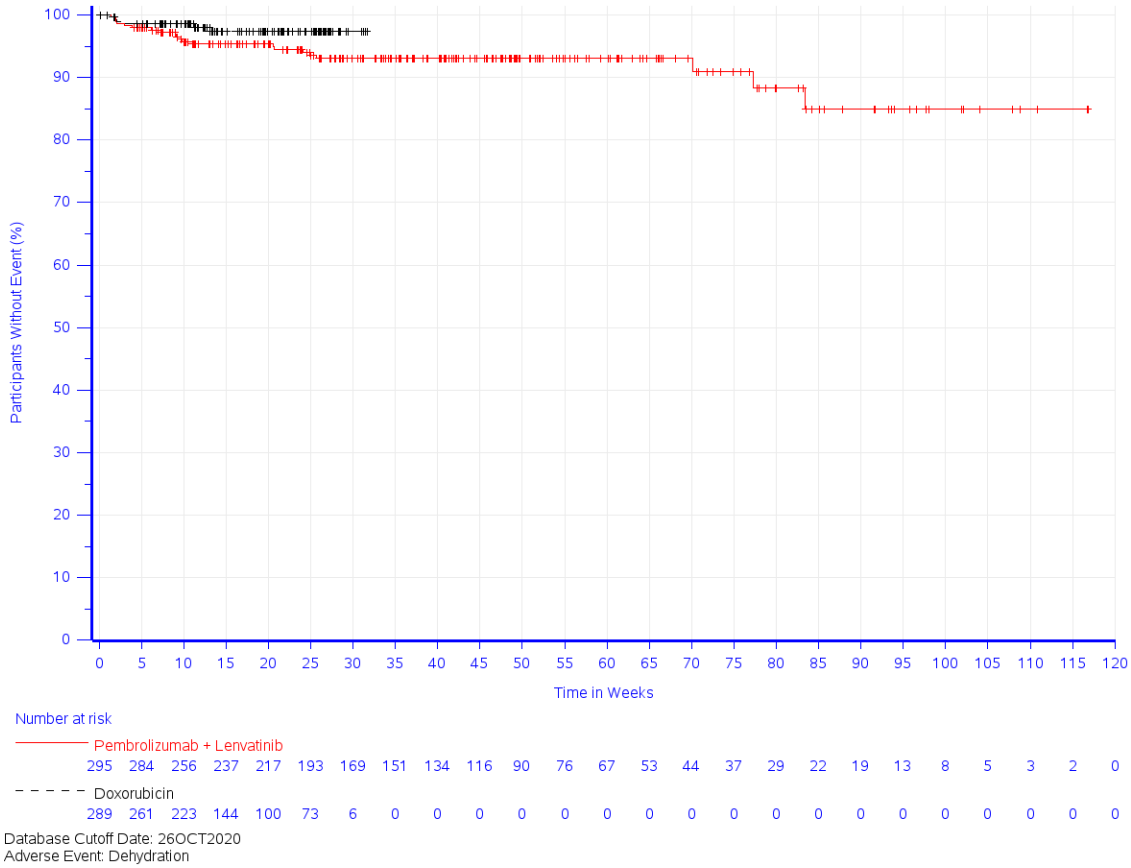
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Electrocardiogram QT prolonged



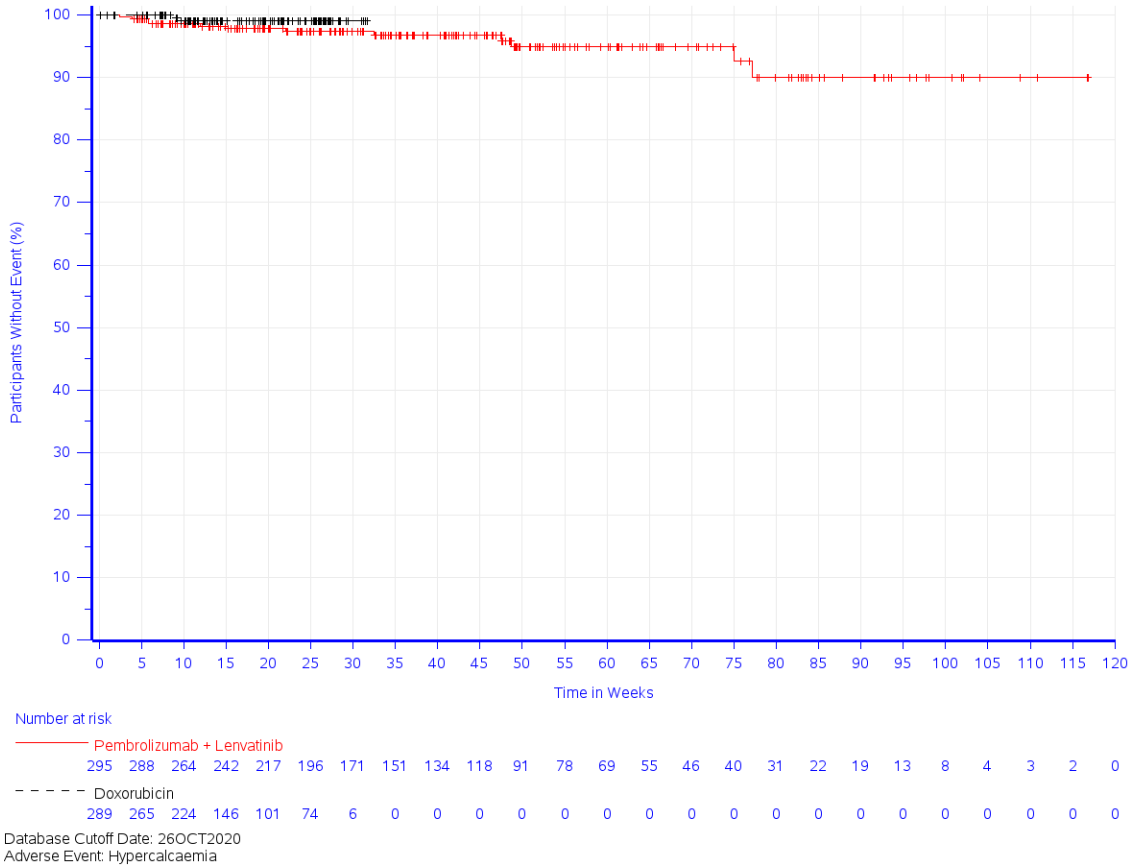
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Gamma-glutamyltransferase increased



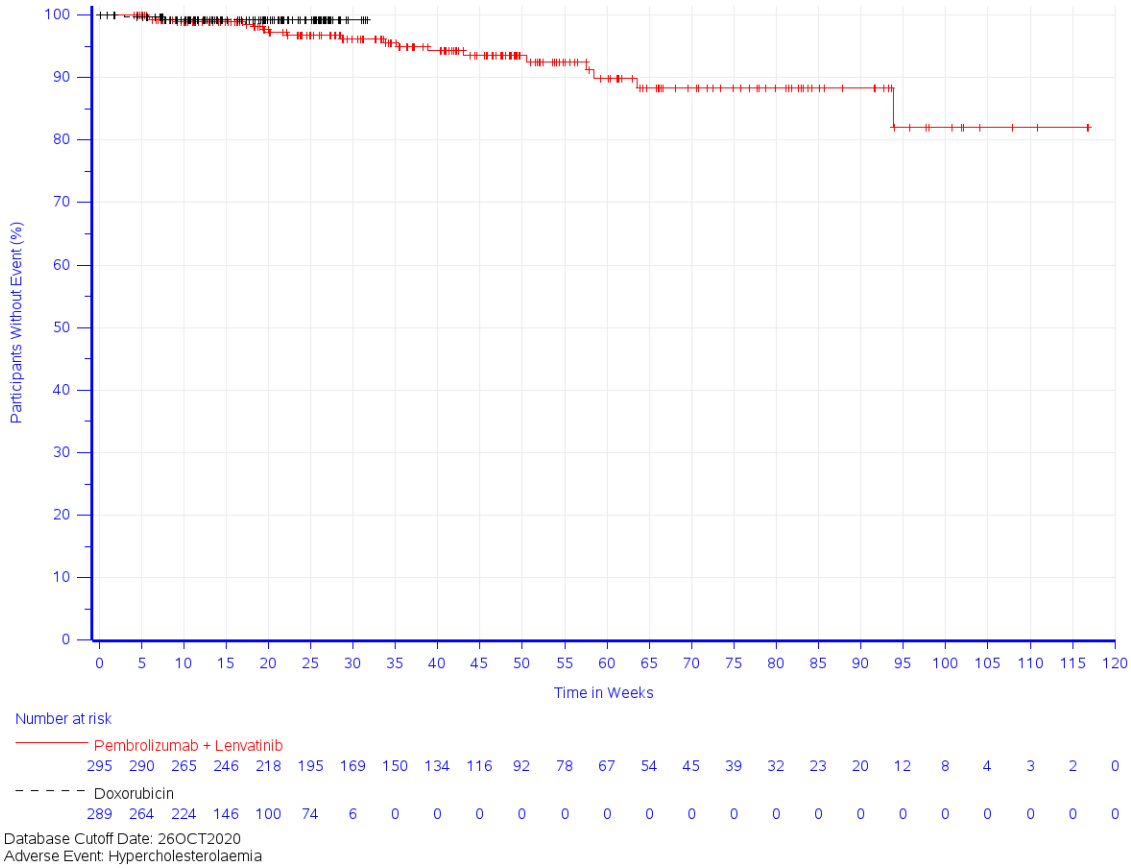
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Platelet count decreased



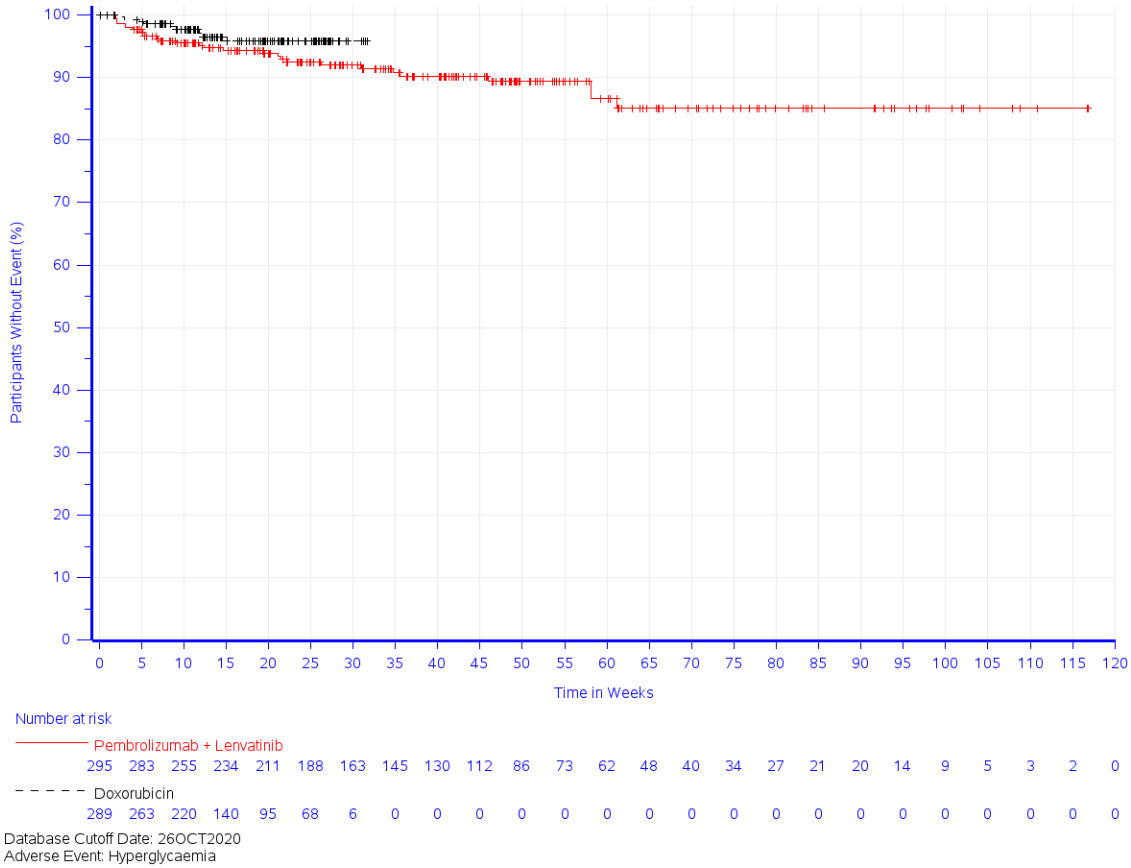
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Dehydration



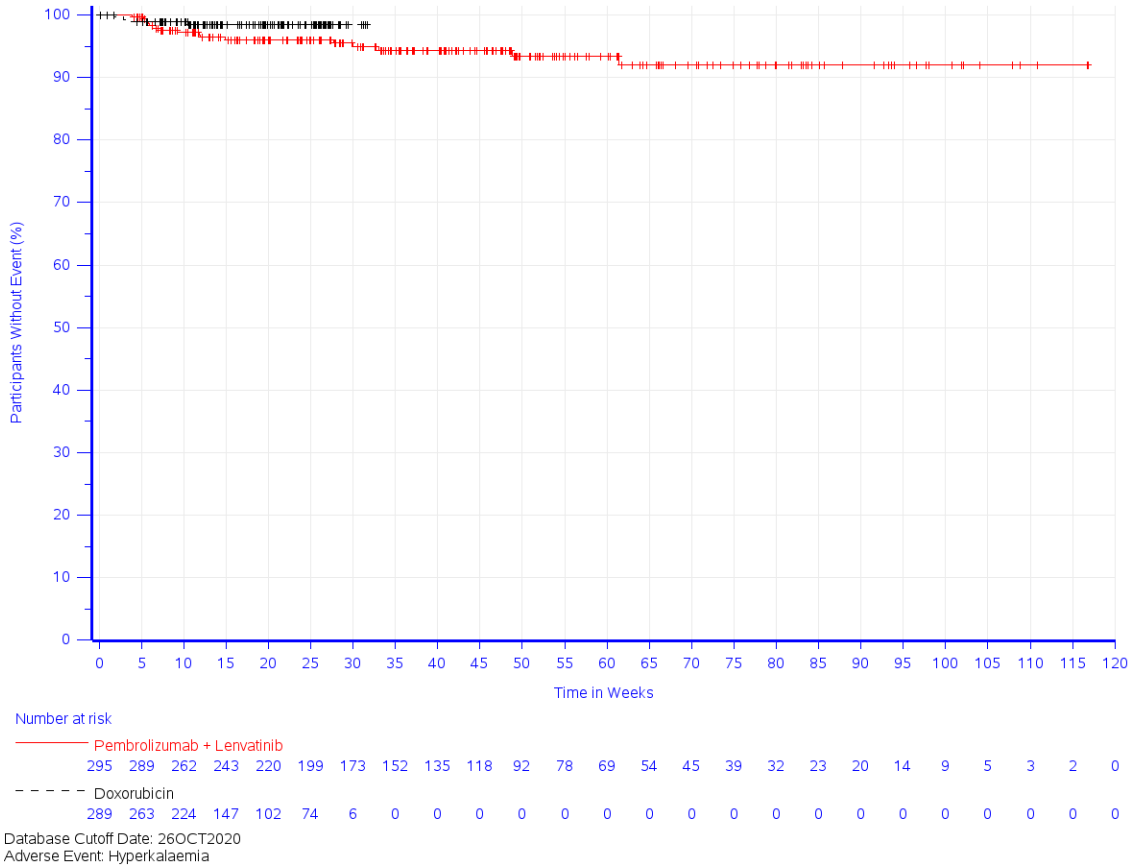
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Hypercalcaemia



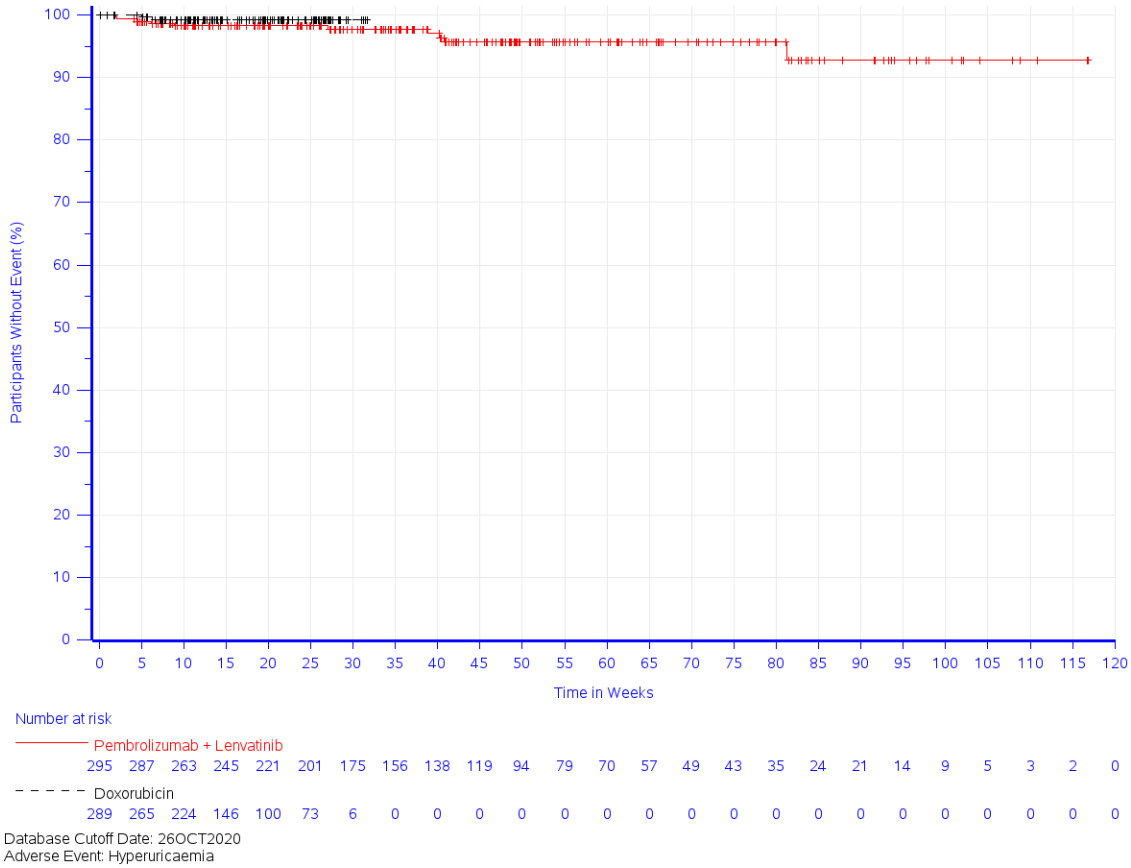
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Hypercholesterolaemia



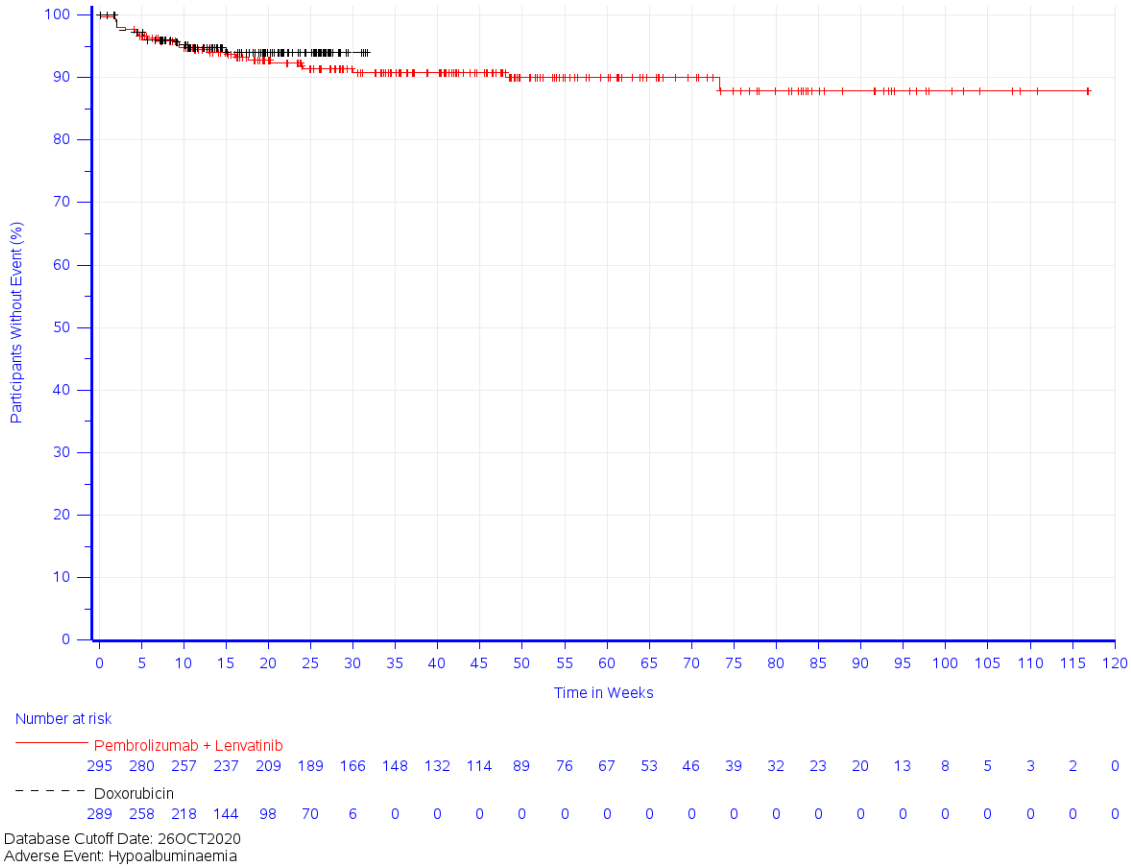
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Hyperglycaemia



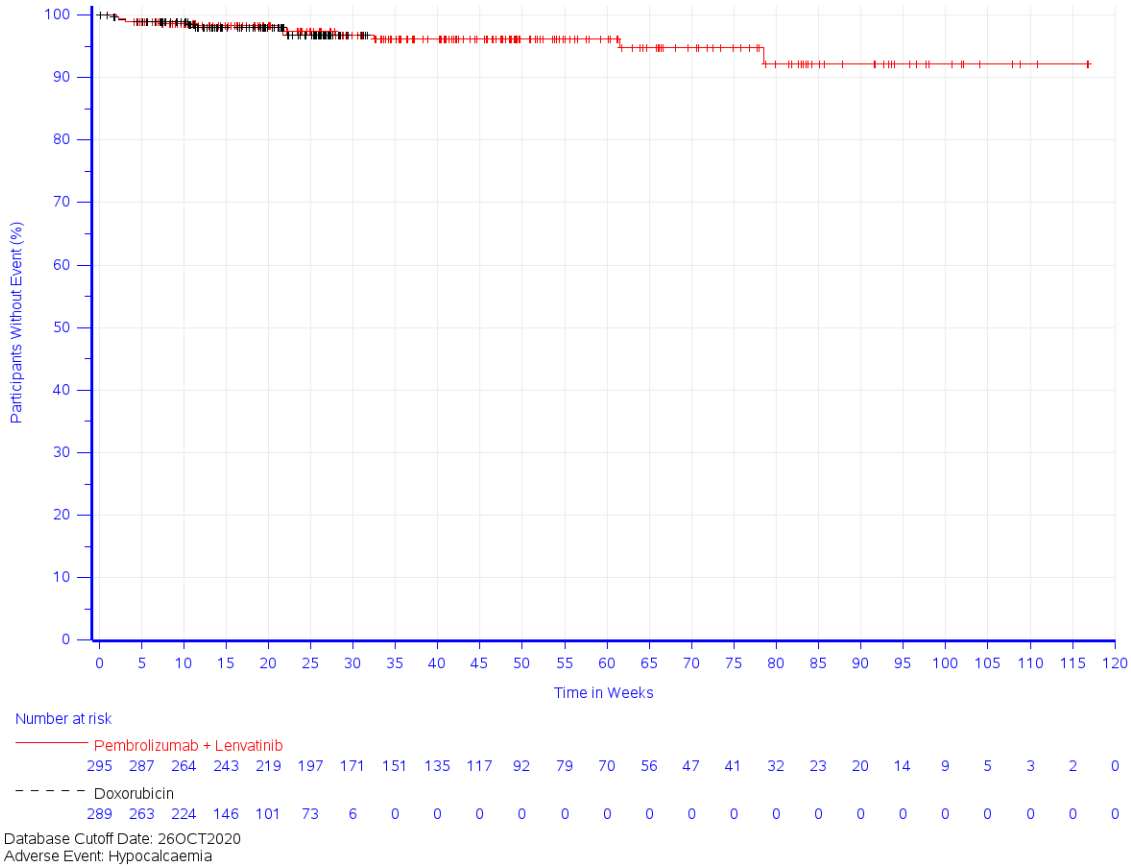
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Hyperkalaemia



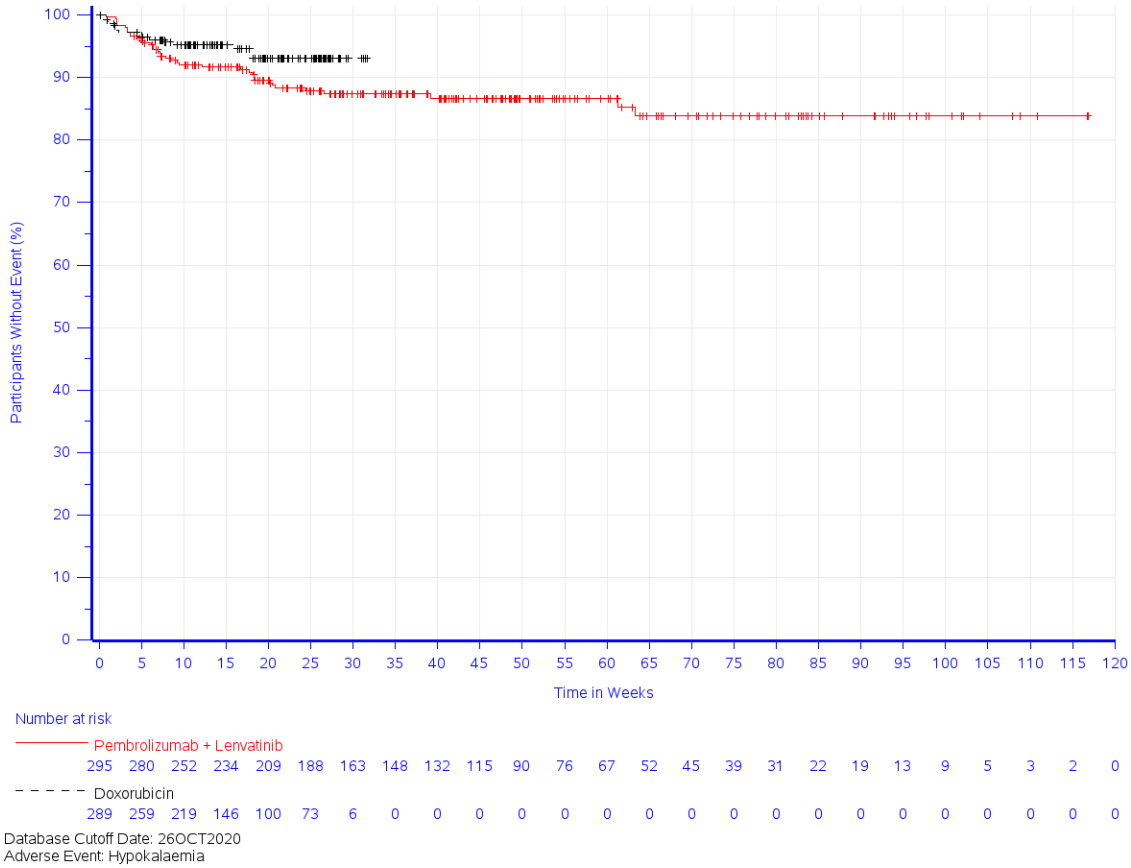
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Hyperuricaemia



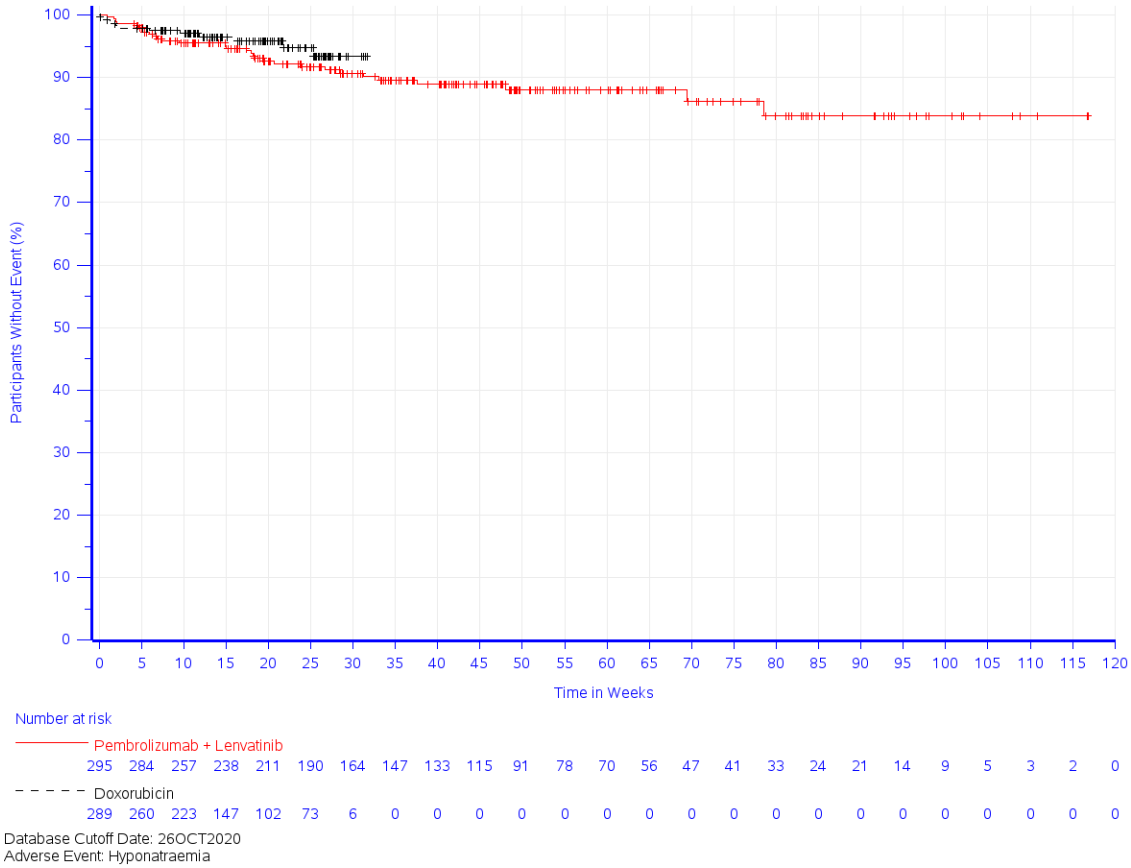
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Hypoalbuminaemia



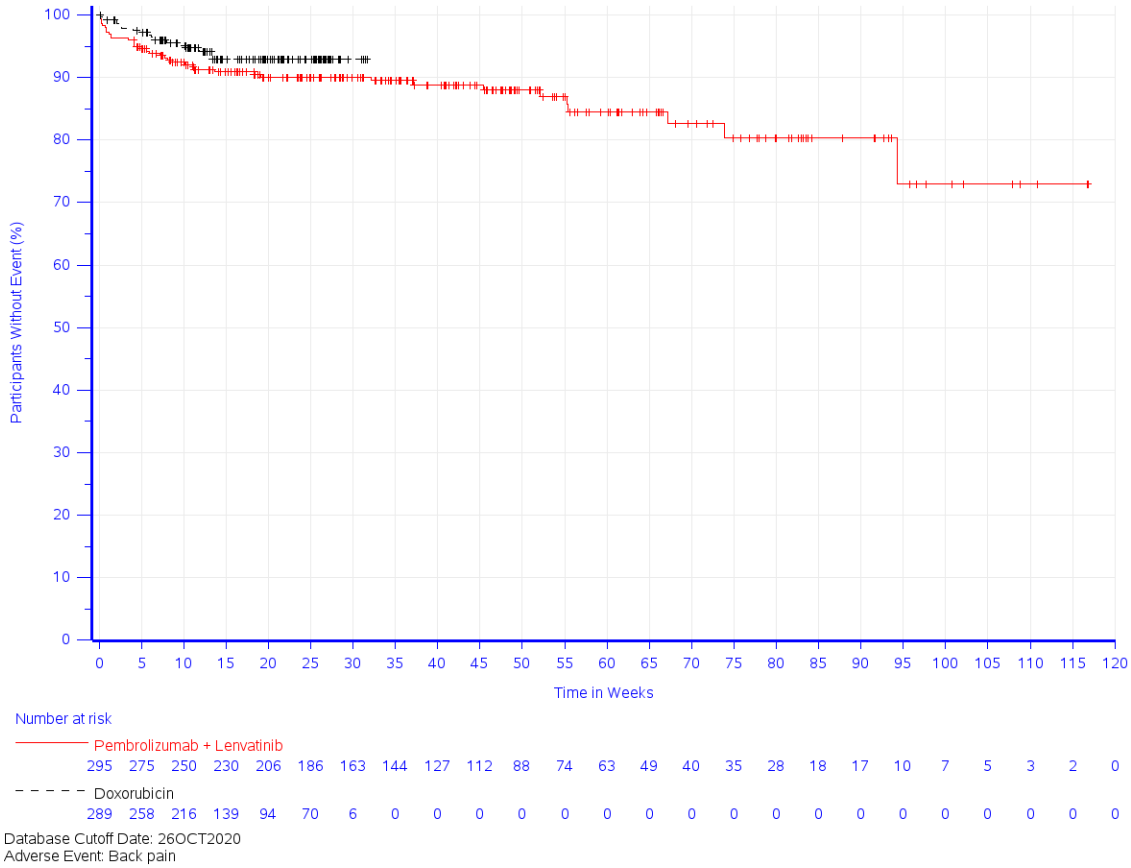
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Hypocalcaemia



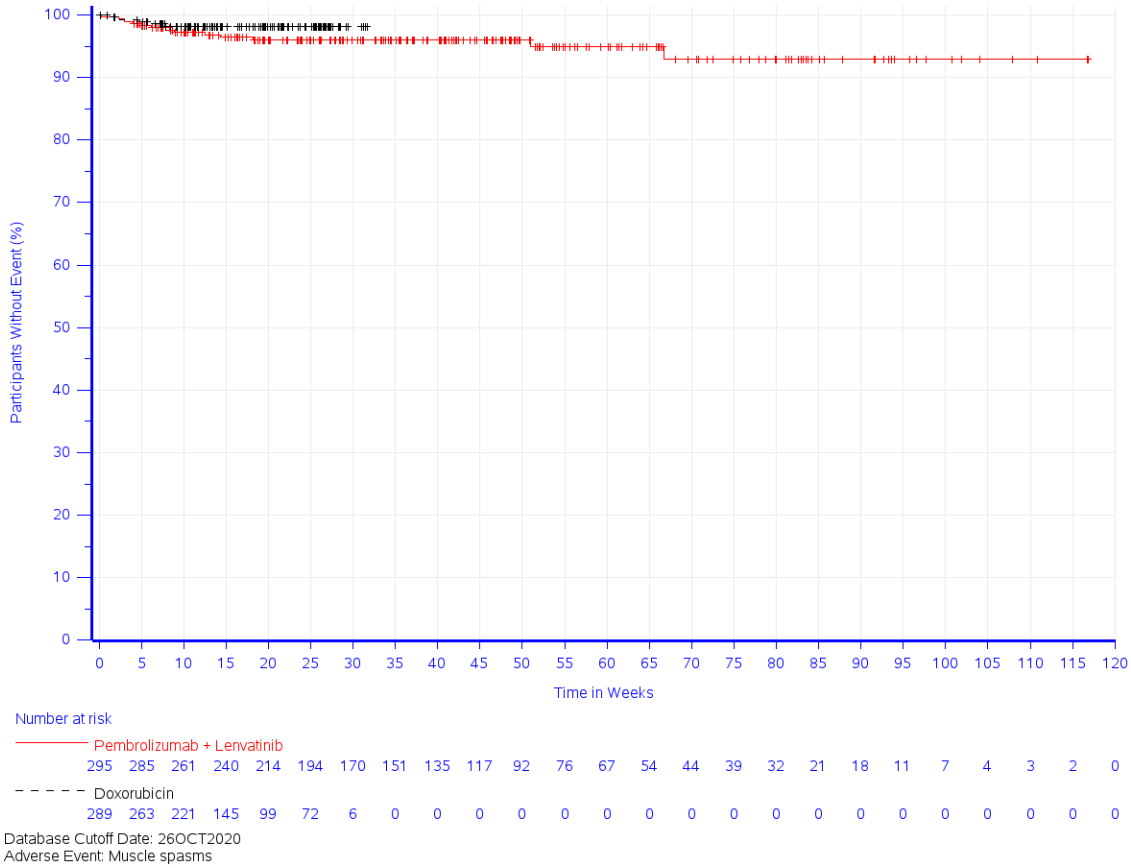
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Hypokalaemia



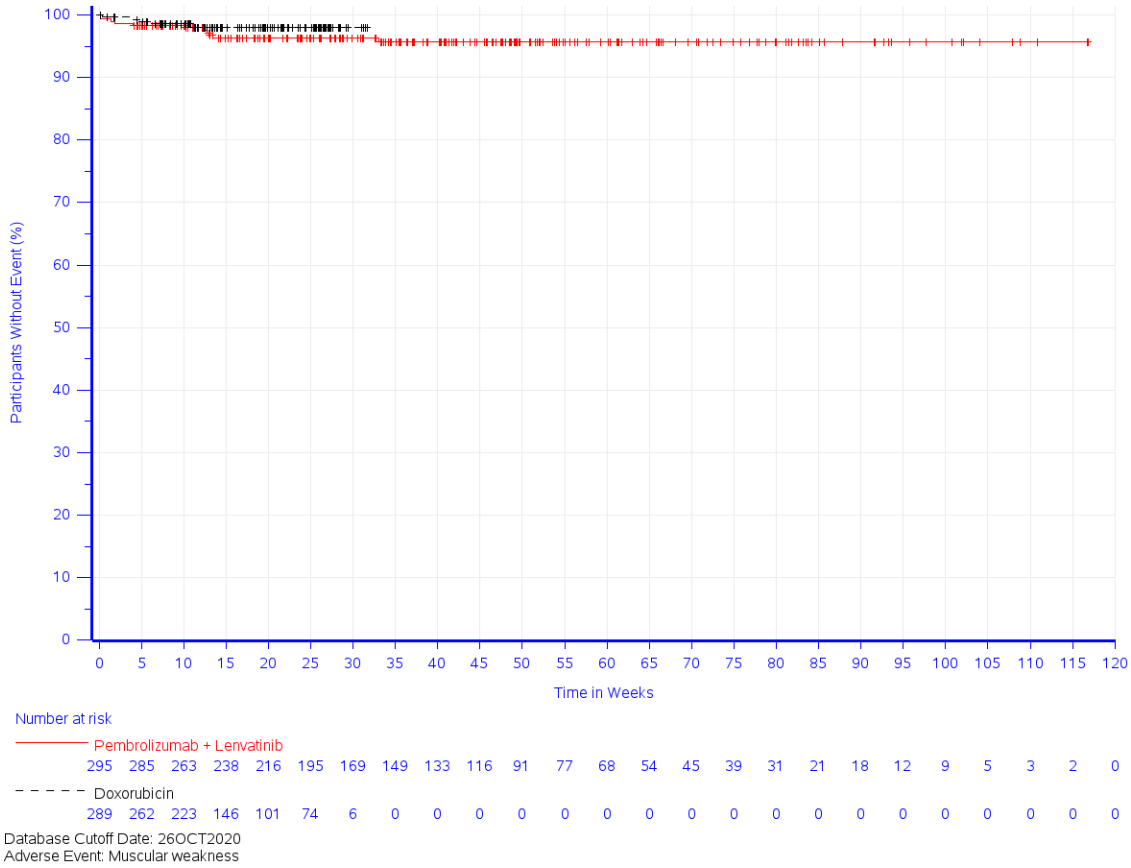
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Hyponatraemia



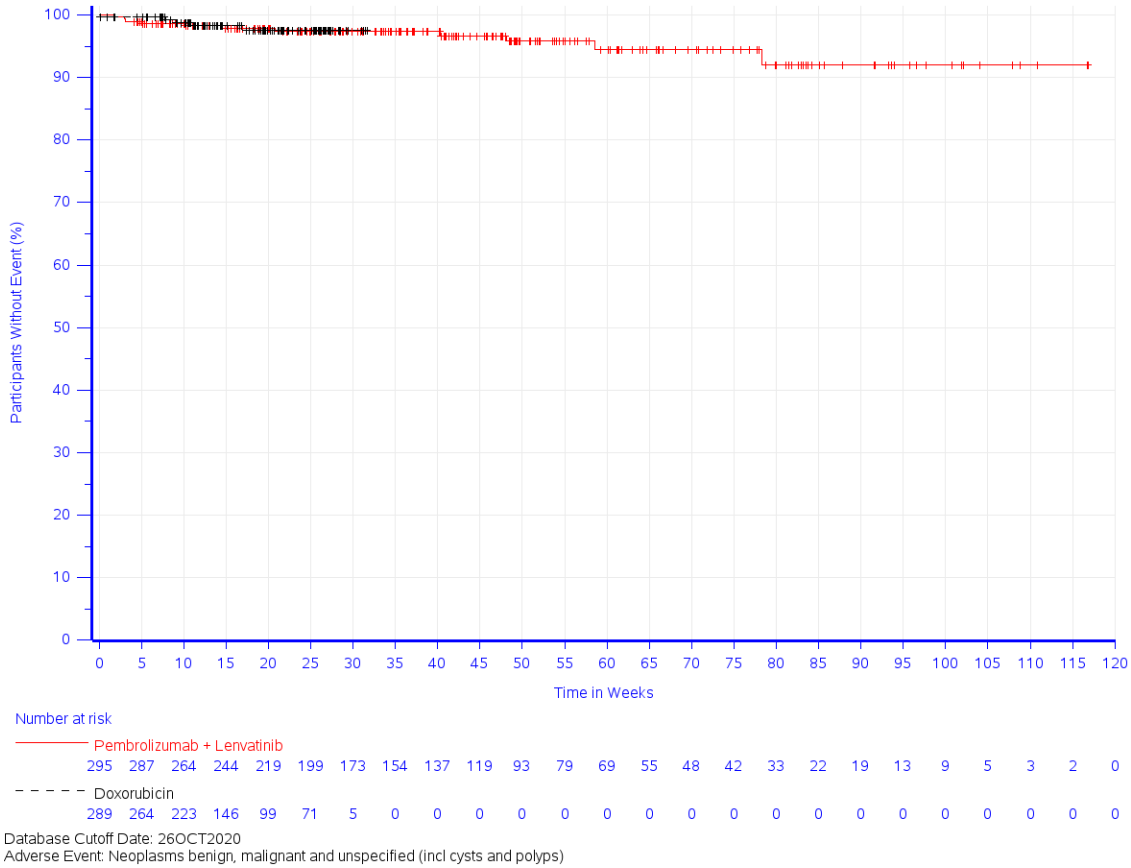
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Back pain



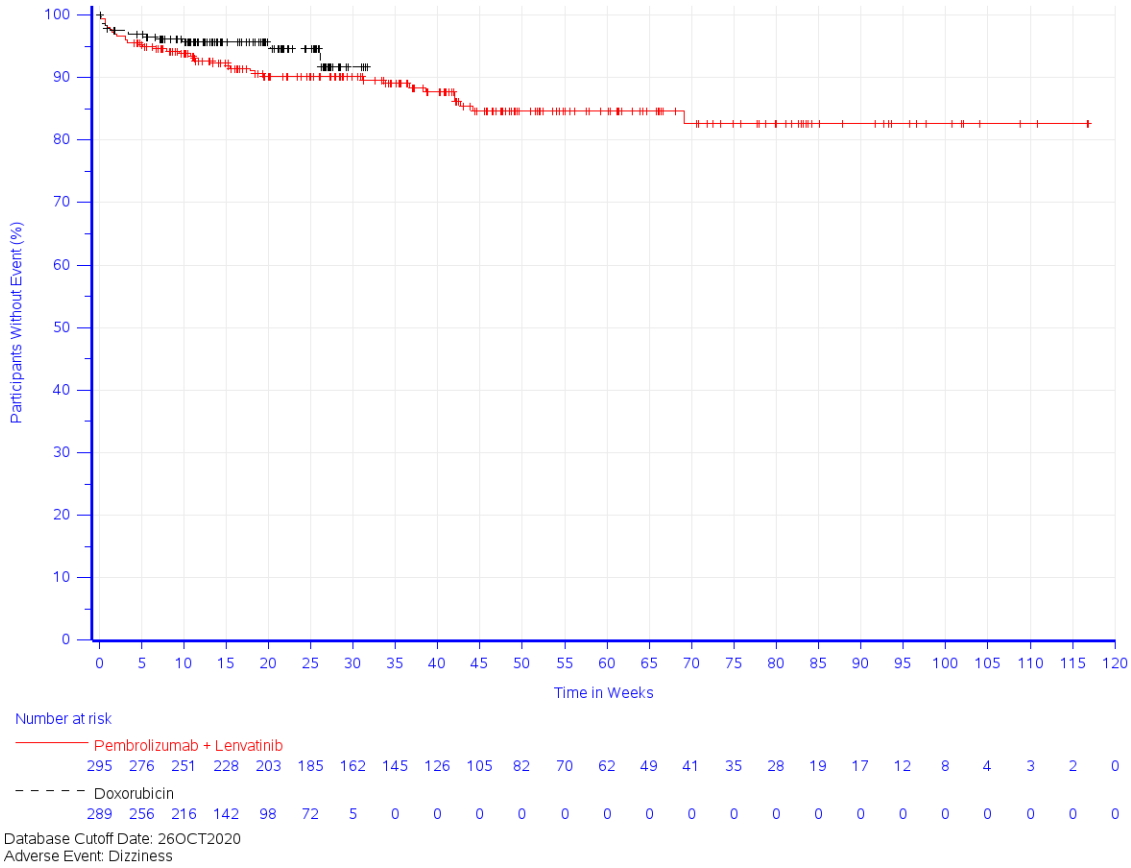
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Muscle spasms



