Dokumentvorlage, Version vom 21.02.2019

Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD Sharp & Dohme GmbH

Modul 4A

Behandlung des fortgeschrittenen oder rezidiverenden 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

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Stand: 10.12.2021

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Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.2.2 sowie 4.3.1.3.1.3 die Rücklaufquoten des EORTC QLQ-C30, die Rücklaufquoten des EORTC QLQ-EN24 und die Rücklaufquoten des EQ-5D VAS der Nutzenbewertungsrelevanten Population dargestellt.

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 26. Oktober 2020 (Interimsanalyse I, präspezifiziert).

Anhang 4-G1.1: Rücklaufquoten des EORTC QLQ-C30

Tabelle 4G-1: Gründe für das Fehlen von Werten im EORTC QLQ-C30

Study: KEYNOTE 775[a]		**Pembrolizumab + Lenvatinib[b]**	**Doxorubicin[b]**
Visit	**EORTC QLQ-C30**	**N[c] = 282 n (%)**	**N[c] = 267 n (%)**
BASELINE	Expected to Complete Questionnaires[d]	280 (99.3)	266 (99.6)
	Completed	270 (95.7)	256 (95.9)
	Compliance (% in those expected to complete questionnaires)[e]	270 (96.4)	256 (96.2)
	Not completed	10 (3.5)	10 (3.7)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	1 (0.4)	5 (1.9)
	Subject refused for other reasons	2 (0.7)	1 (0.4)
	Other	6 (2.1)	3 (1.1)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	2 (0.7)	1 (0.4)
	Translation not available in subjects language	2 (0.7)	1 (0.4)
WEEK 3	Expected to Complete Questionnaires[d]	278 (98.6)	265 (99.3)
	Completed	258 (91.5)	244 (91.4)
	Compliance (% in those expected to complete questionnaires)[e]	258 (92.8)	244 (92.1)
	Not completed	20 (7.1)	21 (7.9)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	2 (0.7)	2 (0.7)
	Subject in hospital or hospice	2 (0.7)	1 (0.4)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.4)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	6 (2.1)	3 (1.1)
	With visit, no record	10 (3.5)	12 (4.5)
	Missing by Design[f]	4 (1.4)	2 (0.7)
	Translation not available in subjects language	2 (0.7)	1 (0.4)
	Visit not scheduled	2 (0.7)	1 (0.4)
WEEK 6	Expected to Complete Questionnaires[d]	265 (94.0)	252 (94.4)
	Completed	242 (85.8)	226 (84.6)
	Compliance (% in those expected to complete questionnaires)[e]	242 (91.3)	226 (89.7)
	Not completed	23 (8.2)	26 (9.7)
	Subject did not complete due to disease under study	1 (0.4)	1 (0.4)
	Not completed due to site staff error	3 (1.1)	4 (1.5)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.7)	4 (1.5)
	Other	3 (1.1)	6 (2.2)
	With visit, no record	13 (4.6)	11 (4.1)
	Missing by Design[f]	17 (6.0)	15 (5.6)
	Discontinued due to adverse event	1 (0.4)	0 (0.0)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	9 (3.2)	50 (18.7)

Study: KEYNOTE 775[a]		**Pembrolizumab + Lenvatinib[b]**	**Doxorubicin[b]**
Visit	**EORTC QLQ-C30**	**N[c] = 282 n (%)**	**N[c] = 267 n (%)**
	Discontinued due to withdrawal by subject	4 (1.4)	6 (2.2)
	Completed study treatment	0 (0.0)	1 (0.4)
	Translation not available in subjects language	2 (0.7)	3 (1.1)
	Subject died	2 (0.7)	1 (0.4)
	Visit not scheduled	17 (6.0)	8 (3.0)
WEEK 15	Expected to Complete Questionnaires[d]	226 (80.1)	154 (57.7)
	Completed	209 (74.1)	131 (49.1)
	Compliance (% in those expected to complete questionnaires)[e]	209 (92.5)	131 (85.1)
	Not completed	17 (6.0)	23 (8.6)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	5 (1.8)	2 (0.7)
	Subject in hospital or hospice	2 (0.7)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.4)
	Subject refused for other reasons	3 (1.1)	6 (2.2)
	Other	6 (2.1)	4 (1.5)
	With visit, no record	1 (0.4)	9 (3.4)
	Missing by Design[f]	56 (19.9)	113 (42.3)
	Discontinued due to adverse event	8 (2.8)	11 (4.1)
	Discontinued due to clinical progression	3 (1.1)	13 (4.9)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	1 (0.4)	3 (1.1)
	Discontinued due to progressive disease	13 (4.6)	67 (25.1)
	Discontinued due to withdrawal by subject	5 (1.8)	6 (2.2)
	Completed study treatment	0 (0.0)	1 (0.4)
	Translation not available in subjects language	2 (0.7)	3 (1.1)
	Subject died	1 (0.4)	2 (0.7)
	Visit not scheduled	23 (8.2)	6 (2.2)
WEEK 18	Expected to Complete Questionnaires[d]	219 (77.7)	125 (46.8)
	Completed	204 (72.3)	106 (39.7)
	Compliance (% in those expected to complete questionnaires)[e]	204 (93.2)	106 (84.8)
	Not completed	15 (5.3)	19 (7.1)
	Not completed due to site staff error	4 (1.4)	5 (1.9)
	Subject in hospital or hospice	1 (0.4)	1 (0.4)
	Subject did not complete due to side effects of treatment	2 (0.7)	1 (0.4)
	Subject refused for other reasons	2 (0.7)	1 (0.4)
	Other	6 (2.1)	6 (2.2)
	With visit, no record	0 (0.0)	5 (1.9)
	Missing by Design[f]	63 (22.3)	142 (53.2)
	Discontinued due to adverse event	11 (3.9)	11 (4.1)
	Discontinued due to clinical progression	3 (1.1)	15 (5.6)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	1 (0.4)	5 (1.9)
	Discontinued due to progressive disease	21 (7.4)	79 (29.6)
	Discontinued due to withdrawal by subject	6 (2.1)	10 (3.7)
	Completed study treatment	0 (0.0)	6 (2.2)
	Translation not available in subjects language	2 (0.7)	1 (0.4)
	Subject died	4 (1.4)	2 (0.7)
	Visit not scheduled	15 (5.3)	11 (4.1)
WEEK 21	Expected to Complete Questionnaires[d]	208 (73.8)	109 (40.8)
	Completed	189 (67.0)	85 (31.8)
	Compliance (% in those expected to complete questionnaires)[e]	189 (90.9)	85 (78.0)
	Not completed	19 (6.7)	24 (9.0)
	Not completed due to site staff error	4 (1.4)	2 (0.7)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Physically unable to complete	2 (0.7)	1 (0.4)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-C30	N[c] = 282 n (%)	N[c] = 267 n (%)
	Other	6 (2.1)	4 (1.5)
	With visit, no record	7 (2.5)	16 (6.0)
	Missing by Design[f]	74 (26.2)	158 (59.2)
	Discontinued due to adverse event	19 (6.7)	14 (5.2)
	Discontinued due to clinical progression	4 (1.4)	16 (6.0)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	2 (0.7)	6 (2.2)
	Discontinued due to progressive disease	28 (9.9)	87 (32.6)
	Discontinued due to withdrawal by subject	6 (2.1)	13 (4.9)
	Completed study treatment	0 (0.0)	13 (4.9)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	0 (0.0)	1 (0.4)
	Visit not scheduled	14 (5.0)	6 (2.2)
WEEK 24	Expected to Complete Questionnaires[d]	193 (68.4)	65 (24.3)
	Completed	170 (60.3)	47 (17.6)
	Compliance (% in those expected to complete questionnaires)[e]	170 (88.1)	47 (72.3)
	Not completed	23 (8.2)	18 (6.7)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Not completed due to site staff error	2 (0.7)	1 (0.4)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Physically unable to complete	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.7)	1 (0.4)
	Other	9 (3.2)	7 (2.6)
	With visit, no record	7 (2.5)	9 (3.4)
	Missing by Design[f]	89 (31.6)	202 (75.7)
	Discontinued due to adverse event	22 (7.8)	17 (6.4)
	Discontinued due to clinical progression	4 (1.4)	18 (6.7)
	Discontinued due to complete response	0 (0.0)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	2 (0.7)	11 (4.1)
	Discontinued due to progressive disease	33 (11.7)	99 (37.1)
	Discontinued due to withdrawal by subject	7 (2.5)	12 (4.5)
	Completed study treatment	0 (0.0)	29 (10.9)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	2 (0.7)
	Visit not scheduled	19 (6.7)	11 (4.1)
WEEK 27	Expected to Complete Questionnaires[d]	183 (64.9)	50 (18.7)
	Completed	164 (58.2)	34 (12.7)
	Compliance (% in those expected to complete questionnaires)[e]	164 (89.6)	34 (68.0)
	Not completed	19 (6.7)	16 (6.0)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Not completed due to site staff error	3 (1.1)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Physically unable to complete	1 (0.4)	0 (0.0)
	Subject lost to follow-up/unable to contact	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.7)	0 (0.0)
	Other	7 (2.5)	1 (0.4)
	With visit, no record	4 (1.4)	14 (5.2)
	Missing by Design[f]	99 (35.1)	217 (81.3)
	Discontinued due to adverse event	24 (8.5)	18 (6.7)
	Discontinued due to clinical progression	4 (1.4)	19 (7.1)
	Discontinued due to complete response	0 (0.0)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)

Study: KEYNOTE 775[a]		**Pembrolizumab + Lenvatinib[b]**	**Doxorubicin[b]**
Visit	**EORTC QLQ-C30**	**N[c] = 282 n (%)**	**N[c] = 267 n (%)**
	Discontinued due to physician decision	2 (0.7)	12 (4.5)
	Discontinued due to progressive disease	47 (16.7)	102 (38.2)
	Discontinued due to withdrawal by subject	7 (2.5)	13 (4.9)
	Completed study treatment	0 (0.0)	44 (16.5)
	Translation not available in subjects language	3 (1.1)	0 (0.0)
	Subject died	1 (0.4)	2 (0.7)
	Visit not scheduled	11 (3.9)	4 (1.5)
WEEK 30	Expected to Complete Questionnaires[d]	171 (60.6)	14 (5.2)
	Completed	157 (55.7)	8 (3.0)
	Compliance (% in those expected to complete questionnaires)[e]	157 (91.8)	8 (57.1)
	Not completed	14 (5.0)	6 (2.2)
	Subject did not complete due to disease under study	1 (0.4)	1 (0.4)
	Not completed due to site staff error	2 (0.7)	3 (1.1)
	Other	7 (2.5)	1 (0.4)
	With visit, no record	4 (1.4)	1 (0.4)
	Missing by Design[f]	111 (39.4)	253 (94.8)
	Discontinued due to adverse event	28 (9.9)	21 (7.9)
	Discontinued due to clinical progression	5 (1.8)	19 (7.1)
	Discontinued due to complete response	0 (0.0)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	2 (0.7)	11 (4.1)
	Discontinued due to progressive disease	57 (20.2)	103 (38.6)
	Discontinued due to withdrawal by subject	9 (3.2)	13 (4.9)
	Completed study treatment	0 (0.0)	80 (30.0)
	Subject died	1 (0.4)	1 (0.4)
	Visit not scheduled	9 (3.2)	2 (0.7)
WEEK 33	Expected to Complete Questionnaires[d]	152 (53.9)	8 (3.0)
	Completed	138 (48.9)	2 (0.7)
	Compliance (% in those expected to complete questionnaires)[e]	138 (90.8)	2 (25.0)
	Not completed	14 (5.0)	6 (2.2)
	Not completed due to site staff error	3 (1.1)	1 (0.4)
	Subject refused for other reasons	1 (0.4)	2 (0.7)
	Other	8 (2.8)	1 (0.4)
	With visit, no record	2 (0.7)	2 (0.7)
	Missing by Design[f]	130 (46.1)	259 (97.0)
	Discontinued due to adverse event	32 (11.3)	21 (7.9)
	Discontinued due to clinical progression	5 (1.8)	19 (7.1)
	Discontinued due to complete response	0 (0.0)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	3 (1.1)	11 (4.1)
	Discontinued due to progressive disease	70 (24.8)	105 (39.3)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	85 (31.8)
	Visit not scheduled	11 (3.9)	1 (0.4)
WEEK 36	Expected to Complete Questionnaires[d]	152 (53.9)	4 (1.5)
	Completed	134 (47.5)	2 (0.7)
	Compliance (% in those expected to complete questionnaires)[e]	134 (88.2)	2 (50.0)
	Not completed	18 (6.4)	2 (0.7)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Physically unable to complete	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.7)	2 (0.7)
	Other	6 (2.1)	0 (0.0)
	With visit, no record	8 (2.8)	0 (0.0)
	Missing by Design[f]	130 (46.1)	263 (98.5)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-C30	N[c] = 282 n (%)	N[c] = 267 n (%)
	Discontinued due to adverse event	32 (11.3)	21 (7.9)
	Discontinued due to clinical progression	5 (1.8)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	3 (1.1)	13 (4.9)
	Discontinued due to progressive disease	74 (26.2)	105 (39.3)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	88 (33.0)
	Visit not scheduled	6 (2.1)	0 (0.0)
WEEK 39	Expected to Complete Questionnaires[d]	138 (48.9)	2 (0.7)
	Completed	124 (44.0)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	124 (89.9)	0 (0.0)
	Not completed	14 (5.0)	2 (0.7)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	7 (2.5)	1 (0.4)
	With visit, no record	4 (1.4)	0 (0.0)
	Missing by Design[f]	144 (51.1)	265 (99.3)
	Discontinued due to adverse event	34 (12.1)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	3 (1.1)	13 (4.9)
	Discontinued due to progressive disease	84 (29.8)	105 (39.3)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	90 (33.7)
	Visit not reached	2 (0.7)	0 (0.0)
	Visit not scheduled	5 (1.8)	0 (0.0)
WEEK 42	Expected to Complete Questionnaires[d]	124 (44.0)	0 (0.0)
	Completed	115 (40.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	115 (92.7)	0 (0.0)
	Not completed	9 (3.2)	0 (0.0)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Other	6 (2.1)	0 (0.0)
	With visit, no record	2 (0.7)	0 (0.0)
	Missing by Design[f]	158 (56.0)	267 (100.0)
	Discontinued due to adverse event	34 (12.1)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	88 (31.2)	106 (39.7)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Subject died	1 (0.4)	0 (0.0)
	Visit not reached	7 (2.5)	0 (0.0)
	Visit not scheduled	8 (2.8)	0 (0.0)
WEEK 45	Expected to Complete Questionnaires[d]	113 (40.1)	0 (0.0)
	Completed	99 (35.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	99 (87.6)	0 (0.0)
	Not completed	14 (5.0)	0 (0.0)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-C30	N[c] = 282 n (%)	N[c] = 267 n (%)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	3 (1.1)	0 (0.0)
	Other	9 (3.2)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	169 (59.9)	267 (100.0)
	Discontinued due to adverse event	36 (12.8)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	3 (1.1)	13 (4.9)
	Discontinued due to progressive disease	94 (33.3)	106 (39.7)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	12 (4.3)	0 (0.0)
	Visit not scheduled	8 (2.8)	0 (0.0)
WEEK 48	Expected to Complete Questionnaires[d]	101 (35.8)	0 (0.0)
	Completed	89 (31.6)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	89 (88.1)	0 (0.0)
	Not completed	12 (4.3)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	8 (2.8)	0 (0.0)
	With visit, no record	2 (0.7)	0 (0.0)
	Missing by Design[f]	181 (64.2)	267 (100.0)
	Discontinued due to adverse event	37 (13.1)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	98 (34.8)	106 (39.7)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	19 (6.7)	0 (0.0)
	Visit not scheduled	7 (2.5)	0 (0.0)
WEEK 51	Expected to Complete Questionnaires[d]	91 (32.3)	1 (0.4)
	Completed	77 (27.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	77 (84.6)	0 (0.0)
	Not completed	14 (5.0)	1 (0.4)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.7)	0 (0.0)
	Other	10 (3.5)	1 (0.4)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	191 (67.7)	266 (99.6)
	Discontinued due to adverse event	40 (14.2)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	99 (35.1)	106 (39.7)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	90 (33.7)
	Subject died	2 (0.7)	0 (0.0)
	Visit not reached	27 (9.6)	0 (0.0)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-C30	N[c] = 282 n (%)	N[c] = 267 n (%)
	Visit not scheduled	3 (1.1)	0 (0.0)
WEEK 54	Expected to Complete Questionnaires[d]	81 (28.7)	0 (0.0)
	Completed	71 (25.2)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	71 (87.7)	0 (0.0)
	Not completed	10 (3.5)	0 (0.0)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	7 (2.5)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	201 (71.3)	267 (100.0)
	Discontinued due to adverse event	42 (14.9)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	103 (36.5)	106 (39.7)
	Discontinued due to withdrawal by subject	10 (3.5)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	33 (11.7)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 57	Expected to Complete Questionnaires[d]	73 (25.9)	0 (0.0)
	Completed	66 (23.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	66 (90.4)	0 (0.0)
	Not completed	7 (2.5)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	5 (1.8)	0 (0.0)
	Missing by Design[f]	209 (74.1)	267 (100.0)
	Discontinued due to adverse event	42 (14.9)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	105 (37.2)	106 (39.7)
	Discontinued due to withdrawal by subject	10 (3.5)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	38 (13.5)	0 (0.0)
	Visit not scheduled	3 (1.1)	0 (0.0)
WEEK 60	Expected to Complete Questionnaires[d]	66 (23.4)	0 (0.0)
	Completed	59 (20.9)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	59 (89.4)	0 (0.0)
	Not completed	7 (2.5)	0 (0.0)
	Other	7 (2.5)	0 (0.0)
	Missing by Design[f]	216 (76.6)	267 (100.0)
	Discontinued due to adverse event	42 (14.9)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	106 (37.6)	106 (39.7)
	Discontinued due to withdrawal by subject	10 (3.5)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Subject died	1 (0.4)	0 (0.0)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-C30	N[c] = 282 n (%)	N[c] = 267 n (%)
	Visit not reached	41 (14.5)	0 (0.0)
	Visit not scheduled	5 (1.8)	0 (0.0)
WEEK 63	Expected to Complete Questionnaires[d]	58 (20.6)	1 (0.4)
	Completed	50 (17.7)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	50 (86.2)	0 (0.0)
	Not completed	8 (2.8)	1 (0.4)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	6 (2.1)	1 (0.4)
	Missing by Design[f]	224 (79.4)	266 (99.6)
	Discontinued due to adverse event	43 (15.2)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	108 (38.3)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	44 (15.6)	0 (0.0)
	Visit not scheduled	7 (2.5)	0 (0.0)
WEEK 66	Expected to Complete Questionnaires[d]	51 (18.1)	0 (0.0)
	Completed	41 (14.5)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	41 (80.4)	0 (0.0)
	Not completed	10 (3.5)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject did not complete due to side effects of treatment	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	6 (2.1)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	231 (81.9)	267 (100.0)
	Discontinued due to adverse event	43 (15.2)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	111 (39.4)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	50 (17.7)	0 (0.0)
	Visit not scheduled	5 (1.8)	0 (0.0)
WEEK 69	Expected to Complete Questionnaires[d]	48 (17.0)	0 (0.0)
	Completed	42 (14.9)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	42 (87.5)	0 (0.0)
	Not completed	6 (2.1)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	5 (1.8)	0 (0.0)
	Missing by Design[f]	234 (83.0)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	112 (39.7)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-C30	N[c] = 282 n (%)	N[c] = 267 n (%)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	51 (18.1)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 72	Expected to Complete Questionnaires[d]	45 (16.0)	0 (0.0)
	Completed	40 (14.2)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	40 (88.9)	0 (0.0)
	Not completed	5 (1.8)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Other	3 (1.1)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	237 (84.0)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	112 (39.7)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	55 (19.5)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 75	Expected to Complete Questionnaires[d]	39 (13.8)	0 (0.0)
	Completed	36 (12.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	36 (92.3)	0 (0.0)
	Not completed	3 (1.1)	0 (0.0)
	Other	2 (0.7)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	243 (86.2)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	112 (39.7)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	57 (20.2)	0 (0.0)
	Visit not scheduled	5 (1.8)	0 (0.0)
WEEK 78	Expected to Complete Questionnaires[d]	39 (13.8)	0 (0.0)
	Completed	37 (13.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	37 (94.9)	0 (0.0)
	Not completed	2 (0.7)	0 (0.0)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Missing by Design[f]	243 (86.2)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	113 (40.1)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-C30	N[c] = 282 n (%)	N[c] = 267 n (%)
	Visit not reached	60 (21.3)	0 (0.0)
	Visit not scheduled	1 (0.4)	0 (0.0)
WEEK 81	Expected to Complete Questionnaires[d]	34 (12.1)	0 (0.0)
	Completed	32 (11.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	32 (94.1)	0 (0.0)
	Not completed	2 (0.7)	0 (0.0)
	Other	1 (0.4)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	248 (87.9)	267 (100.0)
	Discontinued due to adverse event	46 (16.3)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	114 (40.4)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	63 (22.3)	0 (0.0)
	Visit not scheduled	1 (0.4)	0 (0.0)
WEEK 84	Expected to Complete Questionnaires[d]	25 (8.9)	0 (0.0)
	Completed	23 (8.2)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	23 (92.0)	0 (0.0)
	Not completed	2 (0.7)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Missing by Design[f]	257 (91.1)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	115 (40.8)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	72 (25.5)	0 (0.0)
	Visit not scheduled	1 (0.4)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires[d]	19 (6.7)	0 (0.0)
	Completed	18 (6.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	18 (94.7)	0 (0.0)
	Not completed	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Missing by Design[f]	263 (93.3)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	116 (41.1)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	74 (26.2)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-C30	N[c] = 282 n (%)	N[c] = 267 n (%)
WEEK 90	Expected to Complete Questionnaires[d]	19 (6.7)	0 (0.0)
	Completed	19 (6.7)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	19 (100.0)	0 (0.0)
	Missing by Design[f]	263 (93.3)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	116 (41.1)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	74 (26.2)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 93	Expected to Complete Questionnaires[d]	17 (6.0)	0 (0.0)
	Completed	17 (6.0)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	17 (100.0)	0 (0.0)
	Missing by Design[f]	265 (94.0)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	116 (41.1)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	78 (27.7)	0 (0.0)
WEEK 96	Expected to Complete Questionnaires[d]	11 (3.9)	0 (0.0)
	Completed	11 (3.9)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	11 (100.0)	0 (0.0)
	Missing by Design[f]	271 (96.1)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	82 (29.1)	0 (0.0)
	Visit not scheduled	1 (0.4)	0 (0.0)
WEEK 99	Expected to Complete Questionnaires[d]	9 (3.2)	0 (0.0)
	Completed	9 (3.2)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	9 (100.0)	0 (0.0)
	Missing by Design[f]	273 (96.8)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-C30	N[c] = 282 n (%)	N[c] = 267 n (%)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	85 (30.1)	0 (0.0)
WEEK 102	Expected to Complete Questionnaires[d]	8 (2.8)	0 (0.0)
	Completed	8 (2.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	8 (100.0)	0 (0.0)
	Missing by Design[f]	274 (97.2)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	86 (30.5)	0 (0.0)
WEEK 105	Expected to Complete Questionnaires[d]	6 (2.1)	0 (0.0)
	Completed	6 (2.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	6 (100.0)	0 (0.0)
	Missing by Design[f]	276 (97.9)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	88 (31.2)	0 (0.0)
WEEK 108	Expected to Complete Questionnaires[d]	5 (1.8)	0 (0.0)
	Completed	5 (1.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	5 (100.0)	0 (0.0)
	Missing by Design[f]	277 (98.2)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	89 (31.6)	0 (0.0)
WEEK 111	Expected to Complete Questionnaires[d]	2 (0.7)	0 (0.0)
	Completed	1 (0.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	1 (50.0)	0 (0.0)
	Not completed	1 (0.4)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	280 (99.3)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-C30	N[c] = 282 n (%)	N[c] = 267 n (%)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	92 (32.6)	0 (0.0)
WEEK 114	Expected to Complete Questionnaires[d]	2 (0.7)	0 (0.0)
	Completed	1 (0.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	1 (50.0)	0 (0.0)
	Not completed	1 (0.4)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	280 (99.3)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	92 (32.6)	0 (0.0)

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: Expected to complete questionnaire includes all participants who do not have missing data due to a missing by design reason.

e: Compliance is the proportion of participants who completed the PRO questionnaire among these who are expected to complete at each time point, excluding those missing by design. All the other categories are defined as the proportion of participants in the analysis population (N).

f: Missing by design includes: death, disease progression, other discontinuations (reasons may include unacceptable AEs, withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment), and translation not available.

PRO: Patient Reported Outcome; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Anhang 4-G1.2: Rücklaufquoten des EORTC QLQ-EN24

Tabelle 4G-2: Gründe für das Fehlen von Werten im EORTC QLQ-EN24

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-EN24	N[c] = 282 n (%)	N[c] = 267 n (%)
BASELINE	Expected to Complete Questionnaires[d]	280 (99.3)	266 (99.6)
	Completed	222 (78.7)	217 (81.3)
	Compliance (% in those expected to complete questionnaires)[e]	222 (79.3)	217 (81.6)
	Not completed	58 (20.6)	49 (18.4)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	2 (0.7)	5 (1.9)
	Physically unable to complete	0 (0.0)	2 (0.7)
	Subject refused for other reasons	2 (0.7)	1 (0.4)
	Other	8 (2.8)	6 (2.2)
	With visit, no record	46 (16.3)	34 (12.7)
	Missing by Design[f]	2 (0.7)	1 (0.4)
	Translation not available in subjects language	2 (0.7)	1 (0.4)
WEEK 3	Expected to Complete Questionnaires[d]	278 (98.6)	265 (99.3)
	Completed	215 (76.2)	208 (77.9)
	Compliance (% in those expected to complete questionnaires)[e]	215 (77.3)	208 (78.5)
	Not completed	63 (22.3)	57 (21.3)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	2 (0.7)	4 (1.5)
	Subject in hospital or hospice	2 (0.7)	1 (0.4)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.4)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	7 (2.5)	7 (2.6)
	With visit, no record	52 (18.4)	42 (15.7)
	Missing by Design[f]	4 (1.4)	2 (0.7)
	Translation not available in subjects language	2 (0.7)	1 (0.4)
	Visit not scheduled	2 (0.7)	1 (0.4)
WEEK 6	Expected to Complete Questionnaires[d]	265 (94.0)	251 (94.0)
	Completed	202 (71.6)	190 (71.2)
	Compliance (% in those expected to complete questionnaires)[e]	202 (76.2)	190 (75.7)
	Not completed	63 (22.3)	61 (22.8)
	Subject did not complete due to disease under study	1 (0.4)	1 (0.4)
	Not completed due to site staff error	3 (1.1)	4 (1.5)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.7)	3 (1.1)
	Other	4 (1.4)	12 (4.5)
	With visit, no record	52 (18.4)	41 (15.4)
	Missing by Design[f]	17 (6.0)	16 (6.0)
	Discontinued due to adverse event	1 (0.4)	0 (0.0)
	Discontinued due to clinical progression	1 (0.4)	0 (0.0)
	Discontinued due to progressive disease	1 (0.4)	1 (0.4)
	Discontinued due to withdrawal by subject	2 (0.7)	1 (0.4)
	Translation not available in subjects language	3 (1.1)	2 (0.7)
	Subject died	1 (0.4)	3 (1.1)
	Visit not scheduled	8 (2.8)	9 (3.4)
WEEK 9	Expected to Complete Questionnaires[d]	252 (89.4)	225 (84.3)
	Completed	204 (72.3)	172 (64.4)
	Compliance (% in those expected to complete questionnaires)[e]	204 (81.0)	172 (76.4)
	Not completed	48 (17.0)	53 (19.9)
	Subject did not complete due to disease under study	2 (0.7)	2 (0.7)
	Not completed due to site staff error	2 (0.7)	5 (1.9)
	Subject did not complete due to side effects of treatment	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	6 (2.2)
	Other	5 (1.8)	7 (2.6)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-EN24	N[c] = 282 n (%)	N[c] = 267 n (%)
	With visit, no record	37 (13.1)	33 (12.4)
	Missing by Design[f]	30 (10.6)	42 (15.7)
	Discontinued due to adverse event	4 (1.4)	6 (2.2)
	Discontinued due to clinical progression	1 (0.4)	2 (0.7)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to progressive disease	2 (0.7)	10 (3.7)
	Discontinued due to withdrawal by subject	2 (0.7)	4 (1.5)
	Translation not available in subjects language	4 (1.4)	3 (1.1)
	Subject died	3 (1.1)	3 (1.1)
	Visit not scheduled	14 (5.0)	13 (4.9)
WEEK 12	Expected to Complete Questionnaires[d]	237 (84.0)	178 (66.7)
	Completed	183 (64.9)	130 (48.7)
	Compliance (% in those expected to complete questionnaires)[e]	183 (77.2)	130 (73.0)
	Not completed	54 (19.1)	48 (18.0)
	Subject did not complete due to disease under study	2 (0.7)	1 (0.4)
	Not completed due to site staff error	5 (1.8)	2 (0.7)
	Subject in hospital or hospice	2 (0.7)	0 (0.0)
	Physically unable to complete	0 (0.0)	1 (0.4)
	Subject refused for other reasons	0 (0.0)	2 (0.7)
	Other	9 (3.2)	8 (3.0)
	With visit, no record	36 (12.8)	34 (12.7)
	Missing by Design[f]	45 (16.0)	89 (33.3)
	Discontinued due to adverse event	6 (2.1)	7 (2.6)
	Discontinued due to clinical progression	2 (0.7)	8 (3.0)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	9 (3.2)	50 (18.7)
	Discontinued due to withdrawal by subject	4 (1.4)	6 (2.2)
	Completed study treatment	0 (0.0)	1 (0.4)
	Translation not available in subjects language	2 (0.7)	3 (1.1)
	Subject died	2 (0.7)	1 (0.4)
	Visit not scheduled	20 (7.1)	8 (3.0)
WEEK 15	Expected to Complete Questionnaires[d]	226 (80.1)	151 (56.6)
	Completed	177 (62.8)	108 (40.4)
	Compliance (% in those expected to complete questionnaires)[e]	177 (78.3)	108 (71.5)
	Not completed	49 (17.4)	43 (16.1)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	6 (2.1)	3 (1.1)
	Subject in hospital or hospice	2 (0.7)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.4)
	Subject refused for other reasons	2 (0.7)	6 (2.2)
	Other	6 (2.1)	8 (3.0)
	With visit, no record	33 (11.7)	24 (9.0)
	Missing by Design[f]	56 (19.9)	116 (43.4)
	Discontinued due to adverse event	8 (2.8)	11 (4.1)
	Discontinued due to clinical progression	3 (1.1)	13 (4.9)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	1 (0.4)	3 (1.1)
	Discontinued due to progressive disease	13 (4.6)	67 (25.1)
	Discontinued due to withdrawal by subject	5 (1.8)	6 (2.2)
	Completed study treatment	0 (0.0)	1 (0.4)
	Translation not available in subjects language	1 (0.4)	3 (1.1)
	Subject died	1 (0.4)	2 (0.7)
	Visit not scheduled	24 (8.5)	9 (3.4)
WEEK 18	Expected to Complete Questionnaires[d]	215 (76.2)	124 (46.4)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-EN24	N[c] = 282 n (%)	N[c] = 267 n (%)
	Completed	168 (59.6)	87 (32.6)
	Compliance (% in those expected to complete questionnaires)[e]	168 (78.1)	87 (70.2)
	Not completed	47 (16.7)	37 (13.9)
	Not completed due to site staff error	4 (1.4)	5 (1.9)
	Subject in hospital or hospice	1 (0.4)	1 (0.4)
	Subject did not complete due to side effects of treatment	2 (0.7)	1 (0.4)
	Subject refused for other reasons	2 (0.7)	2 (0.7)
	Other	7 (2.5)	9 (3.4)
	With visit, no record	31 (11.0)	19 (7.1)
	Missing by Design[f]	67 (23.8)	143 (53.6)
	Discontinued due to adverse event	11 (3.9)	11 (4.1)
	Discontinued due to clinical progression	3 (1.1)	15 (5.6)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	1 (0.4)	5 (1.9)
	Discontinued due to progressive disease	21 (7.4)	79 (29.6)
	Discontinued due to withdrawal by subject	6 (2.1)	10 (3.7)
	Completed study treatment	0 (0.0)	6 (2.2)
	Translation not available in subjects language	2 (0.7)	1 (0.4)
	Subject died	4 (1.4)	2 (0.7)
	Visit not scheduled	19 (6.7)	12 (4.5)
WEEK 21	Expected to Complete Questionnaires[d]	208 (73.8)	108 (40.4)
	Completed	156 (55.3)	71 (26.6)
	Compliance (% in those expected to complete questionnaires)[e]	156 (75.0)	71 (65.7)
	Not completed	52 (18.4)	37 (13.9)
	Not completed due to site staff error	4 (1.4)	2 (0.7)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Physically unable to complete	2 (0.7)	1 (0.4)
	Other	7 (2.5)	5 (1.9)
	With visit, no record	39 (13.8)	28 (10.5)
	Missing by Design[f]	74 (26.2)	159 (59.6)
	Discontinued due to adverse event	19 (6.7)	14 (5.2)
	Discontinued due to clinical progression	4 (1.4)	16 (6.0)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	2 (0.7)	6 (2.2)
	Discontinued due to progressive disease	28 (9.9)	87 (32.6)
	Discontinued due to withdrawal by subject	6 (2.1)	13 (4.9)
	Completed study treatment	0 (0.0)	13 (4.9)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	0 (0.0)	1 (0.4)
	Visit not scheduled	14 (5.0)	7 (2.6)
WEEK 24	Expected to Complete Questionnaires[d]	193 (68.4)	64 (24.0)
	Completed	138 (48.9)	41 (15.4)
	Compliance (% in those expected to complete questionnaires)[e]	138 (71.5)	41 (64.1)
	Not completed	55 (19.5)	23 (8.6)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Not completed due to site staff error	2 (0.7)	1 (0.4)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Physically unable to complete	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.7)	1 (0.4)
	Other	10 (3.5)	6 (2.2)
	With visit, no record	38 (13.5)	15 (5.6)
	Missing by Design[f]	89 (31.6)	203 (76.0)
	Discontinued due to adverse event	22 (7.8)	17 (6.4)
	Discontinued due to clinical progression	4 (1.4)	18 (6.7)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-EN24	N[c] = 282 n (%)	N[c] = 267 n (%)
	Discontinued due to complete response	0 (0.0)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	2 (0.7)	11 (4.1)
	Discontinued due to progressive disease	33 (11.7)	99 (37.1)
	Discontinued due to withdrawal by subject	7 (2.5)	12 (4.5)
	Completed study treatment	0 (0.0)	30 (11.2)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	2 (0.7)
	Visit not scheduled	19 (6.7)	11 (4.1)
WEEK 27	Expected to Complete Questionnaires[d]	182 (64.5)	50 (18.7)
	Completed	134 (47.5)	26 (9.7)
	Compliance (% in those expected to complete questionnaires)[e]	134 (73.6)	26 (52.0)
	Not completed	48 (17.0)	24 (9.0)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Not completed due to site staff error	3 (1.1)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Physically unable to complete	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.7)	0 (0.0)
	Other	7 (2.5)	4 (1.5)
	With visit, no record	34 (12.1)	19 (7.1)
	Missing by Design[f]	100 (35.5)	217 (81.3)
	Discontinued due to adverse event	24 (8.5)	18 (6.7)
	Discontinued due to clinical progression	4 (1.4)	19 (7.1)
	Discontinued due to complete response	0 (0.0)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	2 (0.7)	12 (4.5)
	Discontinued due to progressive disease	47 (16.7)	102 (38.2)
	Discontinued due to withdrawal by subject	7 (2.5)	13 (4.9)
	Completed study treatment	0 (0.0)	44 (16.5)
	Translation not available in subjects language	3 (1.1)	0 (0.0)
	Subject died	1 (0.4)	2 (0.7)
	Visit not scheduled	12 (4.3)	4 (1.5)
WEEK 30	Expected to Complete Questionnaires[d]	169 (59.9)	14 (5.2)
	Completed	130 (46.1)	8 (3.0)
	Compliance (% in those expected to complete questionnaires)[e]	130 (76.9)	8 (57.1)
	Not completed	39 (13.8)	6 (2.2)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	2 (0.7)	3 (1.1)
	Other	7 (2.5)	1 (0.4)
	With visit, no record	30 (10.6)	1 (0.4)
	Missing by Design[f]	113 (40.1)	253 (94.8)
	Discontinued due to adverse event	29 (10.3)	21 (7.9)
	Discontinued due to clinical progression	5 (1.8)	19 (7.1)
	Discontinued due to complete response	0 (0.0)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	2 (0.7)	11 (4.1)
	Discontinued due to progressive disease	57 (20.2)	103 (38.6)
	Discontinued due to withdrawal by subject	9 (3.2)	13 (4.9)
	Completed study treatment	0 (0.0)	80 (30.0)
	Subject died	1 (0.4)	1 (0.4)
	Visit not scheduled	10 (3.5)	2 (0.7)
WEEK 33	Expected to Complete Questionnaires[d]	151 (53.5)	8 (3.0)
	Completed	111 (39.4)	2 (0.7)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-EN24	N[c] = 282 n (%)	N[c] = 267 n (%)
	Compliance (% in those expected to complete questionnaires)[e]	111 (73.5)	2 (25.0)
	Not completed	40 (14.2)	6 (2.2)
	Not completed due to site staff error	3 (1.1)	1 (0.4)
	Subject refused for other reasons	1 (0.4)	2 (0.7)
	Other	8 (2.8)	1 (0.4)
	With visit, no record	28 (9.9)	2 (0.7)
	Missing by Design[f]	131 (46.5)	259 (97.0)
	Discontinued due to adverse event	32 (11.3)	21 (7.9)
	Discontinued due to clinical progression	5 (1.8)	19 (7.1)
	Discontinued due to complete response	0 (0.0)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	3 (1.1)	11 (4.1)
	Discontinued due to progressive disease	70 (24.8)	105 (39.3)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	85 (31.8)
	Visit not scheduled	12 (4.3)	1 (0.4)
WEEK 36	Expected to Complete Questionnaires[d]	152 (53.9)	4 (1.5)
	Completed	109 (38.7)	2 (0.7)
	Compliance (% in those expected to complete questionnaires)[e]	109 (71.7)	2 (50.0)
	Not completed	43 (15.2)	2 (0.7)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Physically unable to complete	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	2 (0.7)
	Other	6 (2.1)	0 (0.0)
	With visit, no record	34 (12.1)	0 (0.0)
	Missing by Design[f]	130 (46.1)	263 (98.5)
	Discontinued due to adverse event	32 (11.3)	21 (7.9)
	Discontinued due to clinical progression	5 (1.8)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	3 (1.1)	13 (4.9)
	Discontinued due to progressive disease	74 (26.2)	105 (39.3)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	88 (33.0)
	Visit not scheduled	6 (2.1)	0 (0.0)
WEEK 39	Expected to Complete Questionnaires[d]	136 (48.2)	2 (0.7)
	Completed	100 (35.5)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	100 (73.5)	0 (0.0)
	Not completed	36 (12.8)	2 (0.7)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	7 (2.5)	1 (0.4)
	With visit, no record	26 (9.2)	0 (0.0)
	Missing by Design[f]	146 (51.8)	265 (99.3)
	Discontinued due to adverse event	34 (12.1)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	3 (1.1)	13 (4.9)
	Discontinued due to progressive disease	84 (29.8)	105 (39.3)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-EN24	N[c] = 282 n (%)	N[c] = 267 n (%)
	Completed study treatment	0 (0.0)	90 (33.7)
	Visit not reached	2 (0.7)	0 (0.0)
	Visit not scheduled	7 (2.5)	0 (0.0)
WEEK 42	Expected to Complete Questionnaires[d]	123 (43.6)	0 (0.0)
	Completed	91 (32.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	91 (74.0)	0 (0.0)
	Not completed	32 (11.3)	0 (0.0)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Other	6 (2.1)	0 (0.0)
	With visit, no record	25 (8.9)	0 (0.0)
	Missing by Design[f]	159 (56.4)	267 (100.0)
	Discontinued due to adverse event	34 (12.1)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	88 (31.2)	106 (39.7)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Subject died	1 (0.4)	0 (0.0)
	Visit not reached	7 (2.5)	0 (0.0)
	Visit not scheduled	9 (3.2)	0 (0.0)
WEEK 45	Expected to Complete Questionnaires[d]	113 (40.1)	0 (0.0)
	Completed	78 (27.7)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	78 (69.0)	0 (0.0)
	Not completed	35 (12.4)	0 (0.0)
	Subject refused for other reasons	3 (1.1)	0 (0.0)
	Other	8 (2.8)	0 (0.0)
	With visit, no record	24 (8.5)	0 (0.0)
	Missing by Design[f]	169 (59.9)	267 (100.0)
	Discontinued due to adverse event	36 (12.8)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	3 (1.1)	13 (4.9)
	Discontinued due to progressive disease	94 (33.3)	106 (39.7)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	12 (4.3)	0 (0.0)
	Visit not scheduled	8 (2.8)	0 (0.0)
WEEK 48	Expected to Complete Questionnaires[d]	101 (35.8)	0 (0.0)
	Completed	66 (23.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	66 (65.3)	0 (0.0)
	Not completed	35 (12.4)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	8 (2.8)	0 (0.0)
	With visit, no record	25 (8.9)	0 (0.0)
	Missing by Design[f]	181 (64.2)	267 (100.0)
	Discontinued due to adverse event	37 (13.1)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-EN24	N[c] = 282 n (%)	N[c] = 267 n (%)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	98 (34.8)	106 (39.7)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	19 (6.7)	0 (0.0)
	Visit not scheduled	7 (2.5)	0 (0.0)
WEEK 51	Expected to Complete Questionnaires[d]	90 (31.9)	1 (0.4)
	Completed	57 (20.2)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	57 (63.3)	0 (0.0)
	Not completed	33 (11.7)	1 (0.4)
	Subject refused for other reasons	2 (0.7)	0 (0.0)
	Other	10 (3.5)	1 (0.4)
	With visit, no record	21 (7.4)	0 (0.0)
	Missing by Design[f]	192 (68.1)	266 (99.6)
	Discontinued due to adverse event	40 (14.2)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	99 (35.1)	106 (39.7)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	90 (33.7)
	Subject died	2 (0.7)	0 (0.0)
	Visit not reached	27 (9.6)	0 (0.0)
	Visit not scheduled	4 (1.4)	0 (0.0)
WEEK 54	Expected to Complete Questionnaires[d]	81 (28.7)	0 (0.0)
	Completed	51 (18.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	51 (63.0)	0 (0.0)
	Not completed	30 (10.6)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	7 (2.5)	0 (0.0)
	With visit, no record	22 (7.8)	0 (0.0)
	Missing by Design[f]	201 (71.3)	267 (100.0)
	Discontinued due to adverse event	42 (14.9)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	103 (36.5)	106 (39.7)
	Discontinued due to withdrawal by subject	10 (3.5)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	33 (11.7)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 57	Expected to Complete Questionnaires[d]	72 (25.5)	0 (0.0)
	Completed	47 (16.7)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	47 (65.3)	0 (0.0)
	Not completed	25 (8.9)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	5 (1.8)	0 (0.0)
	With visit, no record	19 (6.7)	0 (0.0)
	Missing by Design[f]	210 (74.5)	267 (100.0)
	Discontinued due to adverse event	42 (14.9)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-EN24	N[c] = 282 n (%)	N[c] = 267 n (%)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	105 (37.2)	106 (39.7)
	Discontinued due to withdrawal by subject	10 (3.5)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	38 (13.5)	0 (0.0)
	Visit not scheduled	4 (1.4)	0 (0.0)
WEEK 60	Expected to Complete Questionnaires[d]	65 (23.0)	0 (0.0)
	Completed	42 (14.9)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	42 (64.6)	0 (0.0)
	Not completed	23 (8.2)	0 (0.0)
	Other	6 (2.1)	0 (0.0)
	With visit, no record	17 (6.0)	0 (0.0)
	Missing by Design[f]	217 (77.0)	267 (100.0)
	Discontinued due to adverse event	42 (14.9)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	106 (37.6)	106 (39.7)
	Discontinued due to withdrawal by subject	10 (3.5)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Subject died	1 (0.4)	0 (0.0)
	Visit not reached	41 (14.5)	0 (0.0)
	Visit not scheduled	6 (2.1)	0 (0.0)
WEEK 63	Expected to Complete Questionnaires[d]	57 (20.2)	1 (0.4)
	Completed	33 (11.7)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	33 (57.9)	0 (0.0)
	Not completed	24 (8.5)	1 (0.4)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	5 (1.8)	1 (0.4)
	With visit, no record	18 (6.4)	0 (0.0)
	Missing by Design[f]	225 (79.8)	266 (99.6)
	Discontinued due to adverse event	43 (15.2)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	109 (38.7)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	44 (15.6)	0 (0.0)
	Visit not scheduled	7 (2.5)	0 (0.0)
WEEK 66	Expected to Complete Questionnaires[d]	51 (18.1)	0 (0.0)
	Completed	24 (8.5)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	24 (47.1)	0 (0.0)
	Not completed	27 (9.6)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	6 (2.1)	0 (0.0)
	With visit, no record	19 (6.7)	0 (0.0)
	Missing by Design[f]	231 (81.9)	267 (100.0)
	Discontinued due to adverse event	43 (15.2)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-EN24	N[c] = 282 n (%)	N[c] = 267 n (%)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	111 (39.4)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	50 (17.7)	0 (0.0)
	Visit not scheduled	5 (1.8)	0 (0.0)
WEEK 69	Expected to Complete Questionnaires[d]	47 (16.7)	0 (0.0)
	Completed	25 (8.9)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	25 (53.2)	0 (0.0)
	Not completed	22 (7.8)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	4 (1.4)	0 (0.0)
	With visit, no record	17 (6.0)	0 (0.0)
	Missing by Design[f]	235 (83.3)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	112 (39.7)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	51 (18.1)	0 (0.0)
	Visit not scheduled	3 (1.1)	0 (0.0)
WEEK 72	Expected to Complete Questionnaires[d]	45 (16.0)	0 (0.0)
	Completed	22 (7.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	22 (48.9)	0 (0.0)
	Not completed	23 (8.2)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Other	4 (1.4)	0 (0.0)
	With visit, no record	18 (6.4)	0 (0.0)
	Missing by Design[f]	237 (84.0)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	112 (39.7)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	55 (19.5)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 75	Expected to Complete Questionnaires[d]	39 (13.8)	0 (0.0)
	Completed	20 (7.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	20 (51.3)	0 (0.0)
	Not completed	19 (6.7)	0 (0.0)
	Other	2 (0.7)	0 (0.0)
	With visit, no record	17 (6.0)	0 (0.0)
	Missing by Design[f]	243 (86.2)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-EN24	N[c] = 282 n (%)	N[c] = 267 n (%)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	112 (39.7)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	57 (20.2)	0 (0.0)
	Visit not scheduled	5 (1.8)	0 (0.0)
WEEK 78	Expected to Complete Questionnaires[d]	37 (13.1)	0 (0.0)
	Completed	20 (7.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	20 (54.1)	0 (0.0)
	Not completed	17 (6.0)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	With visit, no record	16 (5.7)	0 (0.0)
	Missing by Design[f]	245 (86.9)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	114 (40.4)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	60 (21.3)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 81	Expected to Complete Questionnaires[d]	33 (11.7)	0 (0.0)
	Completed	17 (6.0)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	17 (51.5)	0 (0.0)
	Not completed	16 (5.7)	0 (0.0)
	With visit, no record	16 (5.7)	0 (0.0)
	Missing by Design[f]	249 (88.3)	267 (100.0)
	Discontinued due to adverse event	46 (16.3)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	114 (40.4)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	63 (22.3)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 84	Expected to Complete Questionnaires[d]	24 (8.5)	0 (0.0)
	Completed	9 (3.2)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	9 (37.5)	0 (0.0)
	Not completed	15 (5.3)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	With visit, no record	14 (5.0)	0 (0.0)
	Missing by Design[f]	258 (91.5)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-EN24	N[c] = 282 n (%)	N[c] = 267 n (%)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	116 (41.1)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	72 (25.5)	0 (0.0)
	Visit not scheduled	1 (0.4)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires[d]	19 (6.7)	0 (0.0)
	Completed	6 (2.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	6 (31.6)	0 (0.0)
	Not completed	13 (4.6)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	With visit, no record	12 (4.3)	0 (0.0)
	Missing by Design[f]	263 (93.3)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	116 (41.1)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	74 (26.2)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 90	Expected to Complete Questionnaires[d]	19 (6.7)	0 (0.0)
	Completed	8 (2.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	8 (42.1)	0 (0.0)
	Not completed	11 (3.9)	0 (0.0)
	With visit, no record	11 (3.9)	0 (0.0)
	Missing by Design[f]	263 (93.3)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	116 (41.1)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	74 (26.2)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 93	Expected to Complete Questionnaires[d]	17 (6.0)	0 (0.0)
	Completed	7 (2.5)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	7 (41.2)	0 (0.0)
	Not completed	10 (3.5)	0 (0.0)
	With visit, no record	10 (3.5)	0 (0.0)
	Missing by Design[f]	265 (94.0)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	116 (41.1)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-EN24	N[c] = 282 n (%)	N[c] = 267 n (%)
	Visit not reached	78 (27.7)	0 (0.0)
WEEK 96	Expected to Complete Questionnaires[d]	10 (3.5)	0 (0.0)
	Completed	2 (0.7)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	2 (20.0)	0 (0.0)
	Not completed	8 (2.8)	0 (0.0)
	Other	1 (0.4)	0 (0.0)
	With visit, no record	7 (2.5)	0 (0.0)
	Missing by Design[f]	272 (96.5)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	82 (29.1)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 99	Expected to Complete Questionnaires[d]	9 (3.2)	0 (0.0)
	Completed	2 (0.7)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	2 (22.2)	0 (0.0)
	Not completed	7 (2.5)	0 (0.0)
	With visit, no record	7 (2.5)	0 (0.0)
	Missing by Design[f]	273 (96.8)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	85 (30.1)	0 (0.0)
WEEK 102	Expected to Complete Questionnaires[d]	8 (2.8)	0 (0.0)
	Completed	2 (0.7)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	2 (25.0)	0 (0.0)
	Not completed	6 (2.1)	0 (0.0)
	With visit, no record	6 (2.1)	0 (0.0)
	Missing by Design[f]	274 (97.2)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	86 (30.5)	0 (0.0)
WEEK 105	Expected to Complete Questionnaires[d]	6 (2.1)	0 (0.0)
	Completed	1 (0.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	1 (16.7)	0 (0.0)
	Not completed	5 (1.8)	0 (0.0)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EORTC QLQ-EN24	N[c] = 282 n (%)	N[c] = 267 n (%)
	With visit, no record	5 (1.8)	0 (0.0)
	Missing by Design[f]	276 (97.9)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	88 (31.2)	0 (0.0)
WEEK 108	Expected to Complete Questionnaires[d]	5 (1.8)	0 (0.0)
	Completed	1 (0.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	1 (20.0)	0 (0.0)
	Not completed	4 (1.4)	0 (0.0)
	With visit, no record	4 (1.4)	0 (0.0)
	Missing by Design[f]	277 (98.2)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	89 (31.6)	0 (0.0)
WEEK 111	Expected to Complete Questionnaires[d]	2 (0.7)	0 (0.0)
	Not completed	2 (0.7)	0 (0.0)
	With visit, no record	2 (0.7)	0 (0.0)
	Missing by Design[f]	280 (99.3)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	92 (32.6)	0 (0.0)
WEEK 114	Expected to Complete Questionnaires[d]	2 (0.7)	0 (0.0)
	Not completed	2 (0.7)	0 (0.0)
	With visit, no record	2 (0.7)	0 (0.0)
	Missing by Design[f]	280 (99.3)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)

Study: KEYNOTE 775[a]		**Pembrolizumab + Lenvatinib[b]**	**Doxorubicin[b]**
Visit	**EORTC QLQ-EN24**	**N[c] = 282 n (%)**	**N[c] = 267 n (%)**
	Visit not reached	92 (32.6)	0 (0.0)

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: Expected to complete questionnaire includes all participants who do not have missing data due to a missing by design reason.

e: Compliance is the proportion of participants who completed the PRO questionnaire among these who are expected to complete at each time point, excluding those missing by design. All the other categories are defined as the proportion of participants in the analysis population (N).

f: Missing by design includes: death, disease progression, other discontinuations (reasons may include unacceptable AEs, withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment), and translation not available.