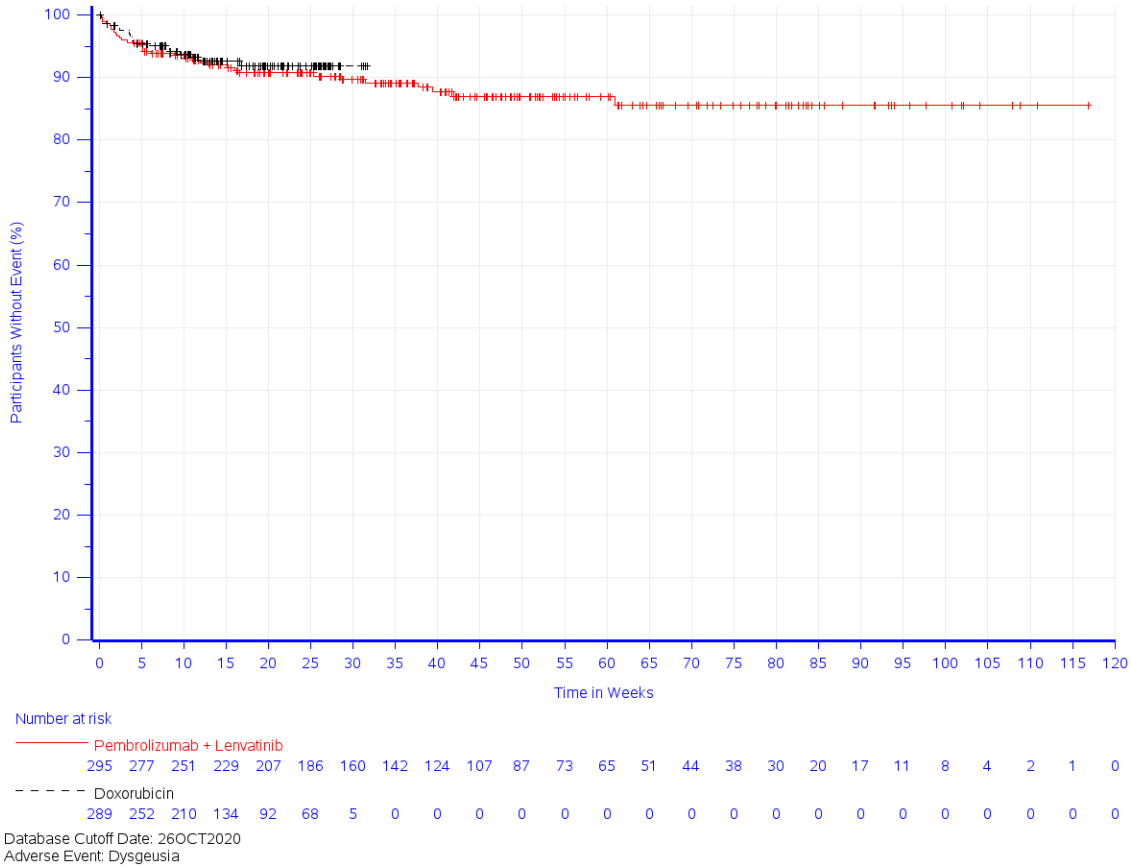
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Muscular weakness



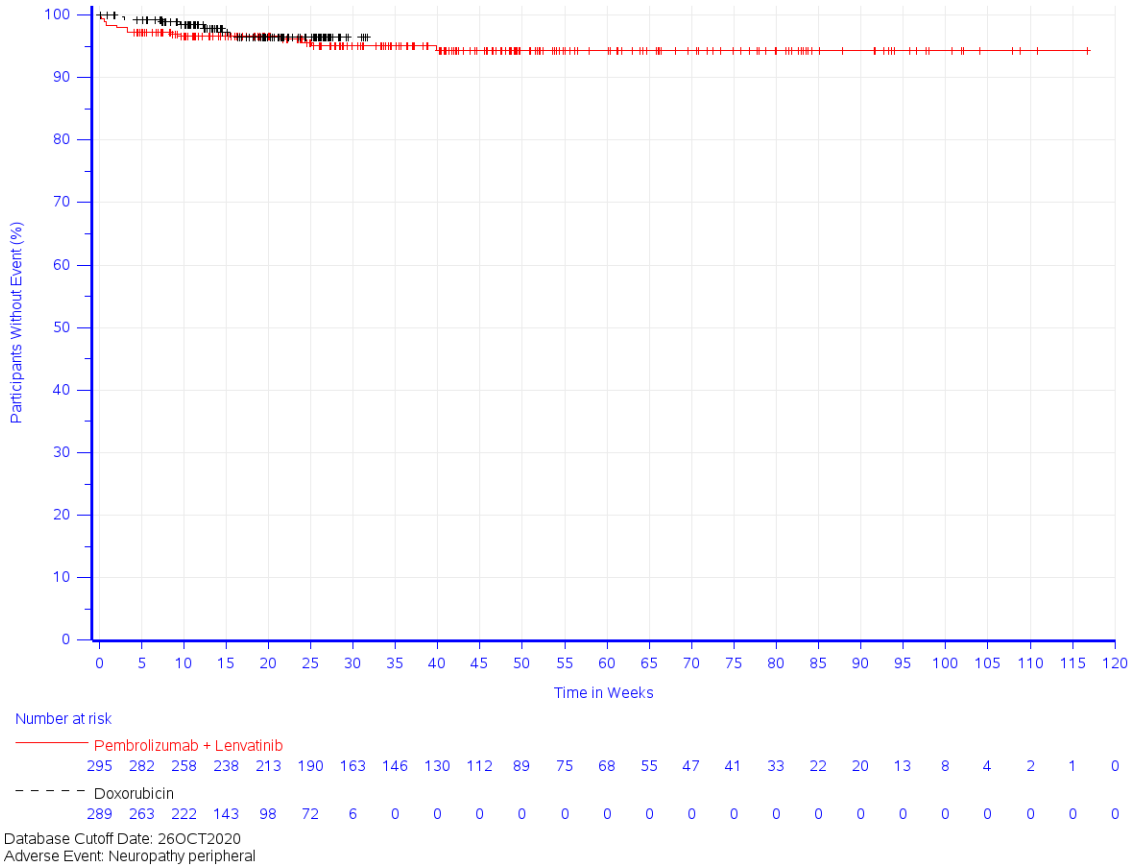
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)



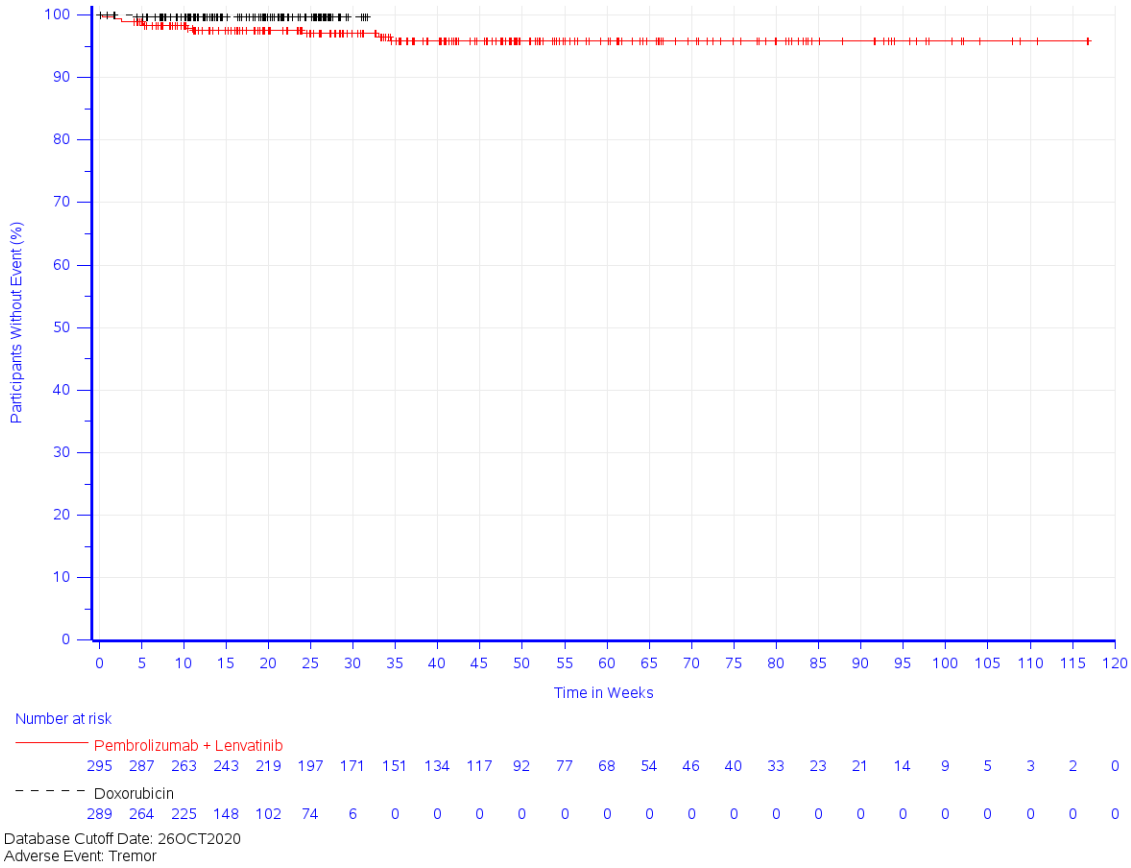
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Dizziness



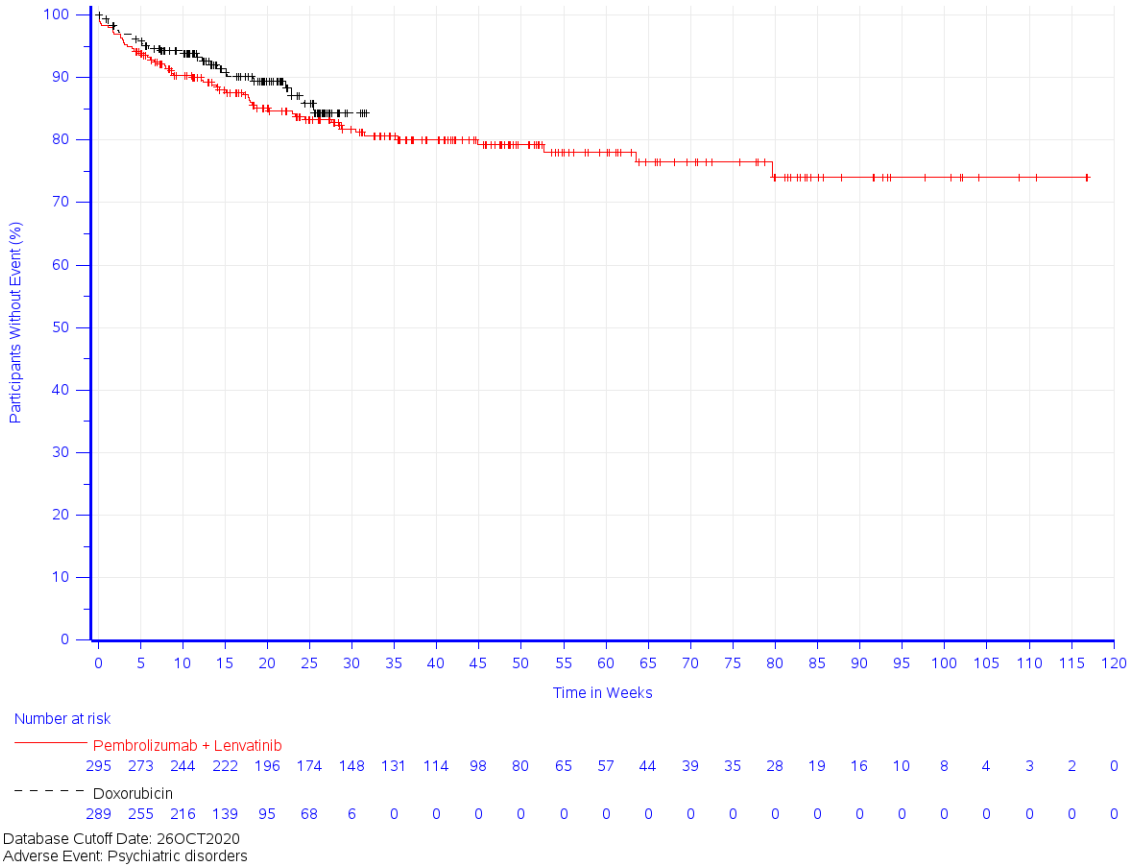
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Dysgeusia



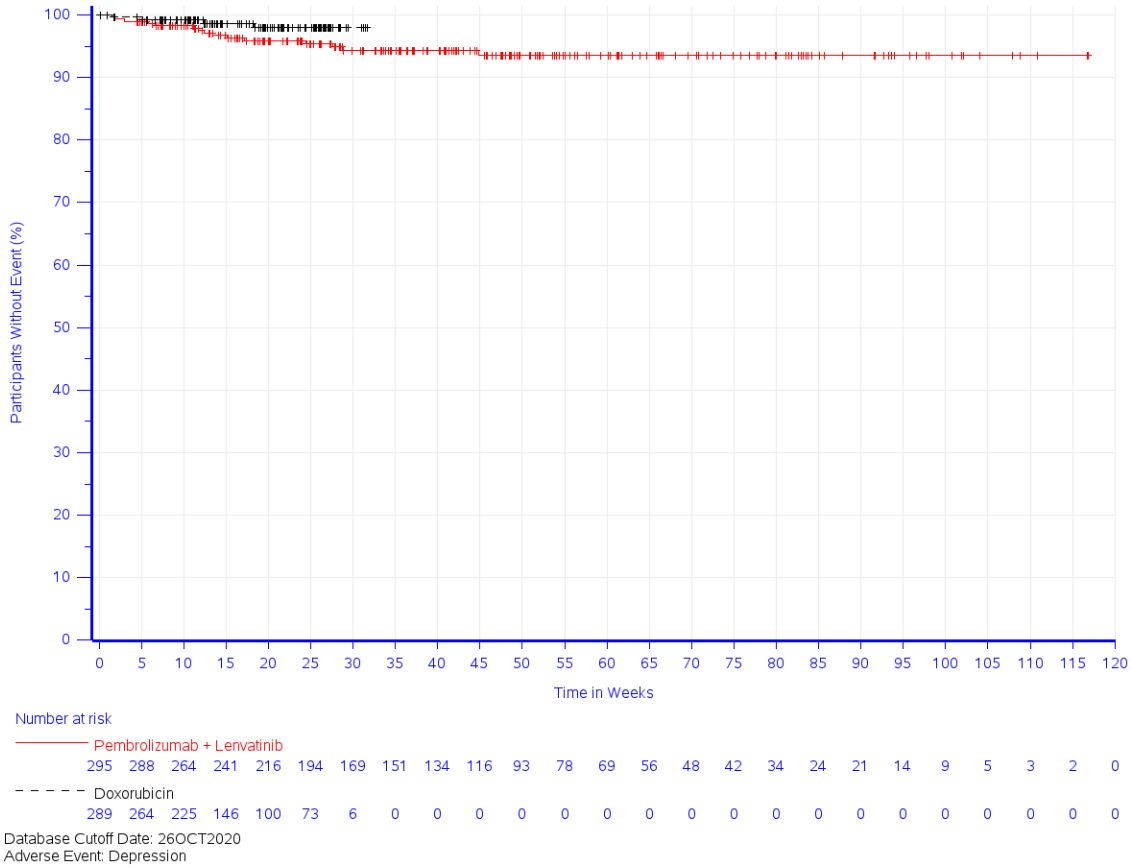
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Neuropathy peripheral



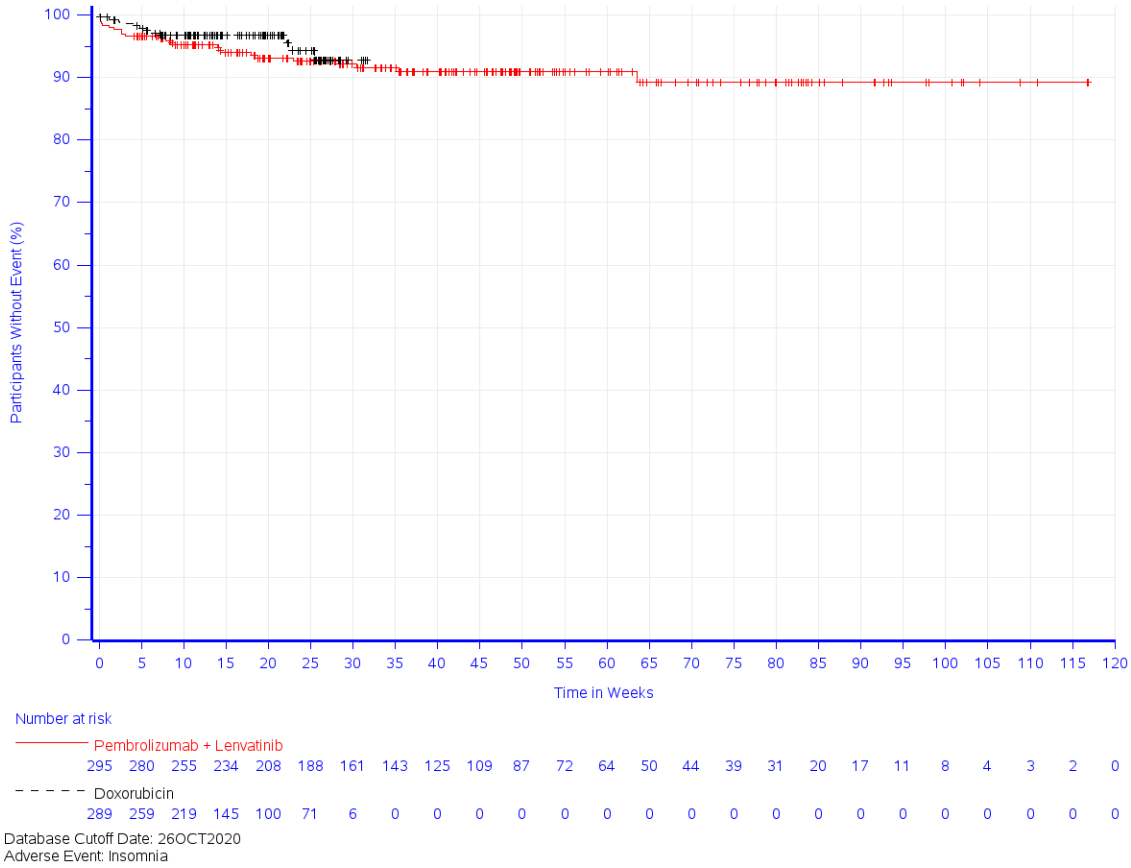
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Tremor



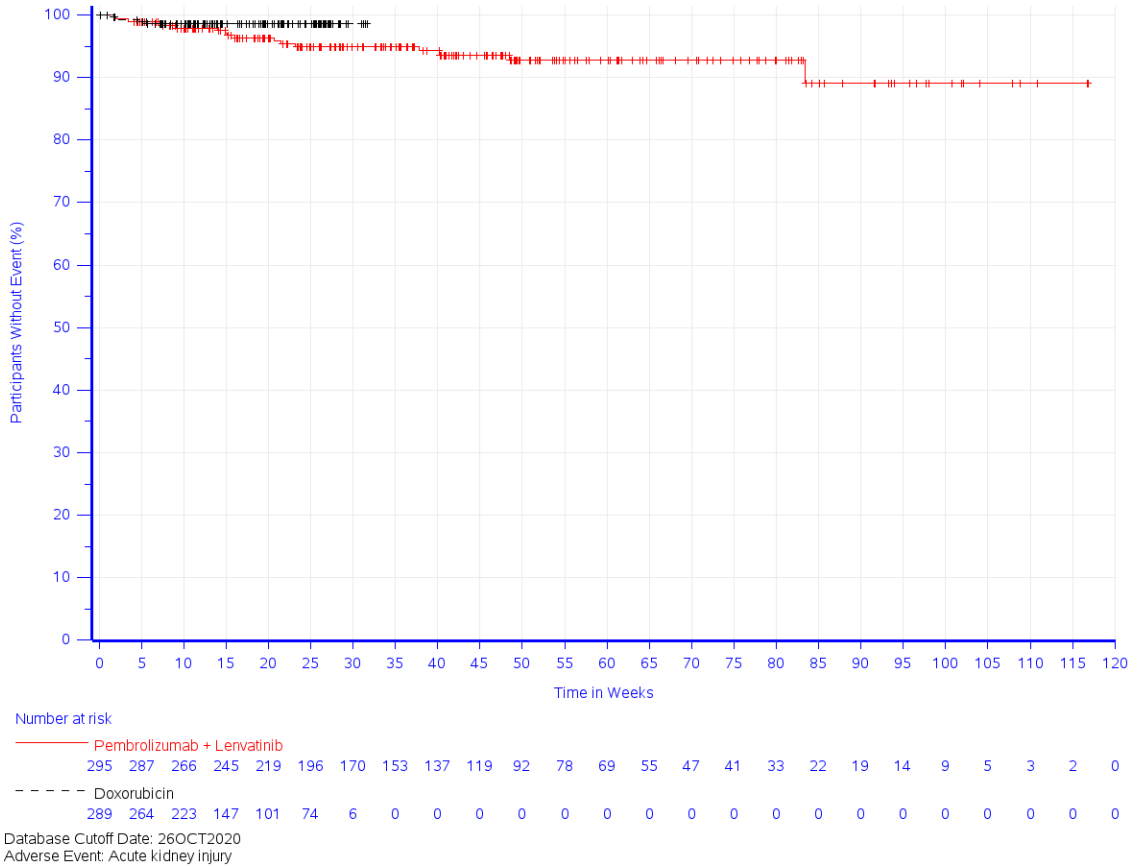
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Psychiatric disorders



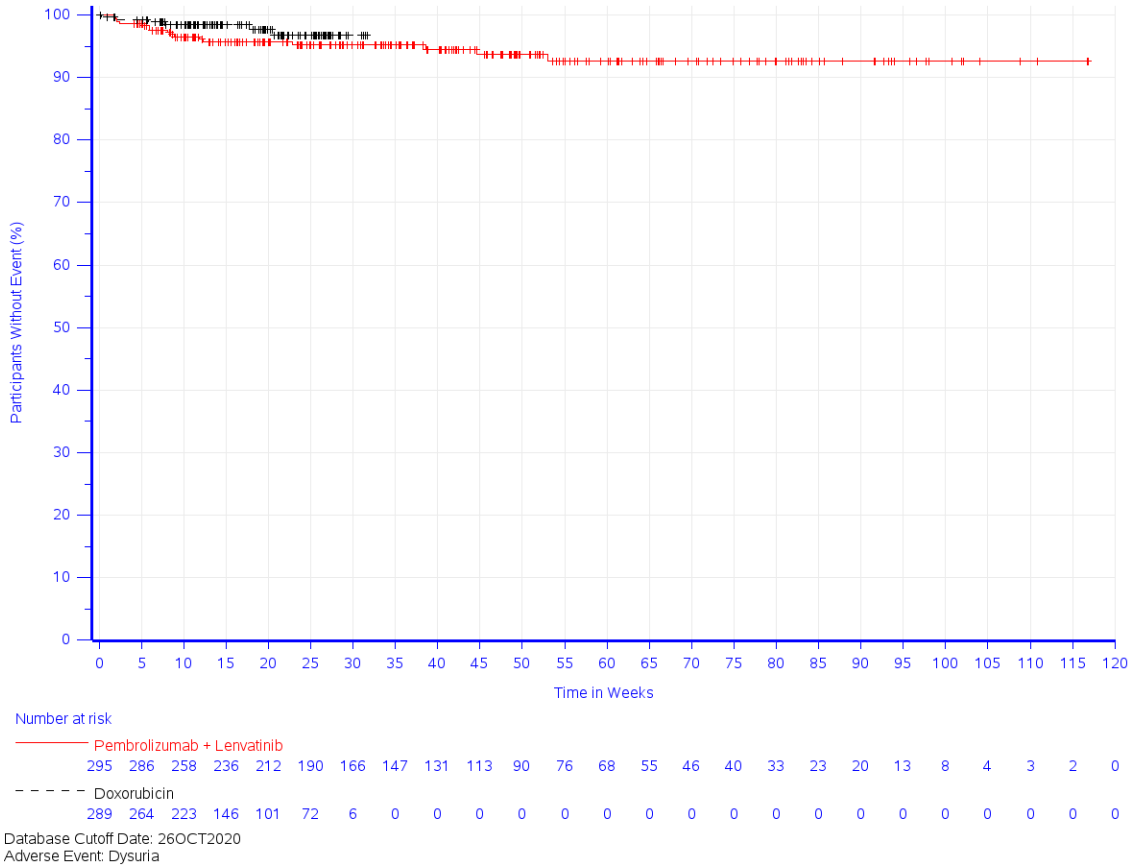
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Depression



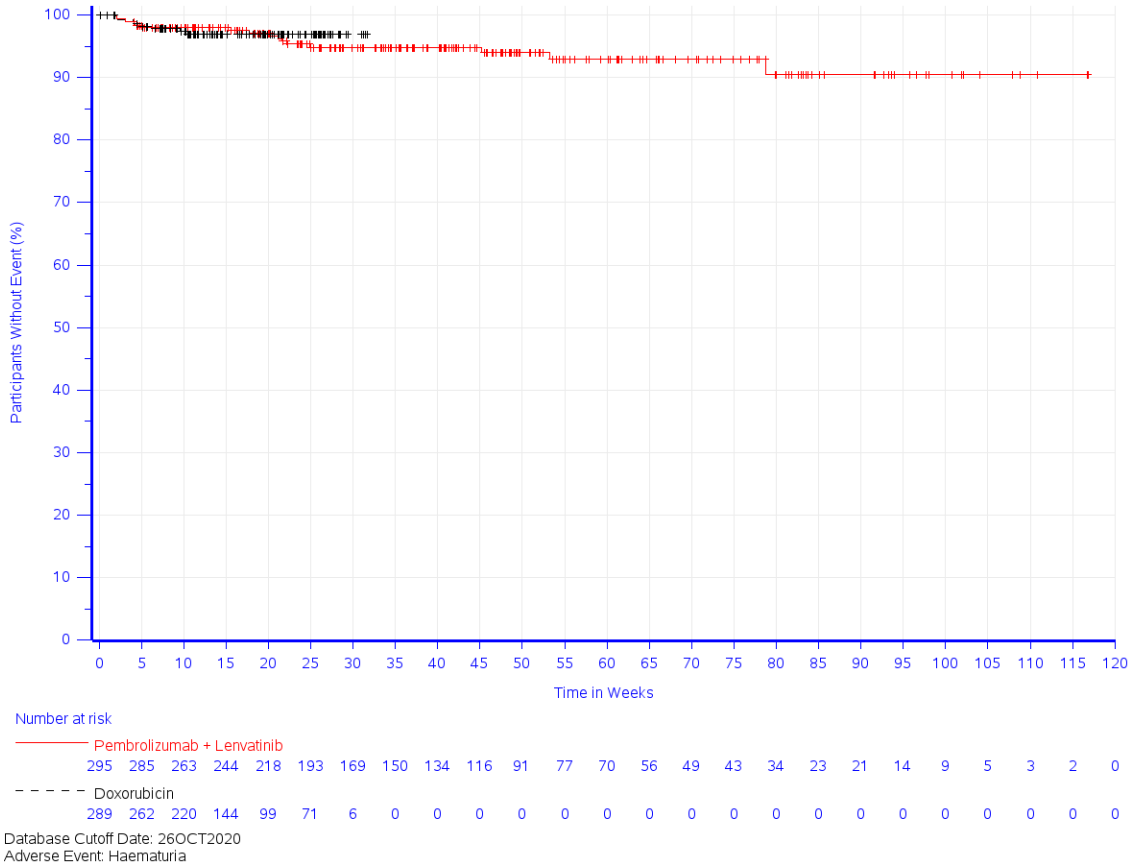
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Insomnia



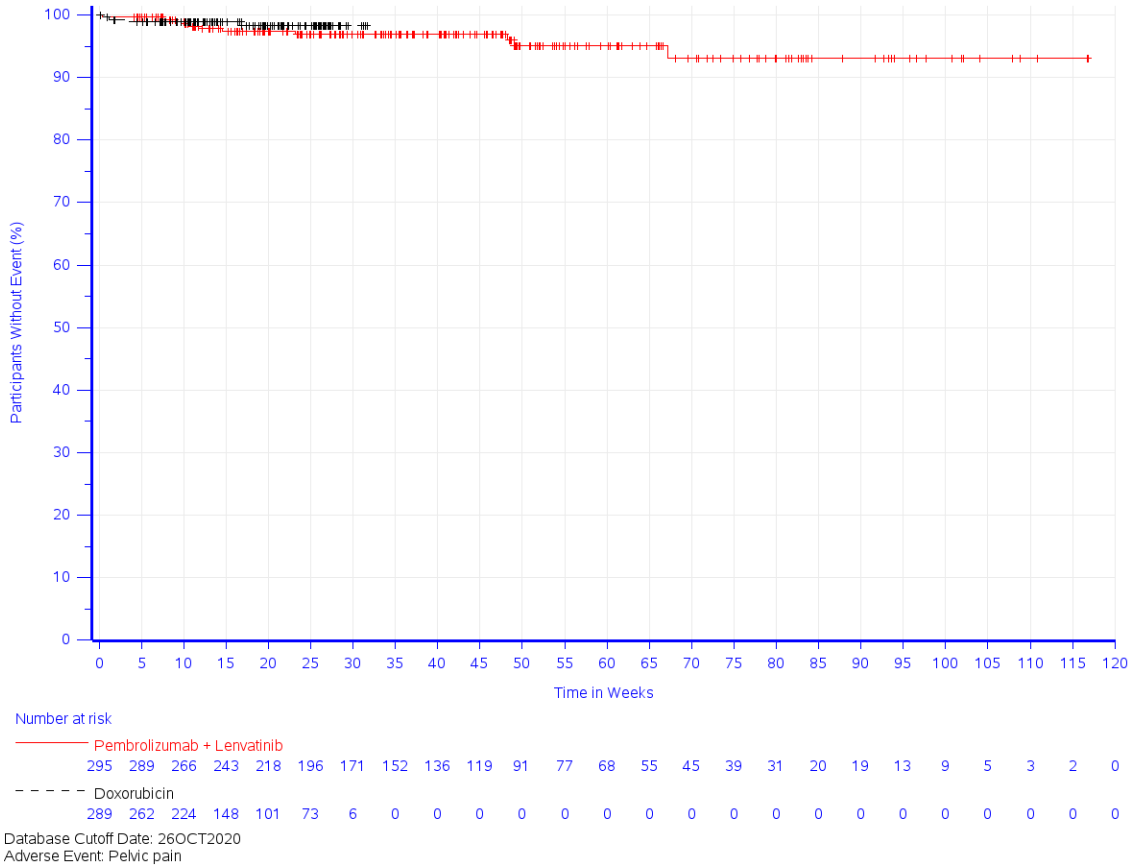
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Acute kidney injury



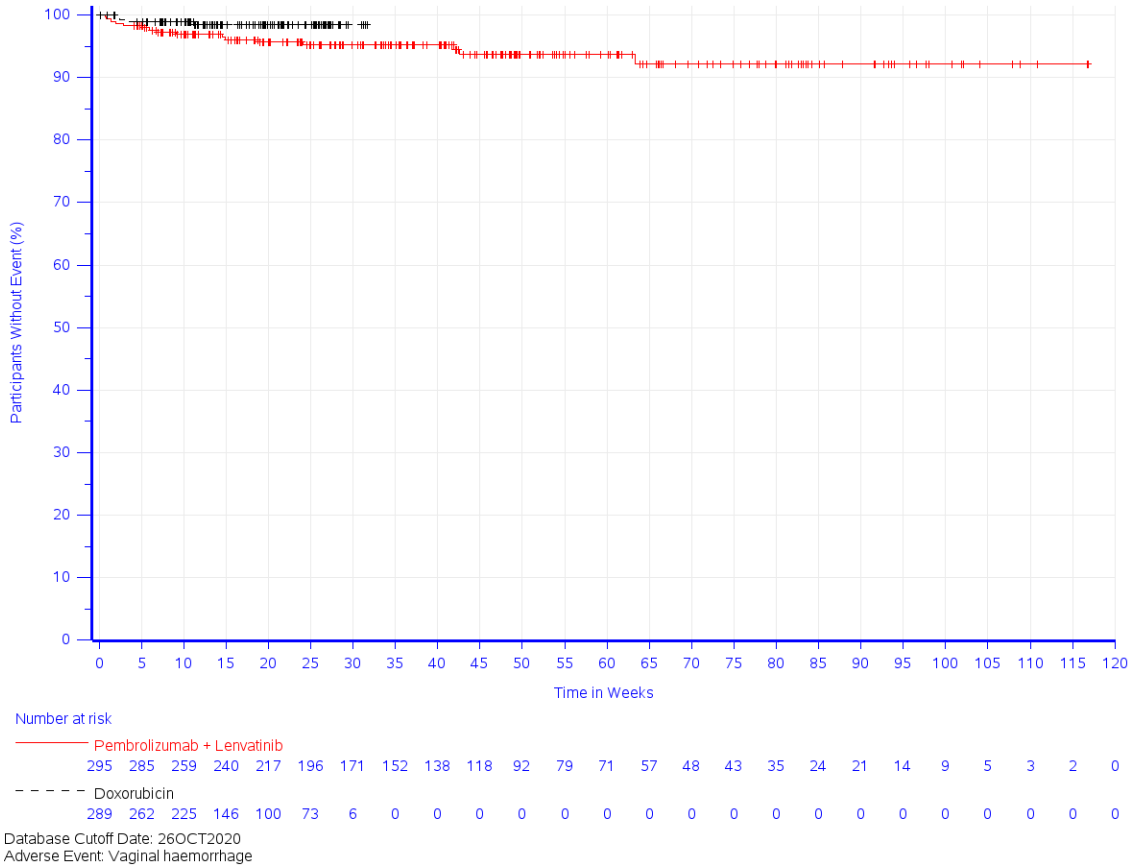
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Dysuria



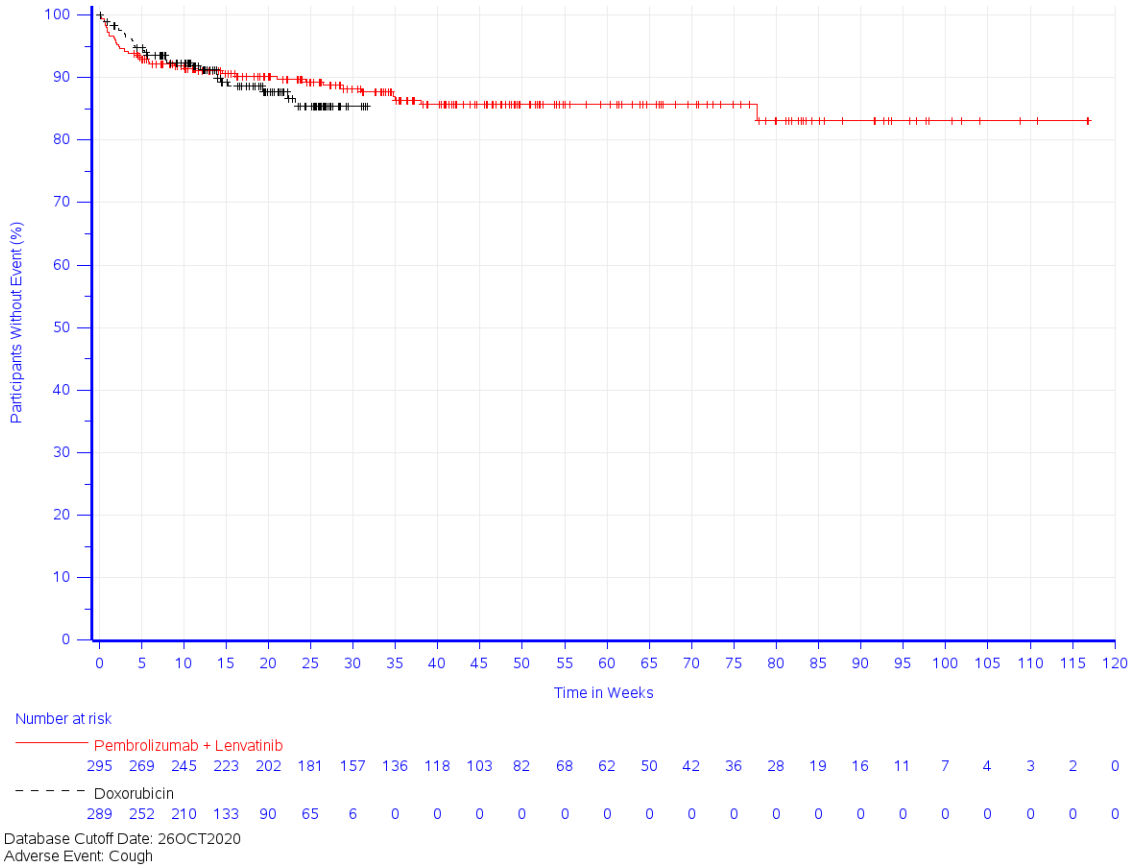
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Haematuria



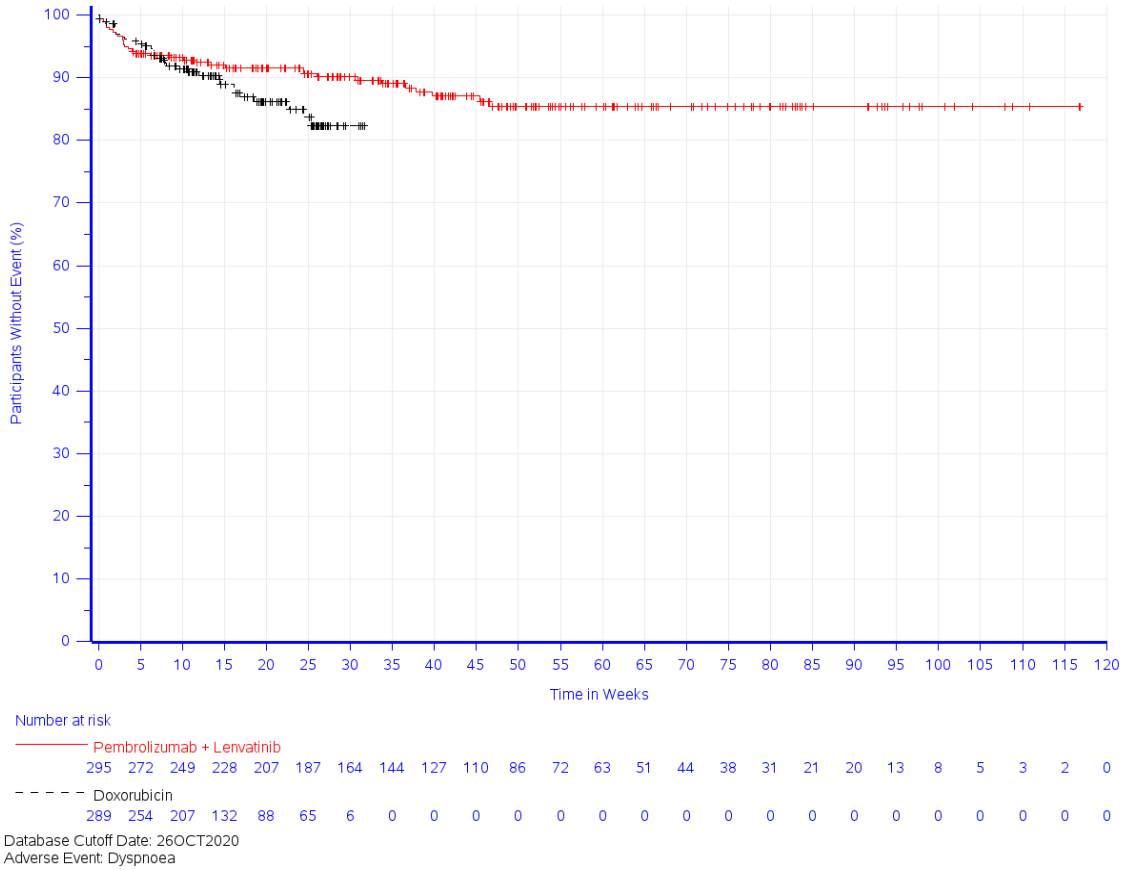
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Pelvic pain



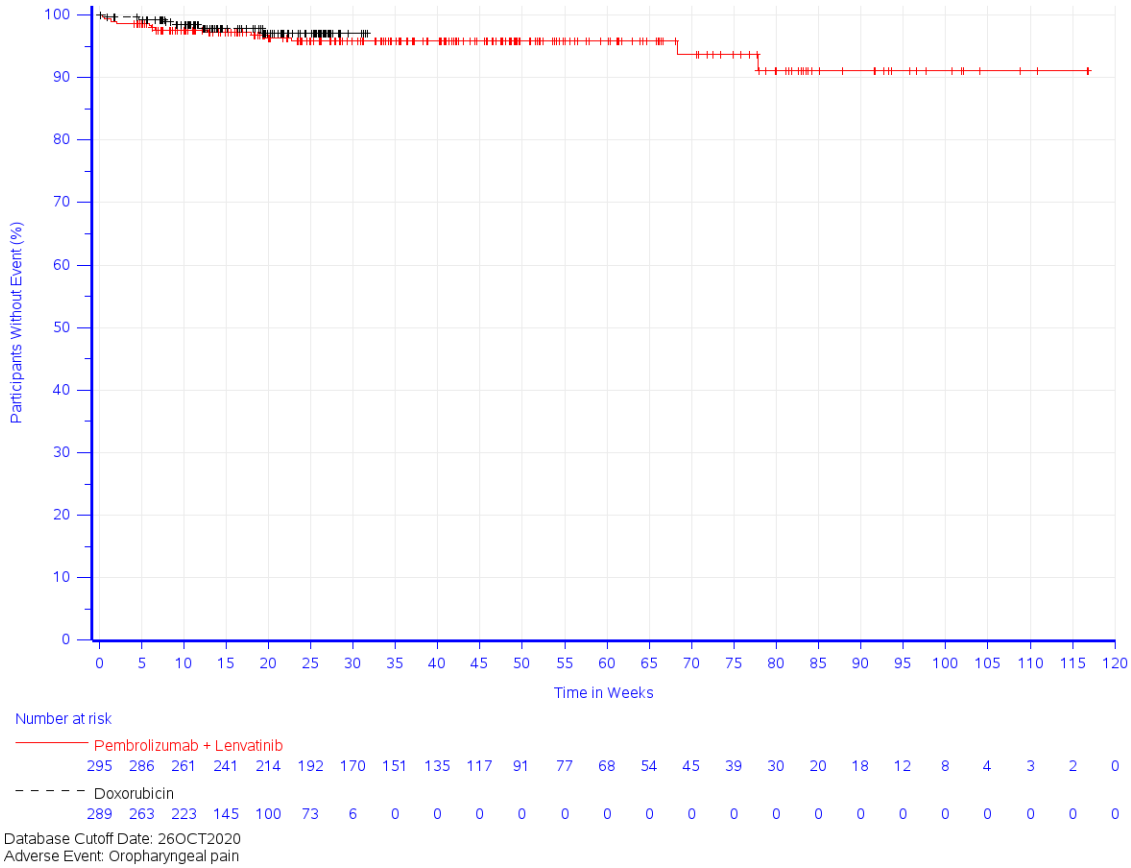
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Vaginal haemorrhage



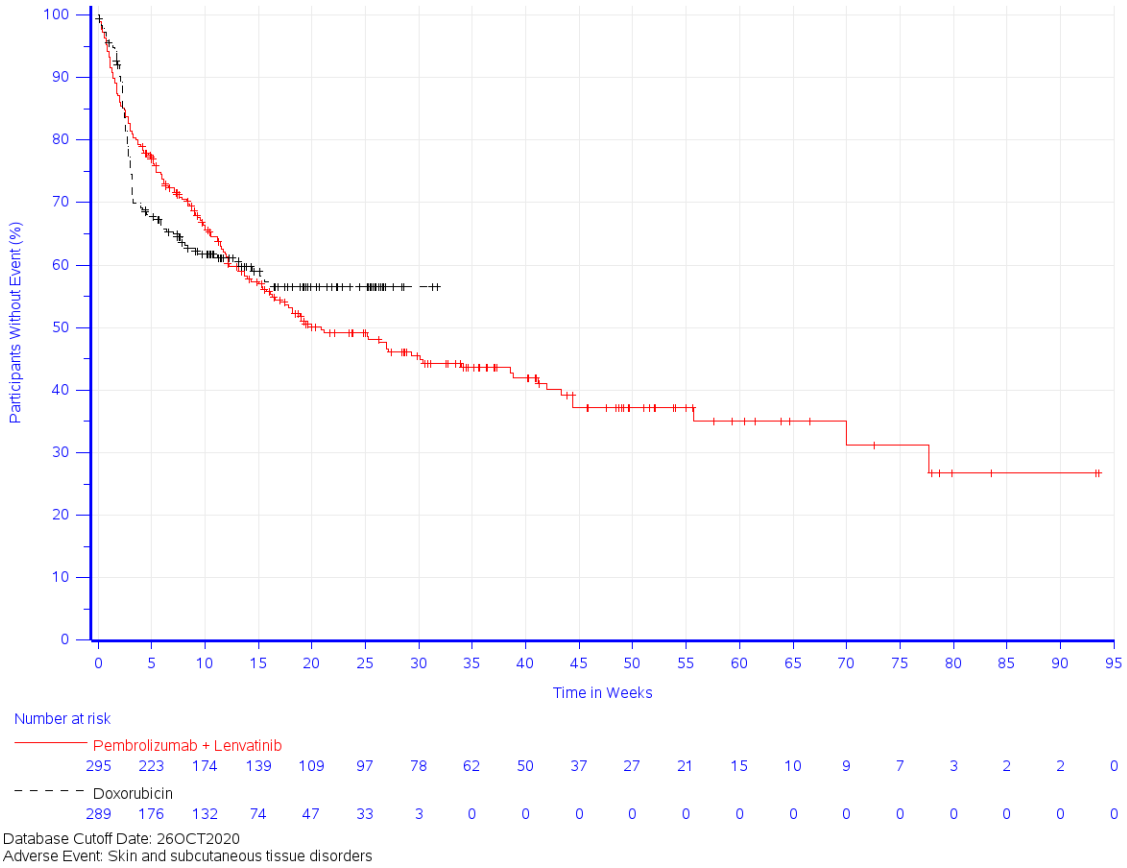
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Cough