PRO: Patient Reported Outcome; EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items

Anhang 4-G1.3: Rücklaufquoten des EQ-5D VAS

Tabelle 4G-3: Gründe für das Fehlen von Werten im EQ-5D VAS

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EQ-5D VAS	N[c] = 282 n (%)	N[c] = 267 n (%)
BASELINE	Expected to Complete Questionnaires[d]	280 (99.3)	266 (99.6)
	Completed	273 (96.8)	261 (97.8)
	Compliance (% in those expected to complete questionnaires)[e]	273 (97.5)	261 (98.1)
	Not completed	7 (2.5)	5 (1.9)
	Not completed due to site staff error	1 (0.4)	4 (1.5)
	Subject refused for other reasons	1 (0.4)	1 (0.4)
	Other	4 (1.4)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	2 (0.7)	1 (0.4)
	Translation not available in subjects language	2 (0.7)	1 (0.4)
WEEK 3	Expected to Complete Questionnaires[d]	278 (98.6)	265 (99.3)
	Completed	260 (92.2)	246 (92.1)
	Compliance (% in those expected to complete questionnaires)[e]	260 (93.5)	246 (92.8)
	Not completed	18 (6.4)	19 (7.1)
	Not completed due to site staff error	2 (0.7)	3 (1.1)
	Subject in hospital or hospice	2 (0.7)	1 (0.4)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.4)
	Other	4 (1.4)	2 (0.7)
	With visit, no record	10 (3.5)	12 (4.5)
	Missing by Design[f]	4 (1.4)	2 (0.7)
	Translation not available in subjects language	2 (0.7)	1 (0.4)
	Visit not scheduled	2 (0.7)	1 (0.4)
WEEK 6	Expected to Complete Questionnaires[d]	265 (94.0)	252 (94.4)
	Completed	242 (85.8)	228 (85.4)
	Compliance (% in those expected to complete questionnaires)[e]	242 (91.3)	228 (90.5)
	Not completed	23 (8.2)	24 (9.0)
	Subject did not complete due to disease under study	1 (0.4)	1 (0.4)
	Not completed due to site staff error	3 (1.1)	4 (1.5)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.7)	3 (1.1)
	Other	3 (1.1)	5 (1.9)
	With visit, no record	13 (4.6)	11 (4.1)
	Missing by Design[f]	17 (6.0)	15 (5.6)
	Discontinued due to adverse event	1 (0.4)	0 (0.0)
	Discontinued due to progressive disease	1 (0.4)	0 (0.0)
	Discontinued due to withdrawal by subject	2 (0.7)	1 (0.4)
	Translation not available in subjects language	3 (1.1)	2 (0.7)
	Subject died	2 (0.7)	3 (1.1)
	Visit not scheduled	8 (2.8)	9 (3.4)
WEEK 9	Expected to Complete Questionnaires[d]	254 (90.1)	227 (85.0)
	Completed	242 (85.8)	206 (77.2)
	Compliance (% in those expected to complete questionnaires)[e]	242 (95.3)	206 (90.7)
	Not completed	12 (4.3)	21 (7.9)
	Subject did not complete due to disease under study	2 (0.7)	2 (0.7)
	Not completed due to site staff error	2 (0.7)	4 (1.5)
	Subject refused for other reasons	1 (0.4)	5 (1.9)
	Other	4 (1.4)	3 (1.1)
	With visit, no record	3 (1.1)	7 (2.6)
	Missing by Design[f]	28 (9.9)	40 (15.0)
	Discontinued due to adverse event	4 (1.4)	5 (1.9)
	Discontinued due to clinical progression	0 (0.0)	2 (0.7)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to progressive disease	2 (0.7)	10 (3.7)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EQ-5D VAS	N[c] = 282 n (%)	N[c] = 267 n (%)
	Discontinued due to withdrawal by subject	2 (0.7)	4 (1.5)
	Translation not available in subjects language	4 (1.4)	3 (1.1)
	Subject died	4 (1.4)	4 (1.5)
	Visit not scheduled	12 (4.3)	11 (4.1)
WEEK 12	Expected to Complete Questionnaires[d]	240 (85.1)	178 (66.7)
	Completed	222 (78.7)	158 (59.2)
	Compliance (% in those expected to complete questionnaires)[e]	222 (92.5)	158 (88.8)
	Not completed	18 (6.4)	20 (7.5)
	Subject did not complete due to disease under study	3 (1.1)	1 (0.4)
	Not completed due to site staff error	5 (1.8)	2 (0.7)
	Subject in hospital or hospice	2 (0.7)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	2 (0.7)
	Other	7 (2.5)	3 (1.1)
	With visit, no record	1 (0.4)	12 (4.5)
	Missing by Design[f]	42 (14.9)	89 (33.3)
	Discontinued due to adverse event	6 (2.1)	7 (2.6)
	Discontinued due to clinical progression	2 (0.7)	8 (3.0)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	9 (3.2)	50 (18.7)
	Discontinued due to withdrawal by subject	4 (1.4)	6 (2.2)
	Completed study treatment	0 (0.0)	1 (0.4)
	Translation not available in subjects language	2 (0.7)	3 (1.1)
	Subject died	2 (0.7)	1 (0.4)
	Visit not scheduled	17 (6.0)	8 (3.0)
WEEK 15	Expected to Complete Questionnaires[d]	226 (80.1)	154 (57.7)
	Completed	209 (74.1)	132 (49.4)
	Compliance (% in those expected to complete questionnaires)[e]	209 (92.5)	132 (85.7)
	Not completed	17 (6.0)	22 (8.2)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	5 (1.8)	2 (0.7)
	Subject in hospital or hospice	2 (0.7)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.4)
	Subject refused for other reasons	3 (1.1)	6 (2.2)
	Other	6 (2.1)	3 (1.1)
	With visit, no record	1 (0.4)	9 (3.4)
	Missing by Design[f]	56 (19.9)	113 (42.3)
	Discontinued due to adverse event	8 (2.8)	11 (4.1)
	Discontinued due to clinical progression	3 (1.1)	13 (4.9)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	1 (0.4)	3 (1.1)
	Discontinued due to progressive disease	13 (4.6)	67 (25.1)
	Discontinued due to withdrawal by subject	5 (1.8)	6 (2.2)
	Completed study treatment	0 (0.0)	1 (0.4)
	Translation not available in subjects language	2 (0.7)	3 (1.1)
	Subject died	1 (0.4)	2 (0.7)
	Visit not scheduled	23 (8.2)	6 (2.2)
WEEK 18	Expected to Complete Questionnaires[d]	219 (77.7)	125 (46.8)
	Completed	205 (72.7)	106 (39.7)
	Compliance (% in those expected to complete questionnaires)[e]	205 (93.6)	106 (84.8)
	Not completed	14 (5.0)	19 (7.1)
	Not completed due to site staff error	3 (1.1)	5 (1.9)
	Subject in hospital or hospice	1 (0.4)	1 (0.4)
	Subject did not complete due to side effects of treatment	2 (0.7)	1 (0.4)
	Subject refused for other reasons	2 (0.7)	1 (0.4)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EQ-5D VAS	N[c] = 282 n (%)	N[c] = 267 n (%)
	Other	6 (2.1)	6 (2.2)
	With visit, no record	0 (0.0)	5 (1.9)
	Missing by Design[f]	63 (22.3)	142 (53.2)
	Discontinued due to adverse event	11 (3.9)	11 (4.1)
	Discontinued due to clinical progression	3 (1.1)	15 (5.6)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	1 (0.4)	5 (1.9)
	Discontinued due to progressive disease	21 (7.4)	79 (29.6)
	Discontinued due to withdrawal by subject	6 (2.1)	10 (3.7)
	Completed study treatment	0 (0.0)	6 (2.2)
	Translation not available in subjects language	2 (0.7)	1 (0.4)
	Subject died	4 (1.4)	2 (0.7)
	Visit not scheduled	15 (5.3)	11 (4.1)
WEEK 21	Expected to Complete Questionnaires[d]	208 (73.8)	109 (40.8)
	Completed	189 (67.0)	86 (32.2)
	Compliance (% in those expected to complete questionnaires)[e]	189 (90.9)	86 (78.9)
	Not completed	19 (6.7)	23 (8.6)
	Not completed due to site staff error	4 (1.4)	2 (0.7)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Physically unable to complete	2 (0.7)	1 (0.4)
	Other	6 (2.1)	3 (1.1)
	With visit, no record	7 (2.5)	16 (6.0)
	Missing by Design[f]	74 (26.2)	158 (59.2)
	Discontinued due to adverse event	19 (6.7)	14 (5.2)
	Discontinued due to clinical progression	4 (1.4)	16 (6.0)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	2 (0.7)	6 (2.2)
	Discontinued due to progressive disease	28 (9.9)	87 (32.6)
	Discontinued due to withdrawal by subject	6 (2.1)	13 (4.9)
	Completed study treatment	0 (0.0)	13 (4.9)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	0 (0.0)	1 (0.4)
	Visit not scheduled	14 (5.0)	6 (2.2)
WEEK 24	Expected to Complete Questionnaires[d]	193 (68.4)	65 (24.3)
	Completed	170 (60.3)	48 (18.0)
	Compliance (% in those expected to complete questionnaires)[e]	170 (88.1)	48 (73.8)
	Not completed	23 (8.2)	17 (6.4)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Not completed due to site staff error	2 (0.7)	1 (0.4)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Physically unable to complete	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.7)	1 (0.4)
	Other	9 (3.2)	6 (2.2)
	With visit, no record	7 (2.5)	9 (3.4)
	Missing by Design[f]	89 (31.6)	202 (75.7)
	Discontinued due to adverse event	22 (7.8)	17 (6.4)
	Discontinued due to clinical progression	4 (1.4)	18 (6.7)
	Discontinued due to complete response	0 (0.0)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	2 (0.7)	11 (4.1)
	Discontinued due to progressive disease	33 (11.7)	99 (37.1)
	Discontinued due to withdrawal by subject	7 (2.5)	12 (4.5)
	Completed study treatment	0 (0.0)	29 (10.9)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EQ-5D VAS	N[c] = 282 n (%)	N[c] = 267 n (%)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	2 (0.7)
	Visit not scheduled	19 (6.7)	11 (4.1)
WEEK 27	Expected to Complete Questionnaires[d]	183 (64.9)	50 (18.7)
	Completed	164 (58.2)	34 (12.7)
	Compliance (% in those expected to complete questionnaires)[e]	164 (89.6)	34 (68.0)
	Not completed	19 (6.7)	16 (6.0)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Not completed due to site staff error	3 (1.1)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Physically unable to complete	1 (0.4)	0 (0.0)
	Subject lost to follow-up/unable to contact	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.7)	0 (0.0)
	Other	7 (2.5)	1 (0.4)
	With visit, no record	4 (1.4)	14 (5.2)
	Missing by Design[f]	99 (35.1)	217 (81.3)
	Discontinued due to adverse event	24 (8.5)	18 (6.7)
	Discontinued due to clinical progression	4 (1.4)	19 (7.1)
	Discontinued due to complete response	0 (0.0)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	2 (0.7)	12 (4.5)
	Discontinued due to progressive disease	47 (16.7)	102 (38.2)
	Discontinued due to withdrawal by subject	7 (2.5)	13 (4.9)
	Completed study treatment	0 (0.0)	44 (16.5)
	Translation not available in subjects language	3 (1.1)	0 (0.0)
	Subject died	1 (0.4)	2 (0.7)
	Visit not scheduled	11 (3.9)	4 (1.5)
WEEK 30	Expected to Complete Questionnaires[d]	171 (60.6)	14 (5.2)
	Completed	158 (56.0)	8 (3.0)
	Compliance (% in those expected to complete questionnaires)[e]	158 (92.4)	8 (57.1)
	Not completed	13 (4.6)	6 (2.2)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	2 (0.7)	3 (1.1)
	Other	7 (2.5)	1 (0.4)
	With visit, no record	4 (1.4)	1 (0.4)
	Missing by Design[f]	111 (39.4)	253 (94.8)
	Discontinued due to adverse event	28 (9.9)	21 (7.9)
	Discontinued due to clinical progression	5 (1.8)	19 (7.1)
	Discontinued due to complete response	0 (0.0)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	2 (0.7)	11 (4.1)
	Discontinued due to progressive disease	57 (20.2)	103 (38.6)
	Discontinued due to withdrawal by subject	9 (3.2)	13 (4.9)
	Completed study treatment	0 (0.0)	80 (30.0)
	Subject died	1 (0.4)	1 (0.4)
	Visit not scheduled	9 (3.2)	2 (0.7)
WEEK 33	Expected to Complete Questionnaires[d]	152 (53.9)	8 (3.0)
	Completed	139 (49.3)	2 (0.7)
	Compliance (% in those expected to complete questionnaires)[e]	139 (91.4)	2 (25.0)
	Not completed	13 (4.6)	6 (2.2)
	Not completed due to site staff error	2 (0.7)	1 (0.4)
	Subject refused for other reasons	1 (0.4)	2 (0.7)
	Other	8 (2.8)	1 (0.4)
	With visit, no record	2 (0.7)	2 (0.7)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EQ-5D VAS	N[c] = 282 n (%)	N[c] = 267 n (%)
	Missing by Design[f]	130 (46.1)	259 (97.0)
	Discontinued due to adverse event	32 (11.3)	21 (7.9)
	Discontinued due to clinical progression	5 (1.8)	19 (7.1)
	Discontinued due to complete response	0 (0.0)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	3 (1.1)	11 (4.1)
	Discontinued due to progressive disease	70 (24.8)	105 (39.3)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	85 (31.8)
	Visit not scheduled	11 (3.9)	1 (0.4)
WEEK 36	Expected to Complete Questionnaires[d]	152 (53.9)	4 (1.5)
	Completed	134 (47.5)	2 (0.7)
	Compliance (% in those expected to complete questionnaires)[e]	134 (88.2)	2 (50.0)
	Not completed	18 (6.4)	2 (0.7)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Physically unable to complete	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.7)	2 (0.7)
	Other	6 (2.1)	0 (0.0)
	With visit, no record	8 (2.8)	0 (0.0)
	Missing by Design[f]	130 (46.1)	263 (98.5)
	Discontinued due to adverse event	32 (11.3)	21 (7.9)
	Discontinued due to clinical progression	5 (1.8)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	3 (1.1)	13 (4.9)
	Discontinued due to progressive disease	74 (26.2)	105 (39.3)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	88 (33.0)
	Visit not scheduled	6 (2.1)	0 (0.0)
WEEK 39	Expected to Complete Questionnaires[d]	138 (48.9)	2 (0.7)
	Completed	124 (44.0)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	124 (89.9)	0 (0.0)
	Not completed	14 (5.0)	2 (0.7)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	7 (2.5)	1 (0.4)
	With visit, no record	4 (1.4)	0 (0.0)
	Missing by Design[f]	144 (51.1)	265 (99.3)
	Discontinued due to adverse event	34 (12.1)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	3 (1.1)	13 (4.9)
	Discontinued due to progressive disease	84 (29.8)	105 (39.3)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	90 (33.7)
	Visit not reached	2 (0.7)	0 (0.0)
	Visit not scheduled	5 (1.8)	0 (0.0)
WEEK 42	Expected to Complete Questionnaires[d]	124 (44.0)	0 (0.0)
	Completed	115 (40.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	115 (92.7)	0 (0.0)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EQ-5D VAS	N[c] = 282 n (%)	N[c] = 267 n (%)
	Not completed	9 (3.2)	0 (0.0)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Other	6 (2.1)	0 (0.0)
	With visit, no record	2 (0.7)	0 (0.0)
	Missing by Design[f]	158 (56.0)	267 (100.0)
	Discontinued due to adverse event	34 (12.1)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	88 (31.2)	106 (39.7)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Subject died	1 (0.4)	0 (0.0)
	Visit not reached	7 (2.5)	0 (0.0)
	Visit not scheduled	8 (2.8)	0 (0.0)
WEEK 45	Expected to Complete Questionnaires[d]	113 (40.1)	0 (0.0)
	Completed	99 (35.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	99 (87.6)	0 (0.0)
	Not completed	14 (5.0)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	3 (1.1)	0 (0.0)
	Other	9 (3.2)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	169 (59.9)	267 (100.0)
	Discontinued due to adverse event	36 (12.8)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	3 (1.1)	13 (4.9)
	Discontinued due to progressive disease	94 (33.3)	106 (39.7)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	12 (4.3)	0 (0.0)
	Visit not scheduled	8 (2.8)	0 (0.0)
WEEK 48	Expected to Complete Questionnaires[d]	101 (35.8)	0 (0.0)
	Completed	89 (31.6)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	89 (88.1)	0 (0.0)
	Not completed	12 (4.3)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	8 (2.8)	0 (0.0)
	With visit, no record	2 (0.7)	0 (0.0)
	Missing by Design[f]	181 (64.2)	267 (100.0)
	Discontinued due to adverse event	37 (13.1)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	98 (34.8)	106 (39.7)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	19 (6.7)	0 (0.0)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EQ-5D VAS	N[c] = 282 n (%)	N[c] = 267 n (%)
	Visit not scheduled	7 (2.5)	0 (0.0)
WEEK 51	Expected to Complete Questionnaires[d]	91 (32.3)	1 (0.4)
	Completed	77 (27.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	77 (84.6)	0 (0.0)
	Not completed	14 (5.0)	1 (0.4)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.7)	0 (0.0)
	Other	10 (3.5)	1 (0.4)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	191 (67.7)	266 (99.6)
	Discontinued due to adverse event	40 (14.2)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	99 (35.1)	106 (39.7)
	Discontinued due to withdrawal by subject	9 (3.2)	14 (5.2)
	Completed study treatment	0 (0.0)	90 (33.7)
	Subject died	2 (0.7)	0 (0.0)
	Visit not reached	27 (9.6)	0 (0.0)
	Visit not scheduled	3 (1.1)	0 (0.0)
WEEK 54	Expected to Complete Questionnaires[d]	81 (28.7)	0 (0.0)
	Completed	71 (25.2)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	71 (87.7)	0 (0.0)
	Not completed	10 (3.5)	0 (0.0)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	7 (2.5)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	201 (71.3)	267 (100.0)
	Discontinued due to adverse event	42 (14.9)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	103 (36.5)	106 (39.7)
	Discontinued due to withdrawal by subject	10 (3.5)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	33 (11.7)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 57	Expected to Complete Questionnaires[d]	73 (25.9)	0 (0.0)
	Completed	66 (23.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	66 (90.4)	0 (0.0)
	Not completed	7 (2.5)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	5 (1.8)	0 (0.0)
	Missing by Design[f]	209 (74.1)	267 (100.0)
	Discontinued due to adverse event	42 (14.9)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EQ-5D VAS	N[c] = 282 n (%)	N[c] = 267 n (%)
	Discontinued due to progressive disease	105 (37.2)	106 (39.7)
	Discontinued due to withdrawal by subject	10 (3.5)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	38 (13.5)	0 (0.0)
	Visit not scheduled	3 (1.1)	0 (0.0)
WEEK 60	Expected to Complete Questionnaires[d]	66 (23.4)	0 (0.0)
	Completed	59 (20.9)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	59 (89.4)	0 (0.0)
	Not completed	7 (2.5)	0 (0.0)
	Other	7 (2.5)	0 (0.0)
	Missing by Design[f]	216 (76.6)	267 (100.0)
	Discontinued due to adverse event	42 (14.9)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	106 (37.6)	106 (39.7)
	Discontinued due to withdrawal by subject	10 (3.5)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Subject died	1 (0.4)	0 (0.0)
	Visit not reached	41 (14.5)	0 (0.0)
	Visit not scheduled	5 (1.8)	0 (0.0)
WEEK 63	Expected to Complete Questionnaires[d]	58 (20.6)	1 (0.4)
	Completed	51 (18.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	51 (87.9)	0 (0.0)
	Not completed	7 (2.5)	1 (0.4)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	6 (2.1)	1 (0.4)
	Missing by Design[f]	224 (79.4)	266 (99.6)
	Discontinued due to adverse event	43 (15.2)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	108 (38.3)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	44 (15.6)	0 (0.0)
	Visit not scheduled	7 (2.5)	0 (0.0)
WEEK 66	Expected to Complete Questionnaires[d]	51 (18.1)	0 (0.0)
	Completed	41 (14.5)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	41 (80.4)	0 (0.0)
	Not completed	10 (3.5)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject did not complete due to side effects of treatment	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	6 (2.1)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	231 (81.9)	267 (100.0)
	Discontinued due to adverse event	43 (15.2)	21 (7.9)
	Discontinued due to clinical progression	6 (2.1)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EQ-5D VAS	N[c] = 282 n (%)	N[c] = 267 n (%)
	Discontinued due to progressive disease	111 (39.4)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	50 (17.7)	0 (0.0)
	Visit not scheduled	5 (1.8)	0 (0.0)
WEEK 69	Expected to Complete Questionnaires[d]	48 (17.0)	0 (0.0)
	Completed	42 (14.9)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	42 (87.5)	0 (0.0)
	Not completed	6 (2.1)	0 (0.0)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	4 (1.4)	0 (0.0)
	Missing by Design[f]	234 (83.0)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	112 (39.7)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	51 (18.1)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 72	Expected to Complete Questionnaires[d]	45 (16.0)	0 (0.0)
	Completed	40 (14.2)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	40 (88.9)	0 (0.0)
	Not completed	5 (1.8)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Other	3 (1.1)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	237 (84.0)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	112 (39.7)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	55 (19.5)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 75	Expected to Complete Questionnaires[d]	39 (13.8)	0 (0.0)
	Completed	36 (12.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	36 (92.3)	0 (0.0)
	Not completed	3 (1.1)	0 (0.0)
	Other	2 (0.7)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	243 (86.2)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EQ-5D VAS	N[c] = 282 n (%)	N[c] = 267 n (%)
	Discontinued due to progressive disease	112 (39.7)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	57 (20.2)	0 (0.0)
	Visit not scheduled	5 (1.8)	0 (0.0)
WEEK 78	Expected to Complete Questionnaires[d]	39 (13.8)	0 (0.0)
	Completed	37 (13.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	37 (94.9)	0 (0.0)
	Not completed	2 (0.7)	0 (0.0)
	Subject did not complete due to disease under study	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Missing by Design[f]	243 (86.2)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	113 (40.1)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	60 (21.3)	0 (0.0)
	Visit not scheduled	1 (0.4)	0 (0.0)
WEEK 81	Expected to Complete Questionnaires[d]	34 (12.1)	0 (0.0)
	Completed	32 (11.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	32 (94.1)	0 (0.0)
	Not completed	2 (0.7)	0 (0.0)
	Other	1 (0.4)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	248 (87.9)	267 (100.0)
	Discontinued due to adverse event	46 (16.3)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	114 (40.4)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	63 (22.3)	0 (0.0)
	Visit not scheduled	1 (0.4)	0 (0.0)
WEEK 84	Expected to Complete Questionnaires[d]	25 (8.9)	0 (0.0)
	Completed	23 (8.2)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	23 (92.0)	0 (0.0)
	Not completed	2 (0.7)	0 (0.0)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Missing by Design[f]	257 (91.1)	267 (100.0)
	Discontinued due to adverse event	45 (16.0)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	115 (40.8)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EQ-5D VAS	N[c] = 282 n (%)	N[c] = 267 n (%)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	72 (25.5)	0 (0.0)
	Visit not scheduled	1 (0.4)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires[d]	19 (6.7)	0 (0.0)
	Completed	18 (6.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	18 (94.7)	0 (0.0)
	Not completed	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Missing by Design[f]	263 (93.3)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	116 (41.1)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	74 (26.2)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 90	Expected to Complete Questionnaires[d]	19 (6.7)	0 (0.0)
	Completed	19 (6.7)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	19 (100.0)	0 (0.0)
	Missing by Design[f]	263 (93.3)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	116 (41.1)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	74 (26.2)	0 (0.0)
	Visit not scheduled	2 (0.7)	0 (0.0)
WEEK 93	Expected to Complete Questionnaires[d]	17 (6.0)	0 (0.0)
	Completed	17 (6.0)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	17 (100.0)	0 (0.0)
	Missing by Design[f]	265 (94.0)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	116 (41.1)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	78 (27.7)	0 (0.0)
WEEK 96	Expected to Complete Questionnaires[d]	11 (3.9)	0 (0.0)
	Completed	11 (3.9)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	11 (100.0)	0 (0.0)
	Missing by Design[f]	271 (96.1)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EQ-5D VAS	N[c] = 282 n (%)	N[c] = 267 n (%)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	82 (29.1)	0 (0.0)
	Visit not scheduled	1 (0.4)	0 (0.0)
WEEK 99	Expected to Complete Questionnaires[d]	9 (3.2)	0 (0.0)
	Completed	9 (3.2)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	9 (100.0)	0 (0.0)
	Missing by Design[f]	273 (96.8)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	85 (30.1)	0 (0.0)
WEEK 102	Expected to Complete Questionnaires[d]	8 (2.8)	0 (0.0)
	Completed	8 (2.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	8 (100.0)	0 (0.0)
	Missing by Design[f]	274 (97.2)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	86 (30.5)	0 (0.0)
WEEK 105	Expected to Complete Questionnaires[d]	6 (2.1)	0 (0.0)
	Completed	6 (2.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	6 (100.0)	0 (0.0)
	Missing by Design[f]	276 (97.9)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	88 (31.2)	0 (0.0)
WEEK 108	Expected to Complete Questionnaires[d]	5 (1.8)	0 (0.0)
	Completed	5 (1.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	5 (100.0)	0 (0.0)
	Missing by Design[f]	277 (98.2)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib[b]	Doxorubicin[b]
Visit	EQ-5D VAS	N[c] = 282 n (%)	N[c] = 267 n (%)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	89 (31.6)	0 (0.0)
WEEK 111	Expected to Complete Questionnaires[d]	2 (0.7)	0 (0.0)
	Completed	1 (0.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	1 (50.0)	0 (0.0)
	Not completed	1 (0.4)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	280 (99.3)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	92 (32.6)	0 (0.0)
WEEK 114	Expected to Complete Questionnaires[d]	2 (0.7)	0 (0.0)
	Completed	1 (0.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	1 (50.0)	0 (0.0)
	Not completed	1 (0.4)	0 (0.0)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[f]	280 (99.3)	267 (100.0)
	Discontinued due to adverse event	47 (16.7)	21 (7.9)
	Discontinued due to clinical progression	7 (2.5)	19 (7.1)
	Discontinued due to complete response	2 (0.7)	1 (0.4)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.4)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.4)
	Discontinued due to physician decision	4 (1.4)	13 (4.9)
	Discontinued due to progressive disease	117 (41.5)	106 (39.7)
	Discontinued due to withdrawal by subject	11 (3.9)	14 (5.2)
	Completed study treatment	0 (0.0)	91 (34.1)
	Visit not reached	92 (32.6)	0 (0.0)

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: Expected to complete questionnaire includes all participants who do not have missing data due to a missing by design reason.

e: Compliance is the proportion of participants who completed the PRO questionnaire among these who are expected to complete at each time point, excluding those missing by design. All the other categories are defined as the proportion of participants in the analysis population (N).

f: Missing by design includes: death, disease progression, other discontinuations (reasons may include unacceptable AEs, withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment), and translation not available.

PRO: Patient Reported Outcome; EQ-5D VAS: European Quality of Life 5 Dimensions Visual Analog Scale

Anhang 4-G2: Kaplan-Meier-Kurven der Subgruppen mit signifikantem Interaktionstest (p < 0,05)

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.2 die Kaplan-Meier-Kurven der Subgruppenanalysen, für die ein signifikanter Interaktionstest (p < 0,05) vorliegt, dargestellt.

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 26. Oktober 2020 (Interimsanalyse I, präspezifiziert).

Mortalität

Gesamtüberleben

Im Folgenden werden die Kaplan-Meier-Kurven der Subgruppenanalyse nach MMR-Status dargestellt, für die ein signifikanter Interaktionstest (p < 0,05) vorliegt.

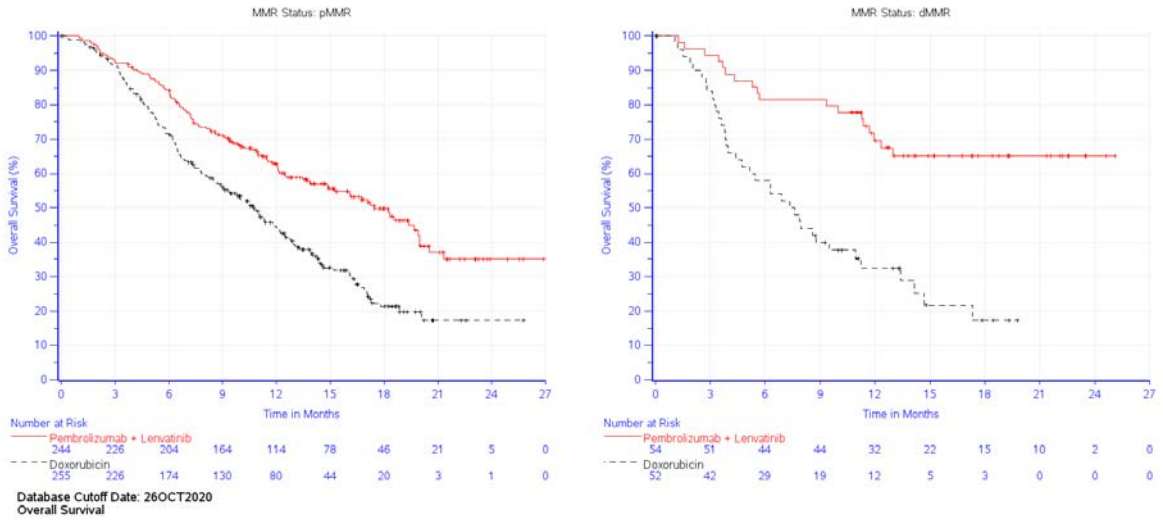

Abbildung 4G-1: Kaplan-Meier-Kurve für die Subgruppenanalyse nach MMR-Status für den Endpunkt Gesamtüberleben der Studie KEYNOTE 775

Morbidität

Zeit bis zur ersten Folgetherapie oder Tod

Im Folgenden werden die Kaplan-Meier-Kurven der Subgruppenanalyse nach MMR-Status dargestellt, für die ein signifikanter Interaktionstest ($p < 0,05$) vorliegt.

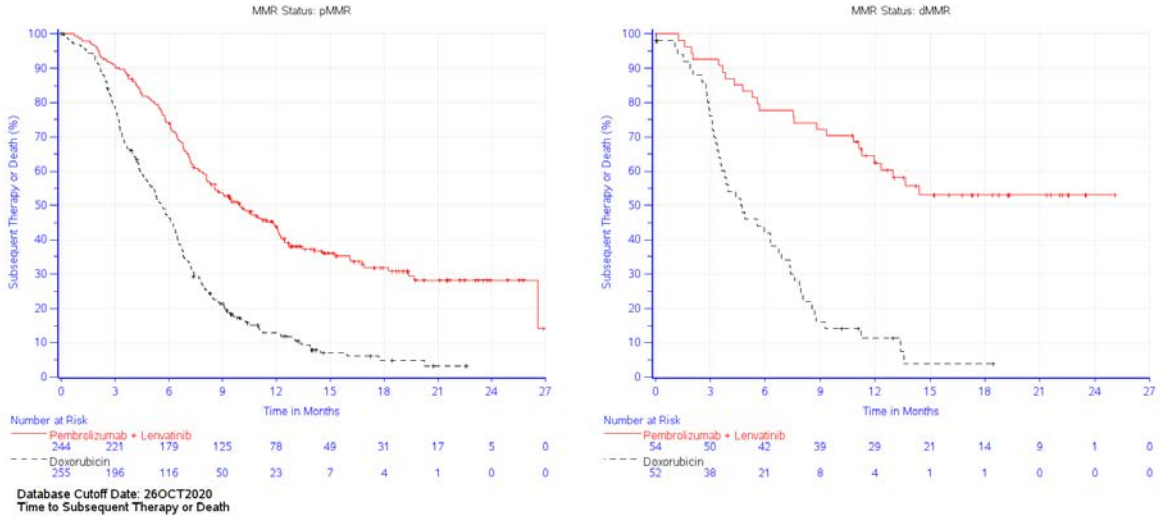

Abbildung 4G-2: Kaplan-Meier-Kurve für die Subgruppenanalyse nach MMR-Status für den Endpunkt Zeit bis zur ersten Folgetherapie oder Tod der Studie KEYNOTE 775

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

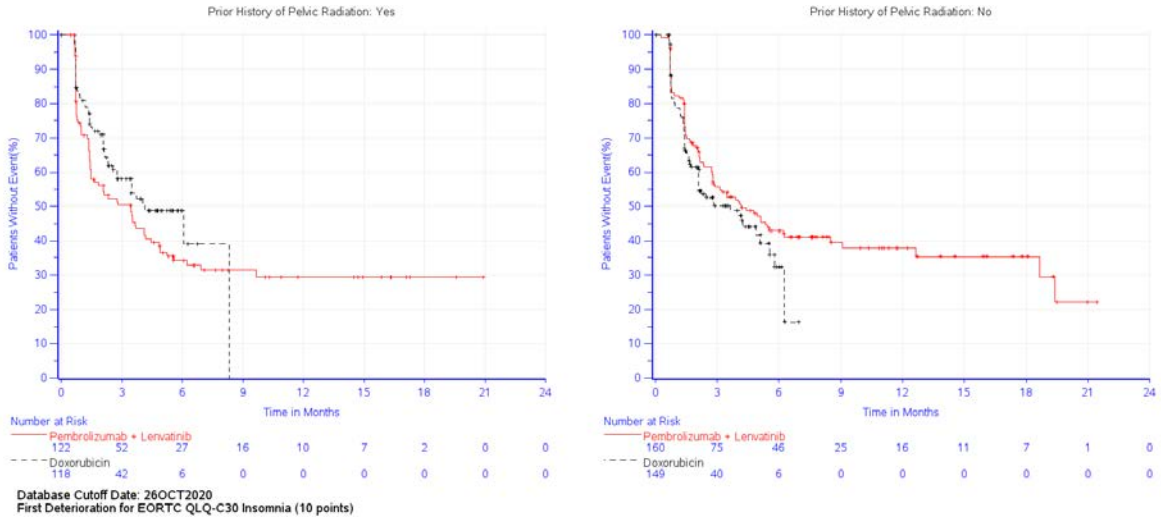

Abbildung 4G-3: Kaplan-Meier-Kurve für die Subgruppenanalyse nach vorheriger Strahlentherapie des Beckens für die Symptomskala Schlaflosigkeit des EORTC QLQ-C30 der Studie KEYNOTE 775

EORTC QLQ-EN24: Symptomskala Gastrointestinale Beschwerden

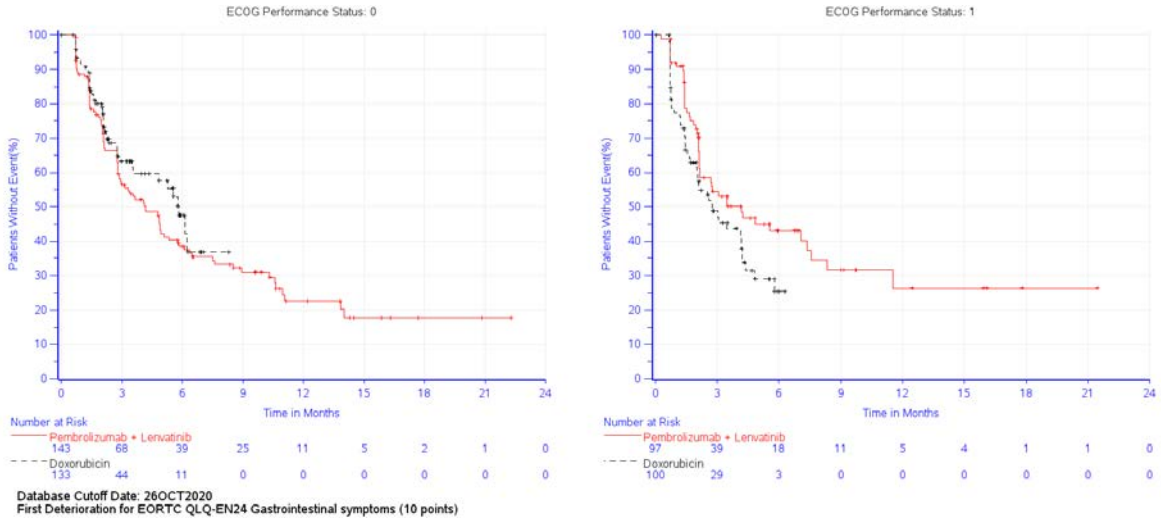

Abbildung 4G-4: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für die Symptomskala Gastrointestinale Beschwerden des EORTC QLQ-EN24 der Studie KEYNOTE 775

EORTC QLQ-EN24: Symptomskala Rücken- und Beckenschmerzen

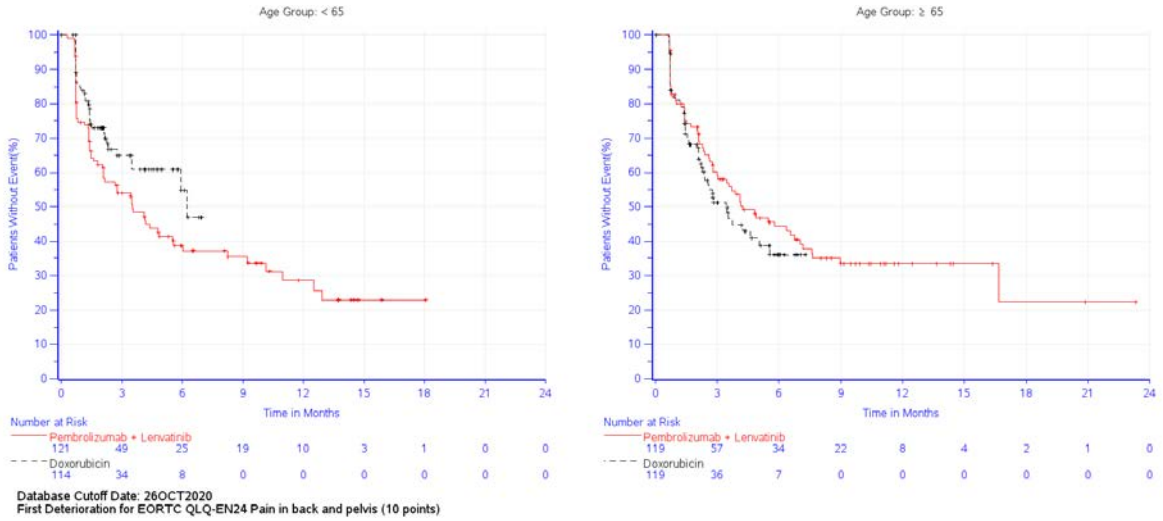

Abbildung 4G-5: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für die Symptomskala Rücken- und Beckenschmerzen des EORTC QLQ-EN24 der Studie KEYNOTE 775

Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

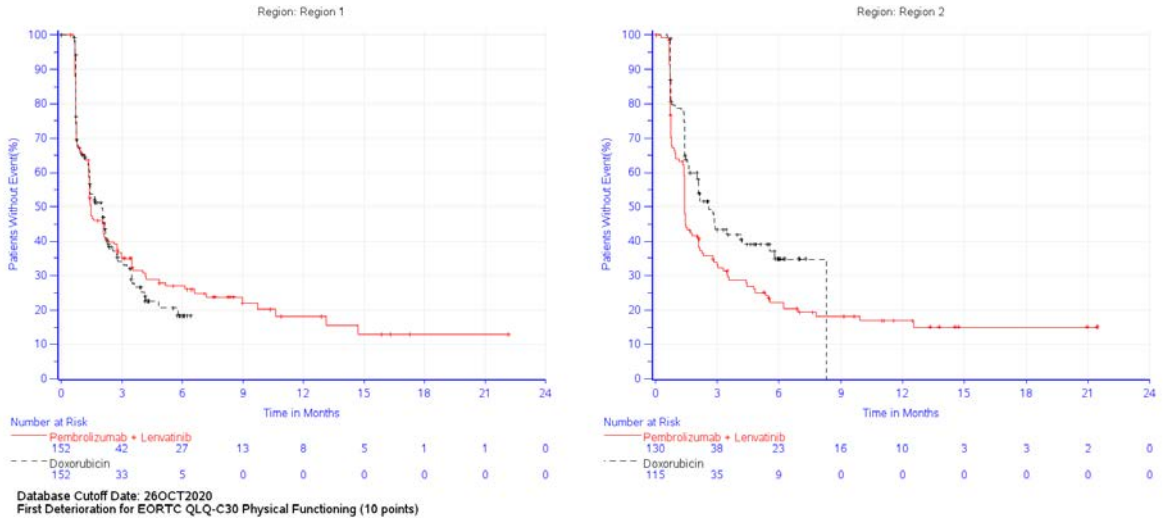

Abbildung 4G-6: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 der Studie KEYNOTE 775

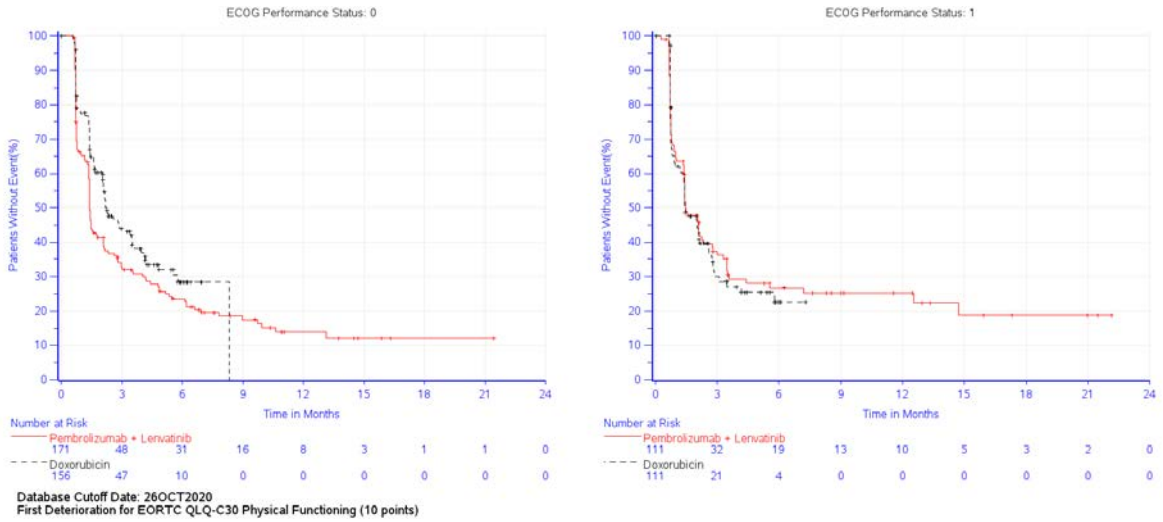

Abbildung 4G-7: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 der Studie KEYNOTE 775

EORTC QLQ-C30: Funktionsskala Rollenfunktion

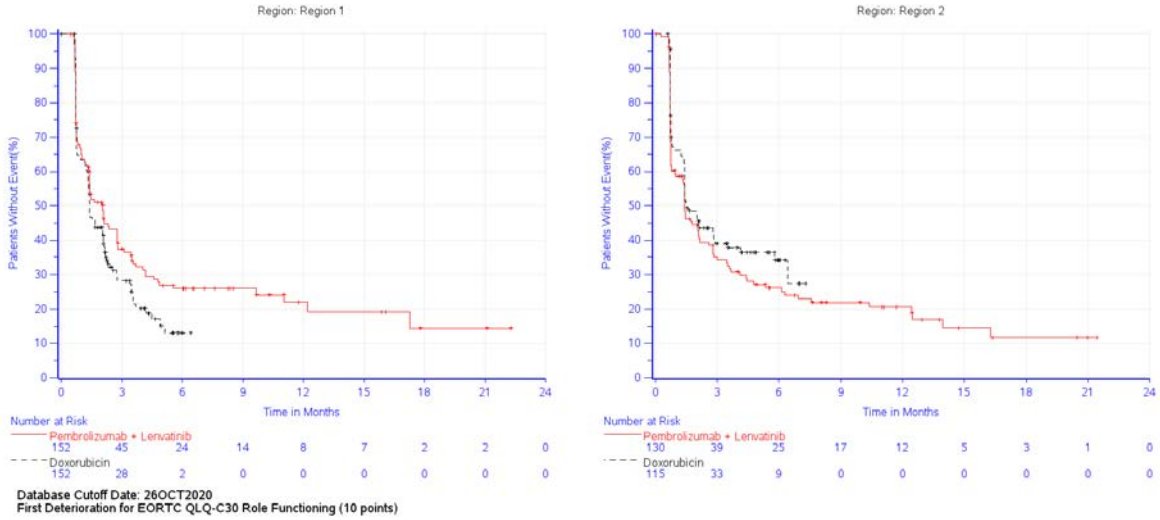

Abbildung 4G-8: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für die Funktionsskala Rollenfunktion des EORTC QLQ-C30 der Studie KEYNOTE 775

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

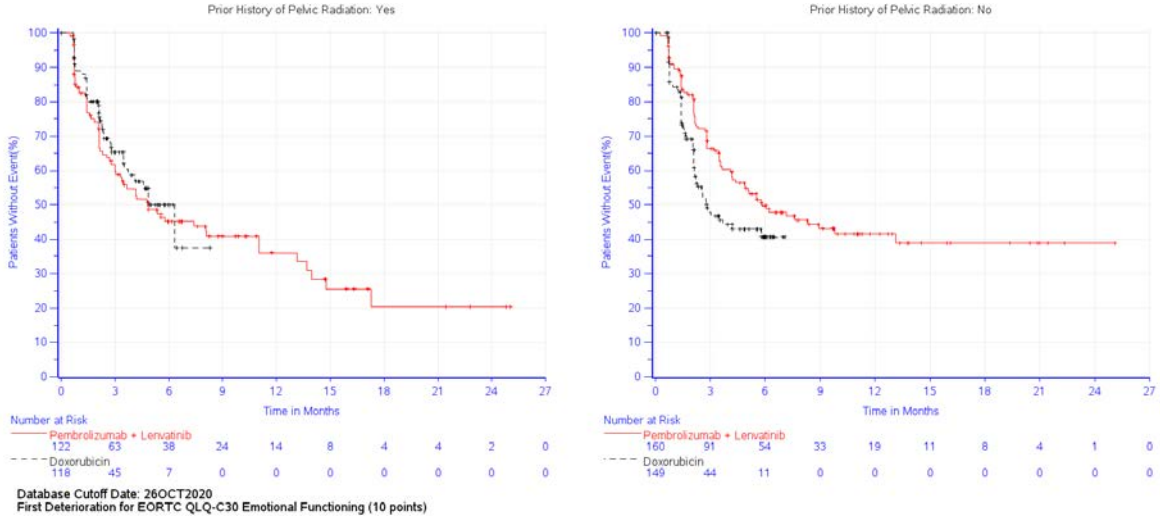

Abbildung 4G-9: Kaplan-Meier-Kurve für die Subgruppenanalyse nach vorheriger Strahlentherapie des Beckens für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 der Studie KEYNOTE 775

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

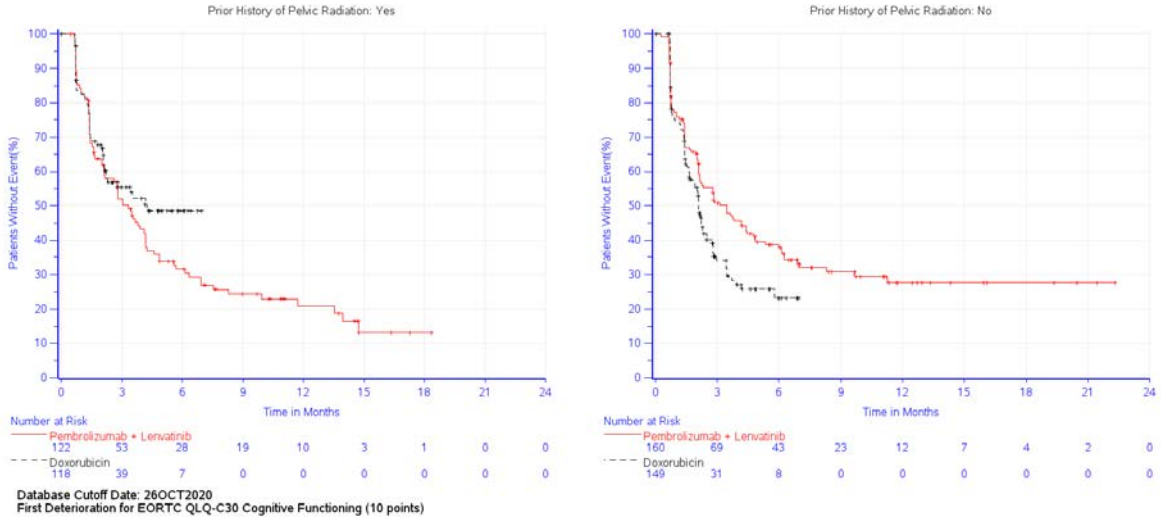

Abbildung 4G-10: Kaplan-Meier-Kurve für die Subgruppenanalyse nach vorheriger Strahlentherapie des Beckens für die Funktionsskala Kognitive Funktion des EORTC QLQ-C30 der Studie KEYNOTE 775

Nebenwirkungen

Unerwünschte Ereignisse Gesamtraten

Unerwünschte Ereignisse gesamt

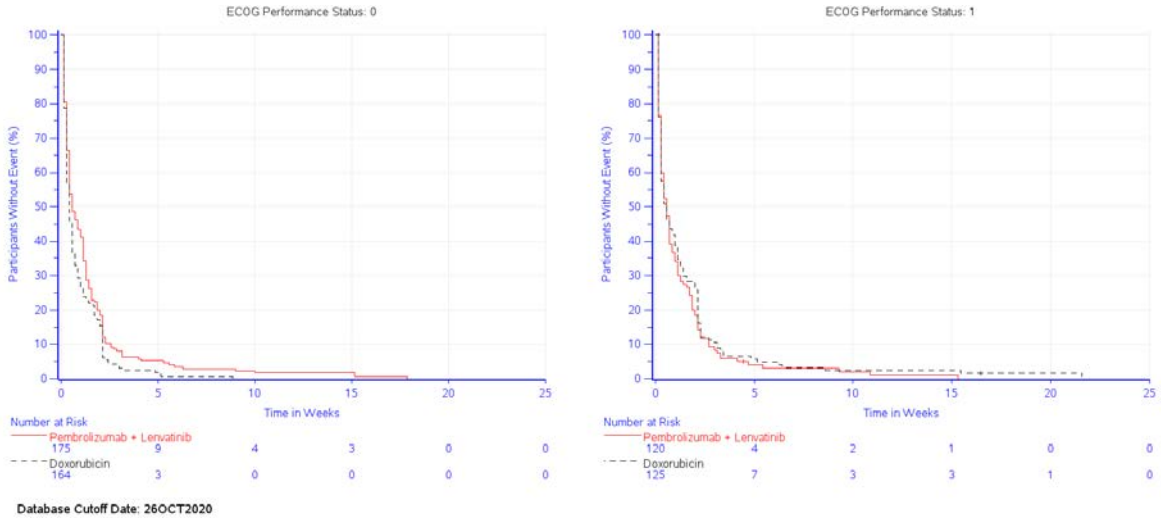

Abbildung 4G-11: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für Unerwünschte Ereignisse gesamt der Studie KEYNOTE 775

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

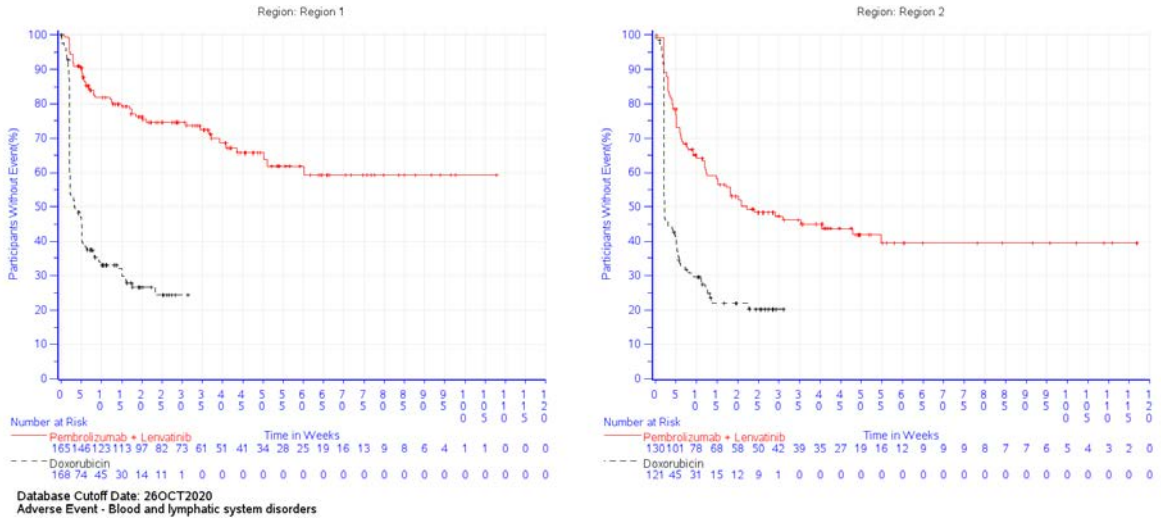

Abbildung 4G-12: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt für die SOC „Erkrankungen des Blutes und des Lymphsystems“ der Studie KEYNOTE 775

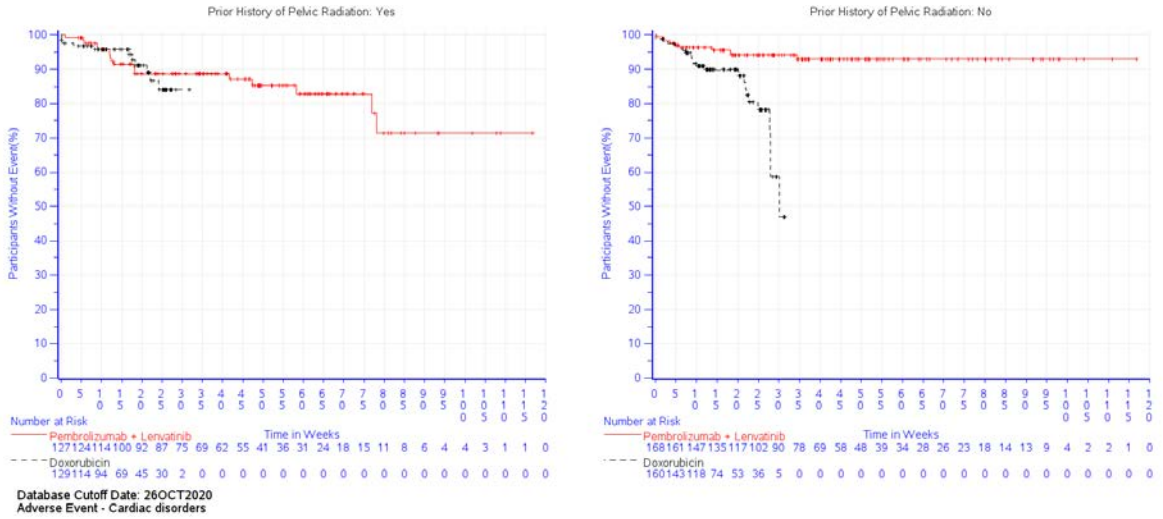

Abbildung 4G-13: Kaplan-Meier-Kurve für die Subgruppenanalyse nach vorheriger Strahlentherapie des Beckens für den Endpunkt Unerwünschte Ereignisse gesamt für die SOC „Herzerkrankungen“ der Studie KEYNOTE 775

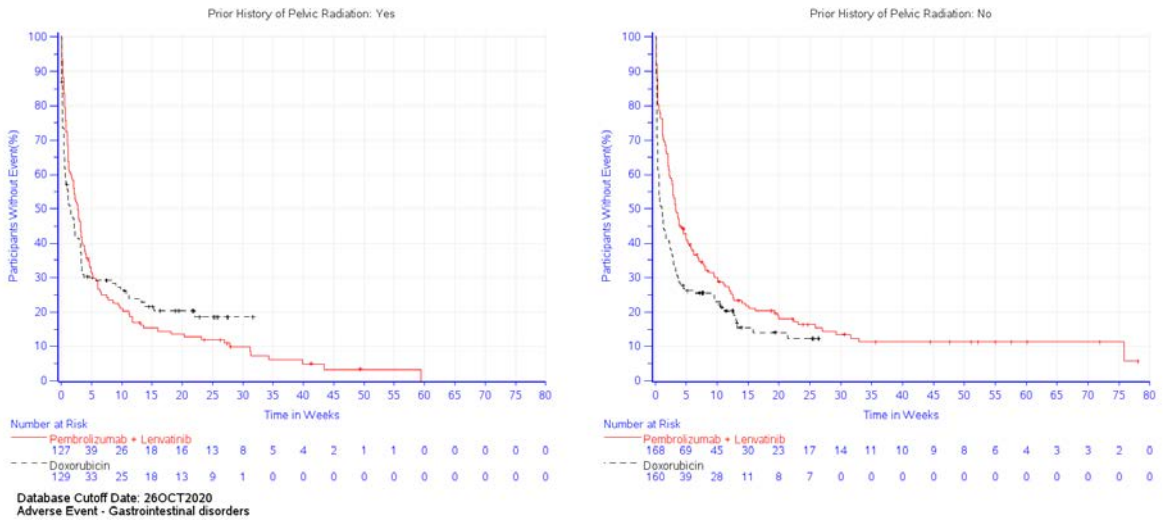

Abbildung 4G-14: Kaplan-Meier-Kurve für die Subgruppenanalyse nach vorheriger Strahlentherapie des Beckens für den Endpunkt Unerwünschte Ereignisse gesamt für die SOC „Erkrankungen des Gastrointestinaltrakts“ der Studie KEYNOTE 775

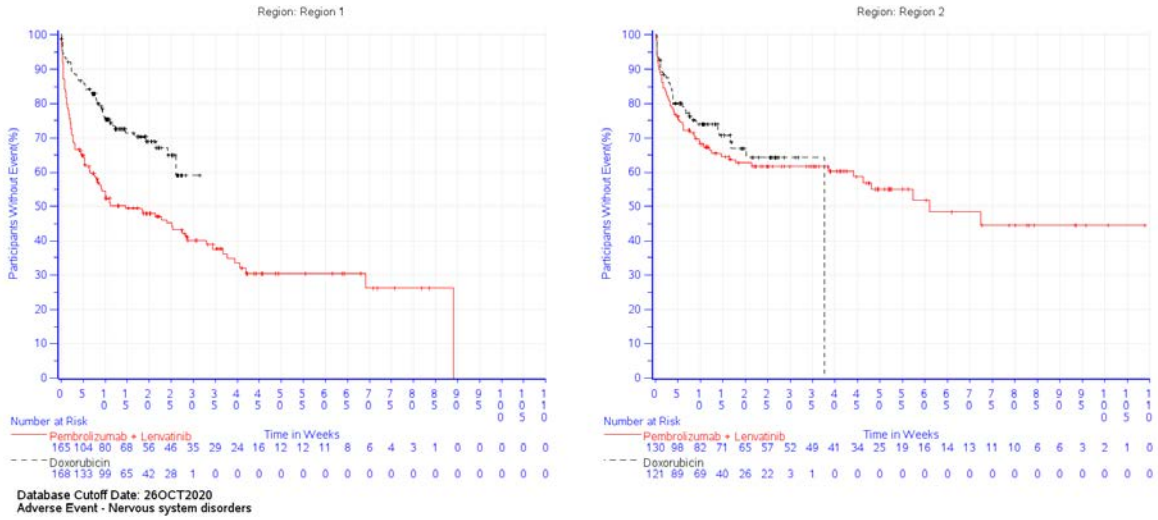

Abbildung 4G-15: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt für die SOC „Erkrankungen des Nervensystems“ der Studie KEYNOTE 775