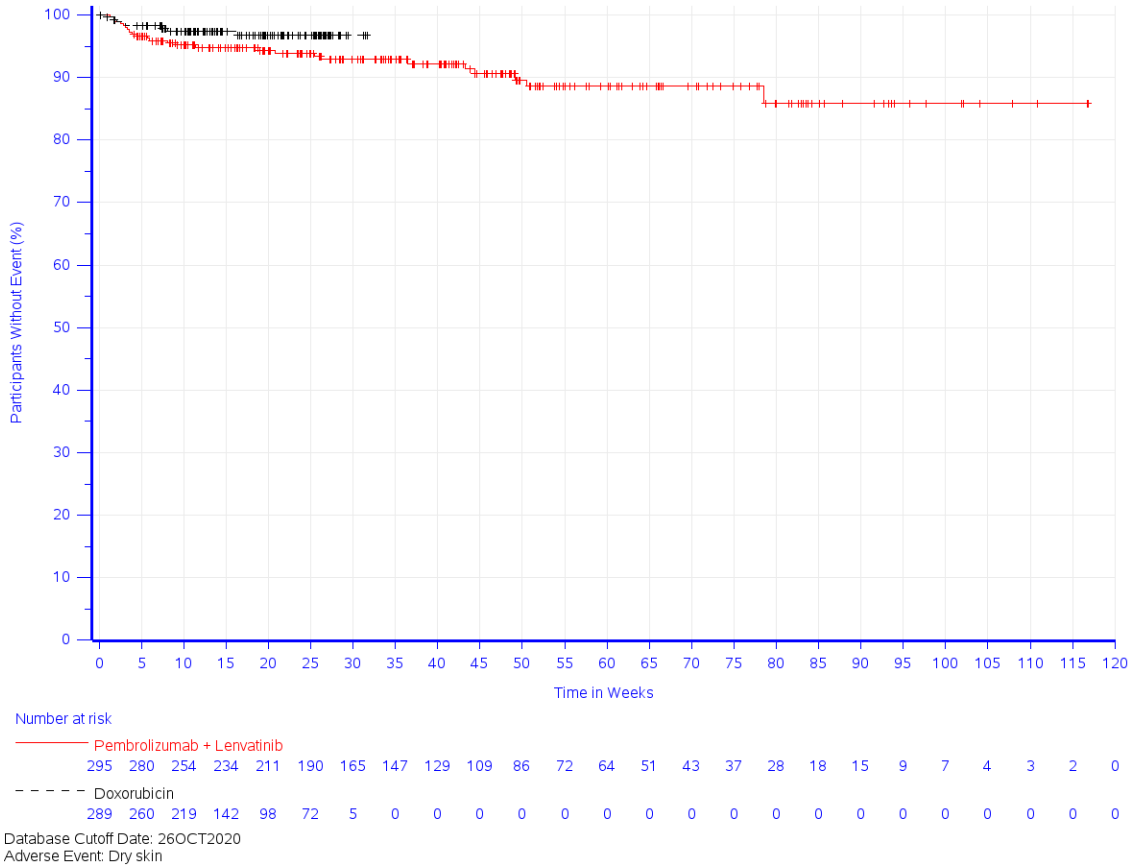
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Dyspnoea



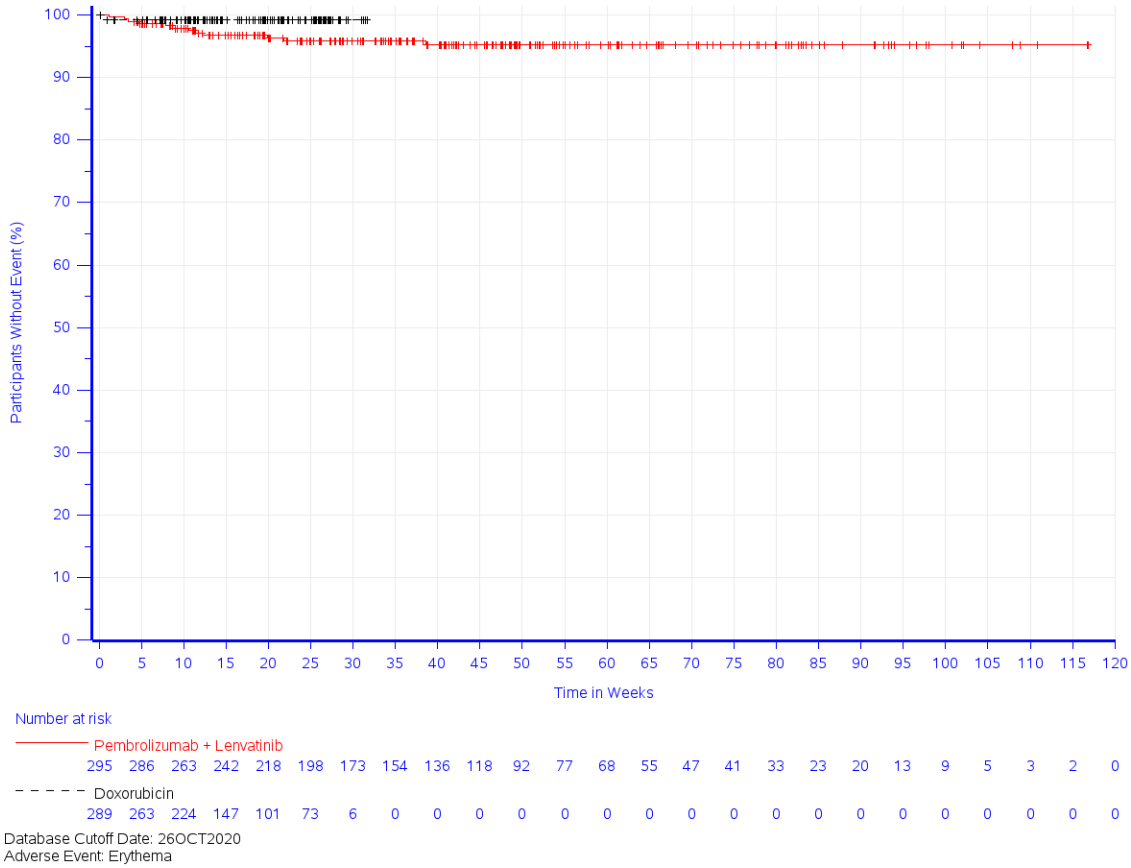
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Oropharyngeal pain



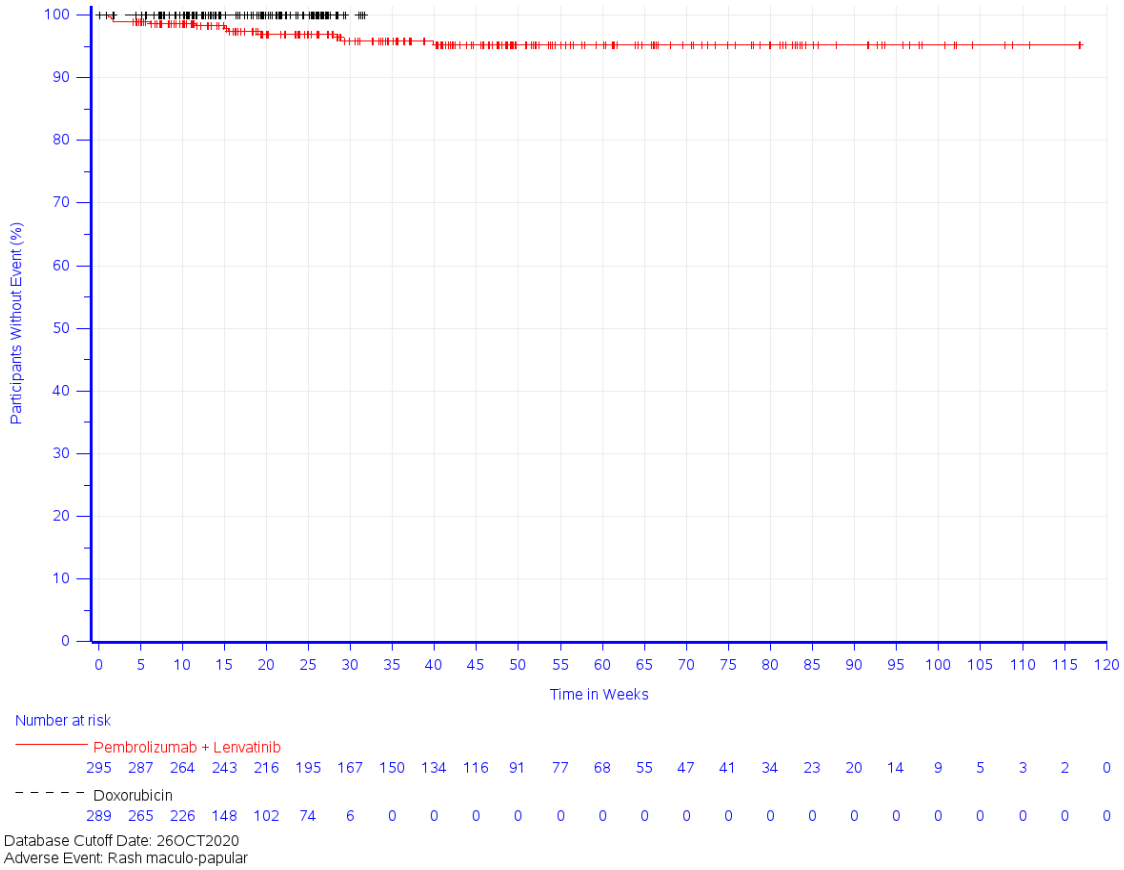
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Skin and subcutaneous tissue disorders



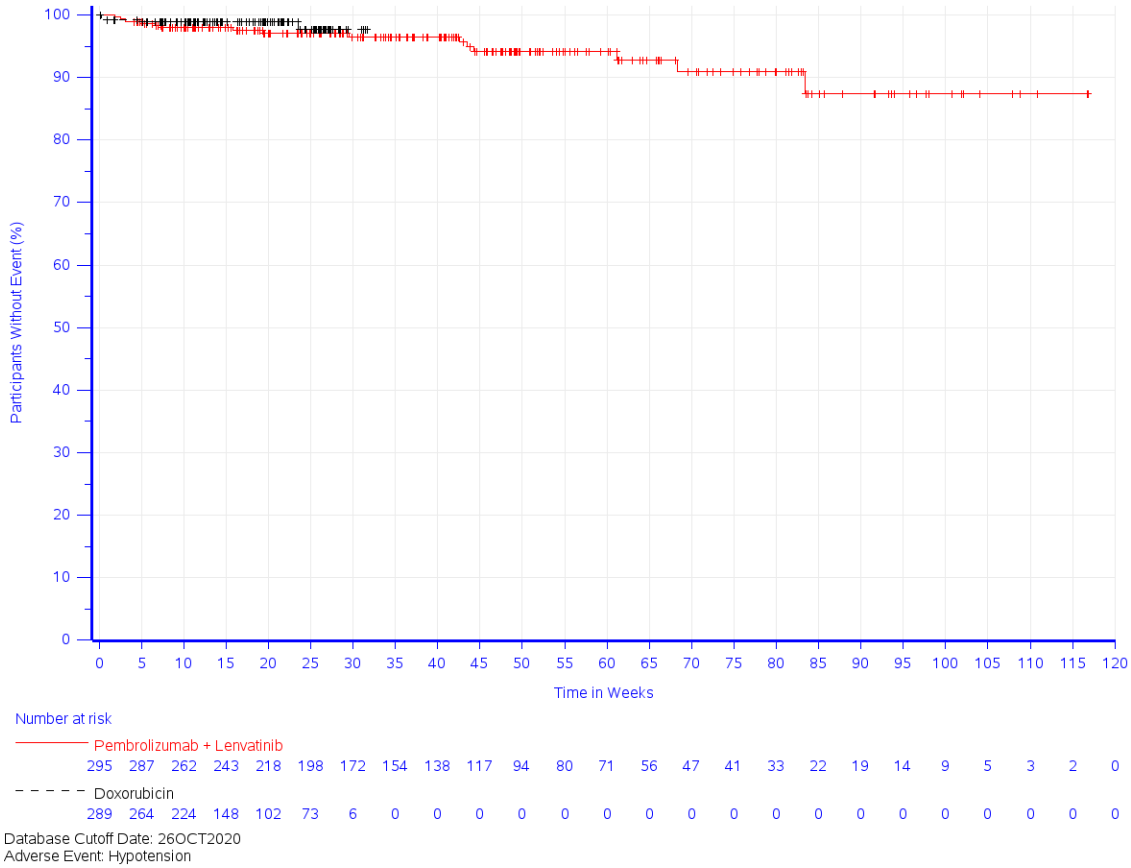
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Dry skin



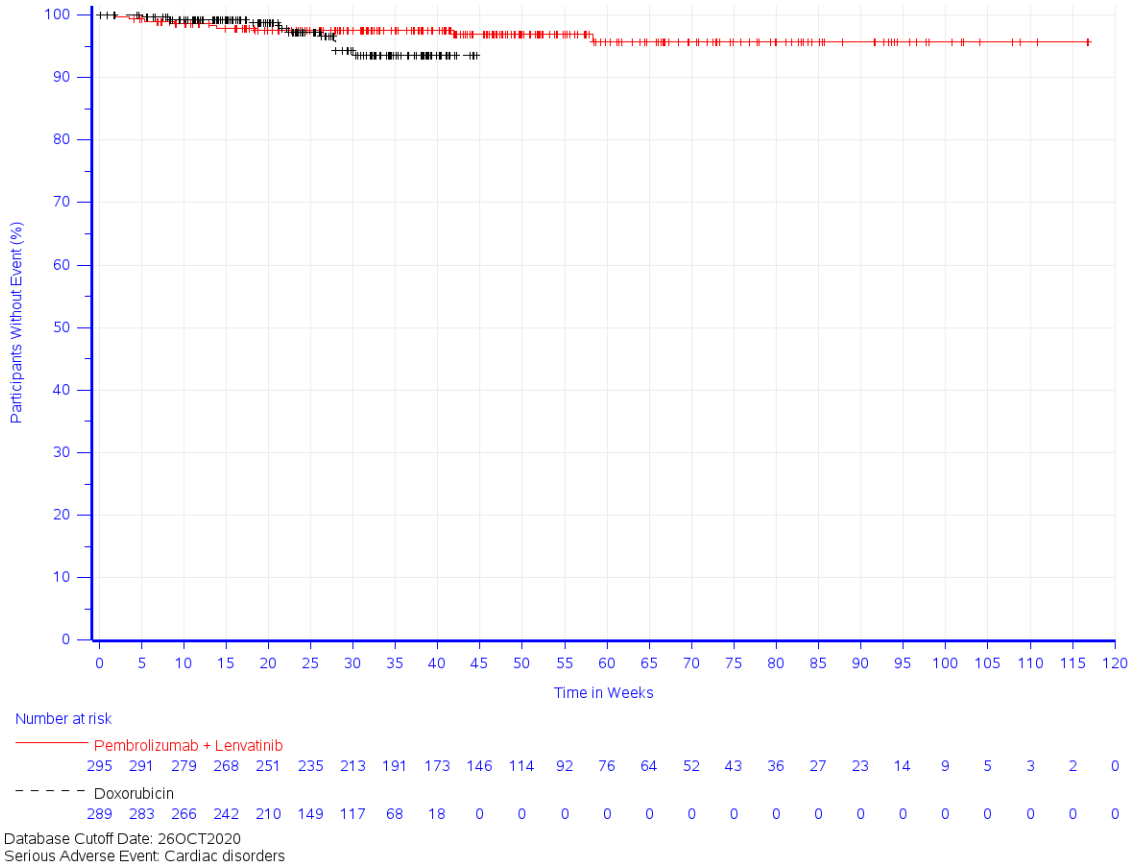
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Erythema



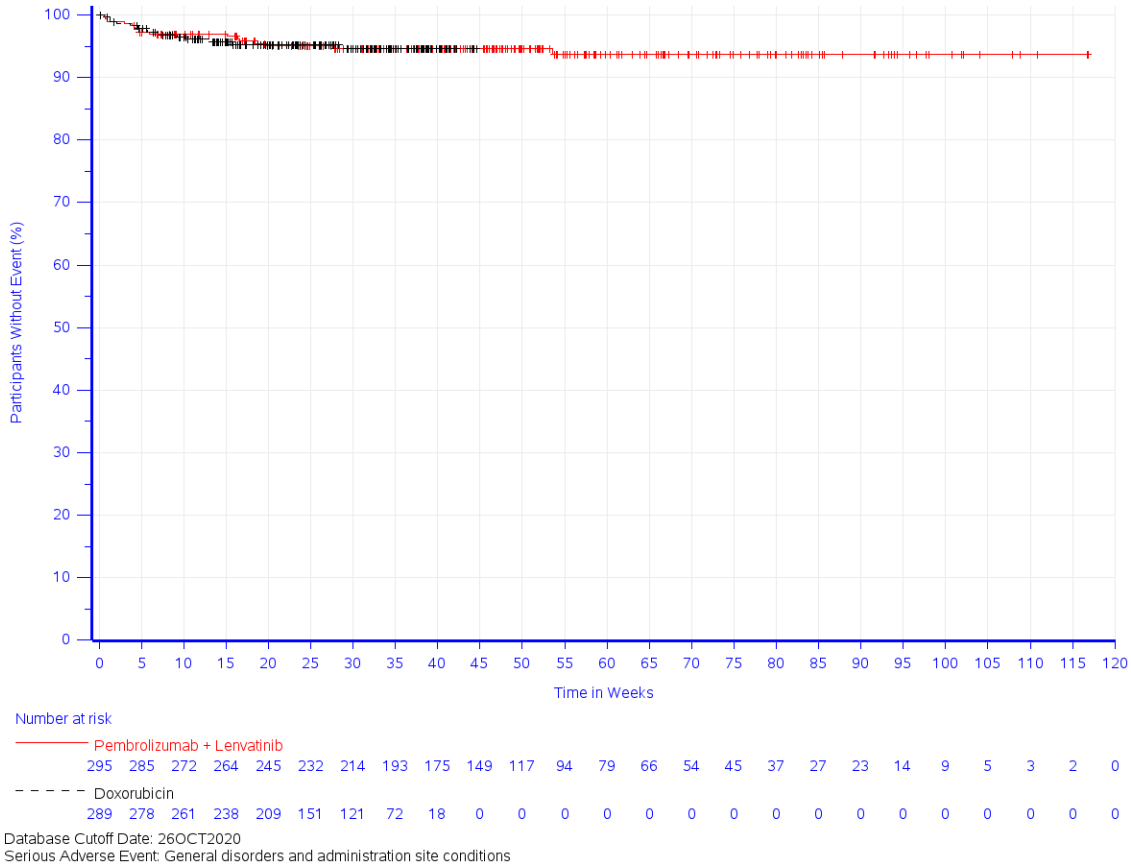
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Rash maculo-papular



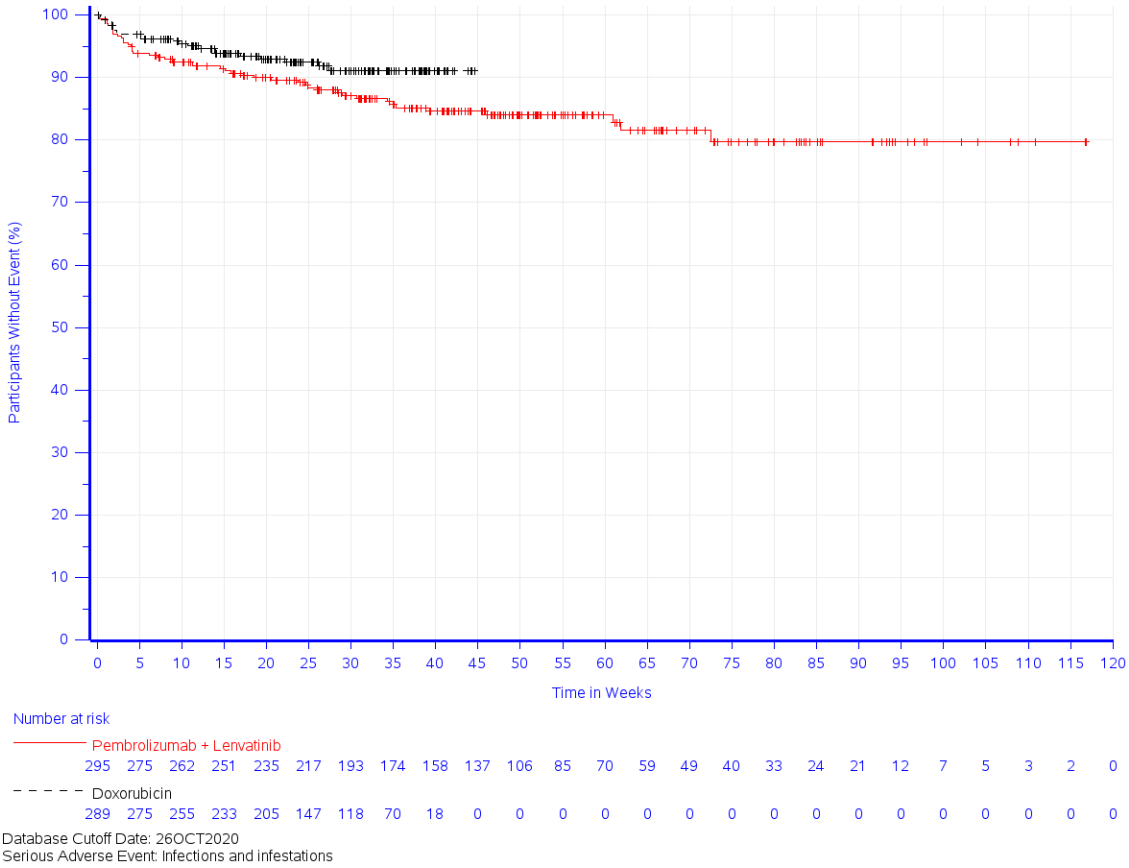
Time to Adverse Event - Kaplan-Meier Curve (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Hypotension



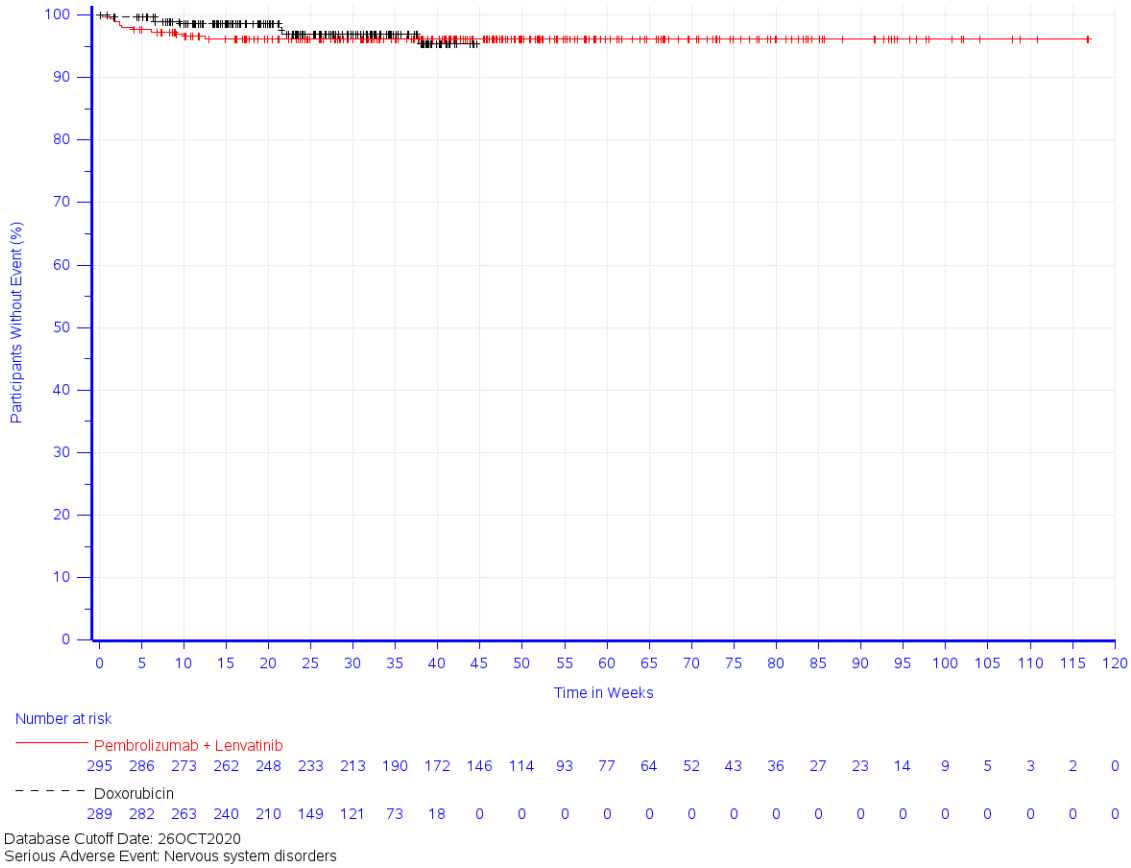
Time to Serious Adverse Event - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Cardiac disorders



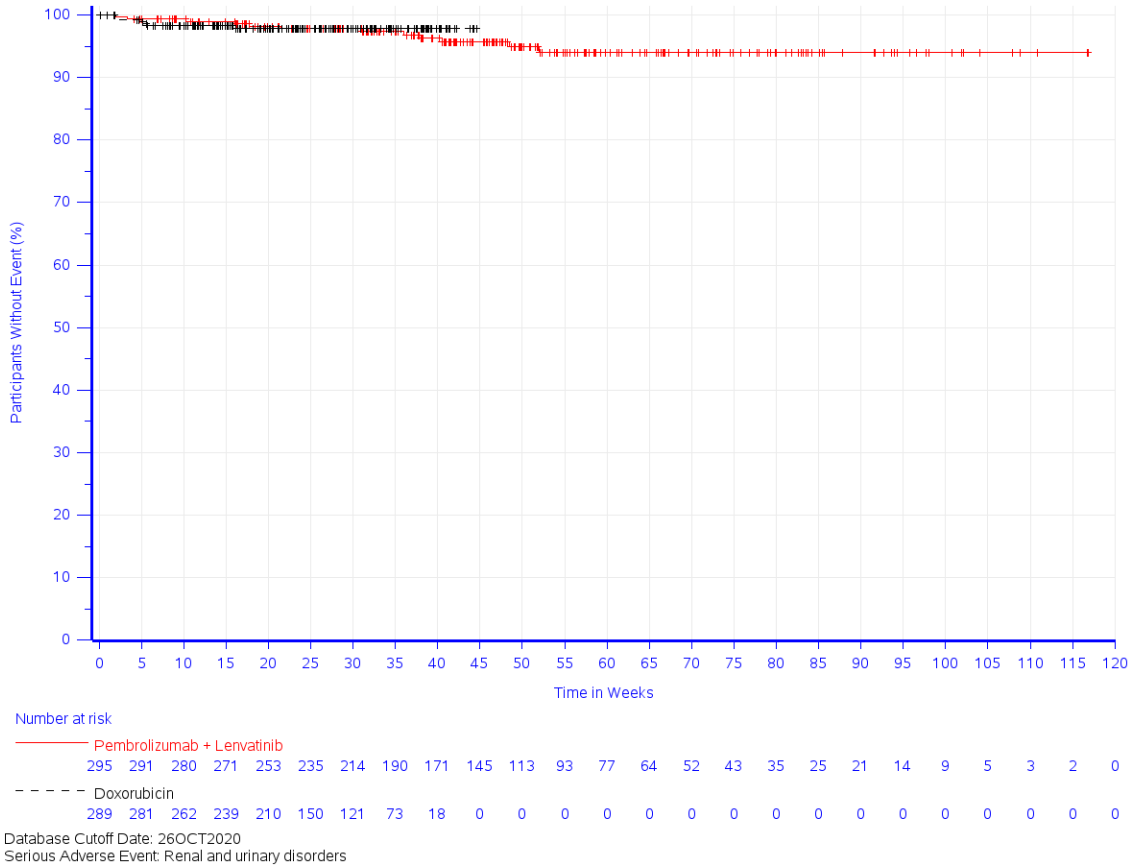
Time to Serious Adverse Event - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: General disorders and administration site conditions



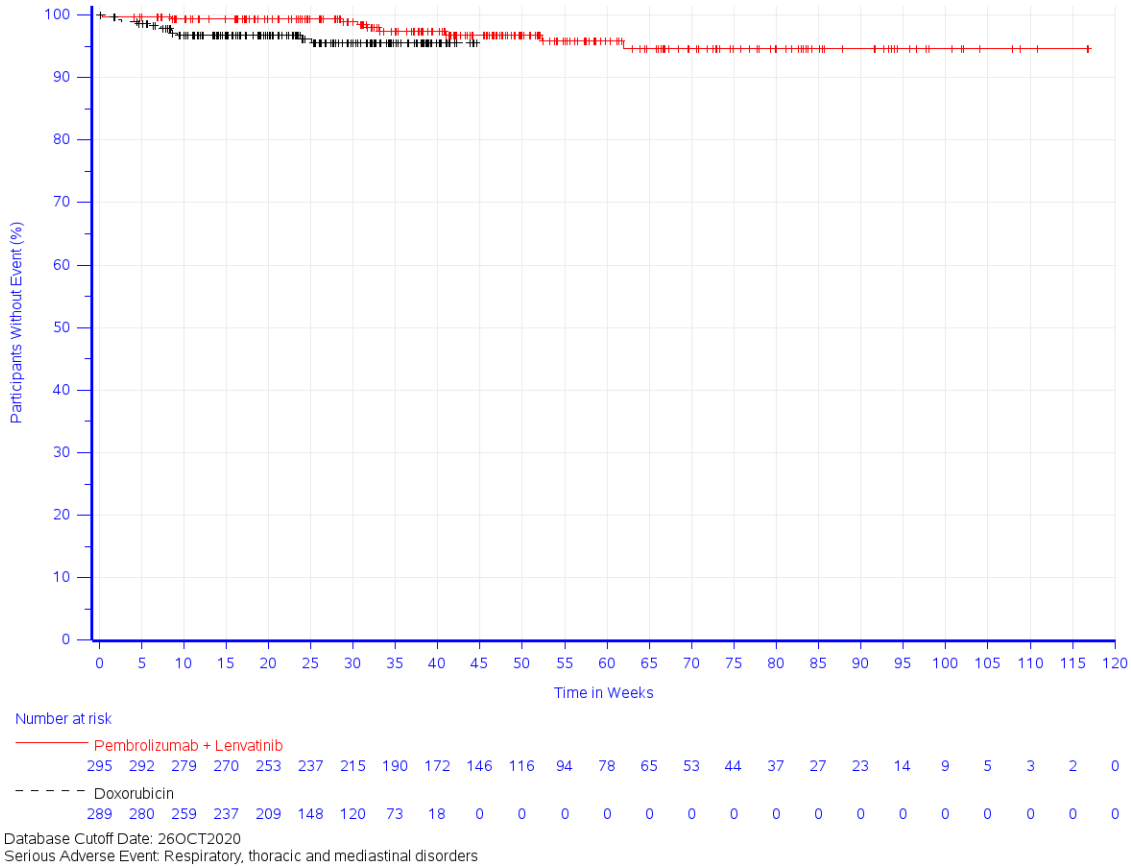
Time to Serious Adverse Event - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Infections and infestations



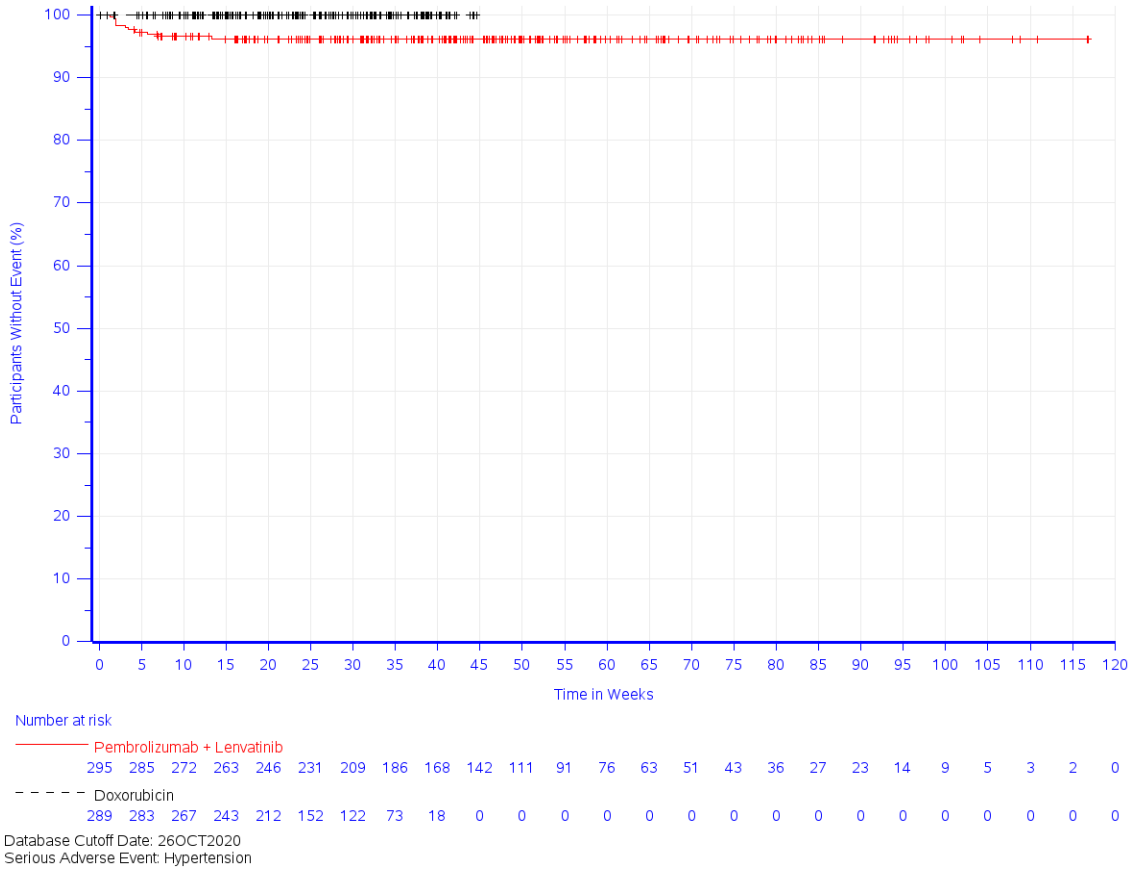
Time to Serious Adverse Event - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Nervous system disorders



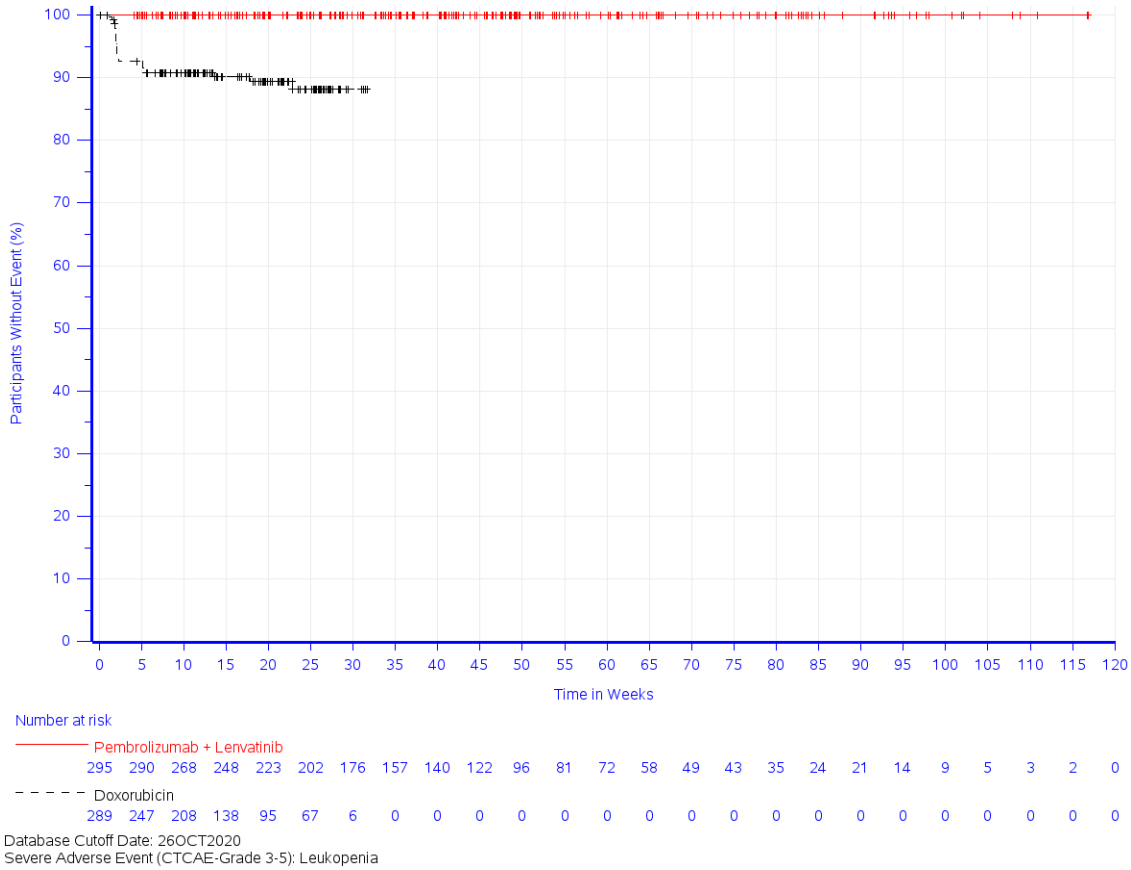
Time to Serious Adverse Event - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Renal and urinary disorders



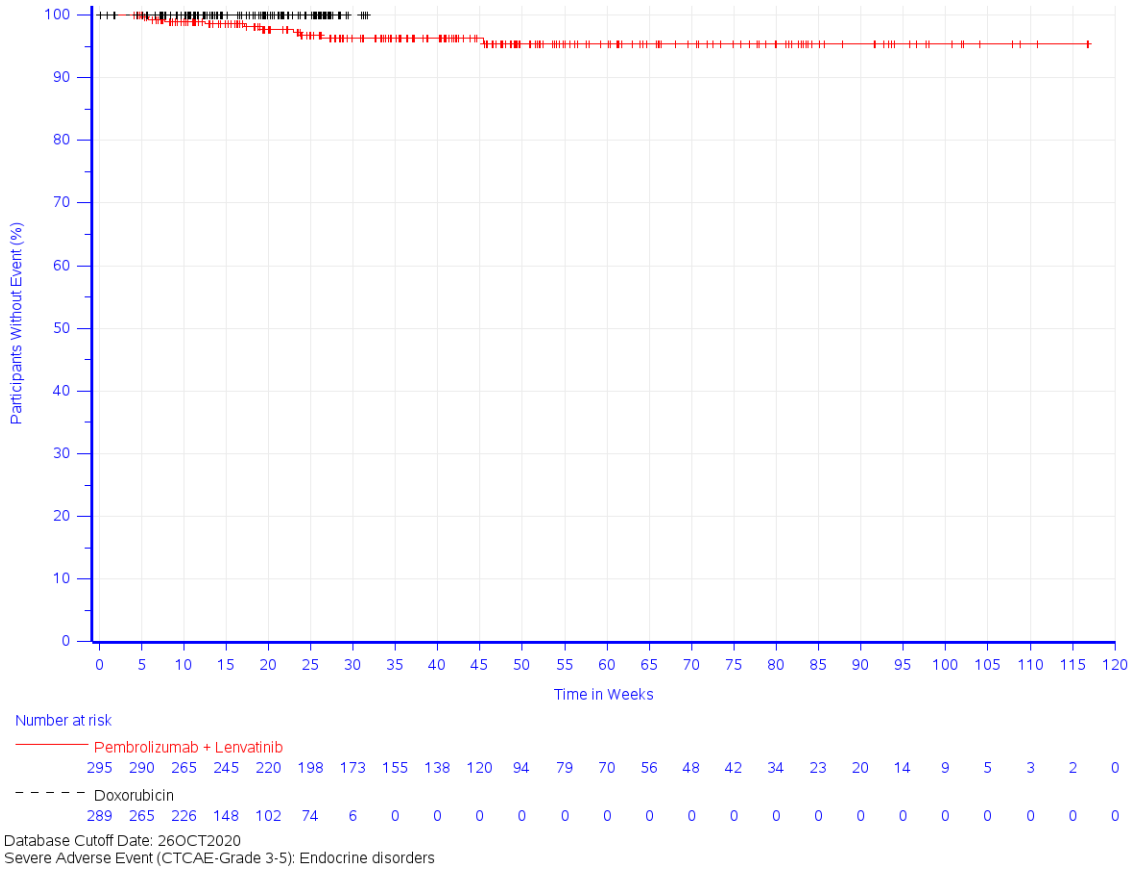
Time to Serious Adverse Event - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Respiratory, thoracic and mediastinal disorders



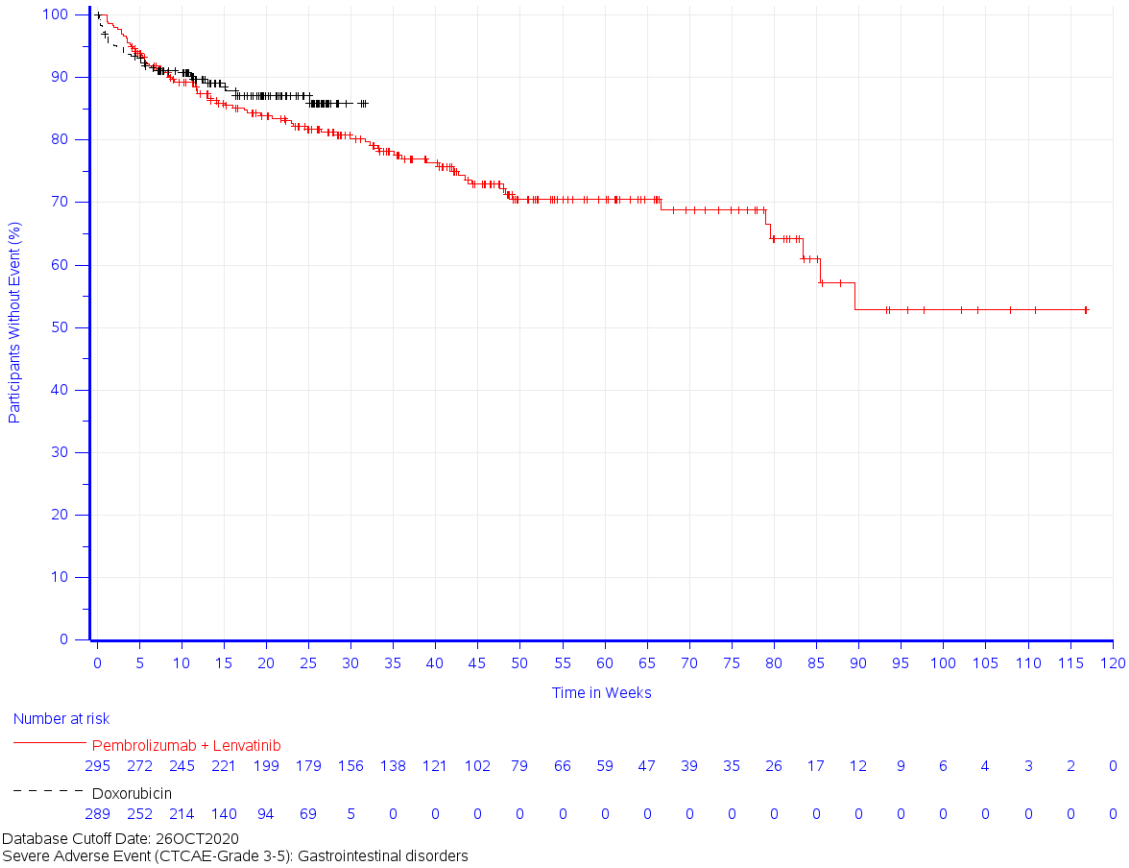
Time to Serious Adverse Event - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Hypertension



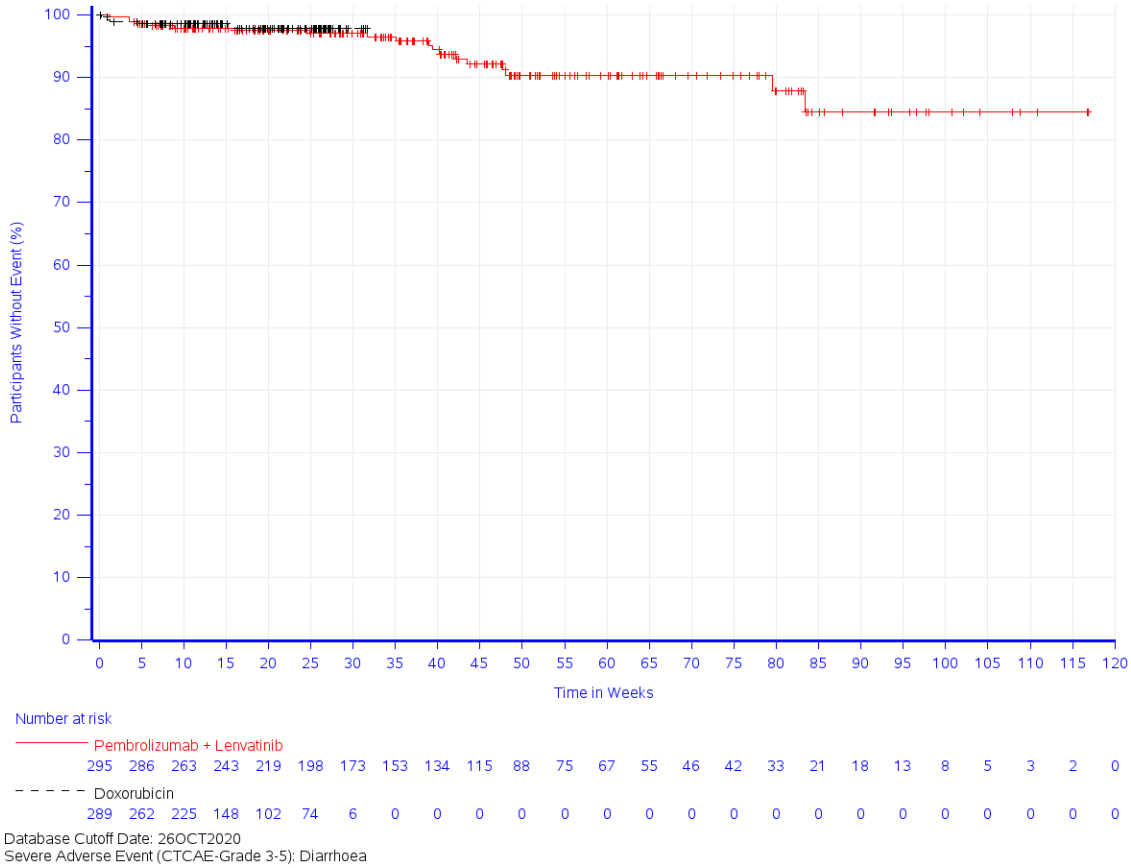
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Gastrointestinal disorders