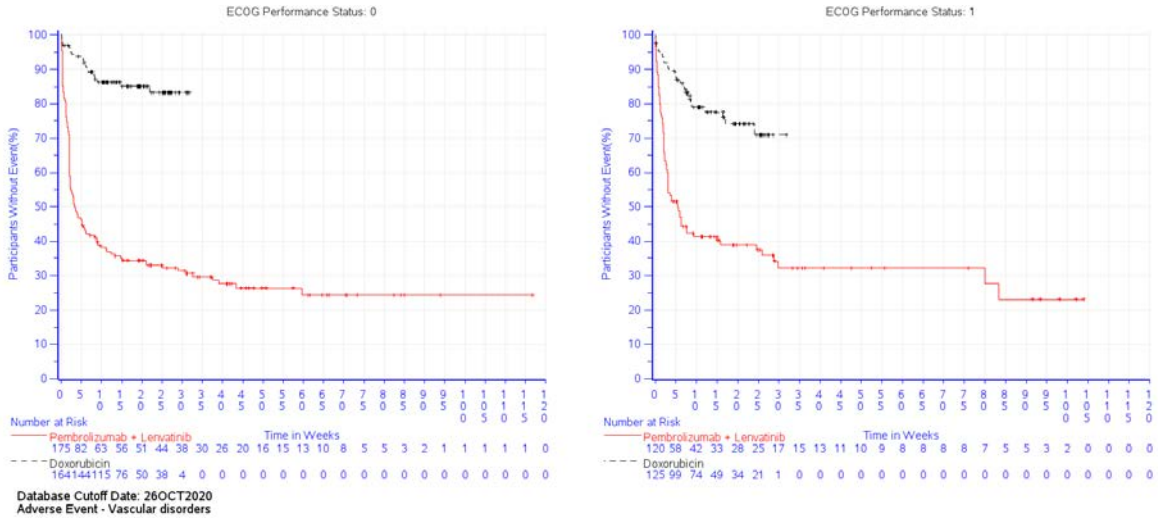

Abbildung 4G-16: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Unerwünschte Ereignisse gesamt für die SOC „Gefäßerkrankungen“ der Studie KEYNOTE 775

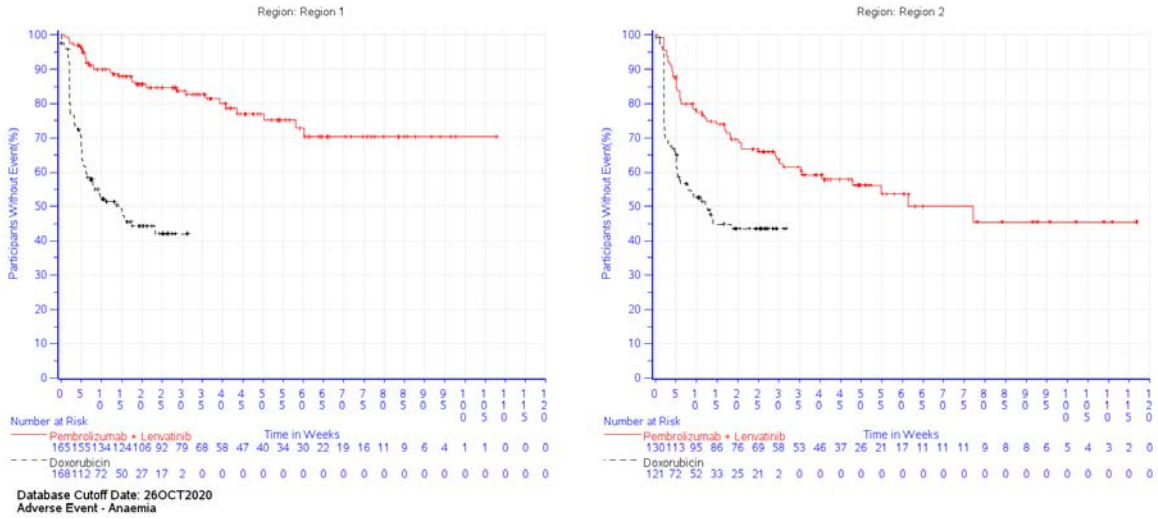

Abbildung 4G-17: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Anämie (SOC: Erkrankungen des Blutes und des Lymphsystems) der Studie KEYNOTE 775

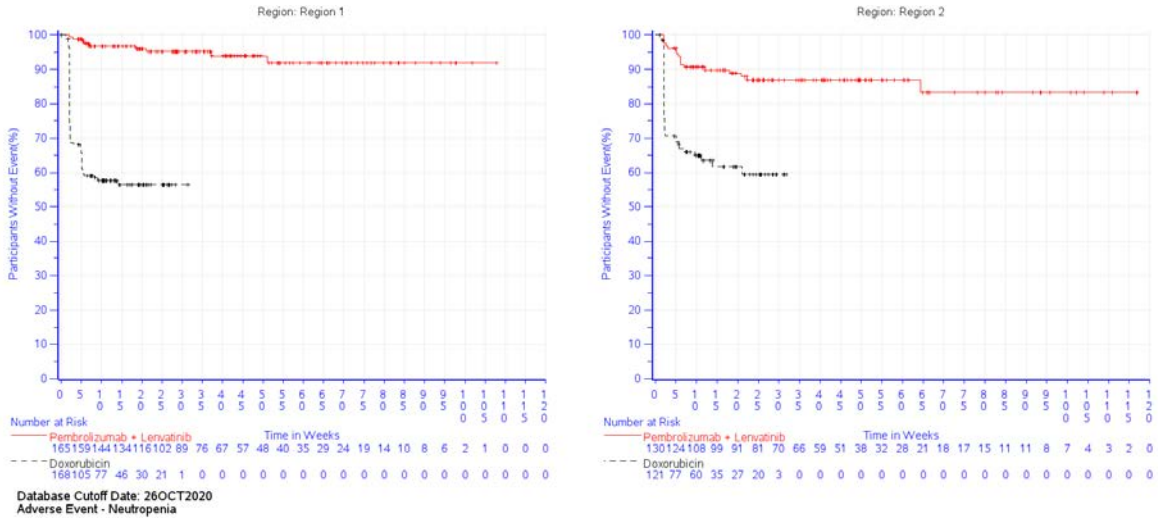

Abbildung 4G-18: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Neutropenie (SOC: Erkrankungen des Blutes und des Lymphsystems) der Studie KEYNOTE 775

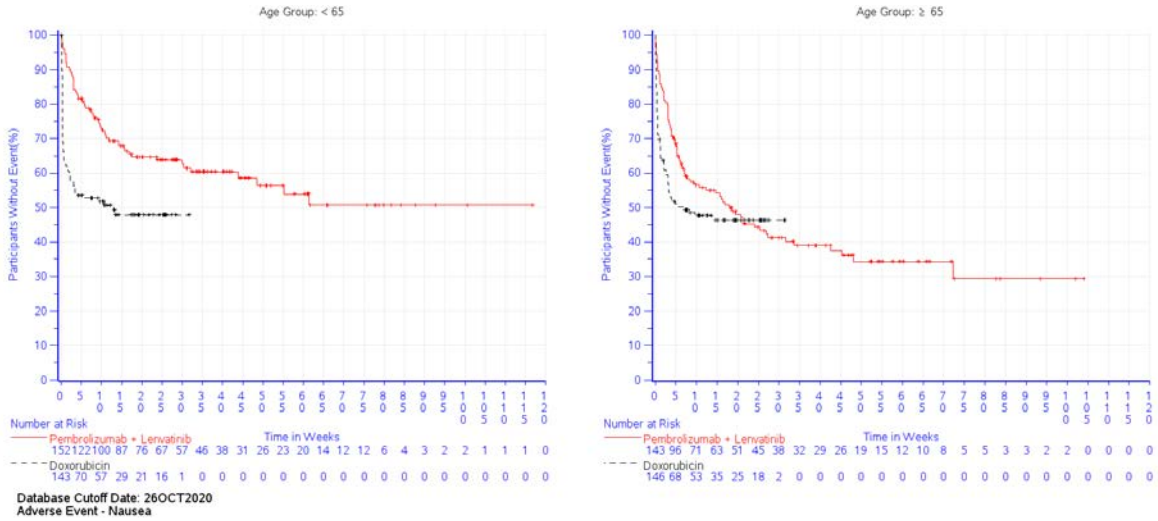

Abbildung 4G-19: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Übelkeit (SOC: Erkrankungen des Gastrointestinaltrakts) der Studie KEYNOTE 775

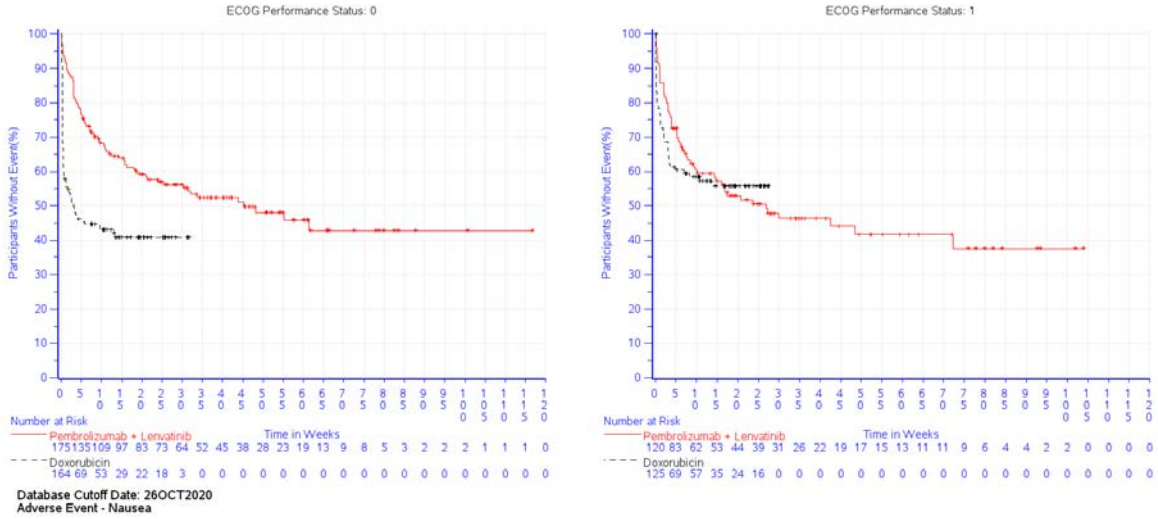

Abbildung 4G-20: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Übelkeit (SOC: Erkrankungen des Gastrointestinaltrakts) der Studie KEYNOTE 775

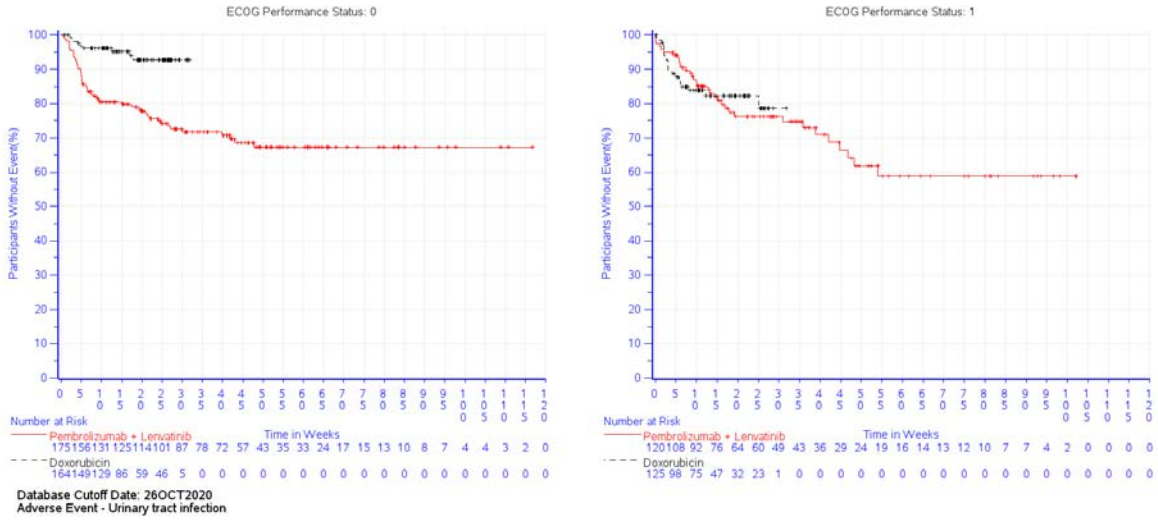

Abbildung 4G-21: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Harnwegsinfektion (SOC: Infektionen und Parasitäre Erkrankungen) der Studie KEYNOTE 775

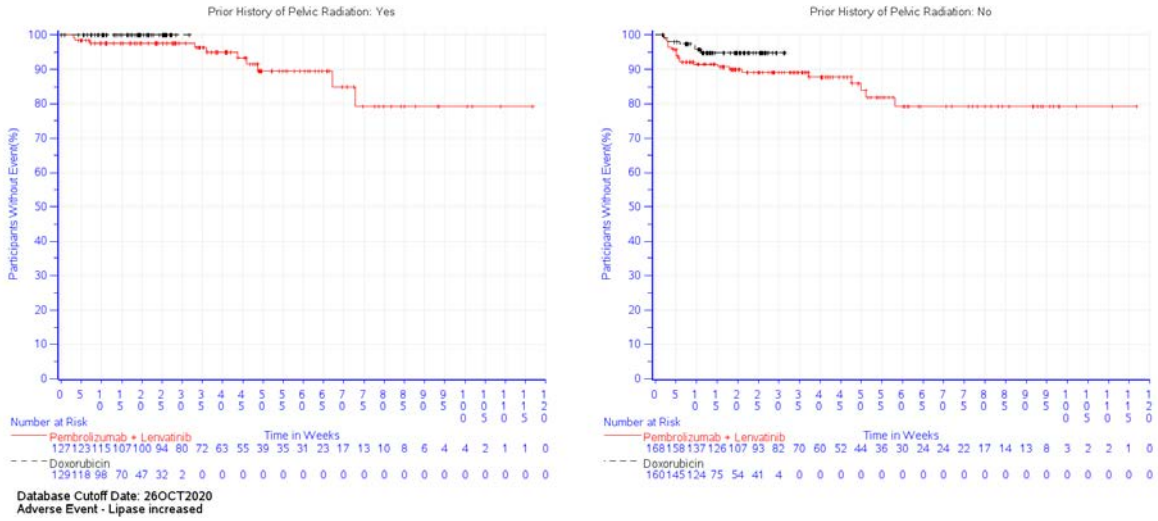

Abbildung 4G-22: Kaplan-Meier-Kurve für die Subgruppenanalyse nach vorheriger Strahlentherapie des Beckens für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Lipase erhöht (SOC: Untersuchungen) der Studie KEYNOTE 775

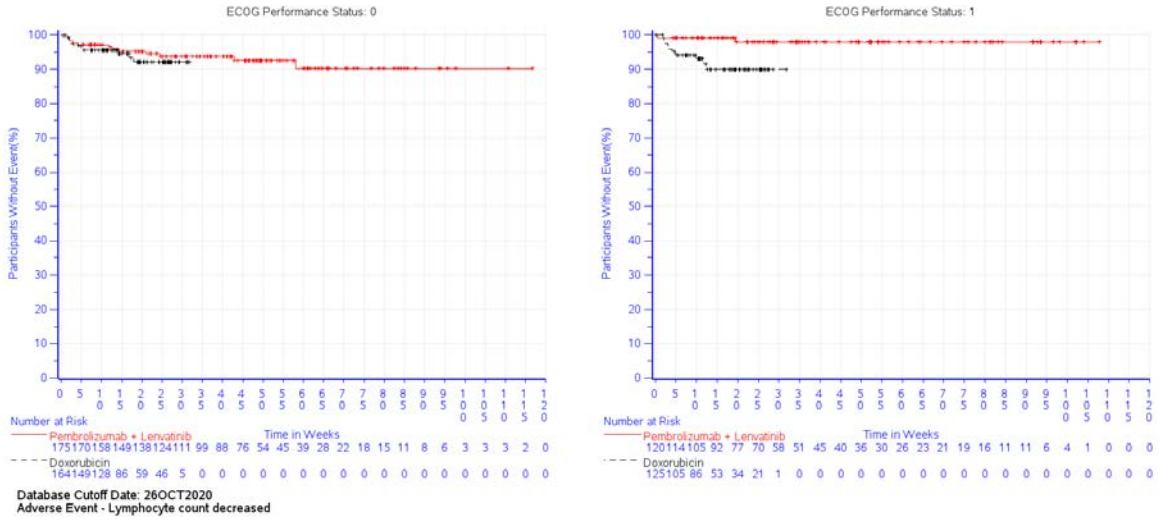

Abbildung 4G-23: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Lymphozytenzahl erniedrigt (SOC: Untersuchungen) der Studie KEYNOTE 775

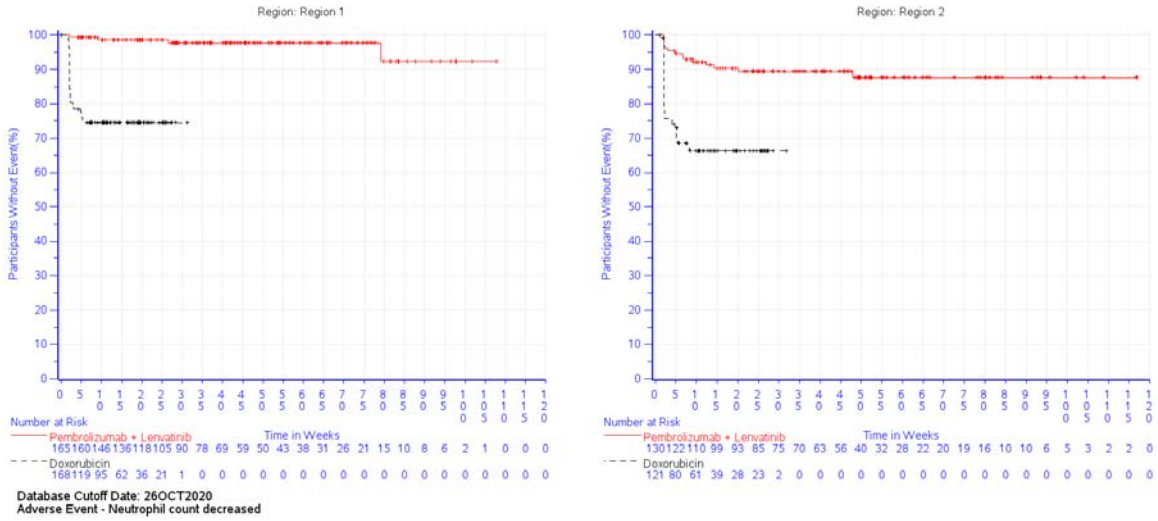

Abbildung 4G-24: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Neutrophilenzahl erniedrigt (SOC: Untersuchungen) der Studie KEYNOTE 775

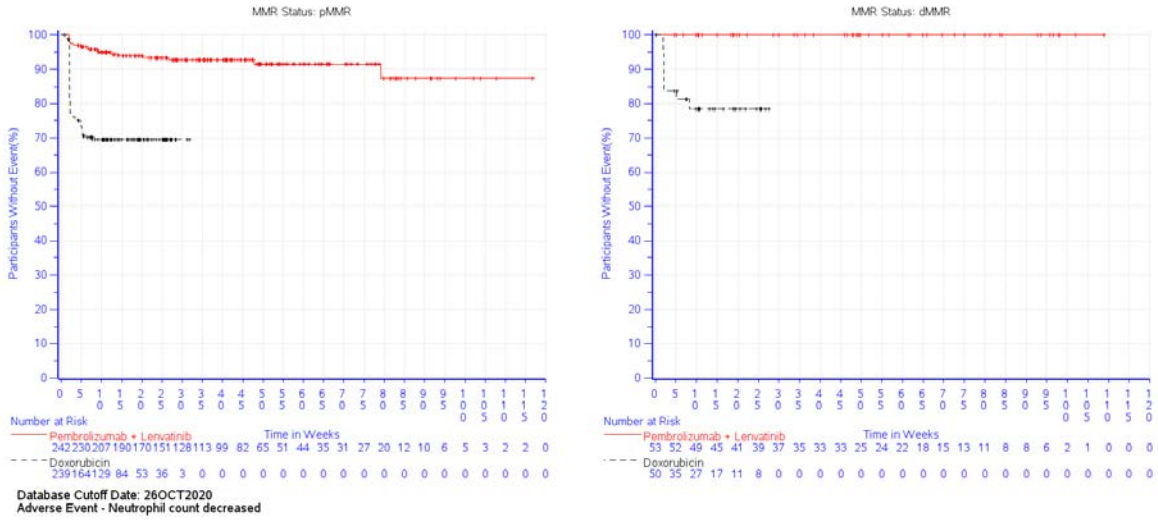

Abbildung 4G-25: Kaplan-Meier-Kurve für die Subgruppenanalyse nach MMR-Status für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Neutrophilenzahl erniedrigt (SOC: Untersuchungen) der Studie KEYNOTE 775

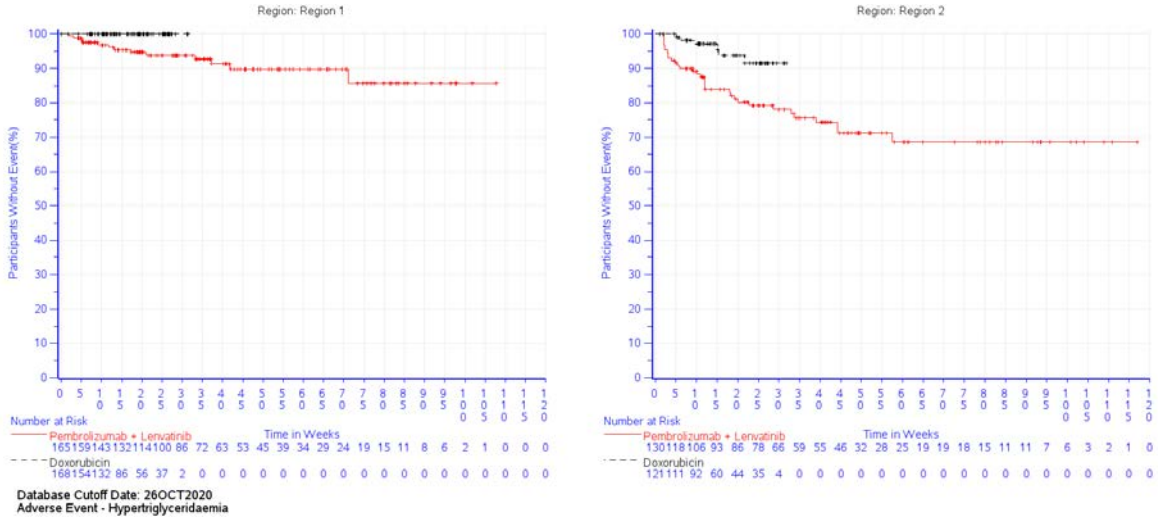

Abbildung 4G-26: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Hypertriglyzeridämie (SOC „Stoffwechsel- und Ernährungsstörungen“) der Studie KEYNOTE 775

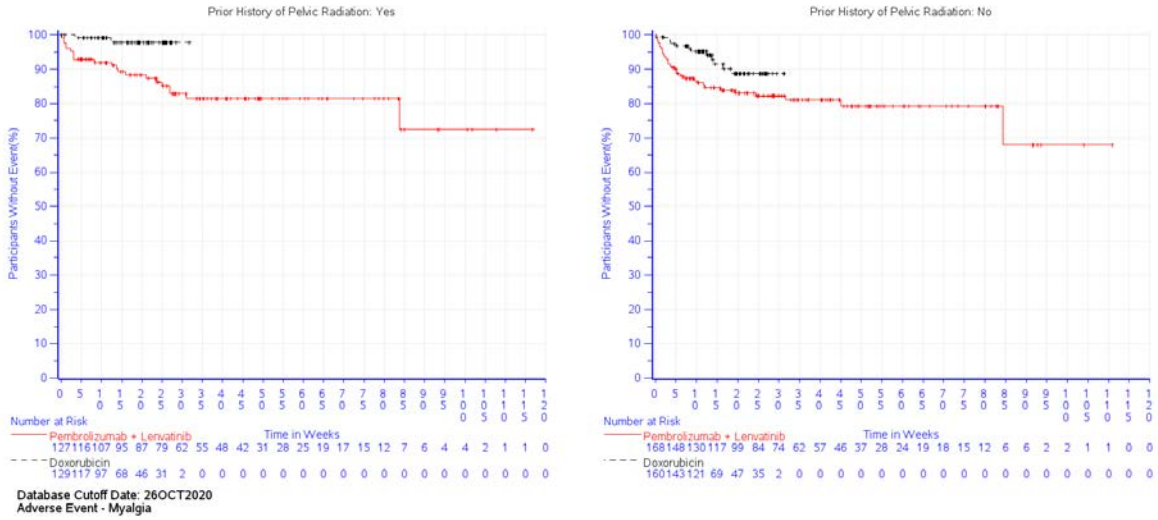

Abbildung 4G-27: Kaplan-Meier-Kurve für die Subgruppenanalyse nach vorheriger Strahlentherapie des Beckens für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Myalgie (SOC „Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen“) der Studie KEYNOTE 775

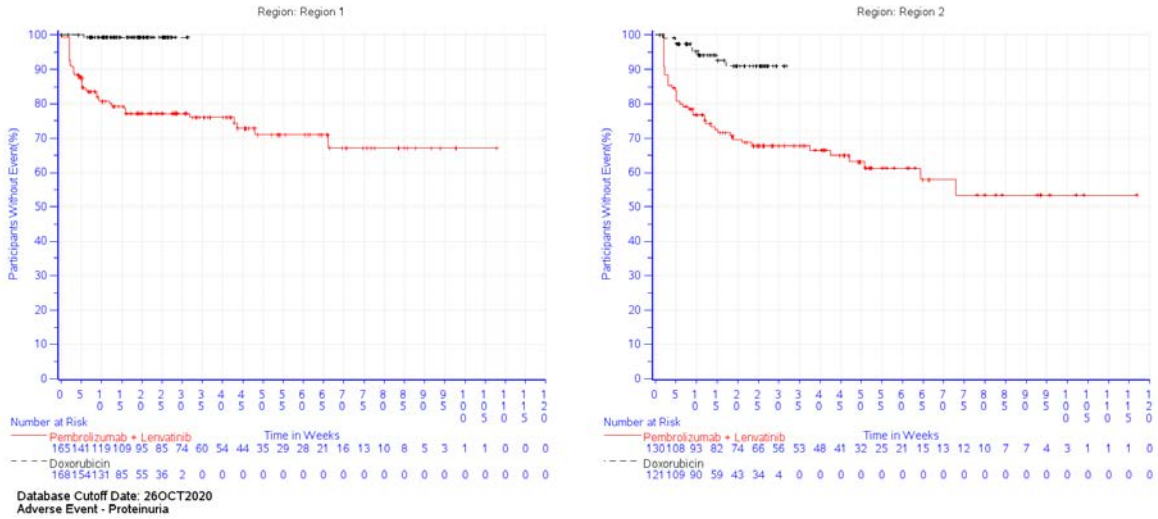

Abbildung 4G-28: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Proteinurie (SOC „Erkrankungen der Nieren und Harnwege“ der Studie KEYNOTE 775