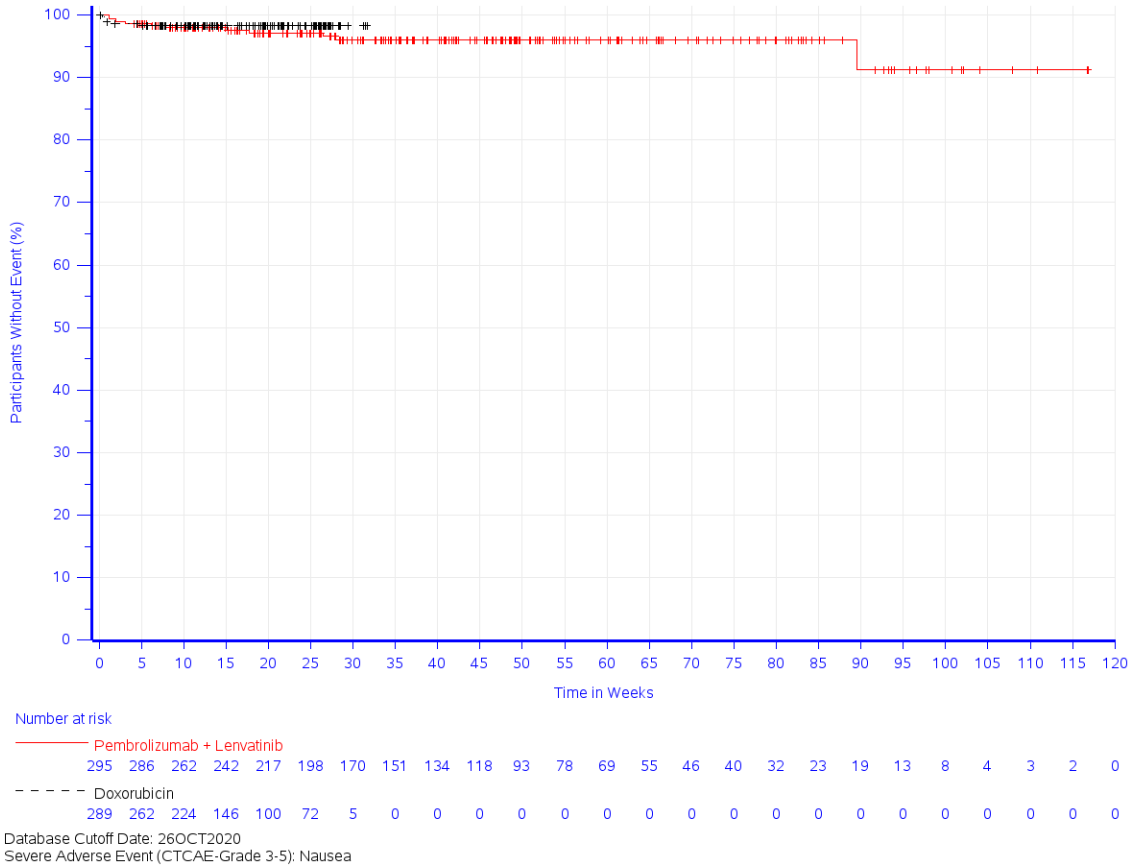
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Endocrine disorders



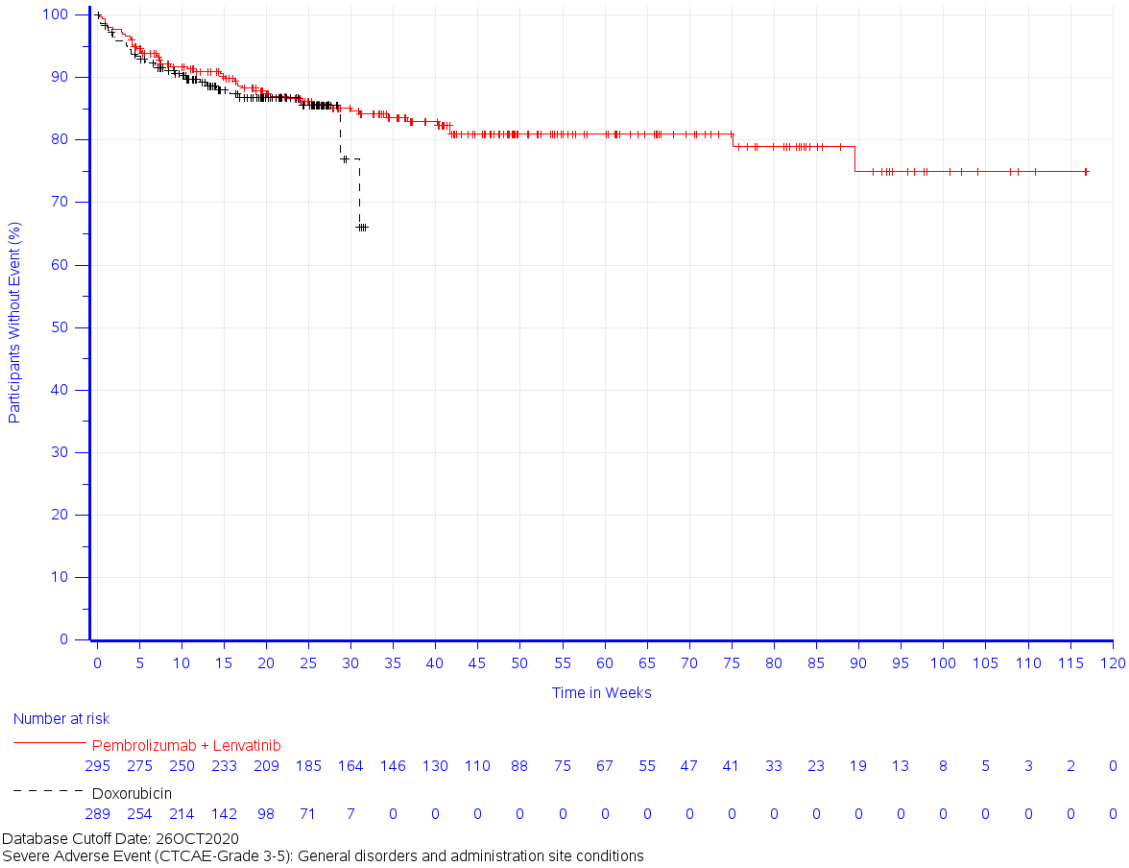
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Gastrointestinal disorders



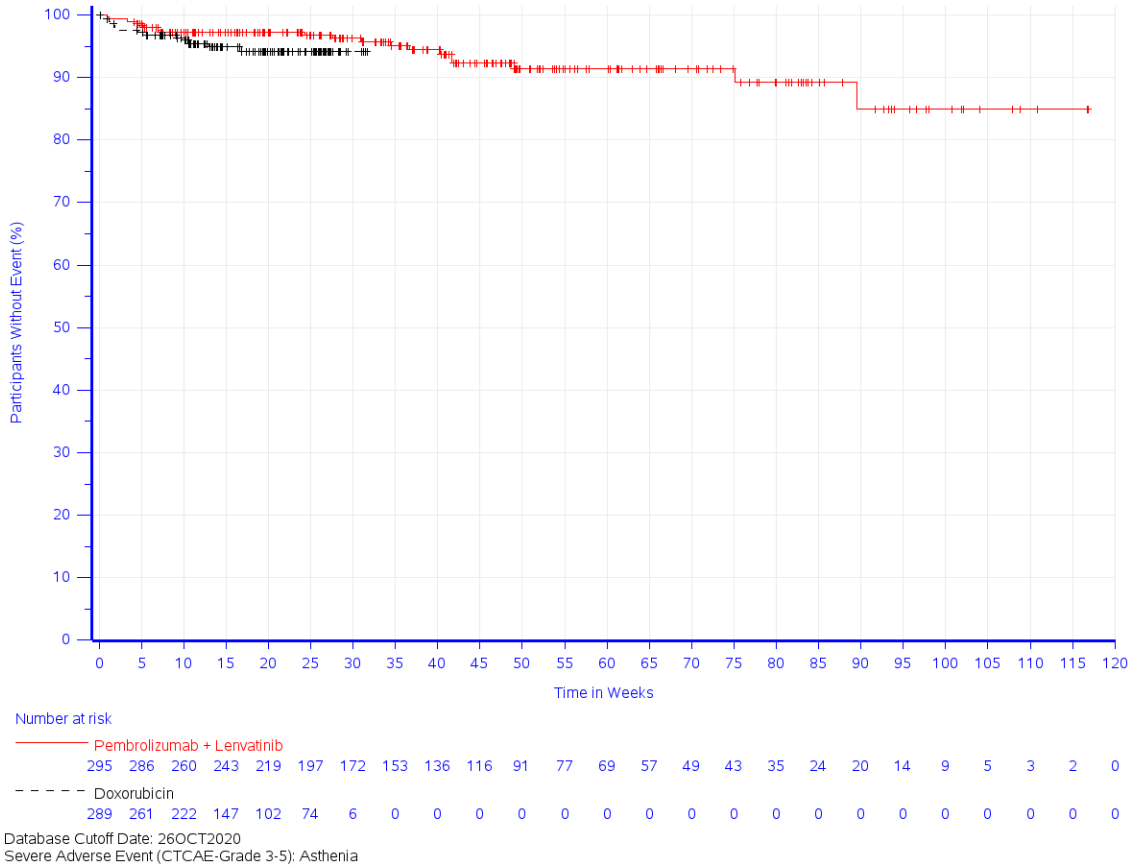
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Diarrhoea



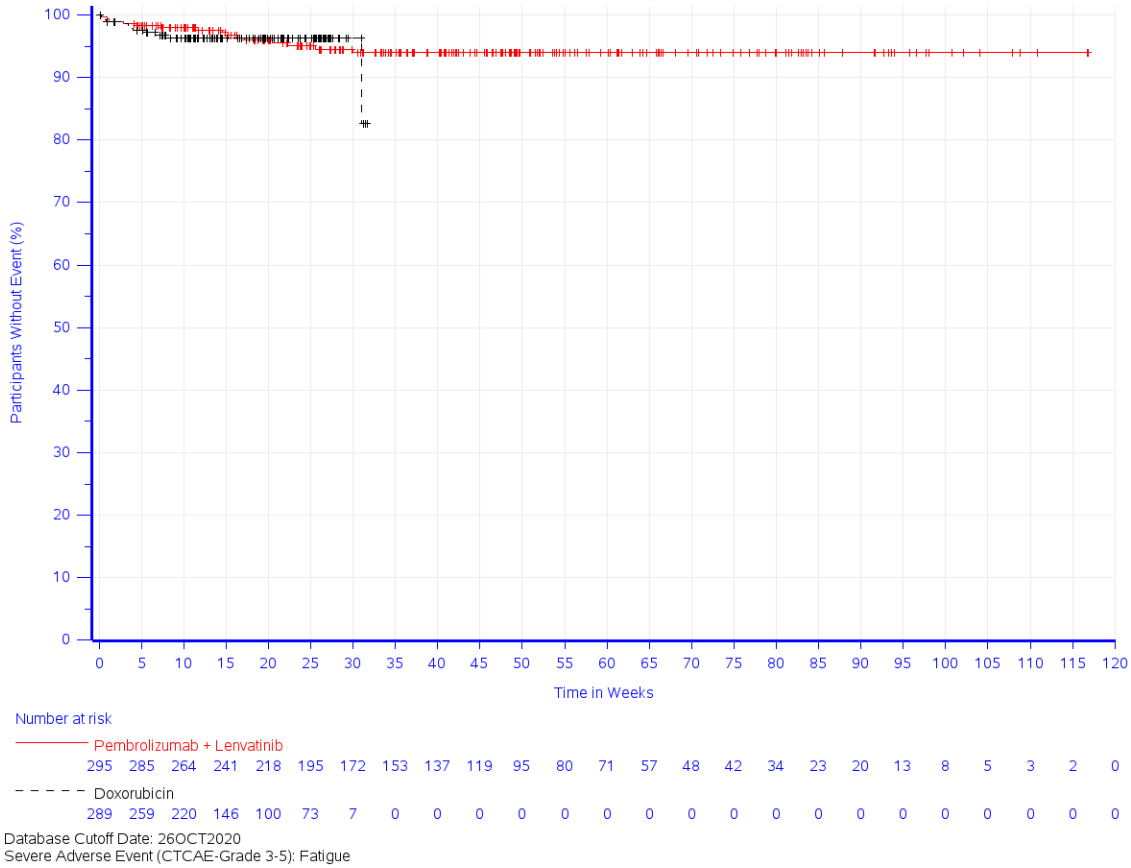
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Nausea



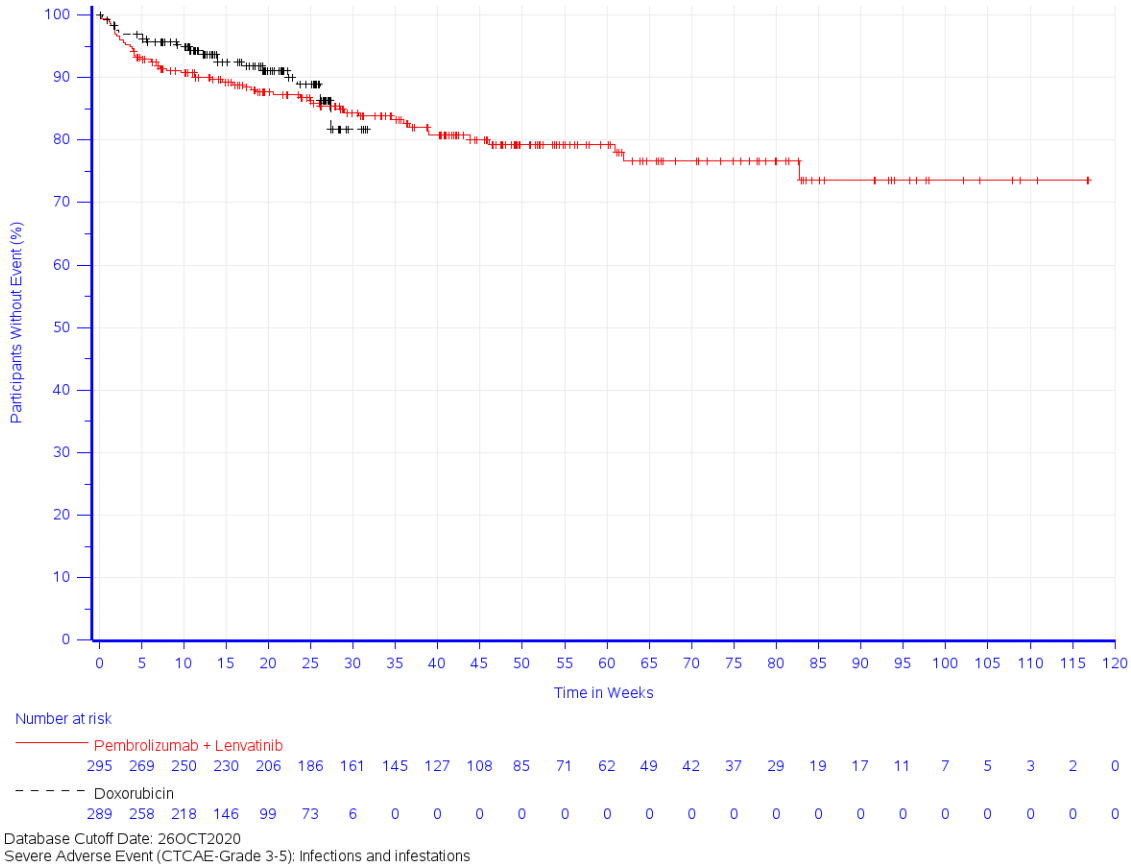
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: General disorders and administration site conditions



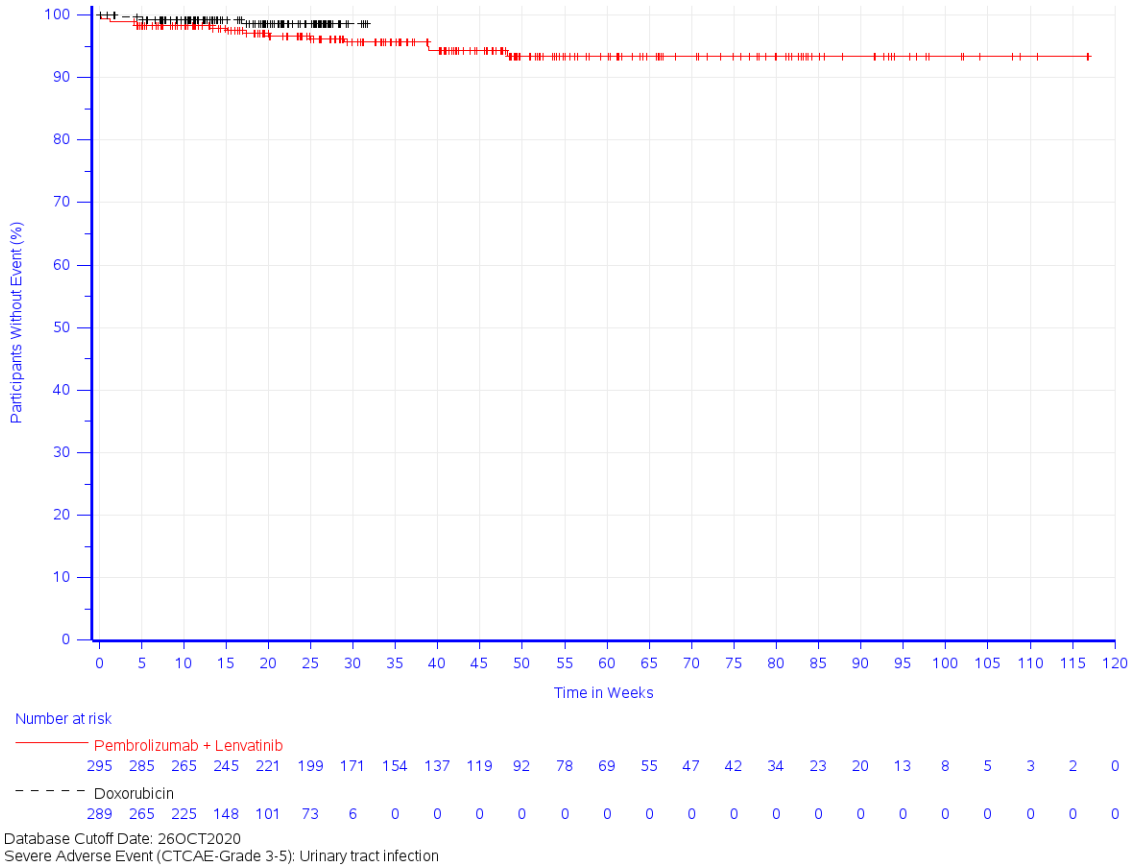
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Asthenia



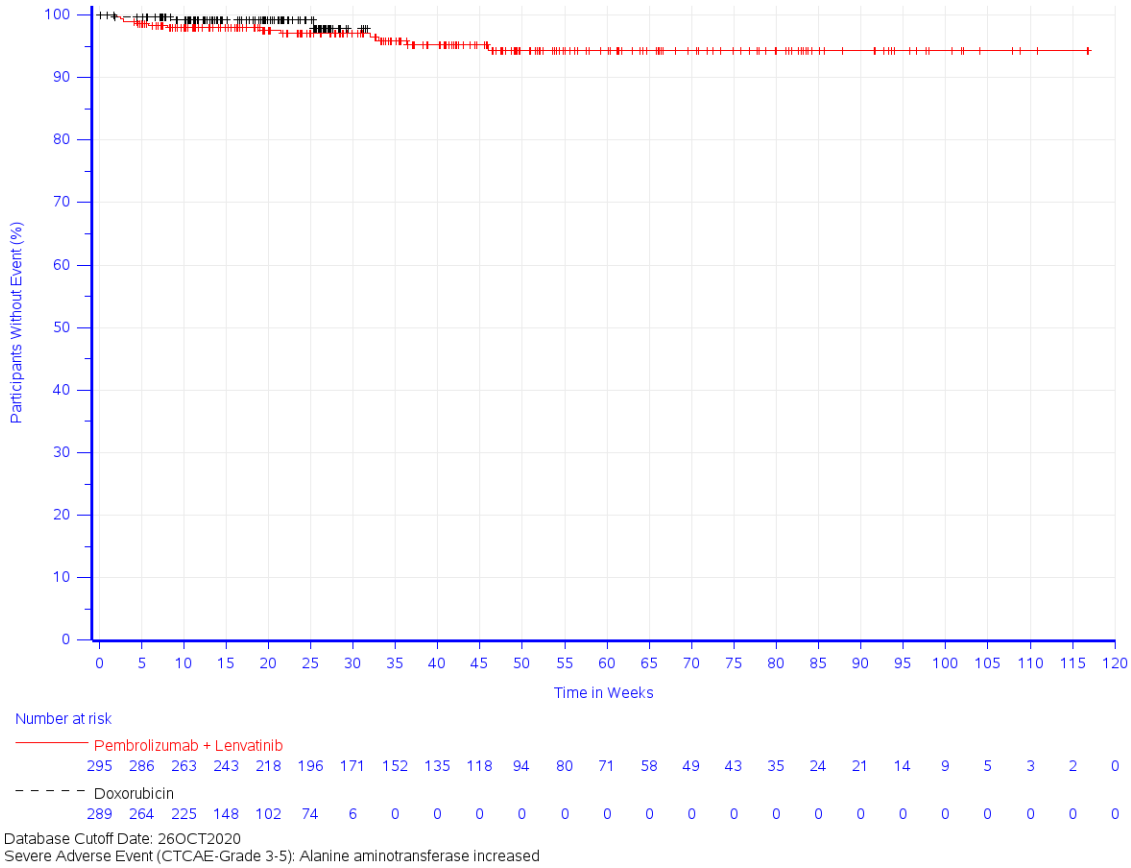
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Fatigue



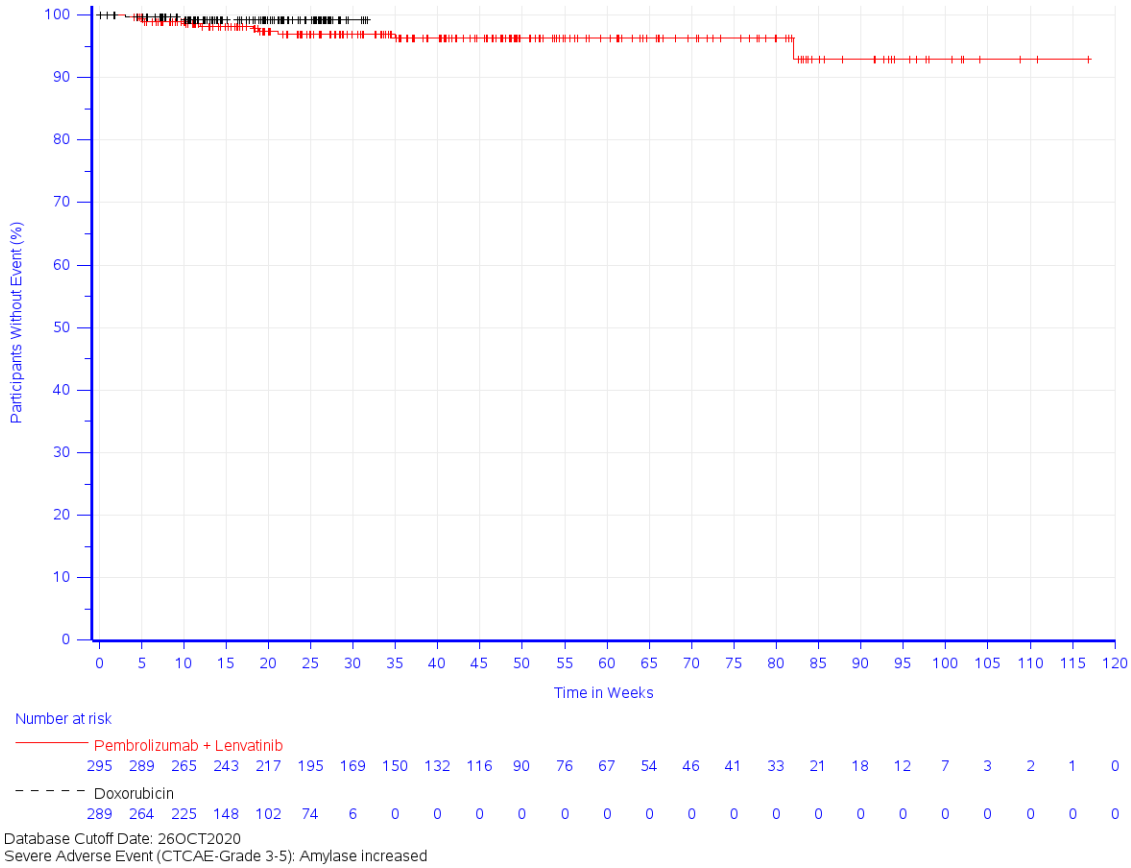
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Infections and infestations



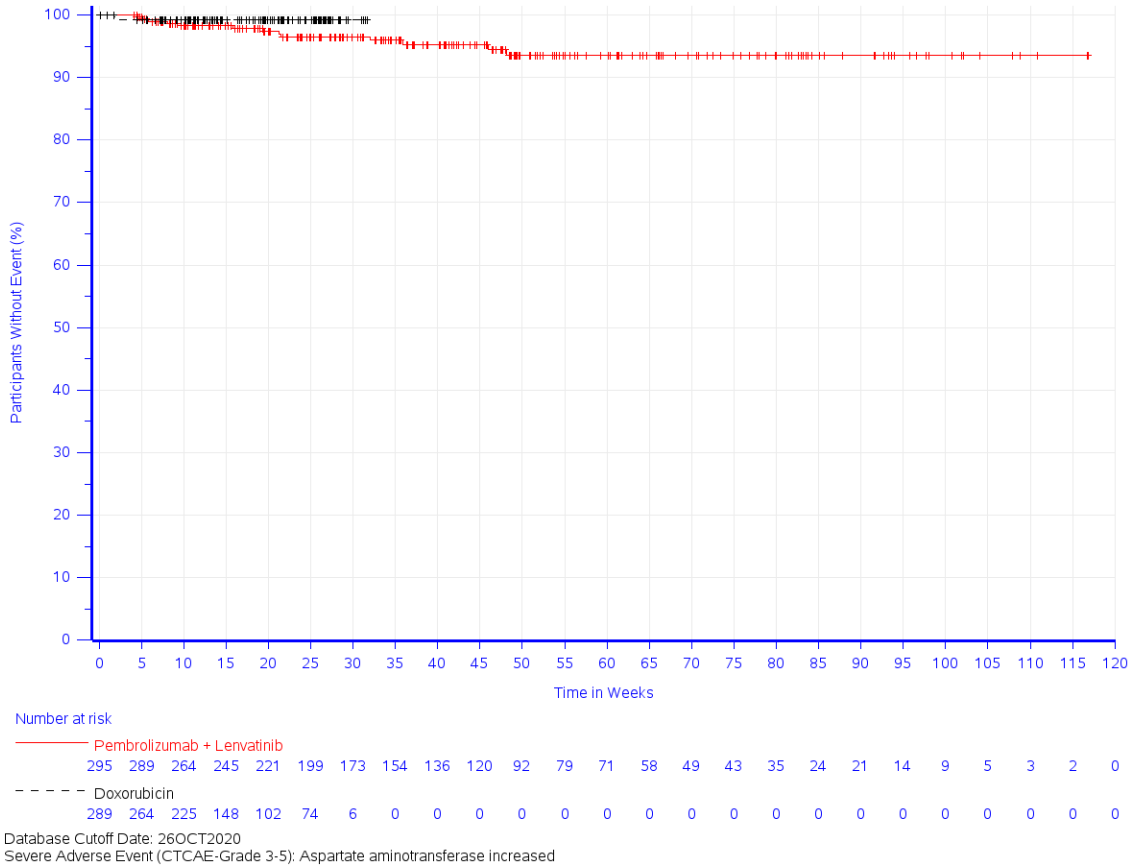
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Urinary tract infection



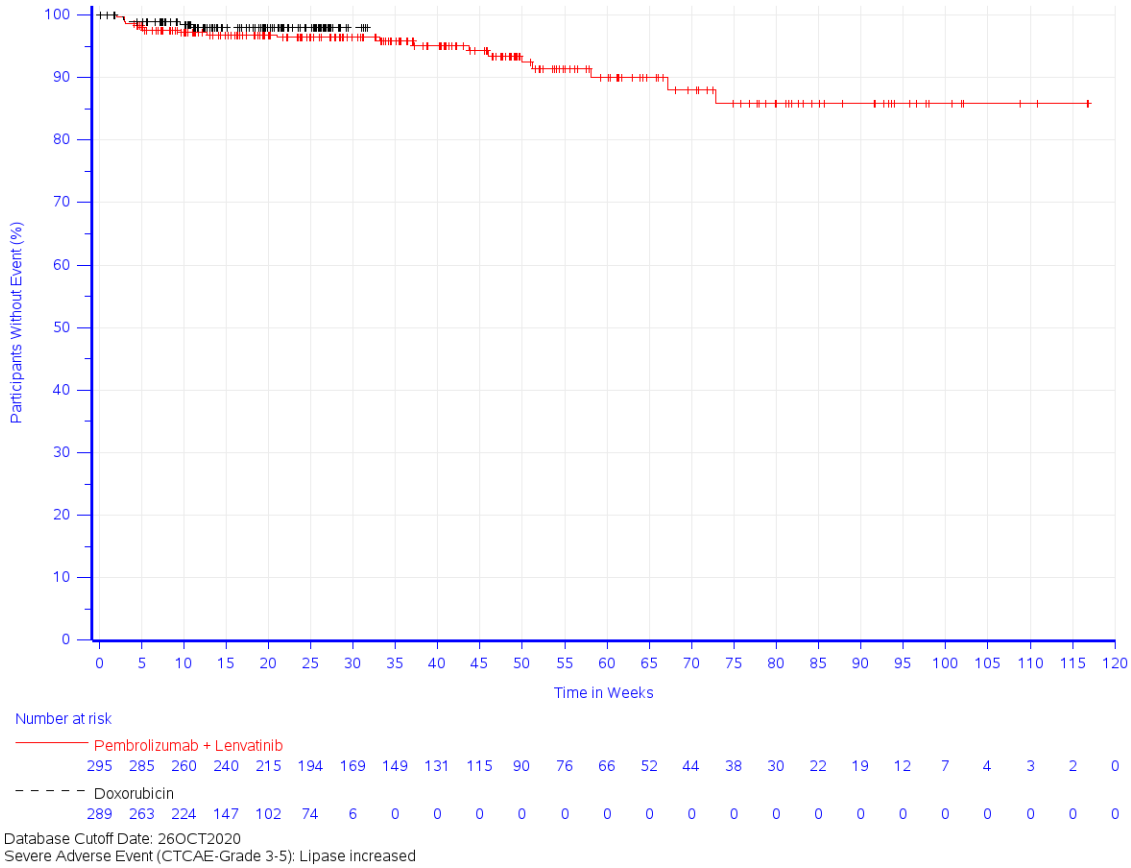
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Alanine aminotransferase increased



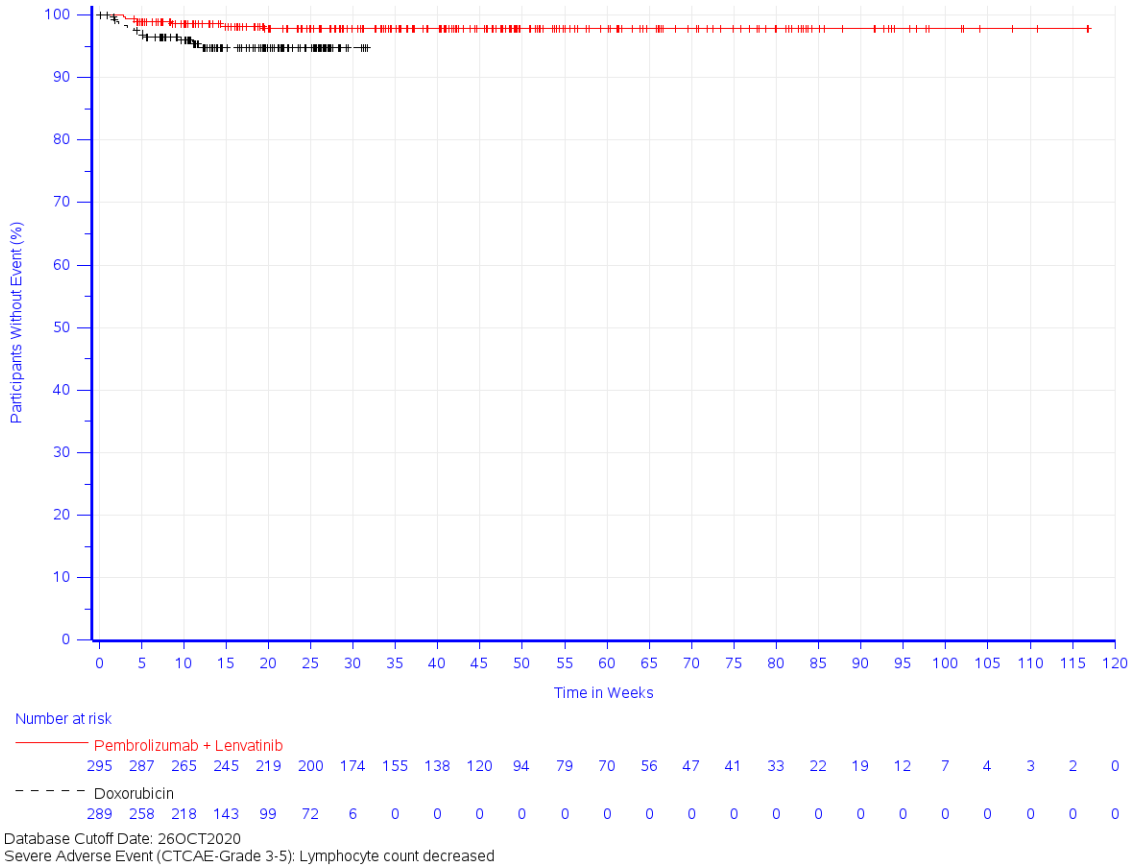
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Amylase increased



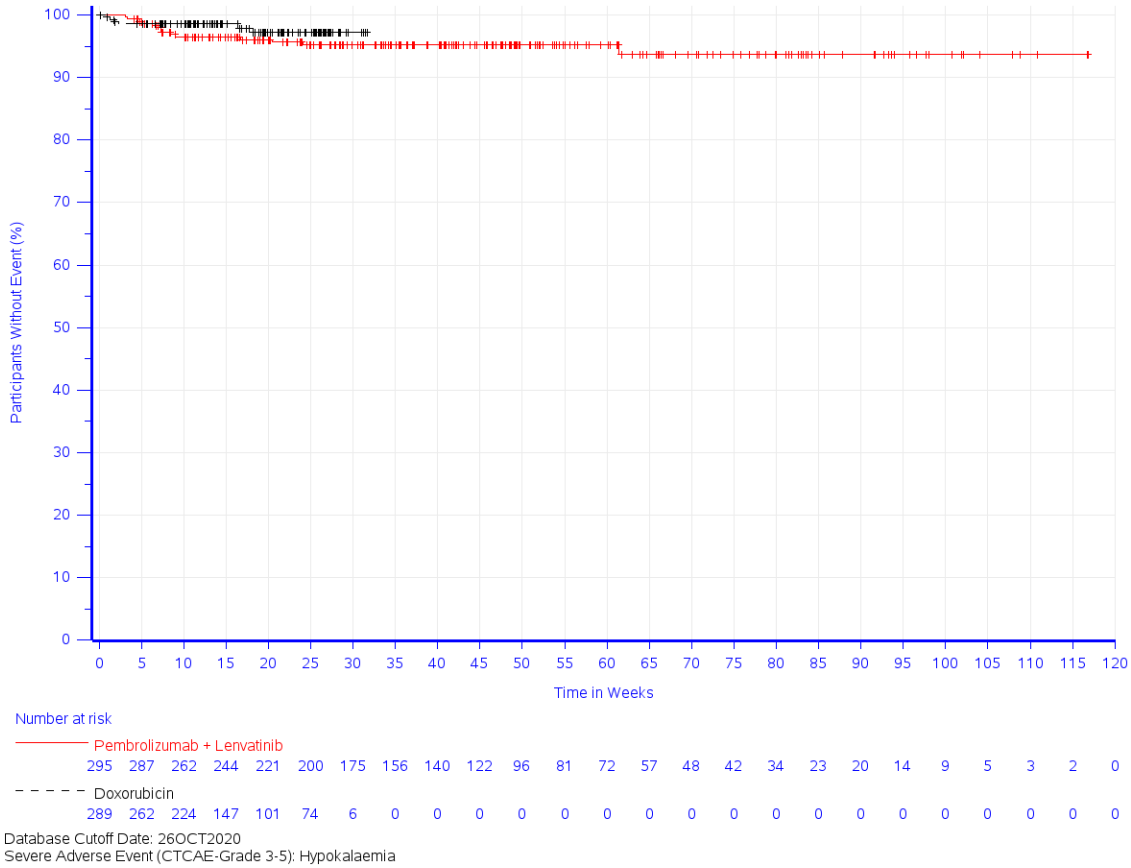
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Aspartate aminotransferase increased



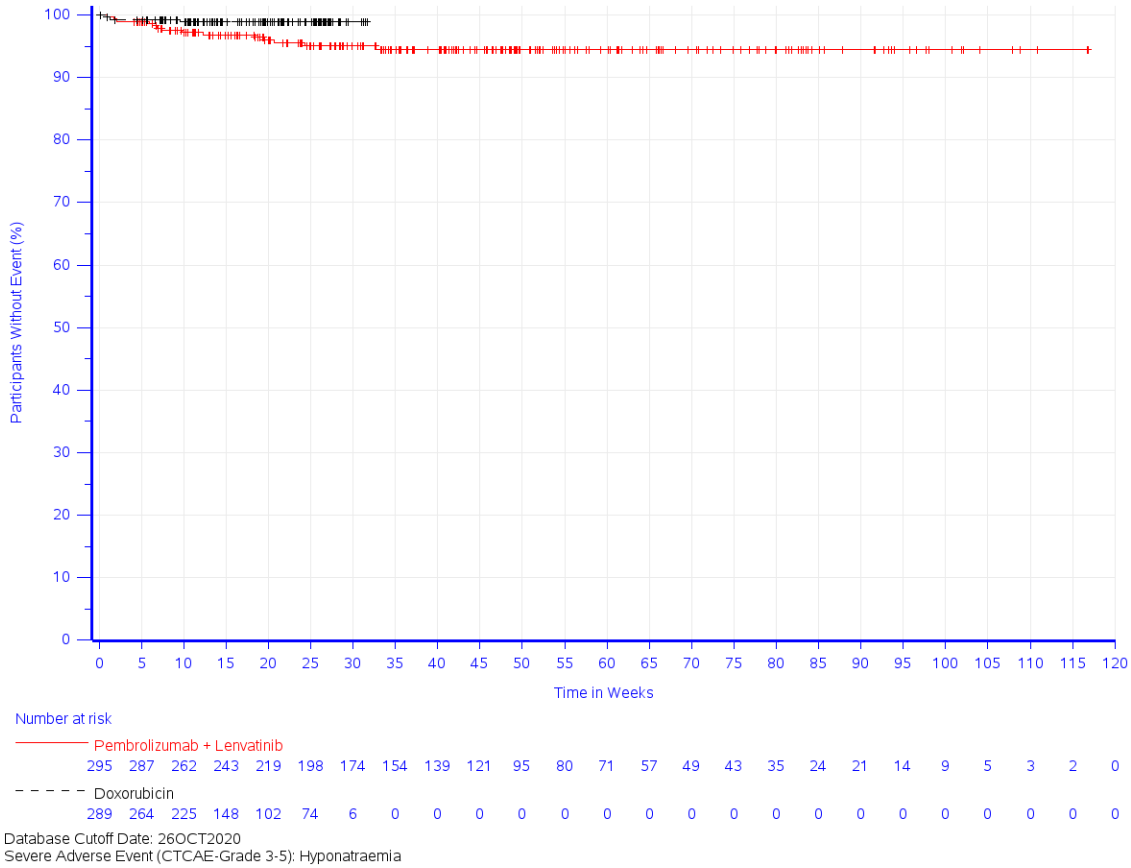
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Lipase increased



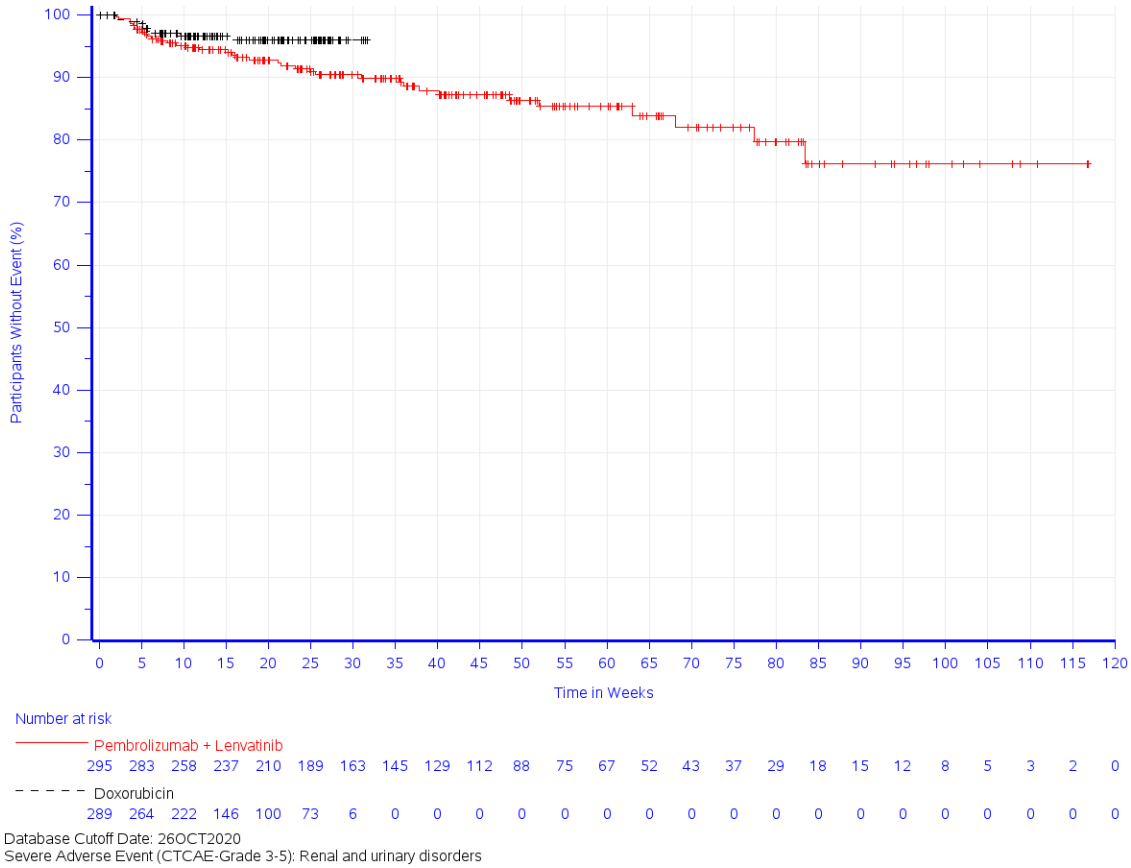
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Lymphocyte count decreased



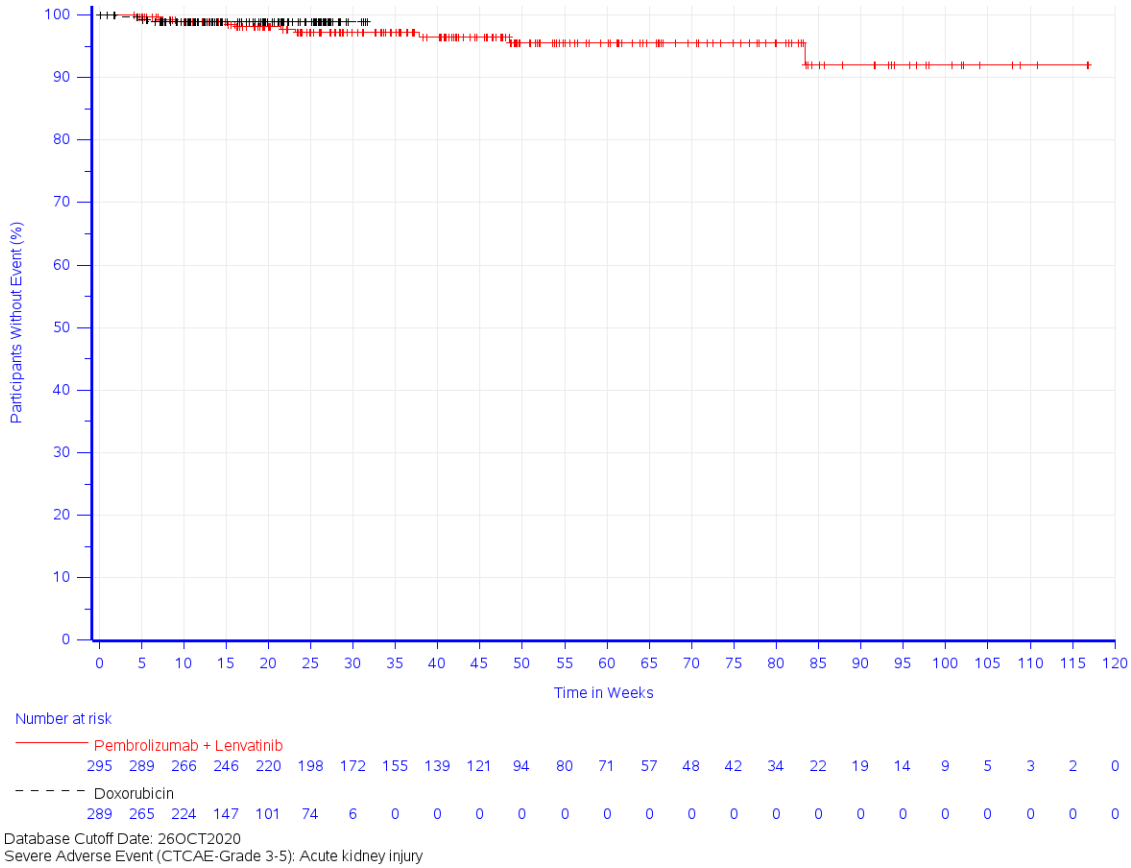
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Hypokalaemia