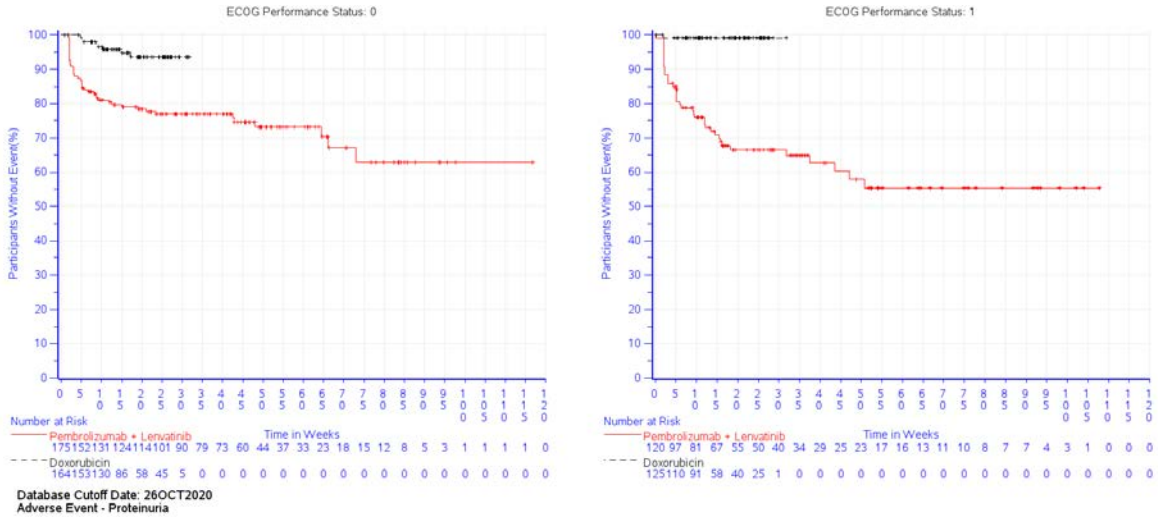

Abbildung 4G-29: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Proteinurie (SOC „Erkrankungen der Nieren und Harnwege“ der Studie KEYNOTE 775

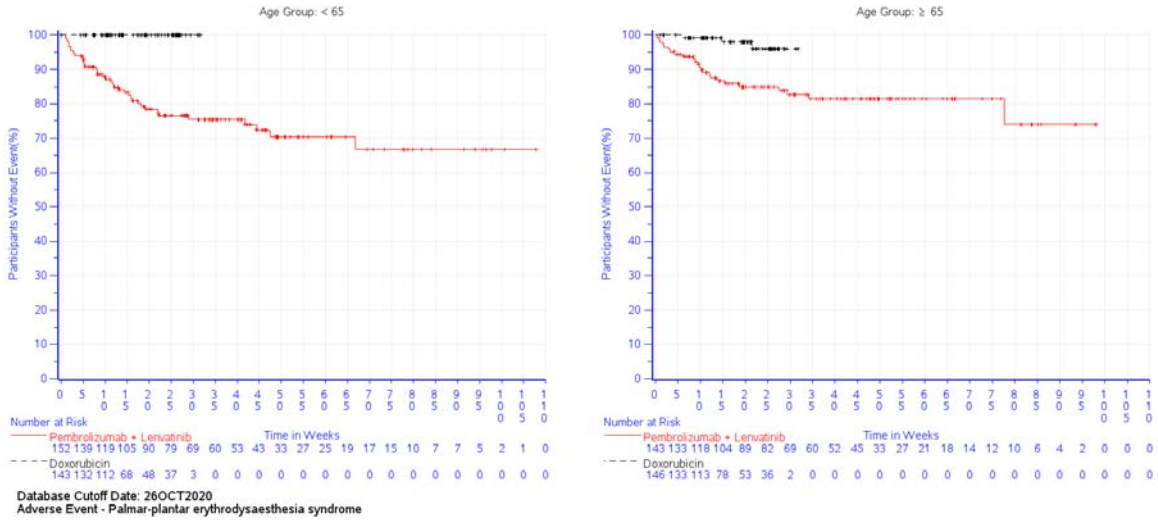

Abbildung 4G-30: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Palmar-plantares Erythrodysaesthesiesyndrom (SOC „Erkrankungen der Haut und des Unterhautgewebes“ der Studie KEYNOTE 775

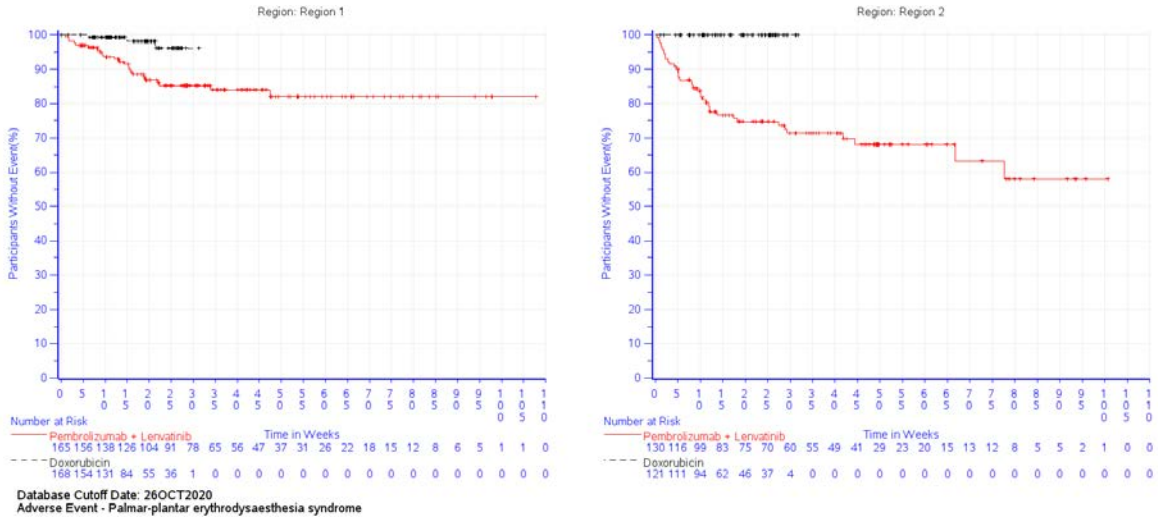

Abbildung 4G-31: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt für den PT Palmar-plantares Erythrodysaesthesiesyndrom (SOC „Erkrankungen der Haut und des Unterhautgewebes“ der Studie KEYNOTE 775

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

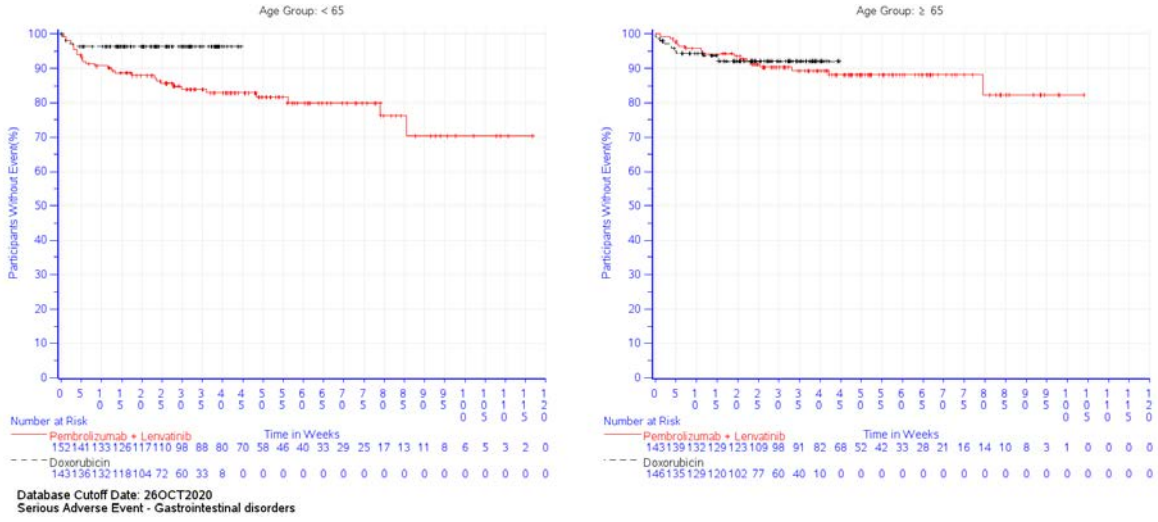

Abbildung 4G-32: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für den Endpunkt Schwerwiegende unerwünschte Ereignisse für die SOC „Erkrankungen des Gastrointestinaltrakts“ der Studie KEYNOTE 775

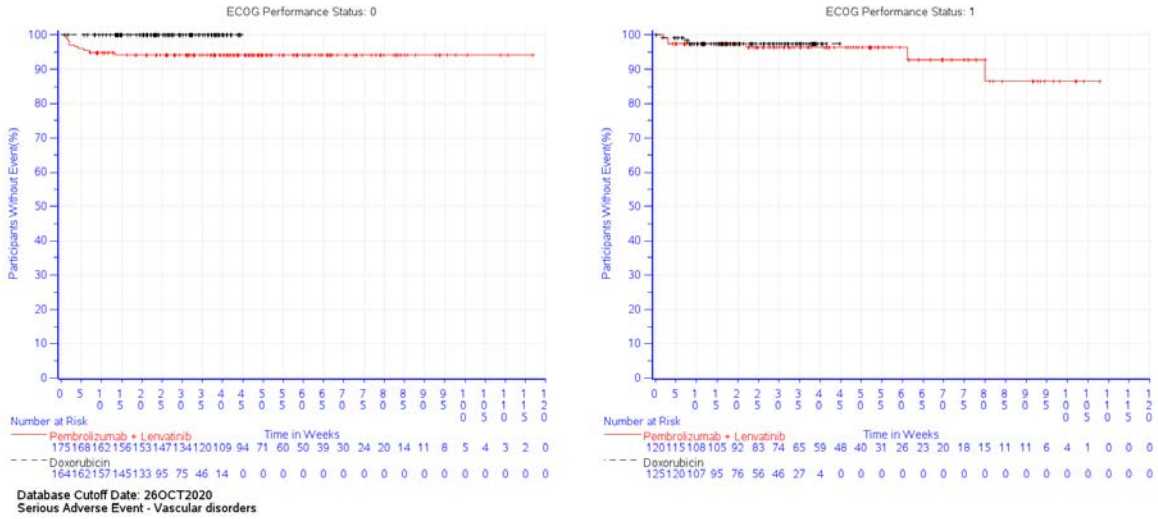

Abbildung 4G-33: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Schwerwiegende unerwünschte Ereignisse für die SOC „Gefäßerkrankungen“ der Studie KEYNOTE 775

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT)

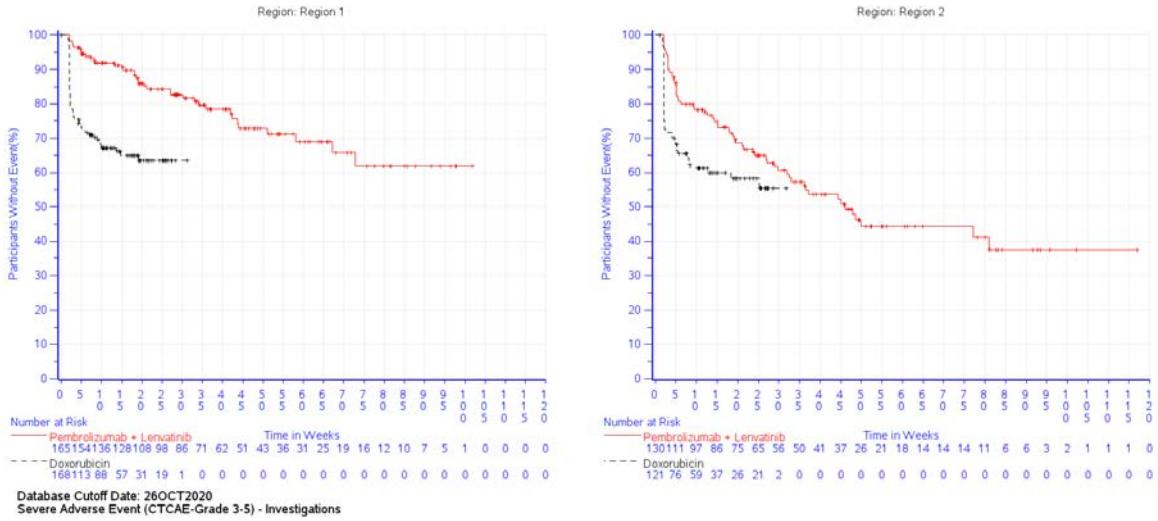

Abbildung 4G-34: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) für die SOC „Untersuchungen“ der Studie KEYNOTE 775

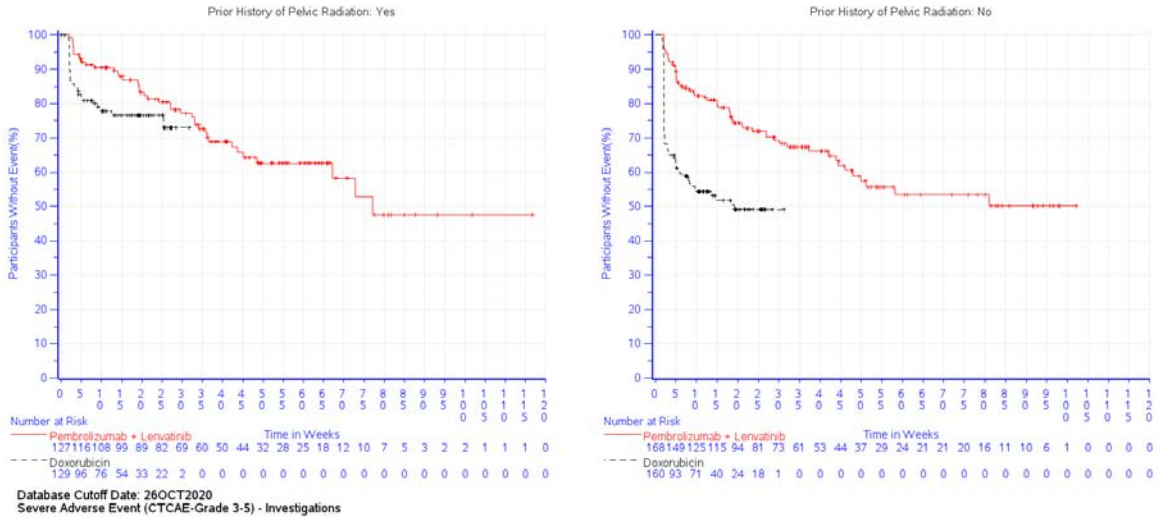

Abbildung 4G-35: Kaplan-Meier-Kurve für die Subgruppenanalyse nach vorheriger Strahlentherapie des Beckens für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) für die SOC „Untersuchungen“ der Studie KEYNOTE 775

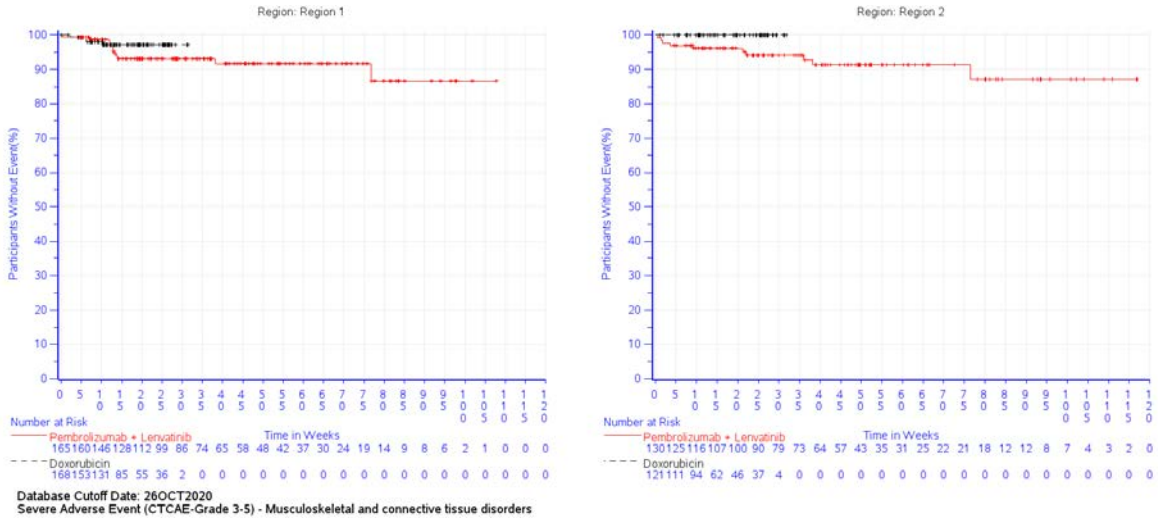

Abbildung 4G-36: Kaplan-Meier-Kurve für die Subgruppenanalyse Region für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) für die SOC „Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen“ der Studie KEYNOTE 775

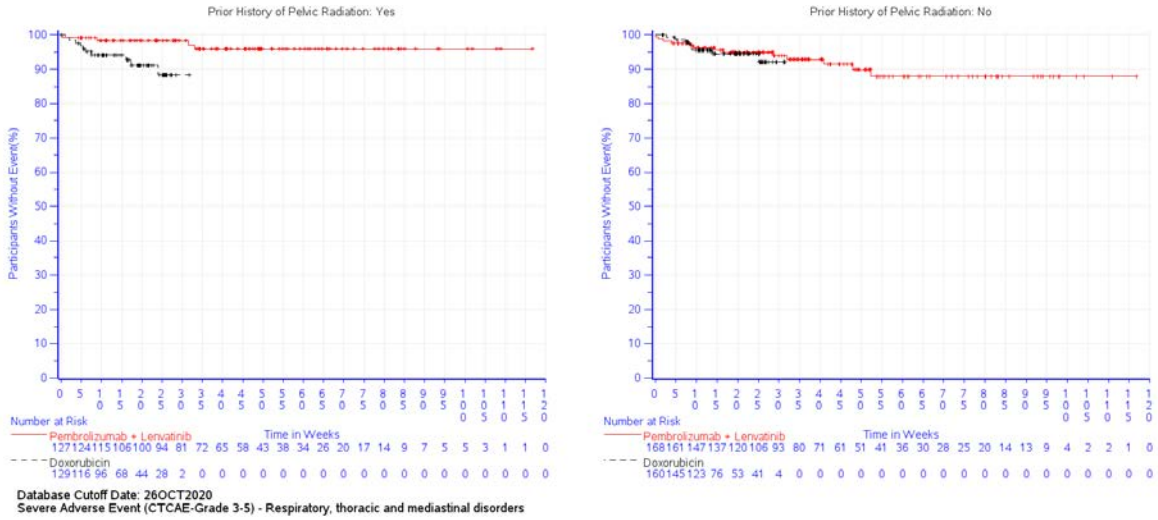

Abbildung 4G-37: Kaplan-Meier-Kurve für die Subgruppenanalyse nach vorheriger Strahlentherapie des Beckens für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) für die SOC „Erkrankungen der Atemwege, des Brustraums und Mediastinums“ der Studie KEYNOTE 775

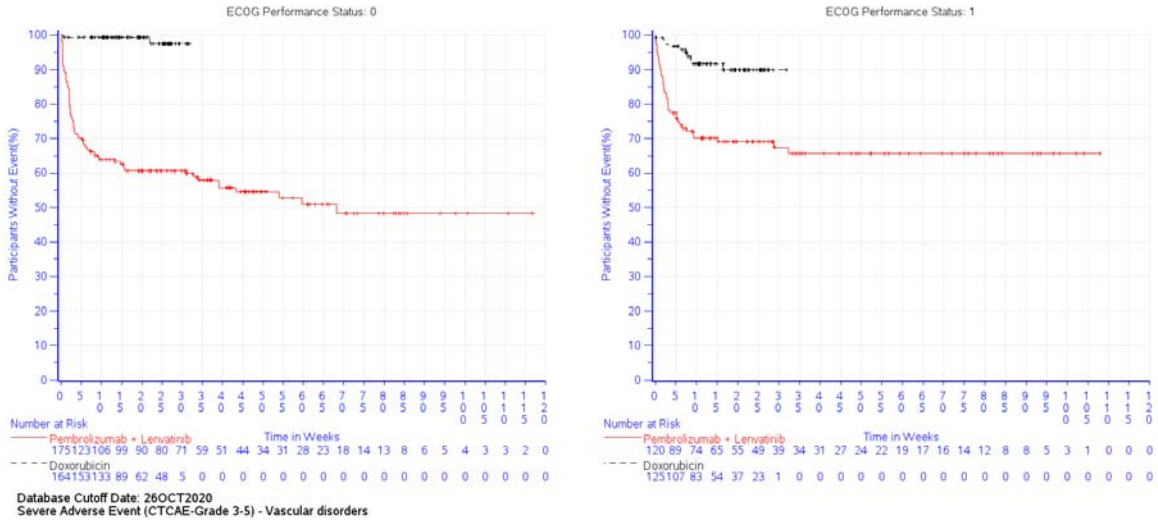

Abbildung 4G-38: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) für die SOC „Gefäßerkrankungen“ der Studie KEYNOTE 775

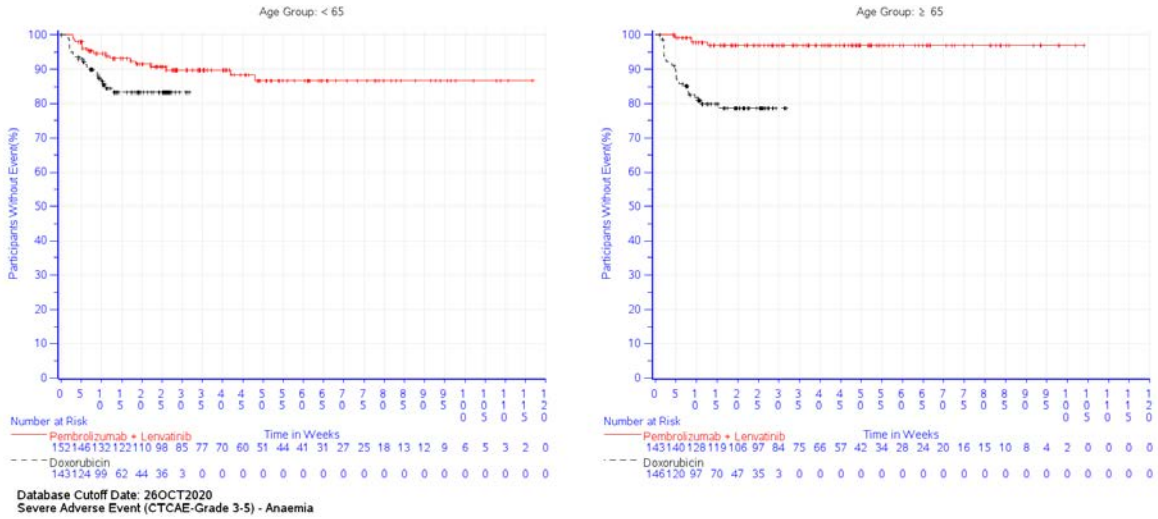

Abbildung 4G-39: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) für den PT Anämie (SOC „Erkrankungen des Blutes und des Lymphsystems“ der Studie KEYNOTE 775

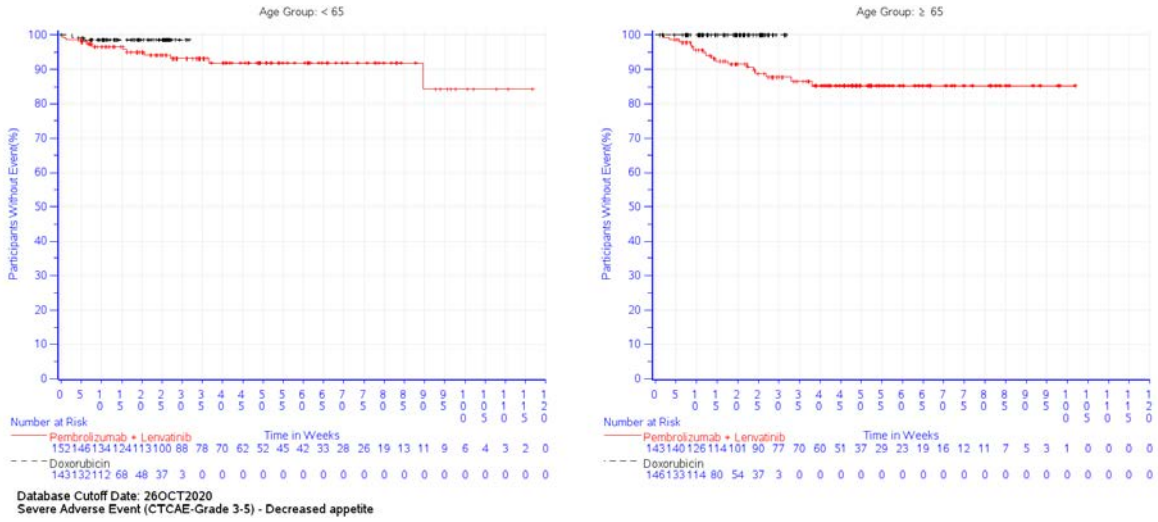

Abbildung 4G-40: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) für den PT Appetit vermindert (SOC „Stoffwechsel- und Ernährungsstörungen“ der Studie KEYNOTE 775

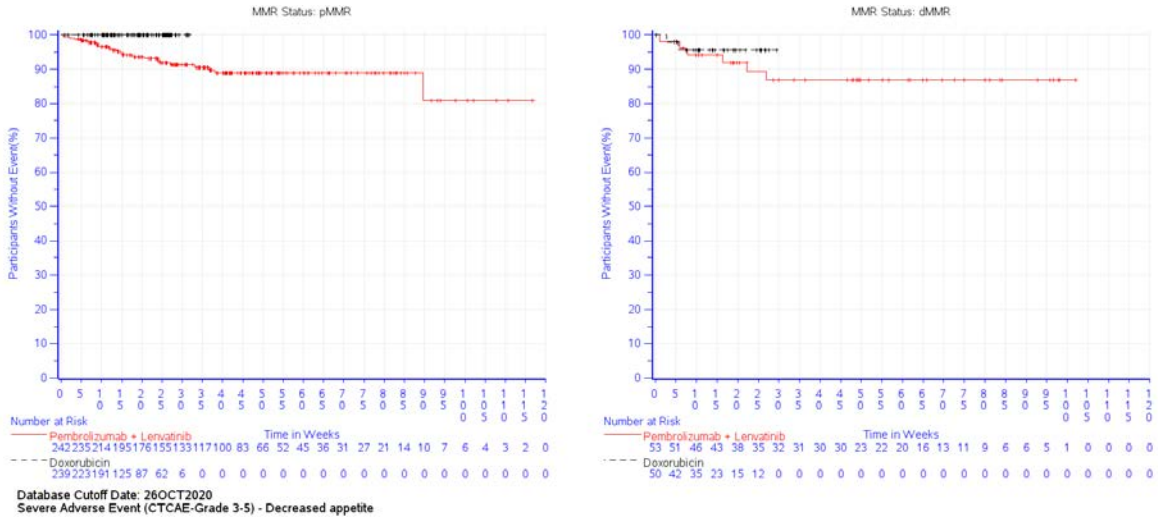

Abbildung 4G-41: Kaplan-Meier-Kurve für die Subgruppenanalyse nach MMR-Status für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) für den PT Appetit vermindert (SOC „Stoffwechsel- und Ernährungsstörungen“ der Studie KEYNOTE 775

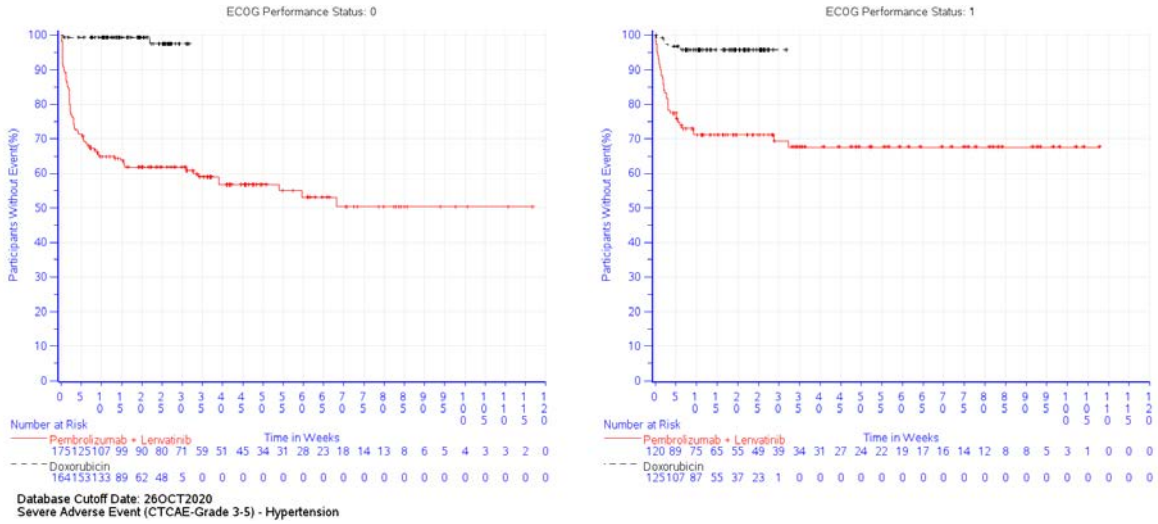

Abbildung 4G-42: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) für den PT Hypertonie (SOC „Gefäßerkrankungen“) der Studie KEYNOTE 775

Anhang 4-G3: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest ($p \geq 0,05$)

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.2 die Ergebnisse der Subgruppenanalysen, für die ein nicht signifikanter Interaktionstest ($p \geq 0,05$) vorliegt, dargestellt.