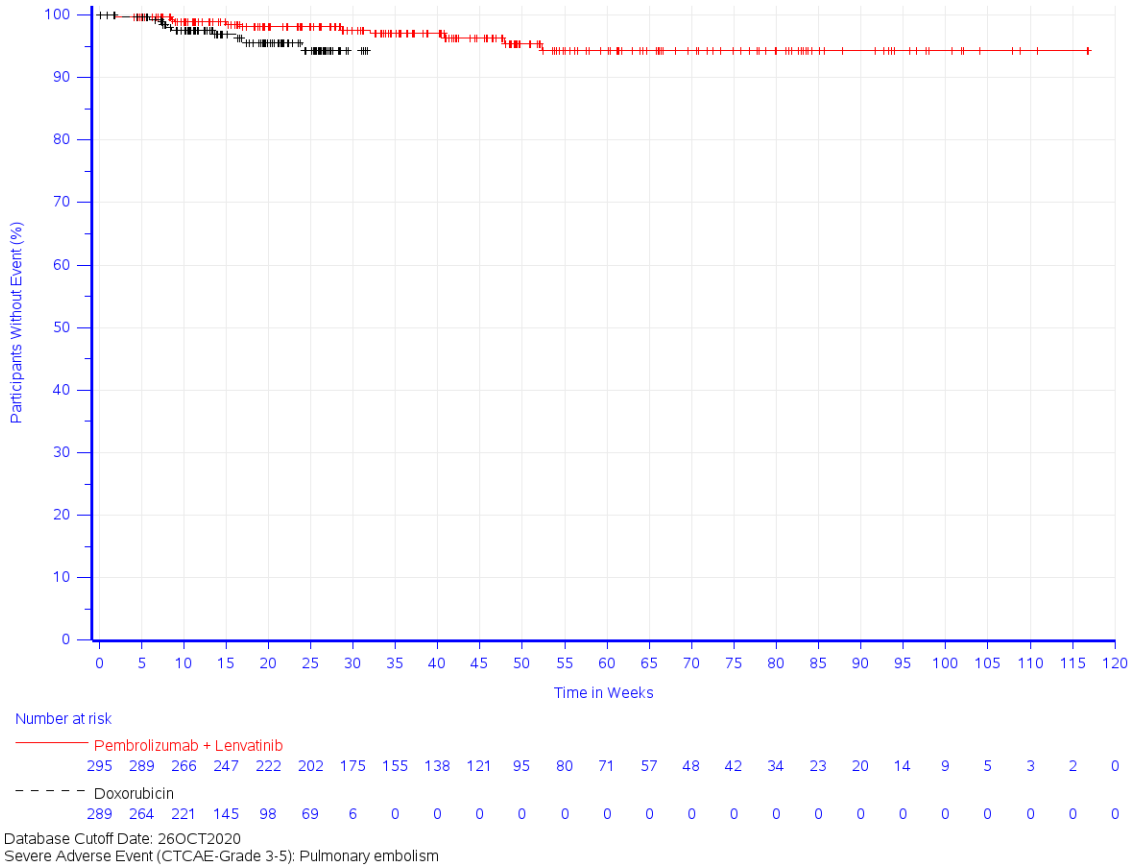
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Hyponatraemia



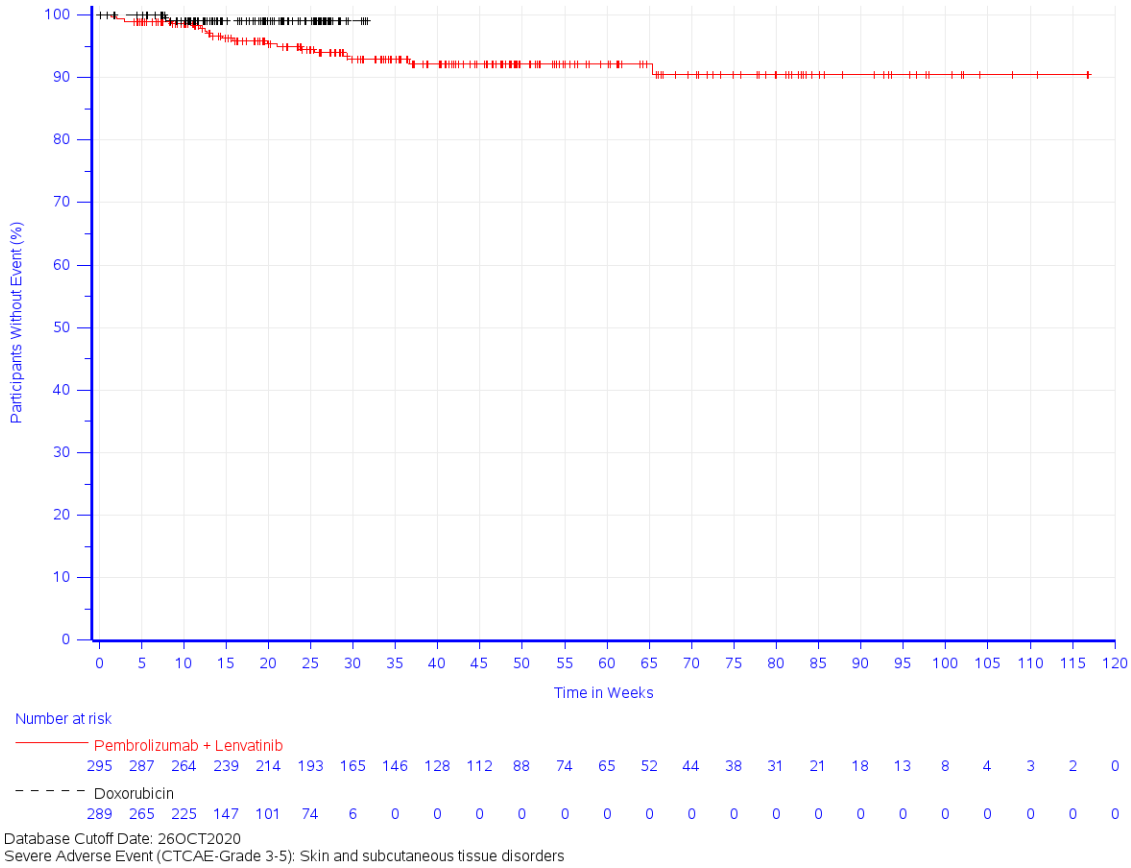
Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Renal and urinary disorders



Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Acute kidney injury



Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for Preferred Term: Pulmonary embolism



Time to Severe Adverse Event (CTCAE-Grade 3-5) - Kaplan-Meier Curve (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Treatment Groups) for System Organ Class: Skin and subcutaneous tissue disorders

Anhang 4-G7.2: Ergebnisse der Subgruppenanalysen mit p-Wert für Interaktionstests ≥ 0.05 für die Verträglichkeitsendpunkte

Analyses of Time to Adverse Event for Subgroups with P-value for Interaction Test ≥ 0.05 or Rule of 10 Not Met

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Age Group									
< 65	152	151 (99.3)	0.6 [0.4; 1.0]	143	142 (99.3)	0.4 [0.3; 0.7]	0.92 [0.73; 1.16]	0.487	0.881
≥ 65	143	143 (100.0)	0.6 [0.4; 0.7]	146	145 (99.3)	0.4 [0.3; 0.6]	0.90 [0.71; 1.13]	0.359	
Region									
Region 1	165	164 (99.4)	0.4 [0.3; 0.7]	168	166 (98.8)	0.4 [0.3; 0.6]	0.99 [0.80; 1.23]	0.932	0.321
Region 2	130	130 (100.0)	0.7 [0.6; 1.0]	121	121 (100.0)	0.6 [0.4; 0.7]	0.85 [0.66; 1.09]	0.209	
MMR Status									
pMMR	242	241 (99.6)	0.6 [0.4; 0.7]	239	238 (99.6)	0.4 [0.4; 0.6]	0.91 [0.76; 1.08]	0.282	0.760
dMMR	53	53 (100.0)	0.7 [0.3; 1.1]	50	49 (98.0)	0.4 [0.3; 1.1]	0.98 [0.66; 1.44]	0.904	
Prior History of Pelvic Radiation									
Yes	127	126 (99.2)	0.6 [0.4; 0.9]	129	127 (98.4)	0.4 [0.3; 0.7]	0.95 [0.74; 1.21]	0.659	0.835
No	168	168 (100.0)	0.6 [0.4; 0.9]	160	160 (100.0)	0.4 [0.3; 0.6]	0.90 [0.72; 1.11]	0.320	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: all-participants-as-treated, population relevant for benefit assessment

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Analyses of Time to Serious Adverse Event for Subgroups with P-value for Interaction Test ≥ 0.05 or Rule of 10 Not Met

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		p-Value for Interaction Test[g]
Serious Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	
Age Group									
< 65	152	82 (53.9)	40.3 [21.1; 79.0]	143	51 (35.7)	Not reached [37.6; -]	1.37 [0.96; 1.96]	0.085	0.591
≥ 65	143	74 (51.7)	45.0 [26.4; -]	146	54 (37.0)	Not reached [-; -]	1.17 [0.81; 1.67]	0.401	
Region									
Region 1	165	87 (52.7)	40.9 [23.1; 61.0]	168	65 (38.7)	Not reached [-; -]	1.14 [0.82; 1.58]	0.438	0.368
Region 2	130	69 (53.1)	44.6 [25.4; 85.4]	121	40 (33.1)	Not reached [-; -]	1.45 [0.97; 2.16]	0.067	
ECOG Performance Status									
0	175	88 (50.3)	46.1 [29.9; -]	164	52 (31.7)	Not reached [-; -]	1.42 [1.00; 2.01]	0.052	0.362
1	120	68 (56.7)	31.0 [19.4; 52.3]	125	53 (42.4)	Not reached [21.9; -]	1.12 [0.77; 1.62]	0.549	
MMR Status									
pMMR	242	120 (49.6)	48.4 [30.6; -]	239	84 (35.1)	Not reached [-; -]	1.23 [0.92; 1.63]	0.161	0.834
dMMR	53	36 (67.9)	16.6 [5.9; 46.1]	50	21 (42.0)	Not reached [9.3; -]	1.40 [0.80; 2.43]	0.235	
Prior History of Pelvic Radiation									
Yes	127	71 (55.9)	34.6 [23.7; 53.9]	129	45 (34.9)	Not reached [-; -]	1.38 [0.94; 2.02]	0.098	0.475
No	168	85 (50.6)	52.0 [27.0; -]	160	60 (37.5)	Not reached [30.1; -]	1.18 [0.84; 1.66]	0.337	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: all-participants-as-treated, population relevant for benefit assessment

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Analyses of Time to Severe Adverse Event (CTCAE-Grade 3-5) for Subgroups with P-value for Interaction Test ≥ 0.05 or Rule of 10 Not Met

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Age Group									
< 65	152	135 (88.8)	5.9 [3.4; 9.3]	143	119 (83.2)	2.1 [2.1; 3.0]	0.67 [0.52; 0.87]	0.003	0.448
≥ 65	143	132 (92.3)	4.3 [3.3; 6.1]	146	122 (83.6)	2.3 [2.1; 2.3]	0.72 [0.56; 0.92]	0.010	
Region									
Region 1	165	147 (89.1)	5.4 [3.4; 7.3]	168	136 (81.0)	2.3 [2.1; 2.4]	0.72 [0.57; 0.92]	0.009	0.607
Region 2	130	120 (92.3)	4.7 [3.1; 8.1]	121	105 (86.8)	2.1 [2.1; 2.3]	0.66 [0.50; 0.87]	0.003	
ECOG Performance Status									
0	175	160 (91.4)	5.7 [3.7; 8.6]	164	141 (86.0)	2.1 [2.1; 2.3]	0.59 [0.47; 0.76]	< 0.001	0.130
1	120	107 (89.2)	4.6 [3.1; 7.3]	125	100 (80.0)	2.3 [2.1; 3.3]	0.83 [0.63; 1.10]	0.196	
MMR Status									
pMMR	242	217 (89.7)	5.7 [3.9; 8.1]	239	201 (84.1)	2.3 [2.1; 2.3]	0.67 [0.54; 0.81]	< 0.001	0.698
dMMR	53	50 (94.3)	3.7 [2.4; 5.9]	50	40 (80.0)	2.1 [2.1; 3.3]	0.82 [0.53; 1.26]	0.369	
Prior History of Pelvic Radiation									
Yes	127	116 (91.3)	6.1 [4.0; 9.0]	129	102 (79.1)	2.3 [2.1; 3.1]	0.74 [0.56; 0.98]	0.037	0.268
No	168	151 (89.9)	4.1 [3.0; 6.6]	160	139 (86.9)	2.1 [2.1; 2.3]	0.65 [0.51; 0.83]	< 0.001	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: all-participants-as-treated, population relevant for benefit assessment

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Analyses of Time to Adverse Event Leading to Treatment Discontinuation for Subgroups with P-value for Interaction Test ≥ 0.05 or Rule of 10 Not Met

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
Adverse Events Leading to Treatment Discontinuation	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Age Group									
< 65	152	46 (30.3)	Not reached [64.4; -]	143	8 (5.6)	Not reached [-; -]	2.71 [1.23; 5.97]	0.013	0.315
≥ 65	143	50 (35.0)	93.0 [52.3; -]	146	17 (11.6)	Not reached [-; -]	2.04 [1.15; 3.62]	0.015	
Region									
Region 1	165	56 (33.9)	93.0 [55.3; -]	168	14 (8.3)	Not reached [-; -]	2.43 [1.31; 4.48]	0.005	0.554
Region 2	130	40 (30.8)	Not reached [64.4; -]	121	11 (9.1)	Not reached [-; -]	2.00 [0.99; 4.05]	0.054	
ECOG Performance Status									
0	175	52 (29.7)	Not reached [64.4; -]	164	14 (8.5)	Not reached [-; -]	2.06 [1.11; 3.82]	0.023	0.574
1	120	44 (36.7)	79.0 [45.1; -]	125	11 (8.8)	Not reached [-; -]	2.47 [1.23; 4.94]	0.011	
MMR Status									
pMMR	242	75 (31.0)	Not reached [62.0; -]	239	21 (8.8)	Not reached [-; -]	2.04 [1.22; 3.40]	0.006	0.795
dMMR	53	21 (39.6)	93.0 [48.3; -]	50	4 (8.0)	Not reached [-; -]	3.23 [1.07; 9.77]	0.038	
Prior History of Pelvic Radiation									
Yes	127	41 (32.3)	93.0 [55.3; -]	129	12 (9.3)	Not reached [-; -]	1.66 [0.83; 3.33]	0.151	0.670
No	168	55 (32.7)	Not reached [62.0; -]	160	13 (8.1)	Not reached [-; -]	2.75 [1.47; 5.14]	0.001	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: all-participants-as-treated, population relevant for benefit assessment

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world

Analyses of Time to Adverse Event by Subgroups with p-Value for Interaction Test ≥ 0.05 or Rule of 10 Not Met (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Groups) For System Organ Classes

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC[h]: Blood and lymphatic system disorders									
Age Group									
< 65	152	66 (43.4)	54.9 [24.1; -]	143	101 (70.6)	3.4 [2.1; 5.1]	0.29 [0.21; 0.41]	< 0.001	0.414
≥ 65	143	53 (37.1)	Not reached [40.4; -]	146	105 (71.9)	2.4 [2.1; 5.0]	0.24 [0.17; 0.34]	< 0.001	
ECOG Performance Status									
0	175	72 (41.1)	Not reached [40.4; -]	164	114 (69.5)	2.3 [2.1; 5.1]	0.28 [0.20; 0.38]	< 0.001	0.820
1	120	47 (39.2)	Not reached [31.0; -]	125	92 (73.6)	3.4 [2.1; 5.1]	0.25 [0.17; 0.36]	< 0.001	
MMR Status									
pMMR	242	90 (37.2)	Not reached [50.1; -]	239	170 (71.1)	3.1 [2.3; 5.1]	0.25 [0.19; 0.33]	< 0.001	0.245
dMMR	53	29 (54.7)	31.0 [12.4; -]	50	36 (72.0)	2.3 [2.1; 5.4]	0.34 [0.20; 0.58]	< 0.001	
Prior History of Pelvic Radiation									
Yes	127	57 (44.9)	50.1 [31.0; -]	129	94 (72.9)	2.4 [2.1; 5.0]	0.25 [0.17; 0.36]	< 0.001	0.856
No	168	62 (36.9)	Not reached [40.9; -]	160	112 (70.0)	3.1 [2.1; 5.1]	0.28 [0.20; 0.39]	< 0.001	
SOC[h]: Cardiac disorders									
Age Group									
< 65	152	14 (9.2)	Not reached [-; -]	143	18 (12.6)	Not reached [-; -]	0.37 [0.17; 0.81]	0.013	0.669
≥ 65	143	14 (9.8)	Not reached [-; -]	146	17 (11.6)	30.1 [28.0; -]	0.39 [0.18; 0.86]	0.020	
Region									
Region 1	165	13 (7.9)	Not reached [-; -]	168	21 (12.5)	28.0 [27.7; -]	0.28 [0.13; 0.63]	0.002	0.346
Region 2	130	15 (11.5)	Not reached [-; -]	121	14 (11.6)	Not reached [30.1; -]	0.51 [0.23; 1.13]	0.099	
ECOG Performance Status									
0	175	19 (10.9)	Not reached [-; -]	164	23 (14.0)	Not reached [30.1; -]	0.35 [0.18; 0.70]	0.003	0.993
1	120	9 (7.5)	Not reached [-; -]	125	12 (9.6)	28.0 [28.0; -]	0.42 [0.16; 1.09]	0.075	
MMR Status									
pMMR	242	22 (9.1)	Not reached [-; -]	239	28 (11.7)	Not reached [28.0; -]	0.38 [0.20; 0.70]	0.002	0.654
dMMR	53	6 (11.3)	Not reached [-; -]	50	7 (14.0)	Not reached [-; -]	0.39 [0.11; 1.37]	0.142	
SOC[h]: Ear and labyrinth disorders									
Age Group									
< 65	152	7	Not reached	143	1	Not reached	3.87	0.223	0.974

		(4.6)	[-; -]		(0.7)	[-; -]	[0.44; 34.12]		
≥ 65	143	12 (8.4)	Not reached [-; -]	146	2 (1.4)	Not reached [-; -]	4.29 [0.93; 19.75]	0.061	
Region									
Region 1	165	11 (6.7)	Not reached [-; -]	168	3 (1.8)	Not reached [-; -]	2.20 [0.57; 8.41]	0.251	0.102
Region 2	130	8 (6.2)	Not reached [-; -]	121	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.020	
ECOG Performance Status									
0	175	12 (6.9)	Not reached [-; -]	164	2 (1.2)	Not reached [-; -]	4.03 [0.87; 18.58]	0.074	0.840
1	120	7 (5.8)	Not reached [-; -]	125	1 (0.8)	Not reached [-; -]	3.94 [0.45; 34.82]	0.217	
MMR Status									
pMMR	242	16 (6.6)	Not reached [-; -]	239	3 (1.3)	Not reached [-; -]	3.78 [1.07; 13.32]	0.039	0.378
dMMR	53	3 (5.7)	Not reached [83.4; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.331	
Prior History of Pelvic Radiation									
Yes	127	7 (5.5)	Not reached [-; -]	129	1 (0.8)	Not reached [-; -]	2.83 [0.31; 25.65]	0.355	0.899
No	168	12 (7.1)	Not reached [-; -]	160	2 (1.3)	Not reached [-; -]	4.62 [1.01; 21.08]	0.048	
SOC[h]: Endocrine disorders									
Age Group									
< 65	152	94 (61.8)	15.1 [12.6; 21.0]	143	2 (1.4)	Not reached [-; -]	46.96 [11.56; 190.86]	< 0.001	0.837
≥ 65	143	95 (66.4)	12.1 [9.1; 17.1]	146	3 (2.1)	Not reached [-; -]	40.98 [12.98; 129.41]	< 0.001	
Region									
Region 1	165	91 (55.2)	19.0 [13.0; 24.4]	168	3 (1.8)	Not reached [-; -]	32.91 [10.41; 104.09]	< 0.001	0.500
Region 2	130	98 (75.4)	11.3 [8.9; 15.0]	121	2 (1.7)	Not reached [-; -]	60.24 [14.84; 244.62]	< 0.001	
ECOG Performance Status									
0	175	123 (70.3)	11.9 [9.0; 15.1]	164	2 (1.2)	Not reached [-; -]	73.51 [18.16; 297.52]	< 0.001	0.200
1	120	66 (55.0)	19.0 [14.6; 23.0]	125	3 (2.4)	Not reached [-; -]	22.99 [7.22; 73.25]	< 0.001	
MMR Status									
pMMR	242	151 (62.4)	14.7 [11.9; 17.1]	239	5 (2.1)	Not reached [-; -]	35.62 [14.60; 86.92]	< 0.001	0.160
dMMR	53	38 (71.7)	15.1 [9.1; 21.0]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Prior History of Pelvic Radiation									
Yes	127	84 (66.1)	15.1 [11.9; 19.4]	129	4 (3.1)	Not reached [-; -]	23.50 [8.60; 64.18]	< 0.001	0.110
No	168	105 (62.5)	14.6 [9.3; 17.1]	160	1 (0.6)	Not reached [-; -]	121.29 [16.92; 869.64]	< 0.001	
SOC[h]: Gastrointestinal disorders									

Age Group									
< 65	152	134 (88.2)	3.3 [2.7; 4.9]	143	108 (75.5)	1.1 [0.6; 2.3]	0.82 [0.64; 1.06]	0.138	0.916
≥ 65	143	126 (88.1)	2.9 [2.0; 3.4]	146	122 (83.6)	1.3 [0.6; 2.1]	0.79 [0.61; 1.02]	0.071	
Region									
Region 1	165	144 (87.3)	2.9 [2.1; 4.1]	168	139 (82.7)	0.7 [0.6; 1.3]	0.76 [0.60; 0.96]	0.020	0.399
Region 2	130	116 (89.2)	3.2 [2.3; 3.9]	121	91 (75.2)	2.0 [1.1; 3.0]	0.87 [0.66; 1.15]	0.339	
ECOG Performance Status									
0	175	158 (90.3)	3.1 [2.3; 4.0]	164	137 (83.5)	0.6 [0.4; 1.1]	0.68 [0.54; 0.86]	0.001	0.054
1	120	102 (85.0)	2.9 [2.0; 3.9]	125	93 (74.4)	2.1 [1.3; 3.1]	0.98 [0.74; 1.30]	0.905	
MMR Status									
pMMR	242	212 (87.6)	3.1 [2.7; 3.9]	239	196 (82.0)	1.1 [0.6; 1.6]	0.74 [0.61; 0.90]	0.002	0.057
dMMR	53	48 (90.6)	2.1 [1.3; 4.0]	50	34 (68.0)	2.3 [0.6; 4.3]	1.19 [0.76; 1.85]	0.455	
SOC[h]: Hepatobiliary disorders									
Age Group									
< 65	152	15 (9.9)	Not reached [-; -]	143	1 (0.7)	Not reached [-; -]	4.91 [0.61; 39.77]	0.136	0.827
≥ 65	143	20 (14.0)	Not reached [-; -]	146	2 (1.4)	Not reached [-; -]	7.00 [1.61; 30.44]	0.009	
Region									
Region 1	165	14 (8.5)	Not reached [-; -]	168	2 (1.2)	Not reached [-; -]	3.96 [0.86; 18.34]	0.078	0.399
Region 2	130	21 (16.2)	Not reached [-; -]	121	1 (0.8)	Not reached [-; -]	10.63 [1.40; 80.53]	0.022	
ECOG Performance Status									
0	175	24 (13.7)	Not reached [-; -]	164	3 (1.8)	Not reached [-; -]	4.49 [1.31; 15.32]	0.017	0.123
1	120	11 (9.2)	Not reached [-; -]	125	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.035	
MMR Status									
pMMR	242	29 (12.0)	Not reached [-; -]	239	3 (1.3)	Not reached [-; -]	5.18 [1.53; 17.49]	0.008	0.346
dMMR	53	6 (11.3)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.092	
Prior History of Pelvic Radiation									
Yes	127	17 (13.4)	Not reached [-; -]	129	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	0.050
No	168	18 (10.7)	Not reached [-; -]	160	3 (1.9)	Not reached [-; -]	2.78 [0.78; 9.92]	0.116	
SOC[h]: Metabolism and nutrition disorders									
Age Group									
< 65	152	108 (71.1)	12.1 [9.3; 21.0]	143	45 (31.5)	Not reached [-; -]	1.87 [1.31; 2.68]	< 0.001	0.160
≥ 65	143	107 (74.8)	6.1 [4.7; 9.3]	146	74 (50.7)	15.3 [9.1; -]	1.38 [1.02; 1.87]	0.036	
Region									
Region 1	165	111 (67.3)	11.9 [7.4; 20.7]	168	65 (38.7)	Not reached [17.0; -]	1.53 [1.11; 2.10]	0.009	0.867

Region 2	130	104 (80.0)	7.1 [5.1; 12.1]	121	54 (44.6)	23.6 [13.1; -]	1.58 [1.13; 2.21]	0.008	
ECOG Performance Status									
0	175	125 (71.4)	12.0 [7.9; 20.6]	164	60 (36.6)	Not reached [22.1; -]	1.63 [1.18; 2.24]	0.003	0.627
1	120	90 (75.0)	7.0 [4.7; 11.7]	125	59 (47.2)	16.1 [8.6; -]	1.52 [1.08; 2.12]	0.015	
MMR Status									
pMMR	242	173 (71.5)	11.9 [7.4; 15.1]	239	96 (40.2)	Not reached [16.1; -]	1.56 [1.21; 2.02]	< 0.001	0.617
dMMR	53	42 (79.2)	5.3 [2.3; 11.0]	50	23 (46.0)	22.1 [5.1; -]	1.52 [0.90; 2.56]	0.117	
Prior History of Pelvic Radiation									
Yes	127	102 (80.3)	9.0 [5.1; 15.0]	129	51 (39.5)	Not reached [15.1; -]	1.74 [1.23; 2.47]	0.002	0.199
No	168	113 (67.3)	11.9 [6.6; 18.0]	160	68 (42.5)	23.6 [15.3; -]	1.42 [1.04; 1.93]	0.025	
SOC[h]: Musculoskeletal and connective tissue disorders									
Age Group									
< 65	152	91 (59.9)	11.1 [5.4; 15.1]	143	40 (28.0)	Not reached [-; -]	2.45 [1.68; 3.56]	< 0.001	0.237
≥ 65	143	80 (55.9)	17.6 [8.9; 40.4]	146	46 (31.5)	Not reached [-; -]	1.71 [1.18; 2.47]	0.004	
Region									
Region 1	165	104 (63.0)	8.3 [5.0; 12.9]	168	54 (32.1)	Not reached [-; -]	2.26 [1.62; 3.15]	< 0.001	0.437
Region 2	130	67 (51.5)	23.6 [12.6; -]	121	32 (26.4)	Not reached [-; -]	1.82 [1.19; 2.79]	0.006	
ECOG Performance Status									
0	175	109 (62.3)	9.7 [5.1; 14.3]	164	52 (31.7)	Not reached [-; -]	2.22 [1.59; 3.10]	< 0.001	0.478
1	120	62 (51.7)	18.3 [11.0; -]	125	34 (27.2)	Not reached [-; -]	1.79 [1.17; 2.74]	0.007	
MMR Status									
pMMR	242	142 (58.7)	12.1 [9.0; 17.6]	239	72 (30.1)	Not reached [-; -]	2.07 [1.56; 2.76]	< 0.001	0.874
dMMR	53	29 (54.7)	21.1 [4.0; -]	50	14 (28.0)	Not reached [17.7; -]	1.95 [1.01; 3.74]	0.045	
Prior History of Pelvic Radiation									
Yes	127	74 (58.3)	16.0 [6.6; 40.4]	129	38 (29.5)	Not reached [-; -]	1.96 [1.31; 2.92]	< 0.001	0.992
No	168	97 (57.7)	11.6 [8.3; 15.9]	160	48 (30.0)	Not reached [-; -]	2.12 [1.49; 2.99]	< 0.001	
SOC[h]: Nervous system disorders									
Age Group									
< 65	152	76 (50.0)	42.0 [21.4; 61.0]	143	38 (26.6)	37.6 [-; -]	1.54 [1.03; 2.30]	0.036	0.825
≥ 65	143	79 (55.2)	17.9 [7.7; 40.6]	146	45 (30.8)	Not reached [26.1; -]	1.76 [1.21; 2.56]	0.003	
ECOG Performance Status									
0	175	90 (51.4)	33.0 [21.3; 61.0]	164	48 (29.3)	Not reached [-; -]	1.50 [1.04; 2.15]	0.028	0.466
1	120	65 (54.2)	14.7 [8.0; 48.1]	125	35 (28.0)	37.6 [24.1; -]	1.87 [1.23; 2.85]	0.004	
MMR Status									

pMMR	242	126 (52.1)	28.3 [11.1; 44.1]	239	74 (31.0)	37.6 [26.1; -]	1.56 [1.16; 2.09]	0.003	0.337
dMMR	53	29 (54.7)	46.3 [8.3; 89.1]	50	9 (18.0)	Not reached [-; -]	2.30 [1.06; 4.97]	0.034	
Prior History of Pelvic Radiation									
Yes	127	66 (52.0)	34.4 [11.0; 69.1]	129	28 (21.7)	Not reached [-; -]	2.18 [1.38; 3.42]	< 0.001	0.113
No	168	89 (53.0)	25.3 [11.0; 57.3]	160	55 (34.4)	37.6 [21.6; -]	1.35 [0.95; 1.91]	0.089	
SOC[h]: Renal and urinary disorders									
Age Group									
< 65	152	63 (41.4)	73.0 [40.6; 83.4]	143	14 (9.8)	Not reached [-; -]	3.23 [1.78; 5.85]	< 0.001	0.801
≥ 65	143	75 (52.4)	40.1 [12.4; 52.0]	146	19 (13.0)	Not reached [-; -]	3.81 [2.29; 6.36]	< 0.001	
Region									
Region 1	165	73 (44.2)	48.0 [31.9; -]	168	16 (9.5)	Not reached [-; -]	4.18 [2.41; 7.25]	< 0.001	0.333
Region 2	130	65 (50.0)	48.4 [21.1; 77.4]	121	17 (14.0)	Not reached [-; -]	2.89 [1.67; 4.99]	< 0.001	
ECOG Performance Status									
0	175	76 (43.4)	64.4 [42.6; 78.7]	164	21 (12.8)	Not reached [-; -]	2.76 [1.68; 4.54]	< 0.001	0.136
1	120	62 (51.7)	31.0 [13.6; 50.9]	125	12 (9.6)	Not reached [-; -]	4.99 [2.67; 9.35]	< 0.001	
MMR Status									
pMMR	242	115 (47.5)	43.6 [29.9; 64.4]	239	29 (12.1)	Not reached [-; -]	3.45 [2.28; 5.23]	< 0.001	0.808
dMMR	53	23 (43.4)	77.4 [30.1; -]	50	4 (8.0)	Not reached [-; -]	4.11 [1.38; 12.22]	0.011	
Prior History of Pelvic Radiation									
Yes	127	63 (49.6)	40.6 [21.1; 78.7]	129	11 (8.5)	Not reached [-; -]	4.80 [2.50; 9.20]	< 0.001	0.147
No	168	75 (44.6)	53.0 [35.0; 83.4]	160	22 (13.8)	Not reached [-; -]	2.91 [1.79; 4.73]	< 0.001	
SOC[h]: Reproductive system and breast disorders									
Age Group									
< 65	152	21 (13.8)	Not reached [-; -]	143	3 (2.1)	Not reached [-; -]	4.14 [1.20; 14.20]	0.024	0.246
≥ 65	143	24 (16.8)	Not reached [-; -]	146	9 (6.2)	Not reached [-; -]	1.68 [0.74; 3.80]	0.212	
Region									
Region 1	165	31 (18.8)	Not reached [-; -]	168	7 (4.2)	Not reached [-; -]	2.78 [1.18; 6.55]	0.020	0.335
Region 2	130	14 (10.8)	Not reached [-; -]	121	5 (4.1)	Not reached [-; -]	1.77 [0.62; 5.05]	0.286	
ECOG Performance Status									
0	175	21 (12.0)	Not reached [-; -]	164	7 (4.3)	Not reached [-; -]	1.78 [0.73; 4.35]	0.204	0.315
1	120	24 (20.0)	Not reached [-; -]	125	5 (4.0)	Not reached [-; -]	3.20 [1.18; 8.70]	0.022	
MMR Status									
pMMR	242	37 (15.3)	Not reached [-; -]	239	9 (3.8)	Not reached [-; -]	2.67 [1.26; 5.70]	0.011	0.357
dMMR	53	8	Not reached	50	3	Not reached	1.25	0.753	

		(15.1)	[-; -]		(6.0)	[-; -]	[0.31; 5.06]		
Prior History of Pelvic Radiation									
Yes	127	23 (18.1)	Not reached [-; -]	129	6 (4.7)	Not reached [-; -]	2.47 [0.97; 6.30]	0.058	0.900
No	168	22 (13.1)	Not reached [-; -]	160	6 (3.8)	Not reached [-; -]	2.22 [0.87; 5.69]	0.096	
SOC[h]: Respiratory, thoracic and mediastinal disorders									
Age Group									
< 65	152	74 (48.7)	36.6 [19.7; -]	143	39 (27.3)	Not reached [-; -]	1.59 [1.06; 2.37]	0.024	0.744
≥ 65	143	77 (53.8)	26.4 [9.9; 50.3]	146	52 (35.6)	Not reached [17.4; -]	1.45 [1.01; 2.08]	0.045	
Region									
Region 1	165	96 (58.2)	12.9 [5.7; 32.0]	168	64 (38.1)	Not reached [17.3; -]	1.55 [1.12; 2.15]	0.008	0.811
Region 2	130	55 (42.3)	64.7 [31.0; -]	121	27 (22.3)	Not reached [-; -]	1.51 [0.93; 2.43]	0.092	
ECOG Performance Status									
0	175	90 (51.4)	33.1 [22.0; 64.7]	164	49 (29.9)	Not reached [25.3; -]	1.48 [1.03; 2.12]	0.034	0.864
1	120	61 (50.8)	20.3 [8.7; -]	125	42 (33.6)	Not reached [17.4; -]	1.54 [1.03; 2.30]	0.033	
MMR Status									
pMMR	242	125 (51.7)	31.0 [16.6; 47.9]	239	81 (33.9)	Not reached [24.1; -]	1.38 [1.03; 1.84]	0.031	0.294
dMMR	53	26 (49.1)	45.6 [5.0; -]	50	10 (20.0)	Not reached [25.1; -]	2.50 [1.19; 5.24]	0.015	
Prior History of Pelvic Radiation									
Yes	127	70 (55.1)	27.7 [6.9; 50.3]	129	40 (31.0)	Not reached [22.3; -]	1.73 [1.16; 2.58]	0.007	0.431
No	168	81 (48.2)	34.7 [19.7; -]	160	51 (31.9)	Not reached [24.1; -]	1.34 [0.94; 1.93]	0.107	
SOC[h]: Vascular disorders									
Age Group									
< 65	152	106 (69.7)	5.1 [2.6; 8.7]	143	25 (17.5)	Not reached [-; -]	5.14 [3.31; 7.99]	< 0.001	0.902
≥ 65	143	95 (66.4)	3.4 [2.3; 6.3]	146	26 (17.8)	Not reached [-; -]	5.07 [3.27; 7.85]	< 0.001	
Region									
Region 1	165	108 (65.5)	3.9 [2.7; 8.9]	168	33 (19.6)	Not reached [-; -]	4.37 [2.95; 6.47]	< 0.001	0.211
Region 2	130	93 (71.5)	3.9 [2.3; 7.6]	121	18 (14.9)	Not reached [-; -]	6.45 [3.88; 10.74]	< 0.001	
MMR Status									
pMMR	242	172 (71.1)	3.1 [2.3; 5.1]	239	46 (19.2)	Not reached [-; -]	5.13 [3.69; 7.12]	< 0.001	0.726
dMMR	53	29 (54.7)	24.6 [3.9; -]	50	5 (10.0)	Not reached [-; -]	5.87 [2.25; 15.31]	< 0.001	
Prior History of Pelvic Radiation									
Yes	127	88 (69.3)	4.0 [2.3; 7.6]	129	18 (14.0)	Not reached [-; -]	6.68 [4.01; 11.13]	< 0.001	0.185
No	168	113 (67.3)	3.9 [2.7; 8.1]	160	33 (20.6)	Not reached [-; -]	4.26 [2.88; 6.31]	< 0.001	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but

actually treated with doxorubicin
c: Number of participants: all-participants-as-treated, population relevant for benefit assessment
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
h: A system organ class appears on this report only if its incidence ≥ 10% or (incidence ≥ 1% and in at least 10 participants) in one or more groups and p-value of main treatment effect is smaller than 0.05, and p-value for interaction test is greater than or equal to 0.05 or rule of 10 is not met
CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; MMR: Mismatch Repair; n.a.: not applicable (when estimation not possible); pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world; SOC: System Organ Class

Analyses of Time to Adverse Event by Subgroups with p-Value for Interaction Test ≥ 0.05 or Rule of 10 Not Met (Incidence ≥ 10% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Groups) For Preferred Terms

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		p-Value for Interaction Test[g]
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	
SOC: Blood and lymphatic system disorders, PT[h]: Anaemia									
Age Group									
< 65	152	46 (30.3)	Not reached [61.4; -]	143	68 (47.6)	13.9 [8.9; -]	0.33 [0.22; 0.50]	< 0.001	0.356
≥ 65	143	39 (27.3)	Not reached [-; -]	146	80 (54.8)	9.1 [5.3; 23.3]	0.26 [0.17; 0.39]	< 0.001	
ECOG Performance Status									
0	175	49 (28.0)	Not reached [77.1; -]	164	75 (45.7)	18.3 [12.1; -]	0.33 [0.22; 0.49]	< 0.001	0.385
1	120	36 (30.0)	Not reached [43.6; -]	125	73 (58.4)	7.3 [5.1; 13.7]	0.24 [0.16; 0.38]	< 0.001	
MMR Status									
pMMR	242	62 (25.6)	Not reached [77.1; -]	239	122 (51.0)	13.3 [7.9; -]	0.26 [0.19; 0.36]	< 0.001	0.176
dMMR	53	23 (43.4)	61.4 [28.6; -]	50	26 (52.0)	14.0 [4.4; -]	0.44 [0.24; 0.81]	0.008	
Prior History of Pelvic Radiation									
Yes	127	42 (33.1)	Not reached [50.1; -]	129	67 (51.9)	11.0 [5.3; -]	0.29 [0.19; 0.46]	< 0.001	0.489
No	168	43 (25.6)	Not reached [-; -]	160	81 (50.6)	13.7 [7.3; -]	0.29 [0.19; 0.43]	< 0.001	
SOC: Blood and lymphatic system disorders, PT[h]: Febrile neutropenia									
Age Group									
< 65	152	1 (0.7)	Not reached [-; -]	143	13 (9.1)	Not reached [-; -]	n.a. [n.a.; n.a.]	> 0.999	0.726
≥ 65	143	1 (0.7)	Not reached [-; -]	146	9 (6.2)	Not reached [-; -]	0.09 [0.01; 0.69]	0.021	
Region									
Region 1	165	0 (0.0)	Not reached [-; -]	168	9 (5.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	0.194
Region 2	130	2 (1.5)	Not reached [-; -]	121	13 (10.7)	Not reached [-; -]	0.06 [0.01; 0.44]	0.006	

ECOG Performance Status									
0	175	2 (1.1)	Not reached [-; -]	164	14 (8.5)	Not reached [-; -]	0.05 [0.01; 0.40]	0.004	0.234
1	120	0 (0.0)	Not reached [-; -]	125	8 (6.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.003	
MMR Status									
pMMR	242	2 (0.8)	Not reached [-; -]	239	18 (7.5)	Not reached [-; -]	0.05 [0.01; 0.35]	0.003	0.294
dMMR	53	0 (0.0)	Not reached [-; -]	50	4 (8.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.014	
Prior History of Pelvic Radiation									
Yes	127	0 (0.0)	Not reached [-; -]	129	9 (7.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	0.148
No	168	2 (1.2)	Not reached [-; -]	160	13 (8.1)	Not reached [-; -]	0.06 [0.01; 0.44]	0.006	
SOC: Blood and lymphatic system disorders, PT[h]: Leukopenia									
Age Group									
< 65	152	13 (8.6)	Not reached [-; -]	143	22 (15.4)	Not reached [-; -]	0.41 [0.20; 0.83]	0.014	0.903
≥ 65	143	9 (6.3)	Not reached [-; -]	146	18 (12.3)	Not reached [-; -]	0.40 [0.17; 0.91]	0.030	
Region									
Region 1	165	5 (3.0)	Not reached [-; -]	168	14 (8.3)	Not reached [-; -]	0.25 [0.08; 0.77]	0.015	0.459
Region 2	130	17 (13.1)	Not reached [-; -]	121	26 (21.5)	Not reached [-; -]	0.46 [0.24; 0.86]	0.015	
ECOG Performance Status									
0	175	15 (8.6)	Not reached [-; -]	164	27 (16.5)	Not reached [-; -]	0.39 [0.20; 0.74]	0.004	0.841
1	120	7 (5.8)	Not reached [-; -]	125	13 (10.4)	Not reached [-; -]	0.44 [0.17; 1.17]	0.101	
MMR Status									
pMMR	242	14 (5.8)	Not reached [-; -]	239	33 (13.8)	Not reached [-; -]	0.29 [0.15; 0.57]	< 0.001	0.144
dMMR	53	8 (15.1)	Not reached [-; -]	50	7 (14.0)	Not reached [-; -]	0.92 [0.33; 2.54]	0.866	
Prior History of Pelvic Radiation									
Yes	127	11 (8.7)	Not reached [-; -]	129	21 (16.3)	Not reached [-; -]	0.38 [0.18; 0.81]	0.012	0.829
No	168	11 (6.5)	Not reached [-; -]	160	19 (11.9)	Not reached [-; -]	0.44 [0.20; 0.95]	0.036	
SOC: Blood and lymphatic system disorders, PT[h]: Neutropenia									
Age Group									
< 65	152	13 (8.6)	Not reached [-; -]	143	54 (37.8)	Not reached [21.0; -]	0.14 [0.07; 0.26]	< 0.001	0.976
≥ 65	143	13 (9.1)	Not reached [-; -]	146	60 (41.1)	Not reached [9.7; -]	0.14 [0.08; 0.27]	< 0.001	
ECOG Performance Status									
0	175	19 (10.9)	Not reached [-; -]	164	67 (40.9)	Not reached [13.9; -]	0.15 [0.09; 0.27]	< 0.001	0.309
1	120	7 (5.8)	Not reached [-; -]	125	47 (37.6)	Not reached [21.0; -]	0.12 [0.05; 0.26]	< 0.001	
MMR Status									
pMMR	242	19 (7.9)	Not reached [-; -]	239	96 (40.2)	Not reached [-; -]	0.12 [0.07; 0.20]	< 0.001	0.292

dMMR	53	7 (13.2)	Not reached [-; -]	50	18 (36.0)	Not reached [5.7; -]	0.24 [0.10; 0.59]	0.002	
Prior History of Pelvic Radiation									
Yes	127	11 (8.7)	Not reached [-; -]	129	57 (44.2)	Not reached [5.6; -]	0.11 [0.05; 0.21]	< 0.001	0.381
No	168	15 (8.9)	Not reached [-; -]	160	57 (35.6)	Not reached [-; -]	0.18 [0.10; 0.32]	< 0.001	
SOC: Endocrine disorders, PT[h]: Hyperthyroidism									
Age Group									
< 65	152	16 (10.5)	Not reached [-; -]	143	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	0.137
≥ 65	143	18 (12.6)	Not reached [-; -]	146	2 (1.4)	Not reached [-; -]	7.98 [1.84; 34.56]	0.005	
Region									
Region 1	165	19 (11.5)	Not reached [-; -]	168	2 (1.2)	Not reached [-; -]	7.59 [1.75; 32.93]	0.007	0.151
Region 2	130	15 (11.5)	Not reached [-; -]	121	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	
ECOG Performance Status									
0	175	21 (12.0)	Not reached [-; -]	164	1 (0.6)	Not reached [-; -]	16.60 [2.22; 123.84]	0.006	0.788
1	120	13 (10.8)	Not reached [-; -]	125	1 (0.8)	Not reached [-; -]	9.15 [1.18; 71.25]	0.035	
MMR Status									
pMMR	242	26 (10.7)	Not reached [-; -]	239	2 (0.8)	Not reached [-; -]	10.27 [2.42; 43.57]	0.002	0.337
dMMR	53	8 (15.1)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.022	
Prior History of Pelvic Radiation									
Yes	127	18 (14.2)	Not reached [-; -]	129	2 (1.6)	Not reached [-; -]	7.13 [1.64; 30.97]	0.009	0.126
No	168	16 (9.5)	Not reached [-; -]	160	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
SOC: Endocrine disorders, PT[h]: Hypothyroidism									
Age Group									
< 65	152	86 (56.6)	20.6 [15.0; 27.0]	143	2 (1.4)	Not reached [-; -]	38.85 [9.54; 158.14]	< 0.001	0.075
≥ 65	143	85 (59.4)	15.3 [11.6; 20.9]	146	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Region									
Region 1	165	80 (48.5)	21.1 [18.0; 39.0]	168	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.127
Region 2	130	91 (70.0)	13.1 [10.0; 15.4]	121	2 (1.7)	Not reached [-; -]	49.47 [12.17; 201.08]	< 0.001	
ECOG Performance Status									
0	175	110 (62.9)	15.0 [11.6; 19.1]	164	1 (0.6)	Not reached [-; -]	120.18 [16.77; 861.29]	< 0.001	0.629
1	120	61 (50.8)	21.1 [15.3; 34.1]	125	1 (0.8)	Not reached [-; -]	58.32 [8.07; 421.31]	< 0.001	
MMR Status									
pMMR	242	134 (55.4)	18.0 [15.0; 21.4]	239	2 (0.8)	Not reached [-; -]	73.37 [18.15; 296.57]	< 0.001	0.360
dMMR	53	37 (69.8)	19.9 [10.1; 23.9]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Prior History of Pelvic Radiation									

Yes	127	78 (61.4)	18.1 [12.6; 21.6]	129	1 (0.8)	Not reached [-; -]	80.65 [11.20; 580.48]	< 0.001	0.929
No	168	93 (55.4)	18.0 [14.6; 21.1]	160	1 (0.6)	Not reached [-; -]	97.63 [13.60; 700.81]	< 0.001	
SOC: Gastrointestinal disorders, PT[h]: Diarrhoea									
Age Group									
< 65	152	77 (50.7)	31.1 [21.1; 46.0]	143	17 (11.9)	Not reached [-; -]	3.33 [1.95; 5.70]	< 0.001	0.201
≥ 65	143	79 (55.2)	23.0 [14.9; 39.9]	146	31 (21.2)	Not reached [-; -]	2.27 [1.49; 3.47]	< 0.001	
Region									
Region 1	165	94 (57.0)	21.1 [13.0; 30.7]	168	31 (18.5)	Not reached [-; -]	2.75 [1.82; 4.16]	< 0.001	0.810
Region 2	130	62 (47.7)	40.0 [25.4; 78.7]	121	17 (14.0)	Not reached [-; -]	2.53 [1.46; 4.38]	< 0.001	
ECOG Performance Status									
0	175	90 (51.4)	31.3 [22.4; 58.7]	164	27 (16.5)	Not reached [-; -]	2.47 [1.59; 3.84]	< 0.001	0.581
1	120	66 (55.0)	20.3 [12.9; 31.1]	125	21 (16.8)	Not reached [-; -]	2.90 [1.76; 4.78]	< 0.001	
MMR Status									
pMMR	242	127 (52.5)	26.9 [20.3; 34.3]	239	40 (16.7)	Not reached [-; -]	2.64 [1.84; 3.79]	< 0.001	0.848
dMMR	53	29 (54.7)	30.7 [8.7; 75.9]	50	8 (16.0)	Not reached [25.1; -]	2.72 [1.21; 6.12]	0.016	
Prior History of Pelvic Radiation									
Yes	127	80 (63.0)	20.0 [11.7; 28.3]	129	23 (17.8)	Not reached [-; -]	2.98 [1.85; 4.78]	< 0.001	0.348
No	168	76 (45.2)	40.0 [23.0; 78.7]	160	25 (15.6)	Not reached [-; -]	2.37 [1.50; 3.76]	< 0.001	
SOC: Gastrointestinal disorders, PT[h]: Dry mouth									
Age Group									
< 65	152	11 (7.2)	Not reached [-; -]	143	3 (2.1)	Not reached [-; -]	2.58 [0.70; 9.54]	0.156	0.924
≥ 65	143	18 (12.6)	Not reached [-; -]	146	6 (4.1)	Not reached [-; -]	2.98 [1.18; 7.52]	0.020	
Region									
Region 1	165	22 (13.3)	Not reached [-; -]	168	7 (4.2)	Not reached [-; -]	2.77 [1.17; 6.55]	0.021	0.988
Region 2	130	7 (5.4)	Not reached [-; -]	121	2 (1.7)	Not reached [-; -]	3.11 [0.64; 14.98]	0.158	
ECOG Performance Status									
0	175	20 (11.4)	Not reached [-; -]	164	6 (3.7)	Not reached [-; -]	2.68 [1.06; 6.77]	0.036	0.984
1	120	9 (7.5)	Not reached [-; -]	125	3 (2.4)	Not reached [-; -]	2.90 [0.78; 10.73]	0.111	
MMR Status									
pMMR	242	24 (9.9)	Not reached [-; -]	239	9 (3.8)	Not reached [-; -]	2.39 [1.10; 5.16]	0.027	0.098
dMMR	53	5 (9.4)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.055	
Prior History of Pelvic Radiation									
Yes	127	17 (13.4)	Not reached [-; -]	129	5 (3.9)	Not reached [-; -]	3.05 [1.12; 8.33]	0.030	0.803
No	168	12	Not reached	160	4	Not reached	2.55	0.109	

		(7.1)	[-; -]		(2.5)	[-; -]	[0.81; 8.02]		
SOC: Gastrointestinal disorders, PT[h]: Gastritis									
Age Group									
< 65	152	13 (8.6)	Not reached [-; -]	143	1 (0.7)	Not reached [-; -]	7.89 [1.00; 62.34]	0.050	0.581
≥ 65	143	5 (3.5)	Not reached [-; -]	146	1 (0.7)	Not reached [-; -]	2.65 [0.27; 25.58]	0.400	
Region									
Region 1	165	4 (2.4)	Not reached [-; -]	168	1 (0.6)	Not reached [-; -]	3.92 [0.44; 35.09]	0.222	0.470
Region 2	130	14 (10.8)	Not reached [-; -]	121	1 (0.8)	Not reached [-; -]	6.50 [0.81; 52.10]	0.078	
ECOG Performance Status									
0	175	14 (8.0)	Not reached [-; -]	164	1 (0.6)	Not reached [-; -]	7.68 [0.97; 60.72]	0.053	0.454
1	120	4 (3.3)	Not reached [-; -]	125	1 (0.8)	Not reached [-; -]	2.88 [0.30; 27.68]	0.360	
MMR Status									
pMMR	242	12 (5.0)	Not reached [-; -]	239	2 (0.8)	Not reached [-; -]	4.14 [0.89; 19.19]	0.069	0.268
dMMR	53	6 (11.3)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.131	
Prior History of Pelvic Radiation									
Yes	127	8 (6.3)	Not reached [-; -]	129	2 (1.6)	Not reached [-; -]	1.87 [0.34; 10.24]	0.471	0.084
No	168	10 (6.0)	Not reached [-; -]	160	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.008	
SOC: Gastrointestinal disorders, PT[h]: Nausea									
Region									
Region 1	165	88 (53.3)	19.4 [10.9; 45.3]	168	90 (53.6)	5.9 [3.1; -]	0.70 [0.52; 0.95]	0.021	0.270
Region 2	130	55 (42.3)	61.4 [42.6; -]	121	57 (47.1)	Not reached [2.6; -]	0.51 [0.34; 0.75]	< 0.001	
MMR Status									
pMMR	242	116 (47.9)	42.6 [20.7; 61.4]	239	127 (53.1)	5.9 [3.1; -]	0.58 [0.45; 0.75]	< 0.001	0.273
dMMR	53	27 (50.9)	30.0 [9.7; -]	50	20 (40.0)	Not reached [2.3; -]	0.84 [0.46; 1.54]	0.582	
Prior History of Pelvic Radiation									
Yes	127	65 (51.2)	30.3 [16.3; -]	129	59 (45.7)	Not reached [3.4; -]	0.75 [0.52; 1.08]	0.124	0.126
No	168	78 (46.4)	43.9 [18.4; -]	160	88 (55.0)	3.6 [2.1; -]	0.52 [0.38; 0.72]	< 0.001	
SOC: Infections and infestations, PT[h]: Urinary tract infection									
Age Group									
< 65	152	35 (23.0)	Not reached [-; -]	143	9 (6.3)	Not reached [-; -]	2.39 [1.12; 5.12]	0.025	0.379
≥ 65	143	48 (33.6)	Not reached [-; -]	146	21 (14.4)	Not reached [-; -]	1.87 [1.11; 3.15]	0.020	
Region									
Region 1	165	47 (28.5)	Not reached [-; -]	168	18 (10.7)	Not reached [-; -]	2.22 [1.28; 3.86]	0.005	0.875
Region 2	130	36 (27.7)	Not reached [-; -]	121	12 (9.9)	Not reached [-; -]	1.70 [0.86; 3.38]	0.128	

MMR Status									
pMMR	242	73 (30.2)	Not reached [-; -]	239	26 (10.9)	Not reached [-; -]	2.06 [1.30; 3.27]	0.002	0.583
dMMR	53	10 (18.9)	Not reached [-; -]	50	4 (8.0)	Not reached [-; -]	1.67 [0.51; 5.48]	0.399	
Prior History of Pelvic Radiation									
Yes	127	38 (29.9)	Not reached [-; -]	129	16 (12.4)	Not reached [-; -]	1.72 [0.94; 3.15]	0.080	0.506
No	168	45 (26.8)	Not reached [-; -]	160	14 (8.8)	Not reached [-; -]	2.28 [1.23; 4.22]	0.009	
SOC: Investigations, PT[h]: Alanine aminotransferase increased									
Age Group									
< 65	152	38 (25.0)	Not reached [78.6; -]	143	8 (5.6)	Not reached [-; -]	2.92 [1.33; 6.43]	0.008	0.389
≥ 65	143	24 (16.8)	Not reached [-; -]	146	3 (2.1)	Not reached [-; -]	6.56 [1.95; 22.11]	0.002	
Region									
Region 1	165	23 (13.9)	Not reached [-; -]	168	4 (2.4)	Not reached [-; -]	4.31 [1.46; 12.73]	0.008	0.865
Region 2	130	39 (30.0)	97.9 [67.3; -]	121	7 (5.8)	Not reached [-; -]	3.66 [1.60; 8.34]	0.002	
ECOG Performance Status									
0	175	46 (26.3)	97.9 [78.6; -]	164	8 (4.9)	Not reached [-; -]	3.73 [1.72; 8.06]	< 0.001	0.994
1	120	16 (13.3)	Not reached [-; -]	125	3 (2.4)	Not reached [-; -]	4.36 [1.25; 15.24]	0.021	
MMR Status									
pMMR	242	53 (21.9)	Not reached [97.9; -]	239	9 (3.8)	Not reached [-; -]	4.35 [2.12; 8.95]	< 0.001	0.545
dMMR	53	9 (17.0)	Not reached [78.6; -]	50	2 (4.0)	Not reached [-; -]	2.19 [0.44; 10.98]	0.342	
Prior History of Pelvic Radiation									
Yes	127	25 (19.7)	Not reached [-; -]	129	3 (2.3)	Not reached [-; -]	5.84 [1.72; 19.79]	0.005	0.386
No	168	37 (22.0)	Not reached [97.9; -]	160	8 (5.0)	Not reached [-; -]	3.20 [1.46; 7.02]	0.004	
SOC: Investigations, PT[h]: Amylase increased									
Age Group									
< 65	152	12 (7.9)	Not reached [-; -]	143	2 (1.4)	Not reached [-; -]	2.48 [0.51; 11.99]	0.260	0.442
≥ 65	143	13 (9.1)	Not reached [-; -]	146	1 (0.7)	Not reached [-; -]	10.47 [1.35; 81.15]	0.025	
Region									
Region 1	165	10 (6.1)	Not reached [-; -]	168	1 (0.6)	Not reached [-; -]	5.04 [0.60; 42.05]	0.135	0.741
Region 2	130	15 (11.5)	Not reached [-; -]	121	2 (1.7)	Not reached [-; -]	4.92 [1.10; 22.04]	0.037	
ECOG Performance Status									
0	175	18 (10.3)	Not reached [-; -]	164	1 (0.6)	Not reached [-; -]	11.06 [1.45; 84.30]	0.020	0.219
1	120	7 (5.8)	Not reached [-; -]	125	2 (1.6)	Not reached [-; -]	1.88 [0.35; 10.28]	0.465	
MMR Status									
pMMR	242	20 (8.3)	Not reached [-; -]	239	2 (0.8)	Not reached [-; -]	5.95 [1.35; 26.25]	0.018	0.482

dMMR	53	5 (9.4)	Not reached [-; -]	50	1 (2.0)	Not reached [-; -]	3.15 [0.35; 28.39]	0.307	
Prior History of Pelvic Radiation									
Yes	127	10 (7.9)	Not reached [-; -]	129	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.026	0.087
No	168	15 (8.9)	Not reached [-; -]	160	3 (1.9)	Not reached [-; -]	3.36 [0.95; 11.95]	0.061	
SOC: Investigations, PT[h]: Aspartate aminotransferase increased									
Age Group									
< 65	152	34 (22.4)	Not reached [97.9; -]	143	7 (4.9)	Not reached [-; -]	3.06 [1.32; 7.07]	0.009	0.940
≥ 65	143	29 (20.3)	Not reached [-; -]	146	7 (4.8)	Not reached [-; -]	3.30 [1.42; 7.67]	0.006	
Region									
Region 1	165	24 (14.5)	Not reached [-; -]	168	7 (4.2)	Not reached [-; -]	2.67 [1.13; 6.33]	0.026	0.476
Region 2	130	39 (30.0)	97.9 [78.6; -]	121	7 (5.8)	Not reached [-; -]	3.68 [1.61; 8.38]	0.002	
ECOG Performance Status									
0	175	44 (25.1)	97.9 [78.6; -]	164	9 (5.5)	Not reached [-; -]	3.14 [1.50; 6.57]	0.002	0.807
1	120	19 (15.8)	Not reached [-; -]	125	5 (4.0)	Not reached [-; -]	3.25 [1.20; 8.83]	0.021	
MMR Status									
pMMR	242	56 (23.1)	Not reached [97.9; -]	239	12 (5.0)	Not reached [-; -]	3.53 [1.87; 6.67]	< 0.001	0.509
dMMR	53	7 (13.2)	Not reached [78.6; -]	50	2 (4.0)	Not reached [-; -]	1.54 [0.28; 8.44]	0.620	
Prior History of Pelvic Radiation									
Yes	127	24 (18.9)	Not reached [-; -]	129	2 (1.6)	Not reached [-; -]	8.54 [1.98; 36.78]	0.004	0.065
No	168	39 (23.2)	Not reached [97.9; -]	160	12 (7.5)	Not reached [-; -]	2.28 [1.17; 4.44]	0.016	
SOC: Investigations, PT[h]: Blood alkaline phosphatase increased									
Age Group									
< 65	152	22 (14.5)	Not reached [-; -]	143	7 (4.9)	Not reached [-; -]	1.80 [0.73; 4.40]	0.200	0.958
≥ 65	143	15 (10.5)	Not reached [-; -]	146	5 (3.4)	Not reached [-; -]	2.68 [0.96; 7.45]	0.059	
Region									
Region 1	165	11 (6.7)	Not reached [-; -]	168	7 (4.2)	Not reached [-; -]	1.19 [0.44; 3.20]	0.734	0.094
Region 2	130	26 (20.0)	Not reached [-; -]	121	5 (4.1)	Not reached [-; -]	3.46 [1.30; 9.22]	0.013	
ECOG Performance Status									
0	175	24 (13.7)	Not reached [-; -]	164	7 (4.3)	Not reached [-; -]	2.04 [0.85; 4.92]	0.113	0.852
1	120	13 (10.8)	Not reached [-; -]	125	5 (4.0)	Not reached [-; -]	2.38 [0.84; 6.75]	0.104	
MMR Status									
pMMR	242	31 (12.8)	Not reached [-; -]	239	11 (4.6)	Not reached [-; -]	2.08 [1.03; 4.23]	0.043	0.603
dMMR	53	6 (11.3)	Not reached [-; -]	50	1 (2.0)	Not reached [-; -]	3.23 [0.36; 28.99]	0.295	
Prior History of Pelvic Radiation									

Yes	127	14 (11.0)	Not reached [-; -]	129	3 (2.3)	Not reached [-; -]	3.43 [0.95; 12.31]	0.059	0.399
No	168	23 (13.7)	Not reached [-; -]	160	9 (5.6)	Not reached [-; -]	1.74 [0.78; 3.87]	0.175	
SOC: Investigations, PT[h]: Blood cholesterol increased									
Age Group									
< 65	152	12 (7.9)	Not reached [-; -]	143	1 (0.7)	Not reached [-; -]	6.27 [0.79; 49.87]	0.083	0.831
≥ 65	143	16 (11.2)	Not reached [-; -]	146	2 (1.4)	Not reached [-; -]	6.20 [1.41; 27.28]	0.016	
Region									
Region 1	165	12 (7.3)	Not reached [-; -]	168	1 (0.6)	Not reached [-; -]	8.65 [1.10; 67.94]	0.040	0.677
Region 2	130	16 (12.3)	Not reached [-; -]	121	2 (1.7)	Not reached [-; -]	4.89 [1.10; 21.67]	0.037	
ECOG Performance Status									
0	175	19 (10.9)	Not reached [-; -]	164	2 (1.2)	Not reached [-; -]	5.98 [1.36; 26.21]	0.018	0.978
1	120	9 (7.5)	Not reached [-; -]	125	1 (0.8)	Not reached [-; -]	6.31 [0.78; 50.82]	0.083	
MMR Status									
pMMR	242	24 (9.9)	Not reached [-; -]	239	2 (0.8)	Not reached [-; -]	8.38 [1.95; 35.97]	0.004	0.334
dMMR	53	4 (7.5)	Not reached [-; -]	50	1 (2.0)	Not reached [-; -]	2.01 [0.21; 19.08]	0.542	
Prior History of Pelvic Radiation									
Yes	127	13 (10.2)	Not reached [-; -]	129	2 (1.6)	Not reached [-; -]	3.89 [0.84; 18.00]	0.082	0.487
No	168	15 (8.9)	Not reached [-; -]	160	1 (0.6)	Not reached [-; -]	10.75 [1.41; 82.07]	0.022	
SOC: Investigations, PT[h]: Blood creatine phosphokinase increased									
Age Group									
< 65	152	7 (4.6)	n.c.	143	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	143	6 (4.2)	n.c.	146	0 (0.0)	n.c.	n.c.	n.c.	
Region									
Region 1	165	7 (4.2)	n.c.	168	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Region 2	130	6 (4.6)	n.c.	121	0 (0.0)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	175	8 (4.6)	n.c.	164	0 (0.0)	n.c.	n.c.	n.c.	n.c.
1	120	5 (4.2)	n.c.	125	0 (0.0)	n.c.	n.c.	n.c.	
MMR Status									
pMMR	242	10 (4.1)	Not reached [-; -]	239	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.007	0.997
dMMR	53	3 (5.7)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.336	
Prior History of Pelvic Radiation									
Yes	127	6 (4.7)	n.c.	129	0 (0.0)	n.c.	n.c.	n.c.	n.c.
No	168	7	n.c.	160	0	n.c.	n.c.	n.c.	

		(4.2)			(0.0)				
SOC: Investigations, PT[h]: Blood creatinine increased									
Age Group									
< 65	152	15 (9.9)	Not reached [-; -]	143	1 (0.7)	Not reached [-; -]	8.85 [1.14; 68.82]	0.037	0.462
≥ 65	143	22 (15.4)	Not reached [-; -]	146	4 (2.7)	Not reached [-; -]	3.57 [1.19; 10.73]	0.023	
Region									
Region 1	165	16 (9.7)	Not reached [-; -]	168	3 (1.8)	Not reached [-; -]	2.70 [0.73; 9.89]	0.135	0.528
Region 2	130	21 (16.2)	Not reached [-; -]	121	2 (1.7)	Not reached [-; -]	7.34 [1.69; 31.82]	0.008	
ECOG Performance Status									
0	175	23 (13.1)	Not reached [-; -]	164	2 (1.2)	Not reached [-; -]	6.27 [1.43; 27.52]	0.015	0.446
1	120	14 (11.7)	Not reached [-; -]	125	3 (2.4)	Not reached [-; -]	3.49 [0.98; 12.44]	0.054	
MMR Status									
pMMR	242	30 (12.4)	Not reached [-; -]	239	5 (2.1)	Not reached [-; -]	4.02 [1.52; 10.61]	0.005	0.217
dMMR	53	7 (13.2)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.084	
Prior History of Pelvic Radiation									
Yes	127	13 (10.2)	Not reached [-; -]	129	2 (1.6)	Not reached [-; -]	3.53 [0.75; 16.53]	0.110	0.820
No	168	24 (14.3)	Not reached [-; -]	160	3 (1.9)	Not reached [-; -]	5.23 [1.54; 17.78]	0.008	
SOC: Investigations, PT[h]: Blood thyroid stimulating hormone increased									
Age Group									
< 65	152	18 (11.8)	Not reached [-; -]	143	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
≥ 65	143	17 (11.9)	Not reached [-; -]	146	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Region									
Region 1	165	23 (13.9)	Not reached [-; -]	168	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
Region 2	130	12 (9.2)	Not reached [-; -]	121	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.008	
ECOG Performance Status									
0	175	25 (14.3)	Not reached [-; -]	164	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
1	120	10 (8.3)	Not reached [-; -]	125	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.005	
MMR Status									
pMMR	242	27 (11.2)	Not reached [-; -]	239	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
dMMR	53	8 (15.1)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.036	
Prior History of Pelvic Radiation									
Yes	127	10 (7.9)	Not reached [-; -]	129	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.007	0.997
No	168	25 (14.9)	Not reached [-; -]	160	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
SOC: Investigations, PT[h]: Lipase increased									

Age Group									
< 65	152	16 (10.5)	Not reached [-; -]	143	4 (2.8)	Not reached [-; -]	1.73 [0.52; 5.75]	0.373	0.587
≥ 65	143	16 (11.2)	Not reached [-; -]	146	3 (2.1)	Not reached [-; -]	3.75 [1.06; 13.33]	0.041	
Region									
Region 1	165	12 (7.3)	Not reached [-; -]	168	4 (2.4)	Not reached [-; -]	0.98 [0.25; 3.94]	0.983	0.390
Region 2	130	20 (15.4)	Not reached [-; -]	121	3 (2.5)	Not reached [-; -]	4.53 [1.32; 15.58]	0.017	
ECOG Performance Status									
0	175	23 (13.1)	Not reached [-; -]	164	3 (1.8)	Not reached [-; -]	4.35 [1.26; 15.07]	0.020	0.191
1	120	9 (7.5)	Not reached [-; -]	125	4 (3.2)	Not reached [-; -]	1.17 [0.31; 4.36]	0.818	
MMR Status									
pMMR	242	26 (10.7)	Not reached [-; -]	239	6 (2.5)	Not reached [-; -]	2.57 [1.01; 6.53]	0.048	0.987
dMMR	53	6 (11.3)	Not reached [-; -]	50	1 (2.0)	Not reached [-; -]	2.51 [0.26; 24.13]	0.426	
SOC: Investigations, PT[h]: Lymphocyte count decreased									
Age Group									
< 65	152	9 (5.9)	Not reached [-; -]	143	10 (7.0)	Not reached [-; -]	0.50 [0.19; 1.32]	0.161	0.512
≥ 65	143	5 (3.5)	Not reached [-; -]	146	10 (6.8)	Not reached [-; -]	0.42 [0.14; 1.25]	0.118	
Region									
Region 1	165	3 (1.8)	Not reached [-; -]	168	8 (4.8)	Not reached [-; -]	0.11 [0.01; 0.86]	0.036	0.303
Region 2	130	11 (8.5)	Not reached [-; -]	121	12 (9.9)	Not reached [-; -]	0.67 [0.29; 1.53]	0.338	
MMR Status									
pMMR	242	13 (5.4)	Not reached [-; -]	239	18 (7.5)	Not reached [-; -]	0.48 [0.23; 1.03]	0.059	0.644
dMMR	53	1 (1.9)	Not reached [-; -]	50	2 (4.0)	Not reached [-; -]	0.35 [0.03; 4.05]	0.404	
Prior History of Pelvic Radiation									
Yes	127	6 (4.7)	Not reached [-; -]	129	9 (7.0)	Not reached [-; -]	0.47 [0.16; 1.42]	0.182	0.945
No	168	8 (4.8)	Not reached [-; -]	160	11 (6.9)	Not reached [-; -]	0.46 [0.18; 1.20]	0.112	
SOC: Investigations, PT[h]: Neutrophil count decreased									
Age Group									
< 65	152	9 (5.9)	Not reached [-; -]	143	42 (29.4)	Not reached [-; -]	0.14 [0.07; 0.30]	< 0.001	0.707
≥ 65	143	9 (6.3)	Not reached [-; -]	146	39 (26.7)	Not reached [-; -]	0.16 [0.07; 0.35]	< 0.001	
ECOG Performance Status									
0	175	14 (8.0)	Not reached [-; -]	164	56 (34.1)	Not reached [-; -]	0.15 [0.08; 0.28]	< 0.001	0.673
1	120	4 (3.3)	Not reached [-; -]	125	25 (20.0)	Not reached [-; -]	0.14 [0.05; 0.41]	< 0.001	
Prior History of Pelvic Radiation									
Yes	127	5 (3.9)	Not reached [-; -]	129	17 (13.2)	Not reached [-; -]	0.18 [0.06; 0.57]	0.003	0.334

No	168	13 (7.7)	Not reached [-; -]	160	64 (40.0)	Not reached [-; -]	0.13 [0.07; 0.25]	< 0.001	
SOC: Investigations, PT[h]: Weight decreased									
Age Group									
< 65	152	54 (35.5)	Not reached [52.9; -]	143	6 (4.2)	Not reached [-; -]	6.93 [2.96; 16.22]	< 0.001	0.059
≥ 65	143	43 (30.1)	Not reached [66.6; -]	146	13 (8.9)	Not reached [-; -]	2.45 [1.30; 4.63]	0.006	
Region									
Region 1	165	48 (29.1)	Not reached [-; -]	168	12 (7.1)	Not reached [-; -]	3.35 [1.77; 6.36]	< 0.001	0.341
Region 2	130	49 (37.7)	Not reached [33.0; -]	121	7 (5.8)	Not reached [-; -]	4.74 [2.12; 10.60]	< 0.001	
ECOG Performance Status									
0	175	51 (29.1)	Not reached [-; -]	164	11 (6.7)	Not reached [-; -]	3.21 [1.65; 6.23]	< 0.001	0.445
1	120	46 (38.3)	Not reached [29.4; -]	125	8 (6.4)	Not reached [-; -]	4.93 [2.31; 10.54]	< 0.001	
MMR Status									
pMMR	242	77 (31.8)	Not reached [66.6; -]	239	15 (6.3)	Not reached [-; -]	3.74 [2.13; 6.56]	< 0.001	0.856
dMMR	53	20 (37.7)	Not reached [15.1; -]	50	4 (8.0)	Not reached [-; -]	4.28 [1.45; 12.61]	0.008	
Prior History of Pelvic Radiation									
Yes	127	51 (40.2)	64.4 [31.0; -]	129	10 (7.8)	Not reached [-; -]	3.53 [1.77; 7.06]	< 0.001	0.976
No	168	46 (27.4)	Not reached [-; -]	160	9 (5.6)	Not reached [-; -]	4.24 [2.06; 8.72]	< 0.001	
SOC: Investigations, PT[h]: White blood cell count decreased									
Age Group									
< 65	152	9 (5.9)	Not reached [-; -]	143	24 (16.8)	Not reached [-; -]	0.20 [0.08; 0.49]	< 0.001	0.528
≥ 65	143	6 (4.2)	Not reached [-; -]	146	26 (17.8)	Not reached [-; -]	0.13 [0.04; 0.37]	< 0.001	
Region									
Region 1	165	5 (3.0)	Not reached [-; -]	168	23 (13.7)	Not reached [-; -]	0.11 [0.03; 0.38]	< 0.001	0.589
Region 2	130	10 (7.7)	Not reached [-; -]	121	27 (22.3)	Not reached [-; -]	0.20 [0.09; 0.45]	< 0.001	
ECOG Performance Status									
0	175	11 (6.3)	Not reached [-; -]	164	39 (23.8)	Not reached [-; -]	0.13 [0.06; 0.30]	< 0.001	0.515
1	120	4 (3.3)	Not reached [-; -]	125	11 (8.8)	Not reached [-; -]	0.27 [0.07; 0.95]	0.042	
MMR Status									
pMMR	242	13 (5.4)	Not reached [-; -]	239	48 (20.1)	Not reached [-; -]	0.13 [0.06; 0.29]	< 0.001	0.328
dMMR	53	2 (3.8)	Not reached [-; -]	50	2 (4.0)	Not reached [-; -]	0.91 [0.13; 6.49]	0.929	
Prior History of Pelvic Radiation									
Yes	127	5 (3.9)	Not reached [-; -]	129	13 (10.1)	Not reached [-; -]	0.14 [0.03; 0.62]	0.009	0.433
No	168	10 (6.0)	Not reached [-; -]	160	37 (23.1)	Not reached [-; -]	0.16 [0.08; 0.35]	< 0.001	
SOC: Metabolism and nutrition disorders, PT[h]: Decreased appetite									

Age Group									
< 65	152	62 (40.8)	75.9 [40.6; -]	143	26 (18.2)	Not reached [-; -]	1.76 [1.10; 2.83]	0.019	0.282
≥ 65	143	67 (46.9)	38.0 [15.6; -]	146	45 (30.8)	Not reached [-; -]	1.43 [0.97; 2.09]	0.068	
Region									
Region 1	165	67 (40.6)	Not reached [33.0; -]	168	39 (23.2)	Not reached [-; -]	1.65 [1.11; 2.46]	0.014	0.819
Region 2	130	62 (47.7)	48.7 [27.0; -]	121	32 (26.4)	Not reached [-; -]	1.39 [0.89; 2.16]	0.145	
ECOG Performance Status									
0	175	73 (41.7)	75.9 [48.0; -]	164	38 (23.2)	Not reached [-; -]	1.47 [0.99; 2.20]	0.058	0.791
1	120	56 (46.7)	33.6 [14.7; -]	125	33 (26.4)	Not reached [-; -]	1.63 [1.05; 2.53]	0.029	
MMR Status									
pMMR	242	101 (41.7)	Not reached [33.6; -]	239	58 (24.3)	Not reached [-; -]	1.50 [1.08; 2.08]	0.017	0.838
dMMR	53	28 (52.8)	25.7 [7.1; -]	50	13 (26.0)	Not reached [-; -]	1.63 [0.83; 3.20]	0.155	
Prior History of Pelvic Radiation									
Yes	127	62 (48.8)	36.3 [16.9; -]	129	34 (26.4)	Not reached [-; -]	1.62 [1.05; 2.49]	0.028	0.686
No	168	67 (39.9)	75.9 [40.6; -]	160	37 (23.1)	Not reached [-; -]	1.47 [0.97; 2.21]	0.068	
SOC: Metabolism and nutrition disorders, PT[h]: Hypertriglyceridaemia									
Age Group									
< 65	152	25 (16.4)	Not reached [-; -]	143	2 (1.4)	Not reached [-; -]	6.58 [1.51; 28.71]	0.012	0.382
≥ 65	143	20 (14.0)	Not reached [-; -]	146	4 (2.7)	Not reached [-; -]	3.69 [1.24; 10.94]	0.019	
ECOG Performance Status									
0	175	30 (17.1)	Not reached [-; -]	164	3 (1.8)	Not reached [-; -]	5.51 [1.65; 18.45]	0.006	0.522
1	120	15 (12.5)	Not reached [-; -]	125	3 (2.4)	Not reached [-; -]	3.68 [1.03; 13.14]	0.045	
MMR Status									
pMMR	242	37 (15.3)	Not reached [-; -]	239	5 (2.1)	Not reached [-; -]	4.36 [1.67; 11.36]	0.003	0.900
dMMR	53	8 (15.1)	Not reached [-; -]	50	1 (2.0)	Not reached [-; -]	5.69 [0.70; 46.51]	0.105	
Prior History of Pelvic Radiation									
Yes	127	20 (15.7)	Not reached [-; -]	129	1 (0.8)	Not reached [-; -]	12.32 [1.62; 93.63]	0.015	0.170
No	168	25 (14.9)	Not reached [-; -]	160	5 (3.1)	Not reached [-; -]	3.07 [1.14; 8.25]	0.026	
SOC: Metabolism and nutrition disorders, PT[h]: Hypomagnesaemia									
Age Group									
< 65	152	19 (12.5)	Not reached [-; -]	143	6 (4.2)	Not reached [-; -]	1.45 [0.54; 3.89]	0.459	0.665
≥ 65	143	39 (27.3)	Not reached [93.3; -]	146	12 (8.2)	Not reached [-; -]	2.25 [1.15; 4.40]	0.018	
Region									
Region 1	165	36 (21.8)	Not reached [-; -]	168	13 (7.7)	Not reached [-; -]	1.85 [0.96; 3.58]	0.068	0.648

Region 2	130	22 (16.9)	Not reached [93.3; -]	121	5 (4.1)	Not reached [-; -]	2.16 [0.77; 6.02]	0.142	
ECOG Performance Status									
0	175	32 (18.3)	Not reached [-; -]	164	8 (4.9)	Not reached [-; -]	2.17 [0.96; 4.89]	0.062	0.637
1	120	26 (21.7)	Not reached [93.3; -]	125	10 (8.0)	Not reached [-; -]	1.74 [0.81; 3.72]	0.153	
MMR Status									
pMMR	242	47 (19.4)	Not reached [93.3; -]	239	17 (7.1)	Not reached [-; -]	1.66 [0.93; 2.98]	0.087	0.220
dMMR	53	11 (20.8)	Not reached [-; -]	50	1 (2.0)	Not reached [-; -]	6.26 [0.77; 50.83]	0.086	
Prior History of Pelvic Radiation									
Yes	127	31 (24.4)	Not reached [77.1; -]	129	6 (4.7)	Not reached [-; -]	2.93 [1.18; 7.30]	0.021	0.101
No	168	27 (16.1)	Not reached [-; -]	160	12 (7.5)	Not reached [-; -]	1.42 [0.70; 2.89]	0.328	
SOC: Musculoskeletal and connective tissue disorders, PT[h]: Arthralgia									
Age Group									
< 65	152	42 (27.6)	Not reached [-; -]	143	6 (4.2)	Not reached [-; -]	5.78 [2.44; 13.70]	< 0.001	0.087
≥ 65	143	44 (30.8)	Not reached [57.9; -]	146	16 (11.0)	Not reached [-; -]	2.35 [1.31; 4.22]	0.004	
Region									
Region 1	165	62 (37.6)	Not reached [34.4; -]	168	18 (10.7)	Not reached [-; -]	3.14 [1.84; 5.36]	< 0.001	0.575
Region 2	130	24 (18.5)	Not reached [-; -]	121	4 (3.3)	Not reached [-; -]	4.54 [1.56; 13.26]	0.006	
ECOG Performance Status									
0	175	53 (30.3)	Not reached [-; -]	164	14 (8.5)	Not reached [-; -]	3.22 [1.77; 5.85]	< 0.001	0.751
1	120	33 (27.5)	Not reached [57.9; -]	125	8 (6.4)	Not reached [-; -]	3.36 [1.53; 7.39]	0.003	
MMR Status									
pMMR	242	72 (29.8)	Not reached [-; -]	239	20 (8.4)	Not reached [-; -]	3.22 [1.95; 5.31]	< 0.001	0.572
dMMR	53	14 (26.4)	Not reached [52.9; -]	50	2 (4.0)	Not reached [-; -]	4.33 [0.95; 19.83]	0.059	
Prior History of Pelvic Radiation									
Yes	127	41 (32.3)	Not reached [62.6; -]	129	11 (8.5)	Not reached [-; -]	2.93 [1.48; 5.78]	0.002	0.856
No	168	45 (26.8)	Not reached [-; -]	160	11 (6.9)	Not reached [-; -]	3.64 [1.87; 7.08]	< 0.001	
SOC: Musculoskeletal and connective tissue disorders, PT[h]: Myalgia									
Age Group									
< 65	152	37 (24.3)	Not reached [83.9; -]	143	7 (4.9)	Not reached [-; -]	4.10 [1.81; 9.27]	< 0.001	0.151
≥ 65	143	15 (10.5)	Not reached [-; -]	146	7 (4.8)	Not reached [-; -]	1.50 [0.58; 3.84]	0.401	
Region									
Region 1	165	26 (15.8)	Not reached [83.9; -]	168	4 (2.4)	Not reached [-; -]	4.91 [1.68; 14.34]	0.004	0.092
Region 2	130	26 (20.0)	Not reached [-; -]	121	10 (8.3)	Not reached [-; -]	1.95 [0.93; 4.09]	0.076	
ECOG Performance Status									

0	175	37 (21.1)	Not reached [83.9; -]	164	13 (7.9)	Not reached [-; -]	2.07 [1.09; 3.95]	0.027	0.052
1	120	15 (12.5)	Not reached [-; -]	125	1 (0.8)	Not reached [-; -]	12.42 [1.62; 95.10]	0.015	
MMR Status									
pMMR	242	38 (15.7)	Not reached [-; -]	239	13 (5.4)	Not reached [-; -]	2.22 [1.16; 4.23]	0.016	0.110
dMMR	53	14 (26.4)	Not reached [84.4; -]	50	1 (2.0)	Not reached [-; -]	10.40 [1.35; 79.82]	0.024	
SOC: Musculoskeletal and connective tissue disorders, PT[h]: Pain in extremity									
Age Group									
< 65	152	23 (15.1)	Not reached [-; -]	143	10 (7.0)	Not reached [-; -]	1.59 [0.74; 3.42]	0.232	0.187
≥ 65	143	12 (8.4)	Not reached [-; -]	146	2 (1.4)	Not reached [-; -]	5.38 [1.19; 24.28]	0.029	
Region									
Region 1	165	22 (13.3)	Not reached [-; -]	168	6 (3.6)	Not reached [-; -]	3.13 [1.26; 7.81]	0.014	0.314
Region 2	130	13 (10.0)	Not reached [-; -]	121	6 (5.0)	Not reached [-; -]	1.44 [0.53; 3.93]	0.471	
ECOG Performance Status									
0	175	21 (12.0)	Not reached [-; -]	164	7 (4.3)	Not reached [-; -]	2.48 [1.05; 5.88]	0.039	0.976
1	120	14 (11.7)	Not reached [-; -]	125	5 (4.0)	Not reached [-; -]	1.89 [0.65; 5.48]	0.239	
MMR Status									
pMMR	242	32 (13.2)	Not reached [-; -]	239	10 (4.2)	Not reached [-; -]	2.47 [1.20; 5.09]	0.015	0.352
dMMR	53	3 (5.7)	Not reached [-; -]	50	2 (4.0)	Not reached [-; -]	1.32 [0.22; 7.89]	0.763	
Prior History of Pelvic Radiation									
Yes	127	14 (11.0)	Not reached [-; -]	129	8 (6.2)	Not reached [-; -]	1.40 [0.58; 3.41]	0.453	0.118
No	168	21 (12.5)	Not reached [-; -]	160	4 (2.5)	Not reached [-; -]	3.92 [1.32; 11.59]	0.014	
SOC: Nervous system disorders, PT[h]: Headache									
Age Group									
< 65	152	39 (25.7)	Not reached [82.0; -]	143	15 (10.5)	Not reached [-; -]	2.11 [1.15; 3.87]	0.016	0.181
≥ 65	143	41 (28.7)	Not reached [-; -]	146	10 (6.8)	Not reached [-; -]	3.97 [1.97; 7.98]	< 0.001	
Region									
Region 1	165	54 (32.7)	Not reached [68.1; -]	168	13 (7.7)	Not reached [-; -]	4.05 [2.19; 7.47]	< 0.001	0.052
Region 2	130	26 (20.0)	Not reached [-; -]	121	12 (9.9)	Not reached [-; -]	1.69 [0.84; 3.41]	0.140	
ECOG Performance Status									
0	175	48 (27.4)	Not reached [-; -]	164	18 (11.0)	Not reached [-; -]	2.38 [1.38; 4.11]	0.002	0.185
1	120	32 (26.7)	Not reached [62.7; -]	125	7 (5.6)	Not reached [-; -]	3.94 [1.71; 9.09]	0.001	
MMR Status									
pMMR	242	71 (29.3)	Not reached [68.1; -]	239	23 (9.6)	Not reached [-; -]	2.81 [1.74; 4.54]	< 0.001	0.912
dMMR	53	9	Not reached	50	2	Not reached	3.44	0.118	

		(17.0)	[82.0; -]		(4.0)	[-; -]	[0.73; 16.21]		
Prior History of Pelvic Radiation									
Yes	127	36 (28.3)	Not reached [68.1; -]	129	7 (5.4)	Not reached [-; -]	4.88 [2.15; 11.05]	< 0.001	0.092
No	168	44 (26.2)	Not reached [82.0; -]	160	18 (11.3)	Not reached [-; -]	2.03 [1.16; 3.56]	0.013	
SOC: Renal and urinary disorders, PT[h]: Proteinuria									
Age Group									
< 65	152	43 (28.3)	Not reached [66.1; -]	143	4 (2.8)	Not reached [-; -]	7.72 [2.74; 21.75]	< 0.001	0.943
≥ 65	143	44 (30.8)	Not reached [-; -]	146	5 (3.4)	Not reached [-; -]	8.77 [3.46; 22.24]	< 0.001	
MMR Status									
pMMR	242	73 (30.2)	Not reached [66.1; -]	239	9 (3.8)	Not reached [-; -]	7.06 [3.51; 14.20]	< 0.001	0.115
dMMR	53	14 (26.4)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Prior History of Pelvic Radiation									
Yes	127	39 (30.7)	Not reached [64.4; -]	129	2 (1.6)	Not reached [-; -]	17.13 [4.11; 71.35]	< 0.001	0.158
No	168	48 (28.6)	Not reached [73.0; -]	160	7 (4.4)	Not reached [-; -]	5.78 [2.60; 12.89]	< 0.001	
SOC: Respiratory, thoracic and mediastinal disorders, PT[h]: Dysphonia									
Age Group									
< 65	152	22 (14.5)	Not reached [-; -]	143	1 (0.7)	Not reached [-; -]	20.20 [2.71; 150.22]	0.003	0.583
≥ 65	143	41 (28.7)	Not reached [-; -]	146	1 (0.7)	Not reached [-; -]	44.34 [6.09; 322.73]	< 0.001	
Region									
Region 1	165	44 (26.7)	Not reached [-; -]	168	2 (1.2)	Not reached [-; -]	23.99 [5.81; 99.11]	< 0.001	0.273
Region 2	130	19 (14.6)	Not reached [-; -]	121	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
ECOG Performance Status									
0	175	35 (20.0)	Not reached [-; -]	164	2 (1.2)	Not reached [-; -]	17.06 [4.10; 71.01]	< 0.001	0.112
1	120	28 (23.3)	Not reached [-; -]	125	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
MMR Status									
pMMR	242	47 (19.4)	Not reached [-; -]	239	2 (0.8)	Not reached [-; -]	23.38 [5.67; 96.39]	< 0.001	0.287
dMMR	53	16 (30.2)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Prior History of Pelvic Radiation									
Yes	127	31 (24.4)	Not reached [-; -]	129	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.094
No	168	32 (19.0)	Not reached [-; -]	160	2 (1.3)	Not reached [-; -]	16.11 [3.86; 67.24]	< 0.001	
SOC: Respiratory, thoracic and mediastinal disorders, PT[h]: Epistaxis									
Age Group									
< 65	152	12 (7.9)	Not reached [-; -]	143	2 (1.4)	Not reached [-; -]	3.73 [0.81; 17.13]	0.091	0.967
≥ 65	143	11 (7.7)	Not reached [-; -]	146	2 (1.4)	Not reached [-; -]	3.91 [0.84; 18.20]	0.082	

Region									
Region 1	165	14 (8.5)	Not reached [-; -]	168	3 (1.8)	Not reached [-; -]	3.27 [0.91; 11.77]	0.070	0.645
Region 2	130	9 (6.9)	Not reached [-; -]	121	1 (0.8)	Not reached [-; -]	5.59 [0.70; 44.94]	0.106	
ECOG Performance Status									
0	175	16 (9.1)	Not reached [-; -]	164	3 (1.8)	Not reached [-; -]	3.44 [0.98; 12.10]	0.054	0.748
1	120	7 (5.8)	Not reached [-; -]	125	1 (0.8)	Not reached [-; -]	4.87 [0.58; 40.97]	0.145	
MMR Status									
pMMR	242	19 (7.9)	Not reached [-; -]	239	4 (1.7)	Not reached [-; -]	3.26 [1.08; 9.79]	0.035	0.274
dMMR	53	4 (7.5)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.135	
Prior History of Pelvic Radiation									
Yes	127	9 (7.1)	Not reached [-; -]	129	2 (1.6)	Not reached [-; -]	2.31 [0.48; 11.16]	0.299	0.680
No	168	14 (8.3)	Not reached [-; -]	160	2 (1.3)	Not reached [-; -]	5.35 [1.20; 23.96]	0.028	
SOC: Respiratory, thoracic and mediastinal disorders, PT[h]: Pulmonary embolism									
Age Group									
< 65	152	5 (3.3)	Not reached [-; -]	143	6 (4.2)	Not reached [-; -]	0.15 [0.02; 0.93]	0.042	0.547
≥ 65	143	7 (4.9)	Not reached [-; -]	146	6 (4.1)	Not reached [-; -]	0.63 [0.19; 2.08]	0.447	
Region									
Region 1	165	7 (4.2)	Not reached [-; -]	168	8 (4.8)	Not reached [-; -]	0.49 [0.16; 1.52]	0.218	0.824
Region 2	130	5 (3.8)	Not reached [-; -]	121	4 (3.3)	Not reached [-; -]	0.22 [0.03; 1.37]	0.105	
ECOG Performance Status									
0	175	7 (4.0)	Not reached [-; -]	164	6 (3.7)	Not reached [-; -]	0.33 [0.09; 1.27]	0.108	0.824
1	120	5 (4.2)	Not reached [-; -]	125	6 (4.8)	Not reached [-; -]	0.43 [0.11; 1.74]	0.237	
MMR Status									
pMMR	242	11 (4.5)	Not reached [-; -]	239	11 (4.6)	Not reached [-; -]	0.34 [0.12; 0.97]	0.043	0.804
dMMR	53	1 (1.9)	Not reached [-; -]	50	1 (2.0)	Not reached [-; -]	0.84 [0.05; 13.45]	0.901	
Prior History of Pelvic Radiation									
Yes	127	2 (1.6)	Not reached [-; -]	129	6 (4.7)	Not reached [-; -]	0.11 [0.01; 0.94]	0.043	0.070
No	168	10 (6.0)	Not reached [-; -]	160	6 (3.8)	Not reached [-; -]	0.64 [0.20; 2.06]	0.450	
SOC: Skin and subcutaneous tissue disorders, PT[h]: Alopecia									
Age Group									
< 65	152	8 (5.3)	Not reached [-; -]	143	38 (26.6)	Not reached [-; -]	0.11 [0.05; 0.25]	< 0.001	0.823
≥ 65	143	8 (5.6)	Not reached [-; -]	146	47 (32.2)	Not reached [-; -]	0.11 [0.05; 0.24]	< 0.001	
Region									
Region 1	165	7 (4.2)	Not reached [-; -]	168	51 (30.4)	Not reached [-; -]	0.09 [0.04; 0.20]	< 0.001	0.347