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 26. Oktober 2020 (Interimsanalyse I, präspezifiziert).

Mortalität

Gesamtüberleben

Tabelle 4G-4: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel

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	

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		p-Value for Interaction Test[g]
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]	
≥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

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

Morbidität

Zeit bis zur ersten Folgetherapie (oder Tod)

Tabelle 4G-5: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Zeit bis zur ersten Folgetherapie oder Tod aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib[b]			Doxorubicin[b]			Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]		p-Value for Interaction Test[g]
Time to Subsequent Therapy or Death	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	91 (59.5)	11.11 [8.58; 16.07]	150	133 (88.7)	5.26 [4.04; 6.24]	0.34 [0.25; 0.44]	< 0.001	0.313
≥ 65	145	88 (60.7)	11.79 [8.74; 12.32]	157	137 (87.3)	5.82 [4.73; 6.67]	0.38 [0.29; 0.50]	< 0.001	
Region									
Region 1	168	109 (64.9)	9.10 [7.56; 11.43]	179	160 (89.4)	5.13 [4.34; 5.82]	0.37 [0.29; 0.48]	< 0.001	0.665
Region 2	130	70 (53.8)	12.45 [10.61; 19.35]	128	110 (85.9)	6.24 [4.93; 7.10]	0.33 [0.24; 0.45]	< 0.001	
ECOG Performance Status									
0	176	100 (56.8)	12.25 [10.61; 14.52]	176	153 (86.9)	5.95 [5.19; 6.47]	0.34 [0.26; 0.44]	< 0.001	0.899
1	121	78 (64.5)	8.31 [6.83; 11.14]	131	117 (89.3)	4.37 [3.78; 6.01]	0.38 [0.29; 0.52]	< 0.001	
Prior History of Pelvic Radiation									
Yes	128	70 (54.7)	12.68 [9.99; 18.23]	138	119 (86.2)	6.01 [4.83; 6.74]	0.29 [0.21; 0.40]	< 0.001	0.281
No	170	109 (64.1)	9.43 [7.36; 11.96]	169	151 (89.3)	5.19 [4.37; 5.91]	0.40 [0.31; 0.52]	< 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 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

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30: Symptomskala Erschöpfung

Tabelle 4G-6: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Erschöpfung aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-7: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Übelkeit und Erbrechen aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-C30: Symptomskala Schmerzen

Tabelle 4G-8: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Schmerzen aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-C30: Symptomskala Dyspnoe

Tabelle 4G-9: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Dyspnoe aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

Tabelle 4G-10: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Schlaflosigkeit aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-C30: Symptomskala Appetitverlust

Tabelle 4G-11: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Appetitverlust aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-C30: Symptomskala Verstopfung

Tabelle 4G-12: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Verstopfung aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-C30: Symptomskala Diarrhoe

Tabelle 4G-13: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Diarrhoe aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-EN24: Symptomskala Lymphödem

Tabelle 4G-14: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Lymphödem aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
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]**	**p-Value for Interaction Test[h]**
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

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

EORTC QLQ-EN24: Symptomskala Urologische Beschwerden

Tabelle 4G-15: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Urologische Beschwerden aus RCT mit dem zu bewertenden Arzneimittel

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

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

EORTC QLQ-EN24: Symptomskala Gastrointestinale Beschwerden

Tabelle 4G-16: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Gastrointestinale Beschwerden aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-EN24: Symptomskala Negativen Körperbild

Tabelle 4G-17: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Negatives Körperbild aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
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]**	**p-Value for Interaction Test[h]**
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

EORTC QLQ-EN24: Symptomskala Sexuelle Probleme

Tabelle 4G-18: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Sexuelle Probleme aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
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]**	**p-Value for Interaction Test[h]**
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

EORTC QLQ-EN24: Symptomskala Rücken- und Beckenschmerzen

Tabelle 4G-19: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Rücken- und Beckenschmerzen aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		**p-Value for Interaction Test[h]**
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]**	
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

EORTC QLQ-EN24: Symptomskala Kribbel-/Taubheitsgefühl

Tabelle 4G-20: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Kribbel-/Taubheitsgefühl aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-EN24: Symptomskala Muskulärer Schmerz

Tabelle 4G-21: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Muskulärer Schmerz aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
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]**	**p-Value for Interaction Test[h]**
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

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EORTC QLQ-EN24: Symptomskala Haarausfall

Tabelle 4G-22: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Haarausfall aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
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]**	**p-Value for Interaction Test[h]**
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

EORTC QLQ-EN24: Symptomskala Geschmacksveränderung

Tabelle 4G-23: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Geschmacksveränderung aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
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]**	**p-Value for Interaction Test[h]**
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

EQ-5D VAS (7 Punkte)

Tabelle 4G-24: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den EQ-5D VAS (7 Punkte) aus RCT mit dem zu bewertenden Arzneimittel

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	105 (71.9)	2.10 [1.45; 2.79]	135	90 (66.7)	1.84 [1.15; 2.56]	0.85 [0.63; 1.13]	0.251	0.855
≥ 65	136	102 (75.0)	1.54 [1.38; 2.33]	132	103 (78.0)	1.41 [1.22; 2.00]	0.83 [0.63; 1.10]	0.204	
Region									
Region 1	152	110 (72.4)	1.84 [1.41; 2.37]	152	112 (73.7)	1.41 [0.95; 1.97]	0.80 [0.62; 1.05]	0.109	0.614
Region 2	130	97 (74.6)	1.81 [1.45; 2.79]	115	81 (70.4)	1.87 [1.38; 2.79]	0.88 [0.65; 1.19]	0.411	
MMR Status									
pMMR	233	175 (75.1)	1.71 [1.41; 2.10]	226	165 (73.0)	1.54 [1.35; 2.07]	0.87 [0.70; 1.08]	0.209	0.375
dMMR	49	32 (65.3)	2.76 [1.45; 4.40]	41	28 (68.3)	1.45 [0.76; 2.79]	0.67 [0.40; 1.13]	0.135	
ECOG Performance Status									
0	171	124 (72.5)	1.81 [1.41; 2.79]	156	112 (71.8)	1.61 [1.35; 2.20]	0.84 [0.65; 1.09]	0.181	0.988
1	111	83 (74.8)	2.07 [1.41; 2.33]	111	81 (73.0)	1.45 [0.82; 2.10]	0.83 [0.61; 1.13]	0.240	
Prior History of Pelvic Radiation									
Yes	122	92 (75.4)	2.04 [1.41; 2.69]	118	79 (66.9)	1.71 [1.35; 2.60]	0.99 [0.73; 1.35]	0.974	0.128
No	160	115 (71.9)	1.81 [1.41; 2.76]	149	114 (76.5)	1.41 [0.82; 2.00]	0.73 [0.56; 0.96]	0.023	

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 7 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

EQ-5D VAS (10 Punkte)

Tabelle 4G-25: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den EQ-5D VAS (10 Punkte) aus RCT mit dem zu bewertenden Arzneimittel

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	101 (69.2)	2.10 [1.81; 3.42]	135	88 (65.2)	2.00 [1.41; 2.79]	0.81 [0.61; 1.09]	0.166	0.843
≥ 65	136	98 (72.1)	1.74 [1.41; 2.76]	132	96 (72.7)	1.94 [1.41; 2.27]	0.88 [0.66; 1.18]	0.391	
Region									
Region 1	152	104 (68.4)	2.10 [1.41; 2.79]	152	105 (69.1)	1.84 [1.41; 2.20]	0.81 [0.62; 1.07]	0.145	0.620
Region 2	130	95 (73.1)	2.04 [1.45; 2.83]	115	79 (68.7)	2.10 [1.41; 2.83]	0.89 [0.66; 1.20]	0.447	
MMR Status									
pMMR	233	168 (72.1)	2.07 [1.45; 2.33]	226	158 (69.9)	1.94 [1.45; 2.27]	0.90 [0.72; 1.12]	0.340	0.296
dMMR	49	31 (63.3)	2.79 [1.48; 7.49]	41	26 (63.4)	1.97 [0.79; 4.11]	0.66 [0.38; 1.13]	0.128	
ECOG Performance Status									
0	171	122 (71.3)	2.04 [1.41; 2.79]	156	108 (69.2)	1.94 [1.51; 2.79]	0.87 [0.67; 1.14]	0.307	0.671
1	111	77 (69.4)	2.10 [1.45; 2.79]	111	76 (68.5)	1.97 [1.35; 2.20]	0.81 [0.58; 1.11]	0.193	
Prior History of Pelvic Radiation									
Yes	122	88 (72.1)	2.10 [1.45; 2.79]	118	76 (64.4)	2.10 [1.41; 2.73]	0.95 [0.70; 1.30]	0.752	0.360
No	160	111 (69.4)	2.10 [1.41; 2.79]	149	108 (72.5)	1.91 [1.41; 2.20]	0.78 [0.60; 1.03]	0.076	

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; 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

Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-26: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den globalen Gesundheitsstatus aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-C30: Funktionsskala Physikalische Funktion

Tabelle 4G-27: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Physikalische Funktion aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-28: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Rollenfunktion aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-29: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Emotionale Funktion aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-30: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Kognitive Funktion aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-31: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Soziale Funktion aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-EN24: Funktionsskala Sexuelles Interesse

Tabelle 4G-32: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Sexuelles Interesse aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-EN24: Funktionsskala Sexuelle Aktivität

Tabelle 4G-33: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Sexuelle Aktivität aus RCT mit dem zu bewertenden Arzneimittel

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

EORTC QLQ-EN24: Funktionsskala Sexueller Genuss

Tabelle 4G-34: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Sexueller Genuss aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		
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]**	**p-Value for Interaction Test[h]**
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

Nebenwirkungen

Unerwünschte Ereignisse Gesamtraten

Unerwünschte Ereignisse gesamt

Tabelle 4G-35: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

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

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-36: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

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]**
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

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

Tabelle 4G-37: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) aus RCT mit dem zu bewertenden Arzneimittel

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

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-38: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

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

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-39: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC) aus RCT mit dem zu bewertenden Arzneimittel

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

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]	
		(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;	< 0.001	

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]
							869.64]		
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

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]
≥ 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	17.9	146	45	Not reached	1.76	0.003	

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]
		(55.2)	[7.7; 40.6]		(30.8)	[26.1; -]	[1.21; 2.56]		
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	

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]
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 (15.1)	Not reached [-; -]	50	3 (6.0)	Not reached [-; -]	1.25 [0.31; 5.06]	0.753	
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									

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]
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

Tabelle 4G-40: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (PT) aus RCT mit dem zu bewertenden Arzneimittel

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: 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									

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	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									

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]
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	21.1	168	31	Not reached	2.75	< 0.001	0.810

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]**
		(57.0)	[13.0; 30.7]		(18.5)	[-; -]	[1.82; 4.16]		
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 (7.1)	Not reached [-; -]	160	4 (2.5)	Not reached [-; -]	2.55 [0.81; 8.02]	0.109	
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

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]
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	Not reached	160	14	Not reached	2.28	0.009	

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]
		(26.8)	[-; -]		(8.8)	[-; -]	[1.23; 4.22]		
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	

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: 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									

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	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 (4.2)	n.c.	160	0 (0.0)	n.c.	n.c.	n.c.	
SOC: Investigations, PT[h]: Blood creatinine increased									
Age Group									

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]
< 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	Not reached	143	4	Not reached	1.73	0.373	0.587

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]
		(10.5)	[-; -]		(2.8)	[-; -]	[0.52; 5.75]		
≥ 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

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]
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	Not reached	160	37	Not reached	0.16	< 0.001	

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]
		(6.0)	[-; -]		(23.1)	[-; -]	[0.08; 0.35]		
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

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]
≥ 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	Not reached	146	7	Not reached	1.50	0.401	

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]
		(10.5)	[-; -]		(4.8)	[-; -]	[0.58; 3.84]		
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	

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]
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 (17.0)	Not reached [82.0; -]	50	2 (4.0)	Not reached [-; -]	3.44 [0.73; 16.21]	0.118	
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									

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]
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	Not reached	129	6	Not reached	0.11	0.043	0.070

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]
		(1.6)	[-; -]		(4.7)	[-; -]	[0.01; 0.94]		
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.

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]
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

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]
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 (15.5)	Not reached [99.3; -]	160	4 (2.5)	Not reached [-; -]	4.68 [1.61; 13.63]	0.005	
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	Not reached	121	3	Not reached	0.56	0.520	

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]
		(1.5)	[-; -]		(2.5)	[-; -]	[0.09; 3.33]		
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

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]**
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									

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-41: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC) aus RCT mit dem zu bewertenden Arzneimittel

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[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 (17.3)	Not reached [-; -]	129	8 (6.2)	Not reached [-; -]	2.34 [1.03; 5.33]	0.042	0.882
No	168	22	Not reached	160	8	Not reached	1.92	0.125	

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]
		(13.1)	[-; -]		(5.0)	[-; -]	[0.83; 4.44]		
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	Not reached	160	4	Not reached	1.61	0.449	

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]
		(4.2)	[-; -]		(2.5)	[-; -]	[0.47; 5.50]		
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

Tabelle 4G-42: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (PT) aus RCT mit dem zu bewertenden Arzneimittel

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	n.c.	146	7	n.c.	n.c.	n.c.	

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]
		(0.7)			(4.8)				
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 (4.1)	Not reached [-; -]	239	1 (0.4)	Not reached [-; -]	7.29 [0.91; 58.10]	0.061	0.589
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	n.c.	146	0	n.c.	n.c.	n.c.	

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]
		(3.5)			(0.0)				
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

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT)

Tabelle 4G-43: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC) aus RCT mit dem zu bewertenden Arzneimittel

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	

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]
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									

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]
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									

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]
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	Not reached	239	2	Not reached	4.60	0.045	0.559

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]**
		(7.0)	[-; -]		(0.8)	[-; -]	[1.03; 20.43]		
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

Tabelle 4G-44: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib[b]**			**Doxorubicin[b]**			**Pembrolizumab + Lenvatinib[b] vs. Doxorubicin[b]**		**p-Value for Interaction Test[g]**
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]**	
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									

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	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									

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]
< 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	Not reached	143	17	Not reached	0.14	0.002	0.394

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]**
		(2.6)	[-; -]		(11.9)	[-; -]	[0.04; 0.47]		
≥ 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

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]
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-G4: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT

Tabelle 4G-45: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) basierend auf der MedDRA Version 23.0 (Version 18.0, 05 Mai 2020) anhand der zugeordneten PT in der Studie KEYNOTE 775

AEOSI	MedDRA Preferred Terms	Immune-Mediated
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,	Yes

	Autoimmune hypothyroidism, Immune-mediated hypothyroidism	
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	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

Anhang 4-G5: Ergebnisse der Gesamtpopulation der Studie KEYNOTE 775

Im Folgenden werden ergänzend die Patientencharakteristika und Ergebnisse der Gesamtpopulation der Studie KEYNOTE 775 dargestellt. Es handelt sich bei der Gesamtpopulation um den Vergleich von Pembrolizumab + Lenvatinib gegenüber der Therapie nach Maßgabe des Arztes (Doxorubicin oder Paclitaxel).

Da die Ergebnisse für die vorliegende Nutzenbewertung nicht zur Ableitung des Zusatznutzens herangezogen werden, werden ausschließlich die Hauptanalysen und keine Subgruppenanalysen dargestellt.

Anhang 4-G5.1: Studienpopulation

Tabelle 4G-45: Charakterisierung der nutzenbewertungsrelevanten Population – RCT mit dem zu bewertenden Arzneimittel

Characteristic	Study: KEYNOTE 775[a]	
	Pembrolizumab + Lenvatinib N[c]=411	TPC[b] N[c]=416
Sex, n (%)		
Female	411 (100.0)	416 (100.0)
Age (Years)		
Mean (SD)	63.2 (9.1)	63.8 (9.2)
Median (Q1; Q3)	64.0 (58.0; 70.0)	65.0 (58.5; 70.0)
Min; Max	30.0; 82.0	35.0; 86.0
Age (Years), n (%)		
< 65	206 (50.1)	204 (49.0)
≥ 65	205 (49.9)	212 (51.0)
Race, n (%)		
American Indian Or Alaska Native	4 (1.0)	7 (1.7)
Asian	85 (20.7)	92 (22.1)
Black Or African American	17 (4.1)	14 (3.4)
Multiple	7 (1.7)	13 (3.1)
Native Hawaiian Or Other Pacific Islander	1 (0.2)	0 (0.0)
White	261 (63.5)	246 (59.1)
Missing	36 (8.8)	44 (10.6)
Ethnicity, n (%)		
Hispanic Or Latino	60 (14.6)	73 (17.5)
Not Hispanic Or Latino	308 (74.9)	287 (69.0)
Not Reported	34 (8.3)	46 (11.1)
Unknown	9 (2.2)	10 (2.4)
Age (Years) Group, n (%)		
< 75	376 (91.5)	373 (89.7)
≥ 75	35 (8.5)	43 (10.3)
Age (Years), n (%)		
<65	206 (50.1)	204 (49.0)
≥ 65 to 74	170 (41.4)	169 (40.6)
≥ 75 to <85	35 (8.5)	41 (9.9)
≥ 85	0 (0.0)	2 (0.5)
Age (Years) at Initial Diagnosis Category		
Mean (SD)	61.3 (9.1)	61.5 (9.3)
Median (Q1; Q3)	62.4 (56.0; 67.5)	62.1 (56.6; 68.0)
Min; Max	29.8; 81.3	27.3; 84.0
Age (Years) at Initial Diagnosis Category, n (%)		
< 65	253 (61.6)	255 (61.3)

Characteristic	Study: KEYNOTE 775[a]	
	Pembrolizumab + Lenvatinib N[c]=411	TPC[b] N[c]=416
≥ 65	158 (38.4)	161 (38.7)
Region[d], n (%)		
Region 1	234 (56.9)	240 (57.7)
Region 2	177 (43.1)	176 (42.3)
MMR Status, n (%)		
pMMR	346 (84.2)	351 (84.4)
dMMR	65 (15.8)	65 (15.6)
ECOG Performance Status, n (%)		
0	246 (59.9)	241 (57.9)
1	164 (39.9)	175 (42.1)
3	1 (0.2)	0 (0.0)
Prior History of Pelvic Radiation, n (%)		
Yes	174 (42.3)	186 (44.7)
No	237 (57.7)	230 (55.3)
Elapsed Time (Years) from Initial Diagnosis		
Mean (SD)	2.4 (2.4)	2.9 (2.8)
Median (Q1; Q3)	1.7 (1.0; 3.1)	2.1 (1.2; 3.6)
Min; Max	0.3; 21.3	0.0; 25.5
Histology of Initial Diagnosis, n (%)		
Clear Cell Carcinoma	30 (7.3)	17 (4.1)
Endometrioid Carcinoma	83 (20.2)	103 (24.8)
Endometrioid Carcinoma With Squamous Differentiation	7 (1.7)	7 (1.7)
High Grade Endometrioid Carcinoma	94 (22.9)	90 (21.6)
High Grade Mucinous Carcinoma	0 (0.0)	1 (0.2)
High Grade Serous	65 (15.8)	65 (15.6)
Low Grade Endometrioid Carcinoma	59 (14.4)	54 (13.0)
Low Grade Mucinous Carcinoma	1 (0.2)	0 (0.0)
Mixed	22 (5.4)	16 (3.8)
Neuroendocrine	2 (0.5)	0 (0.0)
Other	6 (1.5)	7 (1.7)
Serous Carcinoma	38 (9.2)	50 (12.0)
Unclassified	0 (0.0)	3 (0.7)
Undifferentiated Histology	4 (1.0)	3 (0.7)
FIGO Stage at Initial Diagnosis, n (%)		
I	10 (2.4)	11 (2.6)
IA	54 (13.1)	64 (15.4)
IB	47 (11.4)	64 (15.4)
II	32 (7.8)	26 (6.3)
III	5 (1.2)	8 (1.9)
IIIA	28 (6.8)	33 (7.9)
IIIB	11 (2.7)	11 (2.6)
IIIC	30 (7.3)	24 (5.8)
IIIC1	17 (4.1)	25 (6.0)
IIIC2	27 (6.6)	27 (6.5)
IV	27 (6.6)	26 (6.3)
IVA	7 (1.7)	8 (1.9)
IVB	116 (28.2)	89 (21.4)
Missing	0 (0.0)	0 (0.0)
Metastases at Brain[f], n (%)		
No	409 (99.5)	414 (99.5)
Yes	2 (0.5)	2 (0.5)
Metastases at Bone[f], n (%)		
No	372 (90.5)	383 (92.1)
Yes	39 (9.5)	33 (7.9)

Characteristic	Study: KEYNOTE 775[a]	
	Pembrolizumab + Lenvatinib N[c]=411	TPC[b] N[c]=416
Metastases at Liver[f], n (%)		
No	310 (75.4)	318 (76.4)
Yes	101 (24.6)	98 (23.6)
Metastases at Lung[f], n (%)		
No	247 (60.1)	264 (63.5)
Yes	164 (39.9)	152 (36.5)
Metastases at Intra-abdominal[e f], n (%)		
No	247 (60.1)	250 (60.1)
Yes	164 (39.9)	166 (39.9)
Metastases at Lymph Node[f], n (%)		
No	187 (45.5)	191 (45.9)
Yes	224 (54.5)	225 (54.1)

a: Database Cutoff Date: 26OCT2020

b: Treatment of physician's choice of doxorubicin or paclitaxel

c: Number of participants: intention-to-treat population

d: Region 1: Europe, USA, Canada, Australia, New Zealand, Israel; Region 2: Rest of World

e: Includes reported locations of colon, abdominal cavity, omentum, small intestine, peritoneal cavity, and peritoneum. Does not include lymph nodes or other organs

f: Lesion location as determined by investigator review

dMMR: Mismatch Repair deficient; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; Max: Maximum; Min: Minimum; MMR: Mismatch Repair; pMMR: Mismatch Repair Proficient; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation; TPC: Treatment of Physician's Choice

Tabelle 4G-46: Charakterisierung der Gesamtpopulation (Therapieabbrecher, Studienabbrecher) – RCT mit dem zu bewertenden Arzneimittel

	Lenvatinib + Pembrolizumab		TPC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	411		416		827	
Status for Trial						
Discontinued	191	(46.5)	264	(63.5)	455	(55.0)
Death	184	(44.8)	236	(56.7)	420	(50.8)
Lost To Follow-Up	0	(0.0)	2	(0.5)	2	(0.2)
Withdrawal By Subject	7	(1.7)	26	(6.3)	33	(4.0)
Participants Ongoing	220	(53.5)	152	(36.5)	372	(45.0)
Status for Study medication in Trial						
Started	406		388		794	
Completed	0	(0.0)	93	(24.0)	93	(11.7)
Discontinued	282	(69.5)	285	(73.5)	567	(71.4)
Adverse Event	73	(18.0)	33	(8.5)	106	(13.4)
Clinical Progression	15	(3.7)	24	(6.2)	39	(4.9)
Complete Response	2	(0.5)	3	(0.8)	5	(0.6)
Non-Compliance With Study Drug	0	(0.0)	1	(0.3)	1	(0.1)
Non-Study Anti-Cancer Therapy	0	(0.0)	2	(0.5)	2	(0.3)
Physician Decision	4	(1.0)	20	(5.2)	24	(3.0)
Progressive Disease	170	(41.9)	173	(44.6)	343	(43.2)
Withdrawal By Subject	18	(4.4)	29	(7.5)	47	(5.9)
Participants Ongoing	124	(30.5)	10	(2.6)	134	(16.9)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.

Completed study medication: For Lenvatinib + Pembrolizumab, completed 35 infusions of pembrolizumab. For TPC of doxorubicin, received a lifetime maximum cumulative dose of doxorubicin or for TPC of paclitaxel, a maximum tolerable dose was reached per investigator.