Region 2	130	9 (6.9)	Not reached [-; -]	121	34 (28.1)	Not reached [-; -]	0.14 [0.06; 0.30]	< 0.001	
ECOG Performance Status									
0	175	11 (6.3)	Not reached [-; -]	164	57 (34.8)	Not reached [-; -]	0.10 [0.05; 0.20]	< 0.001	0.749
1	120	5 (4.2)	Not reached [-; -]	125	28 (22.4)	Not reached [-; -]	0.13 [0.05; 0.35]	< 0.001	
MMR Status									
pMMR	242	14 (5.8)	Not reached [-; -]	239	74 (31.0)	Not reached [-; -]	0.11 [0.06; 0.20]	< 0.001	0.873
dMMR	53	2 (3.8)	Not reached [-; -]	50	11 (22.0)	Not reached [-; -]	0.13 [0.03; 0.60]	0.009	
Prior History of Pelvic Radiation									
Yes	127	10 (7.9)	Not reached [-; -]	129	39 (30.2)	Not reached [-; -]	0.14 [0.07; 0.30]	< 0.001	0.181
No	168	6 (3.6)	Not reached [-; -]	160	46 (28.8)	Not reached [-; -]	0.08 [0.03; 0.20]	< 0.001	
SOC: Skin and subcutaneous tissue disorders, PT[h]: Nail discolouration									
Age Group									
< 65	152	0 (0.0)	n.c.	143	8 (5.6)	n.c.	n.c.	n.c.	n.c.
≥ 65	143	2 (1.4)	n.c.	146	4 (2.7)	n.c.	n.c.	n.c.	
Region									
Region 1	165	1 (0.6)	n.c.	168	6 (3.6)	n.c.	n.c.	n.c.	n.c.
Region 2	130	1 (0.8)	n.c.	121	6 (5.0)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	175	1 (0.6)	Not reached [-; -]	164	10 (6.1)	Not reached [-; -]	0.07 [0.01; 0.56]	0.012	0.288
1	120	1 (0.8)	Not reached [-; -]	125	2 (1.6)	Not reached [-; -]	0.48 [0.04; 5.29]	0.548	
MMR Status									
pMMR	242	2 (0.8)	Not reached [-; -]	239	11 (4.6)	Not reached [-; -]	0.14 [0.03; 0.65]	0.012	0.546
dMMR	53	0 (0.0)	Not reached [-; -]	50	1 (2.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.298	
Prior History of Pelvic Radiation									
Yes	127	1 (0.8)	n.c.	129	4 (3.1)	n.c.	n.c.	n.c.	n.c.
No	168	1 (0.6)	n.c.	160	8 (5.0)	n.c.	n.c.	n.c.	
SOC: Skin and subcutaneous tissue disorders, PT[h]: Palmar-plantar erythrodysaesthesia syndrome									
ECOG Performance Status									
0	175	39 (22.3)	Not reached [-; -]	164	3 (1.8)	Not reached [-; -]	9.77 [3.00; 31.84]	< 0.001	0.096
1	120	22 (18.3)	Not reached [77.7; -]	125	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
MMR Status									
pMMR	242	50 (20.7)	Not reached [-; -]	239	3 (1.3)	Not reached [-; -]	12.67 [3.93; 40.87]	< 0.001	0.327
dMMR	53	11 (20.8)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.007	
Prior History of Pelvic Radiation									

Yes	127	21 (16.5)	Not reached [-; -]	129	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.124
No	168	40 (23.8)	Not reached [77.7; -]	160	3 (1.9)	Not reached [-; -]	10.40 [3.20; 33.80]	< 0.001	
SOC: Skin and subcutaneous tissue disorders, PT[h]: Pruritus									
Age Group									
< 65	152	12 (7.9)	Not reached [-; -]	143	3 (2.1)	Not reached [-; -]	2.21 [0.59; 8.36]	0.241	0.522
≥ 65	143	18 (12.6)	Not reached [-; -]	146	3 (2.1)	Not reached [-; -]	4.07 [1.16; 14.31]	0.028	
Region									
Region 1	165	22 (13.3)	Not reached [-; -]	168	3 (1.8)	Not reached [-; -]	4.96 [1.44; 17.06]	0.011	0.193
Region 2	130	8 (6.2)	Not reached [-; -]	121	3 (2.5)	Not reached [-; -]	1.41 [0.34; 5.87]	0.634	
ECOG Performance Status									
0	175	20 (11.4)	Not reached [-; -]	164	5 (3.0)	Not reached [-; -]	2.00 [0.70; 5.68]	0.195	0.320
1	120	10 (8.3)	Not reached [-; -]	125	1 (0.8)	Not reached [-; -]	8.63 [1.09; 68.20]	0.041	
MMR Status									
pMMR	242	22 (9.1)	Not reached [-; -]	239	6 (2.5)	Not reached [-; -]	2.33 [0.90; 6.00]	0.080	0.098
dMMR	53	8 (15.1)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.038	
Prior History of Pelvic Radiation									
Yes	127	13 (10.2)	Not reached [-; -]	129	1 (0.8)	Not reached [-; -]	6.39 [0.79; 51.94]	0.083	0.189
No	168	17 (10.1)	Not reached [-; -]	160	5 (3.1)	Not reached [-; -]	2.42 [0.87; 6.74]	0.090	
SOC: Skin and subcutaneous tissue disorders, PT[h]: Rash									
Age Group									
< 65	152	26 (17.1)	Not reached [99.3; -]	143	3 (2.1)	Not reached [-; -]	5.98 [1.78; 20.12]	0.004	0.749
≥ 65	143	21 (14.7)	Not reached [-; -]	146	2 (1.4)	Not reached [-; -]	8.59 [2.00; 36.99]	0.004	
Region									
Region 1	165	25 (15.2)	Not reached [-; -]	168	3 (1.8)	Not reached [-; -]	6.76 [2.02; 22.64]	0.002	0.916
Region 2	130	22 (16.9)	Not reached [99.3; -]	121	2 (1.7)	Not reached [-; -]	7.49 [1.73; 32.36]	0.007	
ECOG Performance Status									
0	175	28 (16.0)	Not reached [-; -]	164	3 (1.8)	Not reached [-; -]	6.68 [2.00; 22.23]	0.002	0.899
1	120	19 (15.8)	Not reached [99.3; -]	125	2 (1.6)	Not reached [-; -]	7.58 [1.74; 33.02]	0.007	
MMR Status									
pMMR	242	36 (14.9)	Not reached [99.3; -]	239	4 (1.7)	Not reached [-; -]	6.95 [2.45; 19.74]	< 0.001	0.973
dMMR	53	11 (20.8)	Not reached [-; -]	50	1 (2.0)	Not reached [-; -]	7.25 [0.91; 57.47]	0.061	
Prior History of Pelvic Radiation									
Yes	127	21 (16.5)	Not reached [-; -]	129	1 (0.8)	Not reached [-; -]	16.55 [2.21; 124.24]	0.006	0.245
No	168	26	Not reached	160	4	Not reached	4.68	0.005	

		(15.5)	[99.3; -]		(2.5)	[-; -]	[1.61; 13.63]		
SOC: Skin and subcutaneous tissue disorders, PT[h]: Rash maculo-papular									
Age Group									
< 65	152	7 (4.6)	n.c.	143	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	143	4 (2.8)	n.c.	146	0 (0.0)	n.c.	n.c.	n.c.	
Region									
Region 1	165	5 (3.0)	n.c.	168	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Region 2	130	6 (4.6)	n.c.	121	0 (0.0)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	175	9 (5.1)	n.c.	164	0 (0.0)	n.c.	n.c.	n.c.	n.c.
1	120	2 (1.7)	n.c.	125	0 (0.0)	n.c.	n.c.	n.c.	
MMR Status									
pMMR	242	9 (3.7)	n.c.	239	0 (0.0)	n.c.	n.c.	n.c.	n.c.
dMMR	53	2 (3.8)	n.c.	50	0 (0.0)	n.c.	n.c.	n.c.	
Prior History of Pelvic Radiation									
Yes	127	4 (3.1)	n.c.	129	0 (0.0)	n.c.	n.c.	n.c.	n.c.
No	168	7 (4.2)	n.c.	160	0 (0.0)	n.c.	n.c.	n.c.	
SOC: Vascular disorders, PT[h]: Deep vein thrombosis									
Age Group									
< 65	152	4 (2.6)	n.c.	143	5 (3.5)	n.c.	n.c.	n.c.	n.c.
≥ 65	143	1 (0.7)	n.c.	146	7 (4.8)	n.c.	n.c.	n.c.	
Region									
Region 1	165	3 (1.8)	Not reached [-; -]	168	9 (5.4)	Not reached [-; -]	0.25 [0.07; 0.95]	0.042	0.610
Region 2	130	2 (1.5)	Not reached [-; -]	121	3 (2.5)	Not reached [-; -]	0.56 [0.09; 3.33]	0.520	
ECOG Performance Status									
0	175	2 (1.1)	Not reached [-; -]	164	2 (1.2)	Not reached [-; -]	0.78 [0.11; 5.59]	0.809	0.342
1	120	3 (2.5)	Not reached [-; -]	125	10 (8.0)	Not reached [-; -]	0.24 [0.06; 0.88]	0.031	
MMR Status									
pMMR	242	5 (2.1)	Not reached [-; -]	239	11 (4.6)	Not reached [-; -]	0.36 [0.12; 1.05]	0.061	0.370
dMMR	53	0 (0.0)	Not reached [-; -]	50	1 (2.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.245	
Prior History of Pelvic Radiation									
Yes	127	2 (1.6)	Not reached [-; -]	129	5 (3.9)	Not reached [-; -]	0.34 [0.07; 1.75]	0.196	0.962
No	168	3 (1.8)	Not reached [-; -]	160	7 (4.4)	Not reached [-; -]	0.32 [0.08; 1.24]	0.098	
SOC: Vascular disorders, PT[h]: Hypertension									

Age Group									
< 65	152	97 (63.8)	5.4 [2.7; 11.1]	143	4 (2.8)	Not reached [-; -]	30.40 [11.16; 82.81]	< 0.001	0.422
≥ 65	143	92 (64.3)	3.6 [2.4; 7.1]	146	7 (4.8)	Not reached [-; -]	18.87 [8.74; 40.78]	< 0.001	
Region									
Region 1	165	99 (60.0)	5.4 [3.0; 14.7]	168	8 (4.8)	Not reached [-; -]	16.86 [8.19; 34.71]	< 0.001	0.183
Region 2	130	90 (69.2)	3.9 [2.3; 8.1]	121	3 (2.5)	Not reached [-; -]	39.42 [12.45; 124.79]	< 0.001	
ECOG Performance Status									
0	175	120 (68.6)	3.9 [2.3; 8.1]	164	5 (3.0)	Not reached [-; -]	31.10 [12.69; 76.22]	< 0.001	0.271
1	120	69 (57.5)	5.9 [3.1; 28.7]	125	6 (4.8)	Not reached [-; -]	16.25 [7.04; 37.52]	< 0.001	
MMR Status									
pMMR	242	163 (67.4)	3.5 [2.6; 5.9]	239	9 (3.8)	Not reached [-; -]	25.63 [13.08; 50.22]	< 0.001	0.475
dMMR	53	26 (49.1)	59.7 [3.9; -]	50	2 (4.0)	Not reached [-; -]	13.78 [3.25; 58.37]	< 0.001	
Prior History of Pelvic Radiation									
Yes	127	84 (66.1)	5.1 [2.3; 9.1]	129	7 (5.4)	Not reached [-; -]	16.57 [7.65; 35.90]	< 0.001	0.234
No	168	105 (62.5)	4.6 [2.9; 10.0]	160	4 (2.5)	Not reached [-; -]	34.35 [12.63; 93.39]	< 0.001	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: all-participants-as-treated, population relevant for benefit assessment

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

h: A specific adverse event appears on this report only if its incidence ≥ 10% or (incidence ≥ 1% and in at least 10 participants) in one or more groups and p-value of main treatment effect is smaller than 0.05, and p-value for interaction test is greater than or equal to 0.05 or rule of 10 is not met

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; MMR: Mismatch Repair; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 participants per subgroup and at least 10 events in one of the subgroups necessary; pMMR: Mismatch Repair Proficient; PT: Preferred Term; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world; SOC: System Organ Class

Analyses of Time to Serious Adverse Event by Subgroups with p-Value for Interaction Test ≥ 0.05 or Rule of 10 Not Met (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Groups) For System Organ Classes

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		p-Value for Interaction Test[g]
Serious Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	
SOC[h]: Blood and lymphatic system disorders									
Age Group									
< 65	152	2 (1.3)	Not reached [-; -]	143	14 (9.8)	Not reached [-; -]	0.07 [0.01; 0.44]	0.004	0.288
≥ 65	143	5 (3.5)	Not reached [-; -]	146	15 (10.3)	Not reached [-; -]	0.31 [0.11; 0.87]	0.025	
Region									
Region 1	165	5 (3.0)	Not reached [-; -]	168	19 (11.3)	Not reached [-; -]	0.25 [0.09; 0.67]	0.006	0.685
Region 2	130	2 (1.5)	Not reached [-; -]	121	10 (8.3)	Not reached [-; -]	0.11 [0.02; 0.61]	0.012	
ECOG Performance Status									
0	175	5 (2.9)	Not reached [-; -]	164	13 (7.9)	Not reached [-; -]	0.28 [0.09; 0.84]	0.023	0.231
1	120	2 (1.7)	Not reached [-; -]	125	16 (12.8)	Not reached [-; -]	0.12 [0.03; 0.52]	0.004	
MMR Status									
pMMR	242	7 (2.9)	Not reached [-; -]	239	23 (9.6)	Not reached [-; -]	0.25 [0.10; 0.60]	0.002	0.067
dMMR	53	0 (0.0)	Not reached [-; -]	50	6 (12.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.008	
Prior History of Pelvic Radiation									
Yes	127	2 (1.6)	Not reached [-; -]	129	14 (10.9)	Not reached [-; -]	0.13 [0.03; 0.59]	0.008	0.343
No	168	5 (3.0)	Not reached [-; -]	160	15 (9.4)	Not reached [-; -]	0.24 [0.08; 0.71]	0.010	
SOC[h]: Gastrointestinal disorders									
Region									
Region 1	165	27 (16.4)	Not reached [-; -]	168	9 (5.4)	Not reached [-; -]	2.54 [1.18; 5.47]	0.017	0.565
Region 2	130	17 (13.1)	Not reached [-; -]	121	7 (5.8)	Not reached [-; -]	1.64 [0.66; 4.08]	0.287	
ECOG Performance Status									
0	175	22 (12.6)	Not reached [-; -]	164	5 (3.0)	Not reached [-; -]	2.93 [1.08; 7.93]	0.034	0.261
1	120	22 (18.3)	Not reached [-; -]	125	11 (8.8)	Not reached [-; -]	1.79 [0.86; 3.74]	0.120	
MMR Status									
pMMR	242	30 (12.4)	Not reached [-; -]	239	12 (5.0)	Not reached [-; -]	2.07 [1.05; 4.08]	0.037	0.787
dMMR	53	14 (26.4)	Not reached [79.6; -]	50	4 (8.0)	Not reached [-; -]	2.22 [0.70; 7.03]	0.175	
Prior History of Pelvic Radiation									
Yes	127	22	Not reached	129	8	Not reached	2.34	0.042	0.882

		(17.3)	[-; -]		(6.2)	[-; -]	[1.03; 5.33]		
No	168	22 (13.1)	Not reached [-; -]	160	8 (5.0)	Not reached [-; -]	1.92 [0.83; 4.44]	0.125	
SOC[h]: Hepatobiliary disorders									
Age Group									
< 65	152	3 (2.0)	n.c.	143	1 (0.7)	n.c.	n.c.	n.c.	n.c.
≥ 65	143	9 (6.3)	n.c.	146	0 (0.0)	n.c.	n.c.	n.c.	
Region									
Region 1	165	3 (1.8)	Not reached [-; -]	168	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.113	0.444
Region 2	130	9 (6.9)	Not reached [-; -]	121	1 (0.8)	Not reached [-; -]	6.91 [0.87; 54.78]	0.067	
ECOG Performance Status									
0	175	7 (4.0)	n.c.	164	1 (0.6)	n.c.	n.c.	n.c.	n.c.
1	120	5 (4.2)	n.c.	125	0 (0.0)	n.c.	n.c.	n.c.	
MMR Status									
pMMR	242	8 (3.3)	n.c.	239	1 (0.4)	n.c.	n.c.	n.c.	n.c.
dMMR	53	4 (7.5)	n.c.	50	0 (0.0)	n.c.	n.c.	n.c.	
Prior History of Pelvic Radiation									
Yes	127	6 (4.7)	n.c.	129	0 (0.0)	n.c.	n.c.	n.c.	n.c.
No	168	6 (3.6)	n.c.	160	1 (0.6)	n.c.	n.c.	n.c.	
SOC[h]: Metabolism and nutrition disorders									
Age Group									
< 65	152	12 (7.9)	Not reached [-; -]	143	2 (1.4)	Not reached [-; -]	4.38 [0.96; 20.03]	0.057	0.454
≥ 65	143	11 (7.7)	Not reached [-; -]	146	4 (2.7)	Not reached [-; -]	2.41 [0.77; 7.61]	0.132	
Region									
Region 1	165	11 (6.7)	Not reached [-; -]	168	3 (1.8)	Not reached [-; -]	2.67 [0.72; 9.91]	0.141	0.990
Region 2	130	12 (9.2)	Not reached [-; -]	121	3 (2.5)	Not reached [-; -]	3.37 [0.95; 11.95]	0.061	
ECOG Performance Status									
0	175	14 (8.0)	Not reached [-; -]	164	3 (1.8)	Not reached [-; -]	3.77 [1.07; 13.24]	0.039	0.696
1	120	9 (7.5)	Not reached [-; -]	125	3 (2.4)	Not reached [-; -]	2.36 [0.62; 8.94]	0.206	
MMR Status									
pMMR	242	18 (7.4)	Not reached [-; -]	239	5 (2.1)	Not reached [-; -]	2.85 [1.04; 7.79]	0.042	0.911
dMMR	53	5 (9.4)	Not reached [-; -]	50	1 (2.0)	Not reached [-; -]	3.83 [0.45; 32.89]	0.221	
Prior History of Pelvic Radiation									
Yes	127	16 (12.6)	Not reached [-; -]	129	2 (1.6)	Not reached [-; -]	6.08 [1.38; 26.80]	0.017	0.094
No	168	7 (4.2)	Not reached [-; -]	160	4 (2.5)	Not reached [-; -]	1.61 [0.47; 5.50]	0.449	

SOC[h]: Vascular disorders									
Age Group									
< 65	152	8 (5.3)	Not reached [-; -]	143	2 (1.4)	Not reached [-; -]	3.32 [0.69; 15.96]	0.135	0.537
≥ 65	143	8 (5.6)	Not reached [-; -]	146	1 (0.7)	Not reached [-; -]	6.87 [0.84; 55.87]	0.072	
Region									
Region 1	165	9 (5.5)	Not reached [-; -]	168	1 (0.6)	Not reached [-; -]	9.29 [1.18; 73.34]	0.034	0.394
Region 2	130	7 (5.4)	Not reached [-; -]	121	2 (1.7)	Not reached [-; -]	2.23 [0.43; 11.50]	0.339	
MMR Status									
pMMR	242	15 (6.2)	Not reached [-; -]	239	3 (1.3)	Not reached [-; -]	4.27 [1.22; 14.98]	0.023	0.587
dMMR	53	1 (1.9)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.336	
Prior History of Pelvic Radiation									
Yes	127	9 (7.1)	Not reached [-; -]	129	2 (1.6)	Not reached [-; -]	3.94 [0.84; 18.56]	0.083	0.774
No	168	7 (4.2)	Not reached [-; -]	160	1 (0.6)	Not reached [-; -]	5.79 [0.70; 48.11]	0.104	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: all-participants-as-treated, population relevant for benefit assessment

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

h: A system organ class appears on this report only if its incidence ≥ 5% or (incidence ≥ 1% and in at least 10 participants) in one or more groups and p-value of main treatment effect is smaller than 0.05, and p-value for interaction test is greater than or equal to 0.05 or rule of 10 is not met

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; MMR: Mismatch Repair; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 participants per subgroup and at least 10 events in one of the subgroups necessary; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world; SOC: System Organ Class

Analyses of Time to Serious Adverse Event by Subgroups with p-Value for Interaction Test ≥ 0.05 or Rule of 10 Not Met (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Groups) For Preferred Terms

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
Serious Adverse Events	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
SOC: Blood and lymphatic system disorders, PT[h]: Febrile neutropenia									
Age Group									
< 65	152	1 (0.7)	n.c.	143	8 (5.6)	n.c.	n.c.	n.c.	n.c.
≥ 65	143	1 (0.7)	n.c.	146	7 (4.8)	n.c.	n.c.	n.c.	
Region									
Region 1	165	0 (0.0)	n.c.	168	8 (4.8)	n.c.	n.c.	n.c.	n.c.
Region 2	130	2 (1.5)	n.c.	121	7 (5.8)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	175	2 (1.1)	Not reached [-; -]	164	10 (6.1)	Not reached [-; -]	0.10 [0.01; 0.64]	0.016	0.258
1	120	0 (0.0)	Not reached [-; -]	125	5 (4.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.026	
MMR Status									
pMMR	242	2 (0.8)	Not reached [-; -]	239	12 (5.0)	Not reached [-; -]	0.09 [0.02; 0.55]	0.009	0.298
dMMR	53	0 (0.0)	Not reached [-; -]	50	3 (6.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.060	
Prior History of Pelvic Radiation									
Yes	127	0 (0.0)	Not reached [-; -]	129	7 (5.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.007	0.129
No	168	2 (1.2)	Not reached [-; -]	160	8 (5.0)	Not reached [-; -]	0.11 [0.01; 0.89]	0.038	
SOC: Infections and infestations, PT[h]: Urinary tract infection									
Age Group									
< 65	152	9 (5.9)	Not reached [-; -]	143	1 (0.7)	Not reached [-; -]	5.88 [0.73; 47.61]	0.097	0.444
≥ 65	143	3 (2.1)	Not reached [-; -]	146	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.087	
Region									
Region 1	165	5 (3.0)	n.c.	168	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Region 2	130	7 (5.4)	n.c.	121	1 (0.8)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	175	4 (2.3)	n.c.	164	1 (0.6)	n.c.	n.c.	n.c.	n.c.
1	120	8 (6.7)	n.c.	125	0 (0.0)	n.c.	n.c.	n.c.	
MMR Status									
pMMR	242	10	Not reached	239	1	Not reached	7.29	0.061	0.589

		(4.1)	[-; -]		(0.4)	[-; -]	[0.91; 58.10]		
dMMR	53	2 (3.8)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.208	
Prior History of Pelvic Radiation									
Yes	127	7 (5.5)	n.c.	129	0 (0.0)	n.c.	n.c.	n.c.	n.c.
No	168	5 (3.0)	n.c.	160	1 (0.6)	n.c.	n.c.	n.c.	
SOC: Vascular disorders, PT[h]: Hypertension									
Age Group									
< 65	152	6 (3.9)	n.c.	143	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	143	5 (3.5)	n.c.	146	0 (0.0)	n.c.	n.c.	n.c.	
Region									
Region 1	165	8 (4.8)	n.c.	168	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Region 2	130	3 (2.3)	n.c.	121	0 (0.0)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	175	9 (5.1)	n.c.	164	0 (0.0)	n.c.	n.c.	n.c.	n.c.
1	120	2 (1.7)	n.c.	125	0 (0.0)	n.c.	n.c.	n.c.	
MMR Status									
pMMR	242	10 (4.1)	Not reached [-; -]	239	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	0.997
dMMR	53	1 (1.9)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.336	
Prior History of Pelvic Radiation									
Yes	127	6 (4.7)	n.c.	129	0 (0.0)	n.c.	n.c.	n.c.	n.c.
No	168	5 (3.0)	n.c.	160	0 (0.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: all-participants-as-treated, population relevant for benefit assessment

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

h: A specific adverse event appears on this report only if its incidence ≥ 5% or (incidence ≥ 1% and in at least 10 participants) in one or more groups and p-value of main treatment effect is smaller than 0.05, and p-value for interaction test is greater than or equal to 0.05 or rule of 10 is not met

CI: Confidence Interval; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; MMR: Mismatch Repair; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 participants per subgroup and at least 10 events in one of the subgroups necessary; pMMR: Mismatch Repair Proficient; PT: Preferred Term; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world; SOC: System Organ Class

Analyses of Time to Severe Adverse Event (CTCAE-Grade 3-5) by Subgroups with p-Value for Interaction Test ≥ 0.05 or Rule of 10 Not Met (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Groups) For System Organ Classes

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
SOC[h]: Blood and lymphatic system disorders									
Age Group									
< 65	152	22 (14.5)	Not reached [-; -]	143	63 (44.1)	Not reached [9.1; -]	0.20 [0.12; 0.33]	< 0.001	0.248
≥ 65	143	18 (12.6)	Not reached [-; -]	146	79 (54.1)	7.1 [4.6; -]	0.14 [0.08; 0.23]	< 0.001	
Region									
Region 1	165	17 (10.3)	Not reached [-; -]	168	81 (48.2)	15.6 [5.1; -]	0.14 [0.08; 0.23]	< 0.001	0.161
Region 2	130	23 (17.7)	Not reached [-; -]	121	61 (50.4)	11.0 [5.1; -]	0.20 [0.12; 0.33]	< 0.001	
ECOG Performance Status									
0	175	24 (13.7)	Not reached [-; -]	164	84 (51.2)	10.3 [5.1; -]	0.16 [0.10; 0.25]	< 0.001	0.652
1	120	16 (13.3)	Not reached [-; -]	125	58 (46.4)	15.6 [6.4; -]	0.17 [0.10; 0.31]	< 0.001	
MMR Status									
pMMR	242	29 (12.0)	Not reached [-; -]	239	120 (50.2)	11.0 [5.3; -]	0.15 [0.10; 0.22]	< 0.001	0.182
dMMR	53	11 (20.8)	Not reached [-; -]	50	22 (44.0)	Not reached [2.3; -]	0.26 [0.12; 0.55]	< 0.001	
Prior History of Pelvic Radiation									
Yes	127	18 (14.2)	Not reached [-; -]	129	66 (51.2)	9.1 [3.1; -]	0.14 [0.08; 0.25]	< 0.001	0.717
No	168	22 (13.1)	Not reached [-; -]	160	76 (47.5)	22.7 [6.4; -]	0.18 [0.11; 0.30]	< 0.001	
SOC[h]: Cardiac disorders									
Age Group									
< 65	152	3 (2.0)	Not reached [-; -]	143	5 (3.5)	Not reached [-; -]	0.17 [0.03; 0.93]	0.041	0.597
≥ 65	143	5 (3.5)	Not reached [-; -]	146	6 (4.1)	Not reached [28.0; -]	0.19 [0.04; 0.81]	0.025	
Region									
Region 1	165	4 (2.4)	Not reached [-; -]	168	5 (3.0)	Not reached [27.7; -]	0.07 [0.01; 0.45]	0.005	0.843
Region 2	130	4 (3.1)	Not reached [-; -]	121	6 (5.0)	Not reached [30.1; -]	0.29 [0.07; 1.12]	0.072	
ECOG Performance Status									
0	175	5 (2.9)	Not reached [-; -]	164	7 (4.3)	Not reached [30.1; -]	0.13 [0.03; 0.59]	0.008	0.903
1	120	3 (2.5)	Not reached [-; -]	125	4 (3.2)	28.0 [28.0; -]	0.25 [0.04; 1.43]	0.119	
MMR Status									
pMMR	242	5 (2.1)	Not reached [-; -]	239	10 (4.2)	Not reached [28.0; -]	0.10 [0.03; 0.37]	< 0.001	0.264

dMMR	53	3 (5.7)	Not reached [-; -]	50	1 (2.0)	Not reached [-; -]	1.47 [0.13; 16.26]	0.756	
Prior History of Pelvic Radiation									
Yes	127	5 (3.9)	Not reached [-; -]	129	4 (3.1)	Not reached [-; -]	0.41 [0.08; 1.97]	0.265	0.328
No	168	3 (1.8)	Not reached [-; -]	160	7 (4.4)	Not reached [28.0; -]	0.10 [0.02; 0.46]	0.003	
SOC[h]: Endocrine disorders									
Age Group									
< 65	152	3 (2.0)	n.c.	143	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	143	7 (4.9)	n.c.	146	0 (0.0)	n.c.	n.c.	n.c.	
Region									
Region 1	165	7 (4.2)	n.c.	168	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Region 2	130	3 (2.3)	n.c.	121	0 (0.0)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	175	6 (3.4)	n.c.	164	0 (0.0)	n.c.	n.c.	n.c.	n.c.
1	120	4 (3.3)	n.c.	125	0 (0.0)	n.c.	n.c.	n.c.	
MMR Status									
pMMR	242	6 (2.5)	n.c.	239	0 (0.0)	n.c.	n.c.	n.c.	n.c.
dMMR	53	4 (7.5)	n.c.	50	0 (0.0)	n.c.	n.c.	n.c.	
Prior History of Pelvic Radiation									
Yes	127	4 (3.1)	n.c.	129	0 (0.0)	n.c.	n.c.	n.c.	n.c.
No	168	6 (3.6)	n.c.	160	0 (0.0)	n.c.	n.c.	n.c.	
SOC[h]: Hepatobiliary disorders									
Age Group									
< 65	152	6 (3.9)	Not reached [-; -]	143	1 (0.7)	Not reached [-; -]	1.89 [0.19; 18.40]	0.584	0.145
≥ 65	143	11 (7.7)	Not reached [-; -]	146	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.016	
Region									
Region 1	165	5 (3.0)	Not reached [-; -]	168	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.199	0.395
Region 2	130	12 (9.2)	Not reached [-; -]	121	1 (0.8)	Not reached [-; -]	5.95 [0.75; 47.40]	0.092	
ECOG Performance Status									
0	175	11 (6.3)	Not reached [-; -]	164	1 (0.6)	Not reached [-; -]	5.02 [0.61; 40.98]	0.132	0.334
1	120	6 (5.0)	Not reached [-; -]	125	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.108	
MMR Status									
pMMR	242	13 (5.4)	Not reached [-; -]	239	1 (0.4)	Not reached [-; -]	5.30 [0.65; 42.92]	0.118	0.515
dMMR	53	4 (7.5)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.118	
Prior History of Pelvic Radiation									

Yes	127	9 (7.1)	n.c.	129	0 (0.0)	n.c.	n.c.	n.c.	n.c.
No	168	8 (4.8)	n.c.	160	1 (0.6)	n.c.	n.c.	n.c.	
SOC[h]: Investigations									
Age Group									
< 65	152	52 (34.2)	81.0 [47.9; -]	143	52 (36.4)	Not reached [25.3; -]	0.42 [0.27; 0.66]	< 0.001	0.902
≥ 65	143	46 (32.2)	Not reached [50.0; -]	146	52 (35.6)	Not reached [-; -]	0.48 [0.31; 0.74]	0.001	
ECOG Performance Status									
0	175	68 (38.9)	72.9 [45.1; -]	164	67 (40.9)	Not reached [19.1; -]	0.42 [0.29; 0.62]	< 0.001	0.968
1	120	30 (25.0)	Not reached [-; -]	125	37 (29.6)	Not reached [-; -]	0.49 [0.29; 0.83]	0.008	
MMR Status									
pMMR	242	81 (33.5)	81.0 [50.0; -]	239	93 (38.9)	Not reached [25.3; -]	0.41 [0.29; 0.57]	< 0.001	0.230
dMMR	53	17 (32.1)	Not reached [43.9; -]	50	11 (22.0)	Not reached [-; -]	0.83 [0.36; 1.88]	0.649	
SOC[h]: Metabolism and nutrition disorders									
Age Group									
< 65	152	36 (23.7)	Not reached [81.3; -]	143	9 (6.3)	Not reached [-; -]	2.48 [1.17; 5.25]	0.018	0.824
≥ 65	143	41 (28.7)	Not reached [-; -]	146	13 (8.9)	Not reached [-; -]	2.04 [1.07; 3.89]	0.031	
Region									
Region 1	165	35 (21.2)	Not reached [-; -]	168	11 (6.5)	Not reached [-; -]	2.06 [1.02; 4.17]	0.044	0.770
Region 2	130	42 (32.3)	89.6 [77.1; -]	121	11 (9.1)	Not reached [-; -]	2.34 [1.19; 4.63]	0.014	
ECOG Performance Status									
0	175	44 (25.1)	Not reached [-; -]	164	9 (5.5)	Not reached [-; -]	3.01 [1.45; 6.25]	0.003	0.220
1	120	33 (27.5)	Not reached [81.3; -]	125	13 (10.4)	Not reached [-; -]	1.65 [0.84; 3.24]	0.145	
MMR Status									
pMMR	242	60 (24.8)	Not reached [81.3; -]	239	14 (5.9)	Not reached [-; -]	2.59 [1.42; 4.72]	0.002	0.093
dMMR	53	17 (32.1)	Not reached [27.0; -]	50	8 (16.0)	Not reached [-; -]	1.45 [0.62; 3.42]	0.393	
Prior History of Pelvic Radiation									
Yes	127	40 (31.5)	Not reached [77.1; -]	129	10 (7.8)	Not reached [-; -]	2.49 [1.21; 5.10]	0.013	0.497
No	168	37 (22.0)	Not reached [89.6; -]	160	12 (7.5)	Not reached [-; -]	1.99 [1.02; 3.87]	0.044	
SOC[h]: Musculoskeletal and connective tissue disorders									
Age Group									
< 65	152	15 (9.9)	Not reached [-; -]	143	3 (2.1)	Not reached [-; -]	3.01 [0.84; 10.74]	0.089	0.704
≥ 65	143	7 (4.9)	Not reached [-; -]	146	1 (0.7)	Not reached [-; -]	3.91 [0.45; 33.77]	0.215	
ECOG Performance Status									
0	175	15 (8.6)	Not reached [-; -]	164	2 (1.2)	Not reached [-; -]	4.33 [0.96; 19.63]	0.057	0.535

1	120	7 (5.8)	Not reached [-; -]	125	2 (1.6)	Not reached [-; -]	2.24 [0.45; 11.20]	0.327	
MMR Status									
pMMR	242	20 (8.3)	Not reached [-; -]	239	3 (1.3)	Not reached [-; -]	3.97 [1.15; 13.77]	0.030	0.318
dMMR	53	2 (3.8)	Not reached [-; -]	50	1 (2.0)	Not reached [-; -]	1.34 [0.12; 15.42]	0.814	
Prior History of Pelvic Radiation									
Yes	127	12 (9.4)	Not reached [-; -]	129	1 (0.8)	Not reached [-; -]	6.42 [0.80; 51.67]	0.081	0.245
No	168	10 (6.0)	Not reached [-; -]	160	3 (1.9)	Not reached [-; -]	2.29 [0.62; 8.50]	0.216	
SOC[h]: Respiratory, thoracic and mediastinal disorders									
Age Group									
< 65	152	10 (6.6)	Not reached [-; -]	143	7 (4.9)	Not reached [-; -]	0.60 [0.19; 1.87]	0.376	0.310
≥ 65	143	7 (4.9)	Not reached [-; -]	146	11 (7.5)	Not reached [-; -]	0.36 [0.12; 1.03]	0.057	
Region									
Region 1	165	10 (6.1)	Not reached [-; -]	168	12 (7.1)	Not reached [-; -]	0.55 [0.22; 1.35]	0.193	0.772
Region 2	130	7 (5.4)	Not reached [-; -]	121	6 (5.0)	Not reached [-; -]	0.30 [0.07; 1.26]	0.100	
ECOG Performance Status									
0	175	10 (5.7)	Not reached [-; -]	164	9 (5.5)	Not reached [-; -]	0.49 [0.17; 1.36]	0.171	0.770
1	120	7 (5.8)	Not reached [-; -]	125	9 (7.2)	Not reached [-; -]	0.40 [0.13; 1.30]	0.128	
MMR Status									
pMMR	242	15 (6.2)	Not reached [-; -]	239	16 (6.7)	Not reached [-; -]	0.47 [0.21; 1.06]	0.069	0.831
dMMR	53	2 (3.8)	Not reached [-; -]	50	2 (4.0)	Not reached [-; -]	0.28 [0.02; 3.34]	0.314	
SOC[h]: Skin and subcutaneous tissue disorders									
Age Group									
< 65	152	9 (5.9)	Not reached [-; -]	143	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.018	0.138
≥ 65	143	10 (7.0)	Not reached [-; -]	146	2 (1.4)	Not reached [-; -]	2.35 [0.49; 11.35]	0.288	
Region									
Region 1	165	11 (6.7)	Not reached [-; -]	168	2 (1.2)	Not reached [-; -]	3.21 [0.69; 15.03]	0.138	0.170
Region 2	130	8 (6.2)	Not reached [-; -]	121	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.050	
ECOG Performance Status									
0	175	13 (7.4)	Not reached [-; -]	164	1 (0.6)	Not reached [-; -]	6.21 [0.78; 49.20]	0.084	0.657
1	120	6 (5.0)	Not reached [-; -]	125	1 (0.8)	Not reached [-; -]	4.17 [0.50; 34.97]	0.188	
MMR Status									
pMMR	242	17 (7.0)	Not reached [-; -]	239	2 (0.8)	Not reached [-; -]	4.60 [1.03; 20.43]	0.045	0.559
dMMR	53	2 (3.8)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.267	
Prior History of Pelvic Radiation									

Yes	127	9 (7.1)	Not reached [-; -]	129	1 (0.8)	Not reached [-; -]	4.39 [0.53; 36.15]	0.169	0.951
No	168	10 (6.0)	Not reached [-; -]	160	1 (0.6)	Not reached [-; -]	5.86 [0.73; 46.98]	0.096	
SOC[h]: Vascular disorders									
Age Group									
< 65	152	56 (36.8)	Not reached [59.7; -]	143	5 (3.5)	Not reached [-; -]	10.68 [4.26; 26.78]	< 0.001	0.778
≥ 65	143	59 (41.3)	Not reached [32.7; -]	146	7 (4.8)	Not reached [-; -]	9.09 [4.13; 19.98]	< 0.001	
Region									
Region 1	165	63 (38.2)	Not reached [43.4; -]	168	9 (5.4)	Not reached [-; -]	7.73 [3.83; 15.59]	< 0.001	0.225
Region 2	130	52 (40.0)	Not reached [39.1; -]	121	3 (2.5)	Not reached [-; -]	15.73 [4.88; 50.66]	< 0.001	
MMR Status									
pMMR	242	99 (40.9)	Not reached [39.1; -]	239	11 (4.6)	Not reached [-; -]	9.57 [5.12; 17.89]	< 0.001	0.736
dMMR	53	16 (30.2)	Not reached [68.3; -]	50	1 (2.0)	Not reached [-; -]	12.83 [1.68; 98.09]	0.014	
Prior History of Pelvic Radiation									
Yes	127	51 (40.2)	Not reached [32.7; -]	129	8 (6.2)	Not reached [-; -]	6.67 [3.15; 14.13]	< 0.001	0.143
No	168	64 (38.1)	Not reached [54.0; -]	160	4 (2.5)	Not reached [-; -]	15.72 [5.70; 43.33]	< 0.001	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: all-participants-as-treated, population relevant for benefit assessment

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

h: A system organ class appears on this report only if its incidence ≥ 5% or (incidence ≥ 1% and in at least 10 participants) in one or more groups and p-value of main treatment effect is smaller than 0.05, and p-value for interaction test is greater than or equal to 0.05 or rule of 10 is not met

CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; MMR: Mismatch Repair; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 participants per subgroup and at least 10 events in one of the subgroups necessary; pMMR: Mismatch Repair Proficient; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world; SOC: System Organ Class

Analyses of Time to Severe Adverse Event (CTCAE-Grade 3-5) by Subgroups with p-Value for Interaction Test ≥ 0.05 or Rule of 10 Not Met (Incidence ≥ 5% or (Incidence ≥ 1% and in at least 10 Participants) in One or More Groups) For Preferred Terms

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
SOC: Blood and lymphatic system disorders, PT[h]: Anaemia									
Region									
Region 1	165	7 (4.2)	Not reached [-; -]	168	29 (17.3)	Not reached [-; -]	0.21 [0.09; 0.47]	< 0.001	0.097
Region 2	130	13 (10.0)	Not reached [-; -]	121	20 (16.5)	Not reached [-; -]	0.40 [0.19; 0.84]	0.016	
ECOG Performance Status									
0	175	12 (6.9)	Not reached [-; -]	164	23 (14.0)	Not reached [-; -]	0.38 [0.19; 0.79]	0.009	0.401
1	120	8 (6.7)	Not reached [-; -]	125	26 (20.8)	Not reached [-; -]	0.20 [0.09; 0.47]	< 0.001	
MMR Status									
pMMR	242	13 (5.4)	Not reached [-; -]	239	38 (15.9)	Not reached [-; -]	0.23 [0.12; 0.45]	< 0.001	0.489
dMMR	53	7 (13.2)	Not reached [-; -]	50	11 (22.0)	Not reached [-; -]	0.46 [0.18; 1.19]	0.108	
Prior History of Pelvic Radiation									
Yes	127	9 (7.1)	Not reached [-; -]	129	20 (15.5)	Not reached [-; -]	0.28 [0.12; 0.66]	0.004	0.724
No	168	11 (6.5)	Not reached [-; -]	160	29 (18.1)	Not reached [-; -]	0.29 [0.15; 0.59]	< 0.001	
SOC: Blood and lymphatic system disorders, PT[h]: Febrile neutropenia									
Age Group									
< 65	152	1 (0.7)	Not reached [-; -]	143	12 (8.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	> 0.999	0.768
≥ 65	143	1 (0.7)	Not reached [-; -]	146	9 (6.2)	Not reached [-; -]	0.09 [0.01; 0.69]	0.021	
Region									
Region 1	165	0 (0.0)	Not reached [-; -]	168	9 (5.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	0.181
Region 2	130	2 (1.5)	Not reached [-; -]	121	12 (9.9)	Not reached [-; -]	0.06 [0.01; 0.48]	0.008	
ECOG Performance Status									
0	175	2 (1.1)	Not reached [-; -]	164	14 (8.5)	Not reached [-; -]	0.05 [0.01; 0.40]	0.004	0.261
1	120	0 (0.0)	Not reached [-; -]	125	7 (5.6)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.006	
MMR Status									
pMMR	242	2 (0.8)	Not reached [-; -]	239	17 (7.1)	Not reached [-; -]	0.05 [0.01; 0.37]	0.003	0.281
dMMR	53	0 (0.0)	Not reached [-; -]	50	4 (8.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.014	
Prior History of Pelvic Radiation									
Yes	127	0 (0.0)	Not reached [-; -]	129	8 (6.2)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.003	0.167

No	168	2 (1.2)	Not reached [-; -]	160	13 (8.1)	Not reached [-; -]	0.06 [0.01; 0.43]	0.006	
SOC: Blood and lymphatic system disorders, PT[h]: Leukopenia									
Age Group									
< 65	152	0 (0.0)	Not reached [-; -]	143	15 (10.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
≥ 65	143	0 (0.0)	Not reached [-; -]	146	14 (9.6)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Region									
Region 1	165	0 (0.0)	Not reached [-; -]	168	8 (4.8)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.003	0.997
Region 2	130	0 (0.0)	Not reached [-; -]	121	21 (17.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
ECOG Performance Status									
0	175	0 (0.0)	Not reached [-; -]	164	22 (13.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
1	120	0 (0.0)	Not reached [-; -]	125	7 (5.6)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.008	
MMR Status									
pMMR	242	0 (0.0)	Not reached [-; -]	239	23 (9.6)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
dMMR	53	0 (0.0)	Not reached [-; -]	50	6 (12.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.009	
Prior History of Pelvic Radiation									
Yes	127	0 (0.0)	Not reached [-; -]	129	16 (12.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
No	168	0 (0.0)	Not reached [-; -]	160	13 (8.1)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
SOC: Blood and lymphatic system disorders, PT[h]: Neutropenia									
Age Group									
< 65	152	2 (1.3)	Not reached [-; -]	143	42 (29.4)	Not reached [-; -]	0.03 [0.01; 0.14]	< 0.001	0.383
≥ 65	143	5 (3.5)	Not reached [-; -]	146	54 (37.0)	Not reached [-; -]	0.07 [0.03; 0.17]	< 0.001	
Region									
Region 1	165	4 (2.4)	Not reached [-; -]	168	62 (36.9)	Not reached [-; -]	0.05 [0.02; 0.14]	< 0.001	0.740
Region 2	130	3 (2.3)	Not reached [-; -]	121	34 (28.1)	Not reached [-; -]	0.06 [0.02; 0.19]	< 0.001	
ECOG Performance Status									
0	175	6 (3.4)	Not reached [-; -]	164	61 (37.2)	Not reached [-; -]	0.07 [0.03; 0.15]	< 0.001	0.288
1	120	1 (0.8)	Not reached [-; -]	125	35 (28.0)	Not reached [-; -]	0.02 [0.00; 0.17]	< 0.001	
MMR Status									
pMMR	242	6 (2.5)	Not reached [-; -]	239	81 (33.9)	Not reached [-; -]	0.06 [0.02; 0.13]	< 0.001	0.852
dMMR	53	1 (1.9)	Not reached [-; -]	50	15 (30.0)	Not reached [-; -]	0.04 [0.01; 0.31]	0.002	
Prior History of Pelvic Radiation									
Yes	127	3 (2.4)	Not reached [-; -]	129	47 (36.4)	Not reached [-; -]	0.05 [0.01; 0.15]	< 0.001	0.755
No	168	4 (2.4)	Not reached [-; -]	160	49 (30.6)	Not reached [-; -]	0.06 [0.02; 0.16]	< 0.001	
SOC: Investigations, PT[h]: Neutrophil count decreased									

Age Group									
< 65	152	5 (3.3)	Not reached [-; -]	143	38 (26.6)	Not reached [-; -]	0.06 [0.02; 0.20]	< 0.001	0.624
≥ 65	143	3 (2.1)	Not reached [-; -]	146	37 (25.3)	Not reached [-; -]	0.05 [0.01; 0.19]	< 0.001	
Region									
Region 1	165	1 (0.6)	Not reached [-; -]	168	37 (22.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	> 0.999	0.066
Region 2	130	7 (5.4)	Not reached [-; -]	121	38 (31.4)	Not reached [-; -]	0.10 [0.04; 0.25]	< 0.001	
ECOG Performance Status									
0	175	6 (3.4)	Not reached [-; -]	164	50 (30.5)	Not reached [-; -]	0.05 [0.02; 0.15]	< 0.001	0.863
1	120	2 (1.7)	Not reached [-; -]	125	25 (20.0)	Not reached [-; -]	0.07 [0.02; 0.30]	< 0.001	
MMR Status									
pMMR	242	8 (3.3)	Not reached [-; -]	239	68 (28.5)	Not reached [-; -]	0.06 [0.03; 0.15]	< 0.001	0.191
dMMR	53	0 (0.0)	Not reached [-; -]	50	7 (14.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	
Prior History of Pelvic Radiation									
Yes	127	1 (0.8)	Not reached [-; -]	129	16 (12.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	> 0.999	0.627
No	168	7 (4.2)	Not reached [-; -]	160	59 (36.9)	Not reached [-; -]	0.06 [0.03; 0.15]	< 0.001	
SOC: Investigations, PT[h]: Weight decreased									
Age Group									
< 65	152	20 (13.2)	Not reached [-; -]	143	1 (0.7)	Not reached [-; -]	6.47 [0.83; 50.34]	0.074	0.295
≥ 65	143	13 (9.1)	Not reached [-; -]	146	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.065	
Region									
Region 1	165	14 (8.5)	Not reached [-; -]	168	1 (0.6)	Not reached [-; -]	4.86 [0.59; 40.05]	0.142	0.208
Region 2	130	19 (14.6)	Not reached [-; -]	121	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.023	
ECOG Performance Status									
0	175	20 (11.4)	Not reached [-; -]	164	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.061	0.193
1	120	13 (10.8)	Not reached [-; -]	125	1 (0.8)	Not reached [-; -]	6.67 [0.84; 52.92]	0.072	
MMR Status									
pMMR	242	25 (10.3)	Not reached [-; -]	239	1 (0.4)	Not reached [-; -]	8.05 [1.04; 62.16]	0.046	0.537
dMMR	53	8 (15.1)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.161	
Prior History of Pelvic Radiation									
Yes	127	17 (13.4)	Not reached [-; -]	129	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.031	0.228
No	168	16 (9.5)	Not reached [-; -]	160	1 (0.6)	Not reached [-; -]	5.39 [0.68; 42.99]	0.112	
SOC: Investigations, PT[h]: White blood cell count decreased									
Age Group									
< 65	152	4 (2.6)	Not reached [-; -]	143	17 (11.9)	Not reached [-; -]	0.14 [0.04; 0.47]	0.002	0.394

≥ 65	143	2 (1.4)	Not reached [-; -]	146	20 (13.7)	Not reached [-; -]	0.09 [0.02; 0.39]	0.001	
Region									
Region 1	165	1 (0.6)	Not reached [-; -]	168	16 (9.5)	Not reached [-; -]	0.05 [0.01; 0.41]	0.005	0.261
Region 2	130	5 (3.8)	Not reached [-; -]	121	21 (17.4)	Not reached [-; -]	0.15 [0.05; 0.44]	< 0.001	
ECOG Performance Status									
0	175	4 (2.3)	Not reached [-; -]	164	28 (17.1)	Not reached [-; -]	0.08 [0.02; 0.27]	< 0.001	0.510
1	120	2 (1.7)	Not reached [-; -]	125	9 (7.2)	Not reached [-; -]	0.22 [0.05; 1.01]	0.052	
MMR Status									
pMMR	242	5 (2.1)	Not reached [-; -]	239	35 (14.6)	Not reached [-; -]	0.10 [0.03; 0.27]	< 0.001	0.420
dMMR	53	1 (1.9)	Not reached [-; -]	50	2 (4.0)	Not reached [-; -]	0.45 [0.04; 4.99]	0.518	
Prior History of Pelvic Radiation									
Yes	127	1 (0.8)	Not reached [-; -]	129	8 (6.2)	Not reached [-; -]	0.12 [0.01; 0.95]	0.045	0.852
No	168	5 (3.0)	Not reached [-; -]	160	29 (18.1)	Not reached [-; -]	0.11 [0.04; 0.30]	< 0.001	
SOC: Metabolism and nutrition disorders, PT[h]: Decreased appetite									
Region									
Region 1	165	16 (9.7)	Not reached [-; -]	168	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.003	0.062
Region 2	130	12 (9.2)	Not reached [-; -]	121	2 (1.7)	Not reached [-; -]	3.69 [0.80; 16.95]	0.094	
ECOG Performance Status									
0	175	18 (10.3)	Not reached [-; -]	164	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.055
1	120	10 (8.3)	Not reached [-; -]	125	2 (1.6)	Not reached [-; -]	2.79 [0.56; 13.78]	0.209	
Prior History of Pelvic Radiation									
Yes	127	11 (8.7)	Not reached [-; -]	129	2 (1.6)	Not reached [-; -]	3.25 [0.69; 15.34]	0.136	0.064
No	168	17 (10.1)	Not reached [-; -]	160	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	
SOC: Renal and urinary disorders, PT[h]: Proteinuria									
Age Group									
< 65	152	7 (4.6)	Not reached [-; -]	143	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.042	0.318
≥ 65	143	9 (6.3)	Not reached [-; -]	146	1 (0.7)	Not reached [-; -]	7.01 [0.87; 56.33]	0.067	
Region									
Region 1	165	8 (4.8)	n.c.	168	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Region 2	130	8 (6.2)	n.c.	121	1 (0.8)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	175	9 (5.1)	Not reached [-; -]	164	1 (0.6)	Not reached [-; -]	6.65 [0.83; 53.24]	0.074	0.273
1	120	7 (5.8)	Not reached [-; -]	125	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.039	
MMR Status									

pMMR	242	14 (5.8)	Not reached [-; -]	239	1 (0.4)	Not reached [-; -]	9.36 [1.20; 72.76]	0.033	0.651
dMMR	53	2 (3.8)	Not reached [-; -]	50	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.187	
Prior History of Pelvic Radiation									
Yes	127	6 (4.7)	Not reached [-; -]	129	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.048	0.336
No	168	10 (6.0)	Not reached [-; -]	160	1 (0.6)	Not reached [-; -]	7.02 [0.88; 56.21]	0.066	
SOC: Vascular disorders, PT[h]: Hypertension									
Age Group									
< 65	152	53 (34.9)	Not reached [68.3; -]	143	1 (0.7)	Not reached [-; -]	50.32 [6.94; 364.76]	< 0.001	0.085
≥ 65	143	57 (39.9)	Not reached [33.9; -]	146	6 (4.1)	Not reached [-; -]	10.35 [4.45; 24.09]	< 0.001	
Region									
Region 1	165	60 (36.4)	Not reached [-; -]	168	6 (3.6)	Not reached [-; -]	11.13 [4.80; 25.80]	< 0.001	0.109
Region 2	130	50 (38.5)	Not reached [54.0; -]	121	1 (0.8)	Not reached [-; -]	45.18 [6.22; 328.25]	< 0.001	
MMR Status									
pMMR	242	94 (38.8)	Not reached [54.0; -]	239	6 (2.5)	Not reached [-; -]	16.67 [7.29; 38.14]	< 0.001	0.867
dMMR	53	16 (30.2)	Not reached [68.3; -]	50	1 (2.0)	Not reached [-; -]	12.83 [1.68; 98.09]	0.014	
Prior History of Pelvic Radiation									
Yes	127	48 (37.8)	Not reached [32.7; -]	129	5 (3.9)	Not reached [-; -]	10.20 [4.05; 25.69]	< 0.001	0.154
No	168	62 (36.9)	Not reached [59.7; -]	160	2 (1.3)	Not reached [-; -]	30.24 [7.38; 124.02]	< 0.001	

a: Database Cutoff Date: 26OCT2020

b: Pre-assigned to doxorubicin according to treatment of physician's choice; rationale was assessed prospectively per investigator's survey. Includes also one participant in the Doxorubicin subpopulation for whom the investigator site selected paclitaxel prior to randomization, but actually treated with doxorubicin

c: Number of participants: all-participants-as-treated, population relevant for benefit assessment

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

h: A specific adverse event appears on this report only if its incidence ≥ 5% or (incidence ≥ 1% and in at least 10 participants) in one or more groups and p-value of main treatment effect is smaller than 0.05, and p-value for interaction test is greater than or equal to 0.05 or rule of 10 is not met

CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; dMMR: Mismatch Repair Deficient; ECOG: Eastern Cooperative Oncology Group; MMR: Mismatch Repair; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 participants per subgroup and at least 10 events in one of the subgroups necessary; pMMR: Mismatch Repair Proficient; PT: Preferred Term; Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2: Rest of the world; SOC: System Organ Class

Anhang 4-G8: AEOSI und CSAE Preferred Terms

MK-3475 AEOSI Preferred Terms

AEOSI	Preferred Term	Immune-mediated (yes/no)
Pneumonitis	Acute interstitial pneumonitis, Autoimmune lung disease, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organising pneumonia, Immune-mediated pneumonitis	Yes
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive, Autoimmune colitis, Immune-mediated enterocolitis	Yes
Hepatitis	Hepatitis, Immune-mediated hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitis fulminant, Drug- induced liver injury	Yes
Nephritis	Nephritis, Autoimmune nephritis, Chronic autoimmune glomerulonephritis, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Mesangioproliferative glomerulonephritis, Nephritis haemorrhagic, Tubulointerstitial nephritis, Nephrotic syndrome, Immune-mediated nephritis	Yes
Adrenal Insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency, Primary adrenal insufficiency, Addison's disease	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis	Yes
Hyperthyroidism	Hyperthyroidism, Basedow’s disease, Thyrotoxic crisis, Immune-mediated hyperthyroidism	Yes
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism, Autoimmune hypothyroidism, Immune-mediated hypothyroidism	Yes
Thyroiditis	Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute, Silent thyroiditis, Autoimmune thyroid disorder, Immune-mediated thyroiditis	Yes
Type 1 Diabetes Mellitus	Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus, Euglycaemic diabetic ketoacidosis, Diabetic ketosis, Ketosis-prone diabetes mellitus	Yes
Severe Skin Reactions Including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): or	Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Pemphigoid, Pemphigus, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, SJS-TEN overlap	Yes
Severe Skin (continued): **If Grade 3 or higher:**	Rash, Rash erythematous, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus genital, Lichen planus, Oral lichen planus, Cutaneous vasculitis, Vasculitic rash	Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis, Vogt-Koyanagi-Harada disease, Chorioretinitis, Choroiditis, Immune-mediated uveitis	Yes

Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Immune-mediated pancreatitis	Yes
Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated myositis, Rhabdomyolysis, Myopathy, Dermatomyositis, Autoimmune myositis	Yes
Guillain-Barre Syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome, Subacute inflammatory demyelinating polyneuropathy	Yes
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis	Yes
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis, Immune-mediated encephalitis	Yes
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis	Yes
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction, Infusion related hypersensitivity reaction	No
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia	Yes
Myelitis	Myelitis, Myelitis transverse	Yes
Vasculitis	Anti-neutrophil cytoplasmic antibody positive vasculitis, Aortitis, Arteritis, Arteritis coronary, Behcet's syndrome, Central nervous system vasculitis, Cerebral arteritis, Diffuse vasculitis, Eosinophilic granulomatosis with polyangiitis, Granulomatosis with polyangiitis, Haemorrhagic vasculitis, Hypersensitivity vasculitis, Microscopic polyangiitis, Ocular vasculitis, Polyarteritis nodosa, Pulmonary vasculitis, Renal arteritis, Renal vasculitis, Retinal vasculitis, Takayasu's arteritis, Giant cell arteritis, Vasculitis, Vasculitis gastrointestinal,Vasculitis necrotising	Yes
Cholangitis Sclerosing	Cholangitis sclerosing, Autoimmune cholangitis, Immune-mediated cholangitis	Yes
Version 19.0 (05-NOV-2020) This list is based on MedDRA Version 23.1		

Lenvatinib CSAE Preferred Terms

CSAE	Preferred Terms
Arterial Thromboembolic Events	Acute aortic syndrome; Acute myocardial infarction; Amaurosis; Amaurosis fugax; Angioplasty; Aortic bypass; Aortic embolus; Aortic surgery; Aortic thrombosis; Aortogram abnormal; Arterectomy; Arterectomy with graft replacement; Arterial angioplasty; Arterial bypass occlusion; Arterial bypass operation; Arterial bypass thrombosis; Arterial graft; Arterial occlusive disease; Arterial revascularisation; Arterial stent insertion; Arterial therapeutic procedure; Arterial thrombosis; Arteriogramabnormal; Arteriogram carotid abnormal; Arteriotomy; Artificial blood vessel occlusion; Atherectomy; Atherosclerotic plaque rupture; Atrial appendage closure; Atrial appendage resection; Basal ganglia infarction; Basilar

	artery occlusion; Basilar artery thrombosis; Blindness transient; Brachiocephalic artery occlusion; Capsular warning syndrome; Cardiac ventricular thrombosis; Carotid angioplasty; Carotid arterial embolus; Carotid artery bypass; Carotid artery occlusion; Carotid artery stent insertion; Carotid artery thrombosis; Carotid endarterectomy; Catheter sitethrombosis; Cerebellar artery occlusion; Cerebellar artery thrombosis; Cerebral artery embolism; Cerebral artery occlusion; Cerebral artery stent insertion; Cerebral artery thrombosis; Cerebral hypoperfusion; Cerebral infarction; Cerebral ischaemia; Cerebral microembolism; Cerebrovascular accident; Cerebrovascular insufficiency; Cerebrovascular stenosis; Coeliac artery occlusion; Coronary angioplasty; Coronary arterial stent insertion; Coronary artery bypass; Coronary artery embolism; Coronary artery occlusion; Coronary artery reocclusion; Coronary artery surgery; Coronary artery thrombosis; Coronary endarterectomy; Coronary revascularisation; Coronary vascular graft occlusion; Device related thrombosis; Diplegia; Embolia cutis medicamentosa; Embolism arterial; Endarterectomy; Femoral artery embolism; Hemiparesis; Hemiplegia; Hepatic artery embolism; Hepatic artery occlusion; Hepatic artery thrombosis; Hypothenar hammer syndrome; Iliac artery embolism; Iliac artery occlusion; Internal capsule infarction; Intra-aortic balloon placement; Intracardiac thrombus; Intraoperative cerebral artery occlusion; Ischaemic cerebral infarction; Ischaemic stroke; Lacunar infarction; Leriche syndrome; Mesenteric arterial occlusion; Mesenteric arteriosclerosis; Mesenteric artery embolism; Mesenteric artery stenosis; Mesenteric artery stent insertion; Mesenteric artery thrombosis; Monoparesis; Monoplegia; Myocardial infarction; Myocardial necrosis; Ophthalmic artery thrombosis; Papillary muscle infarction; Paraneoplastic thrombosis; Paraparesis; Paraplegia; Paresis; Penile artery occlusion; Percutaneous coronary intervention; Peripheral arterial occlusive disease; Peripheral arterial reocclusion; Peripheral artery angioplasty; Peripheral artery bypass; Peripheral artery occlusion; Peripheral artery stent insertion; Peripheral artery surgery; Peripheral artery thrombosis; Peripheral embolism; Peripheral endarterectomy; Popliteal artery entrapment syndrome; Post procedural myocardial infarction; Postinfarction angina; Precerebral artery occlusion; Precerebral artery thrombosis; Profundaplasty; Pulmonary artery occlusion; Pulmonary artery therapeutic procedure; Pulmonary artery thrombosis; Pulmonary endarterectomy; Pulmonary tumour thrombotic microangiopathy; Renal artery angioplasty; Renal artery occlusion; Renal artery thrombosis; Renal embolism; Retinal artery embolism; Retinal artery occlusion; Retinal artery thrombosis; Silent myocardial infarction; Spinal artery embolism;Spinal artery thrombosis; Splenic artery thrombosis; Splenic embolism; Splenic infarction; Stroke in evolution; Subclavian artery embolism; Subclavian artery occlusion; Subclavian artery thrombosis; Thromboembolectomy; Thrombotic cerebral infarction; Thrombotic microangiopathy; Transient ischaemic attack; Truncus coeliacus thrombosis; Vascular pseudoaneurysm thrombosis; Vertebral artery occlusion; Vertebral artery thrombosis; Visual acuity reduced transiently
Cardiac Dysfunction	Acute left ventricular failure; Acute pulmonary oedema; Acute right ventricular failure; Atrial septal defect acquired; Biopsy heart abnormal; Cardiac amyloidosis; Cardiac asthma; Cardiac failure; Cardiac failure acute; Cardiac failure chronic; Cardiac failure congestive; Cardiac failure high output; Cardiac hypertrophy; Cardiac iron overload; Cardiac sarcoidosis; Cardiac septal hypertrophy;

	Cardiogenic shock; Cardiohepatic syndrome; Cardiomyopathy; Cardiomyopathy acute; Cardiomyopathy alcoholic; Cardiomyopathy neonatal; Cardiopulmonary failure; Cardiorenal syndrome; Cardiotoxicity; Chagas' cardiomyopathy; Chronic left ventricular failure; Chronic right ventricular failure; Congestive cardiomyopathy; Congestive hepatopathy; Cor pulmonale; Cor pulmonale acute; Cor pulmonale chronic; Diabetic cardiomyopathy; Echocardiogram abnormal; Ejection fraction abnormal; Ejection fraction decreased; Eosinophilic myocarditis; Giant cell myocarditis; Hepatojugular reflux; HIV cardiomyopathy; Hypertrophic cardiomyopathy; Ischaemic cardiomyopathy; Left ventricular dysfunction; Left ventricular failure; Low cardiac output syndrome; Metabolic cardiomyopathy; Mitochondrial cardiomyopathy; Myocardial calcification; Myocardial fibrosis; Neonatal cardiac failure; Non-obstructive cardiomyopathy; Obesity cardiomyopathy; Obstructive shock; Peripartum cardiomyopathy; Pulmonary arterial wedge pressure increased; Pulmonary congestion; Pulmonary oedema; Pulmonary oedema neonatal; Radiation associated cardiac failure; Restrictive cardiomyopathy; Right ventricular dysfunction;Right ventricular ejection fraction decreased; Right ventricular failure; Stress cardiomyopathy; Tachycardia induced cardiomyopathy; Thyrotoxiccardiomyopathy; Toxic cardiomyopathy; Ventricular dysfunction; Ventricular failure; Ventricular hypokinesia; Ventricular septal defectacquired; Viral cardiomyopathy
Fistula Formation	Acquired tracheo-oesophageal fistula; Anal fistula; Anal fistula infection; Anal fistula repair; Anastomotic fistula; Anovulvar fistula; Aortoenteric fistula; Arterioenteric fistula; Atrio-oesophageal fistula; Biliary fistula; Biliary fistula repair; Biliary-bronchial fistula; Biliary-vascular fistula; Bladder fistula repair; Bone fistula; Bronchial fistula; Bronchial fistula repair; Bronchopleural fistula; Cerebrospinal fistula; Colon fistula repair; Colonic fistula; Congenital aural fistula; Congenital lip fistula; Dental fistula; Diverticular fistula; Enterocolonic fistula; Enterocutaneous fistula;Enterovesical fistula; Female genital tract fistula; Fistula; Fistula discharge; Fistula inflammation; Fistula of small intestine; Fistula repair; Aorto-oesophageal fistula; Gallbladder fistula; Gallbladder fistula repair; Gastric fistula; Gastric fistula repair; Gastrointestinal fistula; Gastrointestinal fistula repair; Gastropleural fistula; Gastrosplenic fistula; Infected fistula; Intestinal fistula; Intestinal fistula infection; Intestinal fistula repair; Intrahepatic portal hepatic venous fistula; Jaw fistula; Labyrinthine fistula; Lacrimal fistula; Laryngeal fistula; Laryngeal fistula repair; Lymphatic fistula; Male genital tract fistula; Mammary fistula; Mammary fistula repair; Neovaginal fistula; Ocular fistula; Oesophageal fistula; Oesophageal fistula repair; Oesophageal-pulmonary fistula; Oesophagobronchial fistula; Oesophagomediastinal fistula; Oesophagopleural fistula; Oral cavity fistula; Oroantral fistula; Pancreatic fistula; Pancreatic fistula repair; Perineal fistula; Peritoneocutaneous fistula; Pharyngeal fistula; Pharyngeal fistula repair; Pleural fistula; Pleurocutaneous fistula; Post procedural fistula; Postauricular fistula; Pulmonary fistula; Rectal fistula repair; Rectoprostatic fistula; Rectourethral fistula; Renal pelvis fistula; Salivary gland fistula; Thyroglossal fistula; Thyroglossal fistula excision; Tracheal fistula; Tracheal fistula repair; Tracheo-oesophageal fistula; Ureteric fistula; Urethral fistula; Urethroperineal fistula; Urinary fistula; Urogenital fistula; Urogenital fistula repair; Uterine fistula; Vaginal fistula; Vaginal fistularepair; Vesical fistula; Vesicocutaneous fistula; Vesicourethral fistula

GI Perforation	Abdominal abscess; Abdominal hernia perforation; Abdominal wall abscess; Abscess intestinal; Anal abscess; Anastomotic ulcer perforation; Appendiceal abscess; Appendicitis perforated; Chemical peritonitis; Colonic abscess; Diverticular perforation; Diverticulitis intestinal perforated; Douglas' abscess; Duodenal perforation; Duodenal ulcer perforation; Duodenal ulcer perforation, obstructive; Duodenal ulcer repair; Focal peritonitis; Gastric perforation; Gastric ulcer perforation; Gastric ulcer perforation, obstructive; Gastrointestinal anastomotic leak; Gastrointestinal perforation; Gastrointestinal ulcer perforation; Ileal perforation; Ileal ulcer perforation; Inguinal hernia perforation; Intestinal perforation; Intestinal ulcer perforation; Jejunal perforation; Jejunal ulcer perforation; Large intestinal ulcer perforation; Large intestine perforation; Lower gastrointestinal perforation; Mesenteric abscess; Neonatal intestinalperforation; Oesophageal abscess; Oesophageal perforation; Oesophageal rupture; Oesophageal ulcer perforation; Peptic ulcer perforation; Peptic ulcer perforation, obstructive; Perforated peptic ulcer oversewing; Perforated ulcer; Perineal abscess; Perirectal abscess; Peritoneal abscess; Peritonitis; Peritonitis bacterial; Pneumoperitoneum; Pneumoretroperitoneum; Procedural intestinal perforation; Rectal abscess;Rectal perforation; Retroperitoneal abscess; Small intestinal perforation; Small intestinal ulcer perforation; Umbilical hernia perforation; Uppergastrointestinal perforation
Hemorrhage	Abdominal wall haematoma; Abdominal wall haemorrhage; Abnormal withdrawal bleeding; Achenbach syndrome; Acute haemorrhagic leukoencephalitis; Acute haemorrhagic ulcerative colitis; Administrationsite bruise; Administration site haematoma; Administration site haemorrhage; Adrenal haematoma; Adrenal haemorrhage; Anal fissure haemorrhage; Anal haemorrhage; Anal ulcer haemorrhage; Anastomotichaemorrhage; Anastomotic ulcer haemorrhage; Aneurysm ruptured; Angina bullosa haemorrhagica; Anorectal varices haemorrhage; Anticoagulant-related nephropathy; Aortic aneurysm rupture; Aortic dissection rupture; Aortic intramural haematoma; Aortic perforation; Aortic rupture; Aponeurosis contusion; Application site bruise; Application site haematoma; Application site haemorrhage; Application site purpura; Arterial haemorrhage; Arterial intramural haematoma; Arterial perforation; Arterial rupture; Arteriovenous fistula site haematoma; Arteriovenous fistula site haemorrhage; Arteriovenous graftsite haematoma; Arteriovenous graft site haemorrhage; Astringent therapy; Atrial rupture; Auricular haematoma; Basal ganglia haematoma; Basal ganglia haemorrhage; Basilar artery perforation; Bladder tamponade; Bleeding varicose vein; Blood blister; Blood loss anaemia; Blood urine; Blood urine present; Bloody discharge; Bloody peritoneal effluent; Bone contusion; Bone marrow haemorrhage; Brain contusion; Brain stem haematoma; Brain stem haemorrhage; Brain stem microhaemorrhage; Breast haematoma; Breast haemorrhage; Broad ligament haematoma; Bronchial haemorrhage; Bronchial varices haemorrhage; Bullous haemorrhagic dermatosis; Bursal haematoma; Cardiac contusion; Carotid aneurysm rupture; Carotid artery perforation; Catheter site bruise; Catheter site haematoma; Catheter site haemorrhage; Central nervous system haemorrhage; Cephalhaematoma; Cerebellar haematoma; Cerebellar haemorrhage; Cerebellar microhaemorrhage; Cerebral aneurysm perforation; Cerebral aneurysm ruptured syphilitic; Cerebral arteriovenous malformation haemorrhagic; Cerebral artery perforation; Cerebral cyst haemorrhage; Cerebral haematoma; Cerebral haemorrhage;

	Cerebral haemorrhage foetal; Cerebral haemorrhage neonatal; Cerebral microhaemorrhage; Cervix haematoma uterine; Cervix haemorrhage uterine; Chest wall haematoma; Choroidal haematoma; Choroidal haemorrhage; Chronic gastrointestinal bleeding; Chronic pigmented purpura; Ciliary body haemorrhage; Coital bleeding; Colonic haematoma; Conjunctival haemorrhage; Contusion; Corneal bleeding; Cullen's sign; Cystitis haemorrhagic; Deep dissecting haematoma; Diarrhoea haemorrhagic; Disseminated intravascular coagulation; Diverticulitis intestinal haemorrhagic; Diverticulum intestinal haemorrhagic; Duodenal ulcer haemorrhage; Duodenitis haemorrhagic; Dysfunctional uterine bleeding; Ear haemorrhage; Ecchymosis; Encephalitis haemorrhagic; Enterocolitis haemorrhagic; Epidural haemorrhage; Epistaxis; Exsanguination; Extra-axial haemorrhage; Extradural haematoma; Extradural haematoma evacuation; Extravasation blood; Eye contusion; Eye haematoma; Eye haemorrhage; Eyelid bleeding; Eyelid contusion; Eyelid haematoma; Femoral artery perforation; Femoral vein perforation; Foetal-maternal haemorrhage; Fothergill sign positive; Gastric haemorrhage; Gastric ulcer haemorrhage; Gastric ulcer haemorrhage, obstructive; Gastric varices haemorrhage; Gastritis alcoholic haemorrhagic; Gastritis haemorrhagic; Gastroduodenal haemorrhage; Gastrointestinal haemorrhage; Gastrointestinal polyp haemorrhage; Gastrointestinal ulcer haemorrhage; Gastrointestinal vascular malformation haemorrhagic; Genital contusion; Genital haemorrhage; Gingival bleeding; Graft haemorrhage; Grey Turner's sign; Haemangioma rupture; Haemarthrosis; Haematemesis; Haematochezia; Haematocoele; Haematoma; Haematoma evacuation; Haematoma infection; Haematoma muscle; Haematosalpinx; Haematospermia; Haematotympanum; Haematuria; Haematuria traumatic; Haemobilia; Haemoperitoneum; Haemophilic arthropathy; Haemophilic pseudotumour;Haemoptysis; Haemorrhage; Haemorrhage coronary artery; Haemorrhage foetal; Haemorrhage in pregnancy; Haemorrhage intracranial; Haemorrhage neonatal; Haemorrhage subcutaneous; Haemorrhage subepidermal; Haemorrhage urinary tract; Haemorrhagic adrenal infarction; Haemorrhagic arteriovenous malformation; Haemorrhagic ascites; Haemorrhagic breast cyst; Haemorrhagic cerebral infarction; Haemorrhagic cyst; Haemorrhagic diathesis; Haemorrhagic disease of newborn; Haemorrhagic disorder; Haemorrhagic erosive gastritis; Haemorrhagic hepatic cyst; Haemorrhagic infarction; Haemorrhagic necrotic pancreatitis; Haemorrhagic ovarian cyst; Haemorrhagic stroke; Haemorrhagic thyroid cyst; Haemorrhagic transformation stroke; Haemorrhagic tumour necrosis; Haemorrhagic urticaria; Haemorrhagic vasculitis; Haemorrhoidal haemorrhage; Haemostasis; Haemothorax; Henoch-Schonlein purpura; Hepatic haematoma; Hepatic haemorrhage; Hereditary haemorrhagic telangiectasia; Hyperfibrinolysis; Hyphaema; Iliac artery perforation; Iliac artery rupture; Iliac vein perforation; Immune thrombocytopenia; Implant site bruising; Implant site haematoma; Implant site haemorrhage; Incision site haematoma; Incision site haemorrhage; Increased tendency to bruise; Induced abortion haemorrhage; Inferior vena cava perforation; Infusion site bruising; Infusion site haematoma; Infusion site haemorrhage; Injection site bruising; Injection site haematoma; Injection site haemorrhage; Instillation site bruise; Instillation site haematoma; Instillation site haemorrhage; Internal haemorrhage; Intestinal haematoma; Intestinal haemorrhage; Intestinal varices haemorrhage; Intra- abdominal haematoma; Intra-abdominal haemorrhage; Intracerebral haematoma evacuation; Intracranial

	haematoma; Intracranial tumour haemorrhage; Intraocular haematoma; Intrapartum haemorrhage; Intratumoural haematoma; Intraventricular haemorrhage; Intraventricular haemorrhage neonatal; Iris haemorrhage; Joint microhaemorrhage; Kidney contusion; Lacrimal haemorrhage; Large intestinal haemorrhage; Large intestinal ulcer haemorrhage; Laryngeal haematoma; Laryngeal haemorrhage; Lip haematoma; Lip haemorrhage; Liver contusion; Lower gastrointestinal haemorrhage; Lower limb artery perforation; Lymph node haemorrhage; Mallory-Weiss syndrome; Mediastinal haematoma; Mediastinal haemorrhage; Medical device site bruise; Medical device site haematoma; Medical device site haemorrhage; Melaena; Melaena neonatal; Meningorrhagia; Menometrorrhagia; Menorrhagia; Mesenteric haematoma; Mesenteric haemorrhage; Metrorrhagia; Mouth haemorrhage; Mucocutaneous haemorrhage; Mucosal haemorrhage; Muscle contusion; Muscle haemorrhage; Myocardial haemorrhage; Myocardial rupture; Naevus haemorrhage; Nail bed bleeding; Nasal septum haematoma; Neonatal gastrointestinal haemorrhage; Nephritis haemorrhagic; Nipple exudate bloody; Ocular retrobulbar haemorrhage; Oesophageal haemorrhage; Oesophageal intramural haematoma; Oesophageal ulcer haemorrhage; Oesophageal varices haemorrhage; Oesophagitis haemorrhagic; Optic disc haemorrhage; Optic nerve sheath haemorrhage; Oral blood blister; Oral contusion; Oral mucosa haematoma; Oral purpura; Orbital haematoma; Orbital haemorrhage; Osteorrhagia; Ovarian haematoma; Ovarian haemorrhage; Palpable purpura; Pancreatic haemorrhage; Pancreatic pseudocyst haemorrhage; Pancreatitis haemorrhagic; Papillary muscle haemorrhage; Paranasal sinus haematoma; Paranasal sinus haemorrhage; Parathyroid haemorrhage; Parotid gland haemorrhage; Pelvic haematoma; Pelvic haematoma obstetric; Pelvic haemorrhage; Penile contusion; Penile haematoma; Penile haemorrhage; Peptic ulcer haemorrhage; Pericardial haemorrhage; Perineal haematoma; Periorbital haematoma; Periorbital haemorrhage; Periosteal haematoma; Peripartum haemorrhage; Peripheral artery aneurysm rupture; Peripheral artery haematoma; Peritoneal haematoma; Periventricular haemorrhage neonatal; Petechiae; Pharyngeal contusion; Pharyngeal haematoma; Pharyngeal haemorrhage; Pituitary apoplexy; Pituitary haemorrhage; Placenta praevia haemorrhage; Polymenorrhagia; Post abortion haemorrhage; Post procedural contusion; Post procedural haematoma; Post procedural haematuria; Post procedural haemorrhage; Post transfusion purpura; Postmenopausal haemorrhage; Postpartum haemorrhage; Post-traumatic punctate intraepidermal haemorrhage; Premature separation of placenta; Procedural haemorrhage; Proctitis haemorrhagic; Prostatic haemorrhage; Pulmonary alveolar haemorrhage; Pulmonary contusion; Pulmonary haematoma; Pulmonary haemorrhage; Pulmonary haemorrhage neonatal; Puncture site bruise; Puncture site haematoma; Puncture site haemorrhage; Purpura; Purpura fulminans; Purpura neonatal; Purpura non-thrombocytopenic; Purpura senile; Putamen haemorrhage; Radiation associated haemorrhage; Rectal haemorrhage; Rectal ulcer haemorrhage; Renal artery perforation; Renal cyst haemorrhage; Renal haematoma; Renal haemorrhage; Respiratory tract haemorrhage; Respiratory tract haemorrhage neonatal; Retinal aneurysm rupture; Retinal haemorrhage; Retinopathy haemorrhagic; Retroperitoneal haematoma; Retroperitoneal haemorrhage; Retroplacental haematoma; Ruptured cerebral aneurysm; Scleral haemorrhage; Scrotal haematocoele; Scrotal haematoma; Scrotal haemorrhage; Shock haemorrhagic; Skin

	haemorrhage; Skin neoplasm bleeding; Skin ulcer haemorrhage; Small intestinal haemorrhage; Small intestinal ulcer haemorrhage; Soft tissue haemorrhage; Spermatic cord haemorrhage; Spinal cord haematoma; Spinal cord haemorrhage; Spinal epidural haematoma; Spinal epidural haemorrhage; Spinal subarachnoid haemorrhage; Spinal subdural haematoma; Spinal subdural haemorrhage; Spleen contusion; Splenic artery perforation; Splenic haematoma; Splenic haemorrhage; Splenic varices haemorrhage; Splinter haemorrhages; Spontaneous haematoma; Spontaneous haemorrhage; Stoma site haemorrhage; Stomatitis haemorrhagic; Subarachnoid haematoma; Subarachnoid haemorrhage; Subarachnoid haemorrhage neonatal; Subcapsular hepatic haematoma; Subcapsular renal haematoma; Subcapsular splenic haematoma; Subchorionic haematoma; Subchorionic haemorrhage; Subclavian artery perforation; Subclavian vein perforation; Subcutaneous haematoma; Subdural haematoma; Subdural haematoma evacuation; Subdural haemorrhage; Subdural haemorrhage neonatal; Subendocardial haemorrhage; Subgaleal haematoma; Subgaleal haemorrhage; Subretinal haematoma; Superior vena cava perforation; Testicular haemorrhage; Thalamus haemorrhage; Third stage postpartum haemorrhage; Thoracic haemorrhage; Thrombocytopenic purpura; Thrombotic thrombocytopenic purpura; Thyroid haemorrhage; Tongue haematoma; Tongue haemorrhage; Tonsillar haemorrhage; Tooth pulp haemorrhage; Tooth socket haemorrhage; Tracheal haemorrhage; Traumatic haematoma; Traumatic haemorrhage; Traumatic haemothorax; Traumatic intracranial haematoma; Traumatic intracranial haemorrhage; Tumour haemorrhage; Ulcer haemorrhage; Umbilical cord haemorrhage; Umbilical haematoma; Umbilical haemorrhage; Upper gastrointestinal haemorrhage; Ureteric haemorrhage; Urethral haemorrhage; Urinary bladder haematoma; Urinary bladder haemorrhage; Urinary occult blood positive; Urogenital haemorrhage; Uterine haematoma; Uterine haemorrhage; Vaccination site bruising; Vaccination site haematoma; Vaccination site haemorrhage; Vaginal haematoma; Vaginal haemorrhage; Varicose vein ruptured; Vascular access site bruising; Vascular access site haematoma; Vascular access site haemorrhage; Vascular access site rupture; Vascular anastomotic haemorrhage; Vascular graft haemorrhage; Vascular pseudoaneurysm ruptured; Vascular purpura; Vascular rupture;Vein rupture; Venous haemorrhage; Venous perforation; Ventricle rupture; Vertebral artery perforation; Vessel puncture site bruise; Vesselpuncture site haematoma; Vessel puncture site haemorrhage; Vitreous haematoma; Vitreous haemorrhage; Vulval haematoma; Vulval haematoma evacuation; Vulval haemorrhage; Withdrawal bleed; Woundhaematoma; Wound haemorrhage
Hepatotoxicity	Acquired antithrombin III deficiency; Acquired factor IX deficiency; Acquired factor VIII deficiency; Acquired factor XI deficiency; Acquired hepatocerebral degeneration; Acquired protein S deficiency; Acute graft versus host disease in liver; Acute hepatic failure; Acute on chronic liver failure; Acute yellow liver atrophy; Alanine aminotransferase abnormal; Alanine aminotransferase increased; Allergic hepatitis; Alloimmune hepatitis; Ammonia abnormal; Ammonia increased; Anti factor X activity abnormal; Anti factor X activity decreased; Anti factor X activity increased; Antithrombin III decreased; Ascites; Aspartate aminotransferase abnormal; Aspartate aminotransferase increased; AST/ALT ratio abnormal; Asterixis; Autoimmune hepatitis; Bacterascites;Benign hepatic neoplasm; Benign hepatobiliary neoplasm; Bile output

	abnormal; Bile output decreased; Biliary ascites; Biliary cirrhosis; Biliary fibrosis; Bilirubin conjugated abnormal; Bilirubin conjugated increased; Bilirubin excretion disorder; Bilirubin urine present; Biopsy liver abnormal; Blood bilirubin abnormal; Blood bilirubin increased; Blood bilirubin unconjugated increased; Blood fibrinogen abnormal; Blood fibrinogen decreased; Blood thrombin abnormal; Blood thrombin decreased; Blood thromboplastin abnormal; Blood thromboplastin decreased; Bromosulphthalein test abnormal; Child-Pugh-Turcotte score abnormal; Child-Pugh-Turcotte score increased; Cholaemia; Cholangiosarcoma; Cholestasis; Cholestatic liver injury; Cholestatic pruritus; Chronic graft versus host disease in liver; Chronic hepatic failure; Chronic hepatitis; Coagulation factor decreased; Coagulation factor IX level abnormal; Coagulation factor IX level decreased; Coagulation factor V level abnormal; Coagulation factor V level decreased; Coagulation factor VII level abnormal; Coagulation factor VII level decreased; Coagulation factor X level abnormal; Coagulation factor X level decreased; Coma hepatic; Computerised tomogram liver abnormal; Cryptogenic cirrhosis; Diabetic hepatopathy; Drug-induced liver injury; Duodenal varices; Encephalopathy; Flood syndrome; Focal nodular hyperplasia; Foetor hepaticus; Galactose elimination capacity test abnormal; Galactose elimination capacity test decreased; Gallbladder varices; Gamma-glutamyltransferase abnormal; Gamma- glutamyltransferase increased; Gastric variceal injection; Gastric variceal ligation; Gastric varices; Gastrooesophageal variceal haemorrhage prophylaxis; Graft versus host disease in liver; Guanase increased; Haemangioma of liver; Hepaplastin abnormal; Hepaplastin decreased; Hepatectomy; Hepatic adenoma; Hepatic angiosarcoma; Hepatic artery flow decreased; Hepatic atrophy; Hepatic calcification; Hepatic cancer; Hepatic cancer metastatic; Hepatic cancer recurrent; Hepatic cancer stage I; Hepatic cancer stage II; Hepatic cancer stage III; Hepatic cancer stage IV; Hepatic cirrhosis; Hepatic cyst; Hepatic cyst ruptured; Hepatic encephalopathy; Hepatic encephalopathy prophylaxis; Hepatic enzyme abnormal; Hepatic enzyme decreased; Hepatic enzyme increased; Hepaticfailure; Hepatic fibrosis; Hepatic function abnormal; Hepatic haemangioma rupture; Hepatic hamartoma; Hepatic hydrothorax; Hepatic hypertrophy; Hepatic hypoperfusion; Hepatic infiltration eosinophilic; Hepatic lesion; Hepatic mass; Hepatic necrosis; Hepatic neoplasm; Hepatic pain; Hepatic sequestration; Hepatic steato-fibrosis; Hepatic steatosis; Hepatic vascular resistance increased; Hepatic venous pressure gradient abnormal; Hepatic venous pressure gradient increased; Hepatitis; Hepatitis acute; Hepatitis cholestatic; Hepatitis chronic active; Hepatitis chronic persistent; Hepatitis fulminant; Hepatitis toxic; Hepatobiliary cancer; Hepatobiliary cancer in situ; Hepatobiliary cyst; Hepatobiliary disease; Hepatobiliary neoplasm; Hepatobiliary scan abnormal; Hepatoblastoma; Hepatoblastoma recurrent; Hepatocellular carcinoma; Hepatocellular foamy cell syndrome; Hepatocellular injury; Hepatomegaly; Hepatopulmonary syndrome; Hepatorenal failure; Hepatorenal syndrome; Hepatosplenomegaly; Hepatotoxicity; Hyperammonaemia; Hyperbilirubinaemia; Hypercholia; Hypertransaminasaemia; Hypocoagulable state; Hypofibrinogenaemia; Hypoprothrombinaemia; Hypothrombinaemia; Hypothromboplastinaemia;Icterus index increased; Immune-mediated cholangitis; Immune-mediated hepatic disorder; Immune-mediated hepatitis; International normalised ratio abnormal; International normalised ratio increased; Intestinal varices;Ischaemic hepatitis;

	Jaundice; Jaundice cholestatic; Jaundice hepatocellular; Kayser-Fleischer ring; Liver carcinoma ruptured; Liver dialysis; Liver disorder; Liver function test abnormal; Liver function test decreased; Liver function test increased; Liver induration; Liver injury; Liver operation; Liver palpable; Liver scan abnormal; Liver tenderness; Liver transplant; Lupoid hepatic cirrhosis; Lupus hepatitis; Magnetic resonance imaging liver abnormal; Magnetic resonance proton density fat fraction measurement; Metabolic encephalopathy; Minimal hepatic encephalopathy; Mitochondrial aspartate aminotransferase increased; Mixed hepatocellular cholangiocarcinoma; Mixed liver injury; Molar ratioof total branched-chain amino acid to tyrosine; Nodular regenerative hyperplasia; Nonalcoholic fatty liver disease; Non-alcoholic steatohepatitis; Non-cirrhotic portal hypertension; Ocular icterus; Oedemadue to hepatic disease; Parenteral nutrition associated liver disease; Perihepatic discomfort; Peripancreatic varices; Portal fibrosis; Portal hypertension; Portal hypertensive colopathy; Portal hypertensive enteropathy; Portal hypertensive gastropathy; Portal vein cavernous transformation; Portal vein dilatation; Portopulmonary hypertension; Primary biliary cholangitis; Protein C decreased; Protein S abnormal; Protein S decreased; Prothrombin level abnormal; Prothrombin level decreased; Prothrombin time abnormal; Prothrombin time prolonged; Prothrombin time ratio abnormal; Prothrombin time ratio increased; Radiation hepatitis; Regenerative siderotic hepatic nodule; Renal and livertransplant; Retrograde portal vein flow; Reye's syndrome; Reynold's syndrome; Splenic varices; Steatohepatitis; Subacute hepatic failure; Sugiura procedure; Thrombin time abnormal; Thrombin time prolonged; Total bile acids increased; Transaminases abnormal; Transaminases increased; Ultrasound liver abnormal; Urine bilirubin increased; Varices oesophageal; Varicose veins of abdominal wall; White nipple sign; X-rayhepatobiliary abnormal
Hypertension	Accelerated hypertension; Blood pressure ambulatory increased; Blood pressure diastolic increased; Blood pressure inadequately controlled; Blood pressure increased; Blood pressure management; Blood pressure orthostatic increased; Blood pressure systolic increased; Catecholamine crisis; Dialysis induced hypertension; Diastolic hypertension; Eclampsia; Endocrine hypertension; Essential hypertension; Gestational hypertension;HELLP syndrome; Hyperaldosteronism; Hypertension; Hypertension neonatal; Hypertensive angiopathy; Hypertensive cardiomegaly; Hypertensive cardiomyopathy; Hypertensive cerebrovascular disease; Hypertensive crisis; Hypertensive emergency; Hypertensive encephalopathy; Hypertensive end-organ damage; Hypertensive heart disease; Hypertensive nephropathy; Hypertensive urgency; Labile hypertension; Malignant hypertension; Malignant hypertensive heart disease; Malignant renal hypertension; Maternal hypertension affecting foetus; Mean arterial pressure increased; Metabolic syndrome; Neurogenichypertension; Orthostatic hypertension; Page kidney; Postoperative hypertension; Pre-eclampsia; Prehypertension; Procedural hypertension; Renal hypertension; Renal sympathetic nerve ablation; Renovascular hypertension; Retinopathy hypertensive; Secondary aldosteronism; Secondary hypertension; Superimposed pre-eclampsia; Supinehypertension; Systolic hypertension; Withdrawal hypertension
Hypocalcemia	Blood calcium decreased; Calcium deficiency; Hypocalcaemia; Hypocalcaemic seizure

Hypothyroidism	Autoimmune hypothyroidism; Blood thyroid stimulating hormone abnormal; Blood thyroid stimulating hormone increased; Congenital hypothyroidism; Generalised resistance to thyroid hormone; Hypothyroidic goitre; Hypothyroidism; Immune-mediated hypothyroidism; Myxoedema; Myxoedema coma; Post procedural hypothyroidism; Primary hypothyroidism; Secondary hypothyroidism; Tertiary hypothyroidism; Thyroid atrophy; Thyroid stimulating hormonedeficiency; Transient hypothyroxinaemia of prematurity
Palmar-Plantar Erythrodysesthesia Syndrome	Palmar erythema; Palmar-plantar erythrodysaesthesia syndrome; Plantarerythema; Rash erythematous; Skin reaction
Posterior Reversible Encephalopathy Syndrome	Posterior reversible encephalopathy syndrome; Vascular encephalopathy
Proteinuria	Albumin globulin ratio increased; Albumin urine present; Albuminuria;Bence Jones protein urine present; Bence Jones proteinuria; Beta 2 microglobulin urine increased; Globulinuria; Microalbuminuria; Myoglobinuria; Nephrotic syndrome; Orthostatic proteinuria; Protein urine; Protein urine present; Proteinuria; Urine albumin/creatinine ratio increased; Urine protein/creatinine ratio abnormal; Urineprotein/creatinine ratio increased
QT Prolongation	Electrocardiogram QT interval abnormal; Electrocardiogram QT prolonged; Long QT syndrome; Long QT syndrome congenital; Torsadede pointes; Ventricular tachycardia
Renal Events	Acute kidney injury; Acute phosphate nephropathy; Anuria; Azotaemia; Blood creatinine abnormal; Blood creatinine increased; Blood urea abnormal; Blood urea increased; Blood urea nitrogen/creatinine ratio increased; Continuous haemodiafiltration; Creatinine renal clearance abnormal; Creatinine renal clearance decreased; Creatinine urine abnormal; Creatinine urine decreased; Crystal nephropathy; Dialysis; Foetal renal impairment; Fractional excretion of sodium; Glomerular filtration rate abnormal; Glomerular filtration rate decreased; Glomerularvascular disorder; Haemodialysis; Haemofiltration; Hypercreatininaemia; Hyponatriuria; Intradialytic parenteral nutrition; Ischaemic nephropathy;Kidney injury molecule-1; Neonatal anuria; Nephritis; Nephroangiosclerosis; Nephropathy toxic; Neutrophil gelatinase- associated lipocalin increased; Oedema due to renal disease; Oliguria; Peritoneal dialysis; Prerenal failure; Renal aneurysm; Renal arteriosclerosis; Renal arteritis; Renal artery arteriosclerosis; Renal artery dissection; Renal artery fibromuscular dysplasia; Renal artery hyperplasia;Renal artery restenosis; Renal artery stenosis; Renal failure; Renal failure neonatal; Renal function test abnormal; Renal impairment; Renal impairment neonatal; Renal infarct; Renal ischaemia; Renal pseudoaneurysm; Renal transplant; Renal tubular disorder; Renal tubular dysfunction; Renal tubular injury; Renal tubular necrosis; Renal vascular thrombosis; Renal vasculitis; Renal vein compression; Renal vein embolism; Renal vein occlusion; Renal vein stenosis; Renal vein thrombosis; Renal vein varices; Renal vessel disorder; Subacute kidney injury; Tubulointerstitial nephritis; Urea renal clearance decreased; Urineoutput decreased
This list is based on MedDRA Version 23.1 (30-OCT-2020)	