Number of participants: intention to treat population

TPC = Treatment Physician's Choice of doxorubicin or paclitaxel

Database Cutoff Date: 26OCT2020

Anhang 4-G5.1: Mortalität

Gesamtüberleben

Tabelle 4G-47: Ergebnisse für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib			TPC[b]			Pembrolizumab + Lenvatinib vs. TPC[b]	
	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]
Overall Survival	411	188 (45.7)	18.3 [15.2; 20.5]	416	245 (58.9)	11.4 [10.5; 12.9]	0.62 [0.51; 0.75]	< 0.001

a: Database Cutoff Date: 26OCT2020
b: Treatment of physician's choice of doxorubicin or paclitaxel
c: Number of participants: intention-to-treat population
d: From product-limit (Kaplan-Meier) method for censored data
e: 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
f: 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; MMR: Mismatch Repair; TPC: Treatment of Physician's Choice

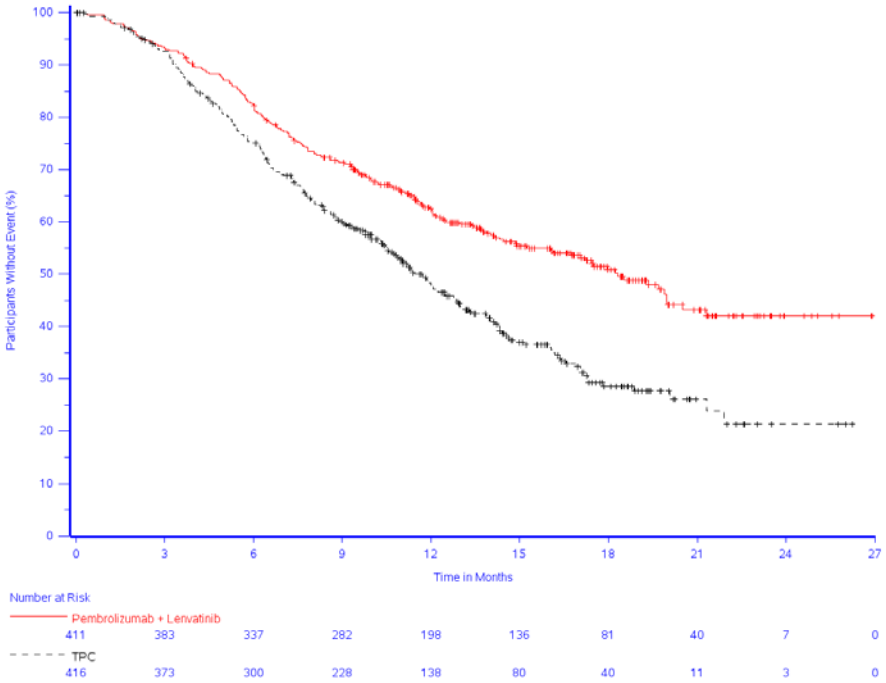

Abbildung 4G-43: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Gesamtüberleben der Studie KEYNOTE 775

Anhang 4-G5.2: Morbidität

Zeit bis zur ersten Folgetherapie (oder Tod)

Tabelle 4G-48: Ergebnisse für den Endpunkt Zeit bis zur ersten Folgetherapie oder Tod aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib			TPC[b]			Pembrolizumab + Lenvatinib vs. TPC[b]	
	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]
Subsequent Oncologic Therapy or Death	411	255 (62.0)	10.7 [9.5; 12.1]	416	351 (84.4)	5.9 [5.3; 6.4]	0.43 [0.36; 0.51]	< 0.001

a: Database Cutoff Date: 26OCT2020
b: Treatment of physician's choice of doxorubicin or paclitaxel
c: Number of participants: intention-to-treat population
d: From product-limit (Kaplan-Meier) method for censored data
e: 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
f: 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; MMR: Mismatch Repair; TPC: Treatment of Physician's Choice

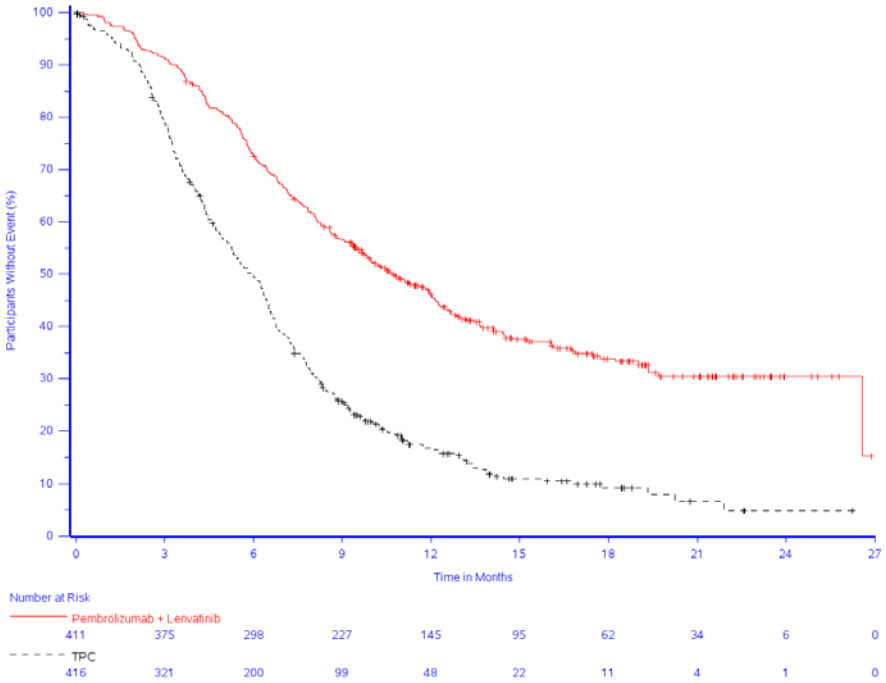

Abbildung 4G-44: Kaplan-Meier-Kurve für den Endpunkt Zeit bis zur ersten Folgetherapie oder Tod der Studie KEYNOTE 775

Tabelle 4G-49: Ergebnisse für den Endpunkt Zeit bis zur ersten Folgetherapie aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib			TPC[b]			Pembrolizumab + Lenvatinib vs. TPC[b]	
	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]
Subsequent Oncologic Therapy	411	131 (31.9)	26.6 [16.9; -]	416	224 (53.8)	7.6 [6.8; 8.3]	0.33 [0.26; 0.41]	< 0.001

a: Database Cutoff Date: 26OCT2020
b: Treatment of physician's choice of doxorubicin or paclitaxel
c: Number of participants: intention-to-treat population
d: From product-limit (Kaplan-Meier) method for censored data
e: 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
f: 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; MMR: Mismatch Repair; TPC: Treatment of Physician's Choice

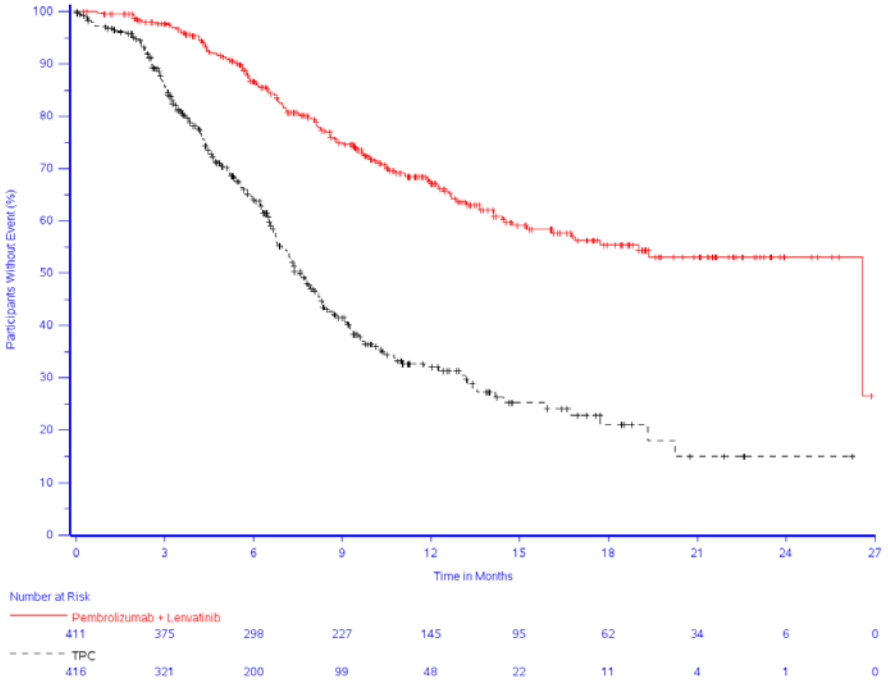

Abbildung 4G-45: Kaplan-Meier-Kurve für den Endpunkt Zeit bis zur ersten Folgetherapie der Studie KEYNOTE 775

Tabelle 4G-50: Übersicht der ersten onkologischen Folgetherapien in der Studie KEYNOTE 775

First Subsequent Oncologic Therapy	Study: KEYNOTE 775[a]	
	Pembrolizumab + Lenvatinib N[c]=411	TPC[b] N[c]=416
Status of First Subsequent Oncologic Therapy, n (%)		
Received first subsequent systemic therapy	105 (25.5)	188 (45.2)
Received first subsequent radiation therapy	24 (5.8)	36 (8.7)
Received first subsequent systemic and radiation therapy	0 (0.0)	0 (0.0)
Received second course treatment	2 (0.5)	0 (0.0)
Died without receiving a subsequent therapy	124 (30.2)	127 (30.5)
Did not receive a subsequent therapy	156 (38.0)	65 (15.6)

a: Database Cutoff Date: 26OCT2020
b: Treatment of physician's choice of doxorubicin or paclitaxel
c: Number of participants: intention-to-treat population
TPC: Treatment of Physician's Choice

Tabelle 4G-51: Übersicht der ersten onkologischen systemischen Folgetherapien in der Studie KEYNOTE 775

Study: KEYNOTE 775[a]	Participants with Event n(%)	
Therapy Class[c] **Therapy Term[d]**	**Pembrolizumab + Lenvatinib (N[e]=411)**	**TPC[b] (N[e]=416)**
Participants whose first subsequent oncologic therapy was systemic	105 (25.5)	188 (45.2)
Any PD1/PD-L1 checkpoint	2 (0.5)	37 (8.9)
Pembrolizumab	2 (0.5)	31 (7.5)
Nivolumab	0 (0.0)	3 (0.7)
Durvalumab	0 (0.0)	2 (0.5)
Atezolizumab	0 (0.0)	1 (0.2)
Any VEGF/VEGFR inhibitor	7 (1.7)	30 (7.2)
Lenvatinib	2 (0.5)	19 (4.6)
Bevacizumab	5 (1.2)	11 (2.6)
Chemotherapy	83 (20.2)	102 (24.5)
Doxorubicin	46 (11.2)	13 (3.1)
Carboplatin	21 (5.1)	32 (7.7)
Paclitaxel	17 (4.1)	36 (8.7)
Gemcitabine	5 (1.2)	24 (5.8)
Cisplatin	8 (1.9)	11 (2.6)
Docetaxel	3 (0.7)	6 (1.4)
Cyclophosphamide	3 (0.7)	4 (1.0)
Epirubicin	3 (0.7)	0 (0.0)
Topotecan	0 (0.0)	3 (0.7)
Oxaliplatin	1 (0.2)	1 (0.2)
Bortezomib	1 (0.2)	0 (0.0)
Capecitabine	1 (0.2)	0 (0.0)
Etoposide	0 (0.0)	1 (0.2)
Irinotecan	0 (0.0)	1 (0.2)
Melphalan	0 (0.0)	1 (0.2)
Mitoxantrone	0 (0.0)	1 (0.2)
Vinorelbine	0 (0.0)	1 (0.2)
Hormonal therapy	16 (3.9)	41 (9.9)
Megestrol	2 (0.5)	16 (3.8)
Letrozole	6 (1.5)	9 (2.2)
Tamoxifen	1 (0.2)	10 (2.4)
Medroxyprogesterone	1 (0.2)	6 (1.4)
Fulvestrant	2 (0.5)	2 (0.5)
Anastrozole	2 (0.5)	1 (0.2)
Goserelin	0 (0.0)	2 (0.5)
Exemestane	1 (0.2)	0 (0.0)
Unspecified	1 (0.2)	0 (0.0)
Other	3 (0.7)	8 (1.9)
Trastuzumab	1 (0.2)	3 (0.7)

Study: KEYNOTE 775[a]	**Participants with Event n(%)**	
Therapy Class[c] **Therapy Term[d]**	**Pembrolizumab + Lenvatinib** **(N[e]=411)**	**TPC[b]** **(N[e]=416)**
Unspecified	0 (0.0)	2 (0.5)
Unspecified Monoclonal Antibody	1 (0.2)	1 (0.2)
Ly 3300054	0 (0.0)	1 (0.2)
Naptumomab Estafenatox	0 (0.0)	1 (0.2)
Pertuzumab	0 (0.0)	1 (0.2)
Sacituzumab	1 (0.2)	0 (0.0)
Other I-O	0 (0.0)	2 (0.5)
Ly 3321367	0 (0.0)	1 (0.2)
Tremelimumab	0 (0.0)	1 (0.2)
Targeted therapy	5 (1.2)	9 (2.2)
Everolimus	2 (0.5)	3 (0.7)
Olaparib	0 (0.0)	3 (0.7)
Temsirolimus	1 (0.2)	1 (0.2)
Abemaciclib	1 (0.2)	0 (0.0)
Adavosertib	0 (0.0)	1 (0.2)
Afatinib	0 (0.0)	1 (0.2)
Mak 683	1 (0.2)	0 (0.0)

a: Database Cutoff Date: 26OCT2020

b: Treatment of physician's choice of doxorubicin or paclitaxel

c: A specific medication class appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding. A participant with multiple first subsequent systemic therapies within a medication class is counted a single time for that medication class

d: Every participant is counted a single time for each applicable systemic therapy

c: Number of participants: intention-to-treat population

I-O: Immuno-Oncology; PD-L1: Programmed Cell Death 1 Ligand 1; PD1: Programmed Cell Death 1; TPC: Treatment of Physician's Choice; VEGF: Vascular Endothelial Growth Factor; VEGFR: Vascular Endothelial Growth Factor Receptor

Krankheitssymptomatik und Gesundheitszustand

Rücklaufquoten des EORTC QLQ-C30

Tabelle 4G-52: Gründe für das Fehlen von Werten im EORTC QLQ-C30

Study: KEYNOTE 775[a]		**Pembrolizumab + Lenvatinib**	**TPC[b]**
Visit	**EORTC QLQ-C30**	**N[c] = 388 n (%)**	**N[c] = 364 n (%)**
BASELINE	Expected to Complete Questionnaires[d]	386 (99.5)	363 (99.7)
	Completed	370 (95.4)	351 (96.4)
	Compliance (% in those expected to complete questionnaires)[e]	370 (95.9)	351 (96.7)
	Not completed	16 (4.1)	12 (3.3)
	Subject did not complete due to disease under study	1 (0.3)	1 (0.3)
	Not completed due to site staff error	2 (0.5)	6 (1.6)
	Physically unable to complete	1 (0.3)	0 (0.0)
	Subject refused for other reasons	2 (0.5)	1 (0.3)
	Other	8 (2.1)	4 (1.1)
	With visit, no record	2 (0.5)	0 (0.0)
	Missing by Design[f]	2 (0.5)	1 (0.3)
	Translation not available in subjects language	2 (0.5)	1 (0.3)
WEEK 3	Expected to Complete Questionnaires[d]	383 (98.7)	362 (99.5)
	Completed	355 (91.5)	325 (89.3)
	Compliance (% in those expected to complete questionnaires)[e]	355 (92.7)	325 (89.8)
	Not completed	28 (7.2)	37 (10.2)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.3)
	Not completed due to site staff error	3 (0.8)	3 (0.8)
	Subject in hospital or hospice	2 (0.5)	1 (0.3)
	Subject did not complete due to side effects of treatment	0 (0.0)	2 (0.5)
	Subject refused for other reasons	2 (0.5)	1 (0.3)
	Other	6 (1.5)	7 (1.9)
	With visit, no record	15 (3.9)	22 (6.0)
	Missing by Design[f]	5 (1.3)	2 (0.5)
	Translation not available in subjects language	2 (0.5)	1 (0.3)
	Visit not scheduled	3 (0.8)	1 (0.3)
WEEK 6	Expected to Complete Questionnaires[d]	368 (94.8)	349 (95.9)
	Completed	339 (87.4)	241 (66.2)
	Compliance (% in those expected to complete questionnaires)[e]	339 (92.1)	241 (69.1)
	Not completed	29 (7.5)	108 (29.7)
	Subject did not complete due to disease under study	1 (0.3)	1 (0.3)
	Not completed due to site staff error	3 (0.8)	4 (1.1)
	Subject in hospital or hospice	1 (0.3)	0 (0.0)
	Subject refused for other reasons	2 (0.5)	5 (1.4)
	Other	4 (1.0)	7 (1.9)
	With visit, no record	18 (4.6)	91 (25.0)
	Missing by Design[f]	20 (5.2)	15 (4.1)
	Discontinued due to adverse event	2 (0.5)	0 (0.0)
	Discontinued due to clinical progression	1 (0.3)	0 (0.0)
	Discontinued due to progressive disease	1 (0.3)	0 (0.0)
	Discontinued due to withdrawal by subject	2 (0.5)	1 (0.3)
	Translation not available in subjects language	3 (0.8)	2 (0.5)
	Subject died	2 (0.5)	3 (0.8)
	Visit not scheduled	9 (2.3)	9 (2.5)
WEEK 9	Expected to Complete Questionnaires[d]	350 (90.2)	321 (88.2)
	Completed	331 (85.3)	290 (79.7)
	Compliance (% in those expected to complete questionnaires)[e]	331 (94.6)	290 (90.3)
	Not completed	19 (4.9)	31 (8.5)
	Subject did not complete due to disease under study	2 (0.5)	3 (0.8)
	Not completed due to site staff error	2 (0.5)	5 (1.4)
	Subject did not complete due to side effects of treatment	1 (0.3)	0 (0.0)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-C30	N[c] = 388 n (%)	N[c] = 364 n (%)
	Subject refused for other reasons	2 (0.5)	8 (2.2)
	Other	6 (1.5)	5 (1.4)
	With visit, no record	6 (1.5)	10 (2.7)
	Missing by Design[f]	38 (9.8)	43 (11.8)
	Discontinued due to adverse event	5 (1.3)	5 (1.4)
	Discontinued due to clinical progression	1 (0.3)	2 (0.5)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to progressive disease	2 (0.5)	10 (2.7)
	Discontinued due to withdrawal by subject	3 (0.8)	6 (1.6)
	Translation not available in subjects language	4 (1.0)	3 (0.8)
	Subject died	5 (1.3)	4 (1.1)
	Visit not scheduled	18 (4.6)	12 (3.3)
WEEK 12	Expected to Complete Questionnaires[d]	334 (86.1)	261 (71.7)
	Completed	310 (79.9)	227 (62.4)
	Compliance (% in those expected to complete questionnaires)[e]	310 (92.8)	227 (87.0)
	Not completed	24 (6.2)	34 (9.3)
	Subject did not complete due to disease under study	3 (0.8)	3 (0.8)
	Not completed due to site staff error	5 (1.3)	3 (0.8)
	Subject in hospital or hospice	2 (0.5)	0 (0.0)
	Subject did not complete due to side effects of treatment	1 (0.3)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	2 (0.5)
	Other	10 (2.6)	6 (1.6)
	With visit, no record	3 (0.8)	20 (5.5)
	Missing by Design[f]	54 (13.9)	103 (28.3)
	Discontinued due to adverse event	9 (2.3)	7 (1.9)
	Discontinued due to clinical progression	3 (0.8)	8 (2.2)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	0 (0.0)	3 (0.8)
	Discontinued due to progressive disease	10 (2.6)	61 (16.8)
	Discontinued due to withdrawal by subject	6 (1.5)	8 (2.2)
	Completed study treatment	0 (0.0)	1 (0.3)
	Translation not available in subjects language	2 (0.5)	3 (0.8)
	Subject died	2 (0.5)	1 (0.3)
	Visit not scheduled	22 (5.7)	9 (2.5)
WEEK 15	Expected to Complete Questionnaires[d]	308 (79.4)	233 (64.0)
	Completed	283 (72.9)	177 (48.6)
	Compliance (% in those expected to complete questionnaires)[e]	283 (91.9)	177 (76.0)
	Not completed	25 (6.4)	56 (15.4)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.3)
	Not completed due to site staff error	7 (1.8)	3 (0.8)
	Subject in hospital or hospice	2 (0.5)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.3)
	Subject refused for other reasons	5 (1.3)	7 (1.9)
	Other	8 (2.1)	5 (1.4)
	With visit, no record	3 (0.8)	39 (10.7)
	Missing by Design[f]	80 (20.6)	131 (36.0)
	Discontinued due to adverse event	13 (3.4)	11 (3.0)
	Discontinued due to clinical progression	4 (1.0)	13 (3.6)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	1 (0.3)	3 (0.8)
	Discontinued due to progressive disease	18 (4.6)	83 (22.8)
	Discontinued due to withdrawal by subject	8 (2.1)	8 (2.2)
	Completed study treatment	0 (0.0)	1 (0.3)
	Translation not available in subjects language	2 (0.5)	3 (0.8)
	Subject died	3 (0.8)	2 (0.5)

Study: KEYNOTE 775[a]		**Pembrolizumab + Lenvatinib**	**TPC[b]**
Visit	**EORTC QLQ-C30**	**N[c] = 388 n (%)**	**N[c] = 364 n (%)**
	Visit not scheduled	31 (8.0)	6 (1.6)
WEEK 18	Expected to Complete Questionnaires[d]	296 (76.3)	200 (54.9)
	Completed	276 (71.1)	142 (39.0)
	Compliance (% in those expected to complete questionnaires)[e]	276 (93.2)	142 (71.0)
	Not completed	20 (5.2)	58 (15.9)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	4 (1.0)	7 (1.9)
	Subject in hospital or hospice	1 (0.3)	1 (0.3)
	Physically unable to complete	1 (0.3)	0 (0.0)
	Subject did not complete due to side effects of treatment	2 (0.5)	1 (0.3)
	Subject refused for other reasons	3 (0.8)	2 (0.5)
	Other	8 (2.1)	7 (1.9)
	With visit, no record	0 (0.0)	40 (11.0)
	Missing by Design[f]	92 (23.7)	164 (45.1)
	Discontinued due to adverse event	19 (4.9)	11 (3.0)
	Discontinued due to clinical progression	4 (1.0)	15 (4.1)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	1 (0.3)	5 (1.4)
	Discontinued due to progressive disease	31 (8.0)	98 (26.9)
	Discontinued due to withdrawal by subject	9 (2.3)	12 (3.3)
	Completed study treatment	0 (0.0)	6 (1.6)
	Translation not available in subjects language	2 (0.5)	1 (0.3)
	Subject died	4 (1.0)	2 (0.5)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	20 (5.2)	12 (3.3)
WEEK 21	Expected to Complete Questionnaires[d]	285 (73.5)	172 (47.3)
	Completed	256 (66.0)	135 (37.1)
	Compliance (% in those expected to complete questionnaires)[e]	256 (89.8)	135 (78.5)
	Not completed	29 (7.5)	37 (10.2)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	5 (1.3)	4 (1.1)
	Subject in hospital or hospice	0 (0.0)	1 (0.3)
	Physically unable to complete	2 (0.5)	1 (0.3)
	Subject refused for other reasons	2 (0.5)	0 (0.0)
	Other	10 (2.6)	5 (1.4)
	With visit, no record	9 (2.3)	26 (7.1)
	Missing by Design[f]	103 (26.5)	192 (52.7)
	Discontinued due to adverse event	28 (7.2)	14 (3.8)
	Discontinued due to clinical progression	6 (1.5)	17 (4.7)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	2 (0.5)	6 (1.6)
	Discontinued due to progressive disease	38 (9.8)	115 (31.6)
	Discontinued due to withdrawal by subject	9 (2.3)	16 (4.4)
	Completed study treatment	0 (0.0)	13 (3.6)
	Translation not available in subjects language	1 (0.3)	0 (0.0)
	Subject died	0 (0.0)	1 (0.3)
	Visit not reached	1 (0.3)	0 (0.0)
	Visit not scheduled	18 (4.6)	8 (2.2)
WEEK 24	Expected to Complete Questionnaires[d]	261 (67.3)	121 (33.2)
	Completed	232 (59.8)	89 (24.5)
	Compliance (% in those expected to complete questionnaires)[e]	232 (88.9)	89 (73.6)
	Not completed	29 (7.5)	32 (8.8)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	3 (0.8)	1 (0.3)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-C30	N[c] = 388 n (%)	N[c] = 364 n (%)
	Subject in hospital or hospice	2 (0.5)	0 (0.0)
	Physically unable to complete	1 (0.3)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.3)
	Subject refused for other reasons	2 (0.5)	1 (0.3)
	Other	12 (3.1)	10 (2.7)
	With visit, no record	8 (2.1)	19 (5.2)
	Missing by Design[f]	127 (32.7)	243 (66.8)
	Discontinued due to adverse event	32 (8.2)	17 (4.7)
	Discontinued due to clinical progression	7 (1.8)	19 (5.2)
	Discontinued due to complete response	0 (0.0)	1 (0.3)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	2 (0.5)	11 (3.0)
	Discontinued due to progressive disease	49 (12.6)	131 (36.0)
	Discontinued due to withdrawal by subject	11 (2.8)	16 (4.4)
	Completed study treatment	0 (0.0)	29 (8.0)
	Translation not available in subjects language	1 (0.3)	0 (0.0)
	Subject died	2 (0.5)	2 (0.5)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	21 (5.4)	15 (4.1)
WEEK 27	Expected to Complete Questionnaires[d]	248 (63.9)	88 (24.2)
	Completed	221 (57.0)	61 (16.8)
	Compliance (% in those expected to complete questionnaires)[e]	221 (89.1)	61 (69.3)
	Not completed	27 (7.0)	27 (7.4)
	Subject did not complete due to disease under study	2 (0.5)	0 (0.0)
	Not completed due to site staff error	4 (1.0)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.3)
	Physically unable to complete	2 (0.5)	0 (0.0)
	Subject lost to follow-up/unable to contact	1 (0.3)	1 (0.3)
	Subject refused for other reasons	3 (0.8)	0 (0.0)
	Other	10 (2.6)	3 (0.8)
	With visit, no record	5 (1.3)	22 (6.0)
	Missing by Design[f]	140 (36.1)	276 (75.8)
	Discontinued due to adverse event	34 (8.8)	20 (5.5)
	Discontinued due to clinical progression	6 (1.5)	20 (5.5)
	Discontinued due to complete response	0 (0.0)	1 (0.3)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	2 (0.5)	13 (3.6)
	Discontinued due to progressive disease	65 (16.8)	139 (38.2)
	Discontinued due to withdrawal by subject	11 (2.8)	17 (4.7)
	Completed study treatment	0 (0.0)	44 (12.1)
	Translation not available in subjects language	3 (0.8)	0 (0.0)
	Subject died	2 (0.5)	3 (0.8)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	15 (3.9)	17 (4.7)
WEEK 30	Expected to Complete Questionnaires[d]	234 (60.3)	40 (11.0)
	Completed	213 (54.9)	27 (7.4)
	Compliance (% in those expected to complete questionnaires)[e]	213 (91.0)	27 (67.5)
	Not completed	21 (5.4)	13 (3.6)
	Subject did not complete due to disease under study	1 (0.3)	1 (0.3)
	Not completed due to site staff error	2 (0.5)	3 (0.8)
	Subject in hospital or hospice	1 (0.3)	0 (0.0)
	Physically unable to complete	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	11 (2.8)	4 (1.1)

Study: KEYNOTE 775[a]		**Pembrolizumab + Lenvatinib**	**TPC[b]**
Visit	**EORTC QLQ-C30**	**N[c] = 388 n (%)**	**N[c] = 364 n (%)**
	With visit, no record	4 (1.0)	5 (1.4)
	Missing by Design[f]	154 (39.7)	324 (89.0)
	Discontinued due to adverse event	39 (10.1)	24 (6.6)
	Discontinued due to clinical progression	8 (2.1)	20 (5.5)
	Discontinued due to complete response	0 (0.0)	2 (0.5)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	2 (0.5)	14 (3.8)
	Discontinued due to progressive disease	76 (19.6)	145 (39.8)
	Discontinued due to withdrawal by subject	13 (3.4)	17 (4.7)
	Completed study treatment	0 (0.0)	81 (22.3)
	Subject died	2 (0.5)	1 (0.3)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	12 (3.1)	18 (4.9)
WEEK 33	Expected to Complete Questionnaires[d]	213 (54.9)	38 (10.4)
	Completed	189 (48.7)	28 (7.7)
	Compliance (% in those expected to complete questionnaires)[e]	189 (88.7)	28 (73.7)
	Not completed	24 (6.2)	10 (2.7)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	3 (0.8)	2 (0.5)
	Subject in hospital or hospice	0 (0.0)	1 (0.3)
	Physically unable to complete	2 (0.5)	0 (0.0)
	Subject did not complete due to side effects of treatment	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	3 (0.8)
	Other	12 (3.1)	2 (0.5)
	With visit, no record	4 (1.0)	2 (0.5)
	Missing by Design[f]	175 (45.1)	326 (89.6)
	Discontinued due to adverse event	43 (11.1)	24 (6.6)
	Discontinued due to clinical progression	8 (2.1)	20 (5.5)
	Discontinued due to complete response	0 (0.0)	2 (0.5)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	3 (0.8)	14 (3.8)
	Discontinued due to progressive disease	92 (23.7)	152 (41.8)
	Discontinued due to withdrawal by subject	13 (3.4)	19 (5.2)
	Completed study treatment	0 (0.0)	86 (23.6)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	14 (3.6)	7 (1.9)
WEEK 36	Expected to Complete Questionnaires[d]	207 (53.4)	25 (6.9)
	Completed	183 (47.2)	18 (4.9)
	Compliance (% in those expected to complete questionnaires)[e]	183 (88.4)	18 (72.0)
	Not completed	24 (6.2)	7 (1.9)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	0 (0.0)	1 (0.3)
	Physically unable to complete	2 (0.5)	0 (0.0)
	Subject refused for other reasons	3 (0.8)	3 (0.8)
	Other	10 (2.6)	1 (0.3)
	With visit, no record	8 (2.1)	2 (0.5)
	Missing by Design[f]	181 (46.6)	339 (93.1)
	Discontinued due to adverse event	47 (12.1)	25 (6.9)
	Discontinued due to clinical progression	9 (2.3)	20 (5.5)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	3 (0.8)	16 (4.4)
	Discontinued due to progressive disease	97 (25.0)	155 (42.6)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-C30	N[c] = 388 n (%)	N[c] = 364 n (%)
	Discontinued due to withdrawal by subject	13 (3.4)	19 (5.2)
	Completed study treatment	0 (0.0)	89 (24.5)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	9 (2.3)	10 (2.7)
WEEK 39	Expected to Complete Questionnaires[d]	189 (48.7)	20 (5.5)
	Completed	171 (44.1)	16 (4.4)
	Compliance (% in those expected to complete questionnaires)[e]	171 (90.5)	16 (80.0)
	Not completed	18 (4.6)	4 (1.1)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	2 (0.5)	0 (0.0)
	Subject in hospital or hospice	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	2 (0.5)
	Other	9 (2.3)	2 (0.5)
	With visit, no record	4 (1.0)	0 (0.0)
	Missing by Design[f]	199 (51.3)	344 (94.5)
	Discontinued due to adverse event	49 (12.6)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	3 (0.8)	17 (4.7)
	Discontinued due to progressive disease	110 (28.4)	157 (43.1)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	91 (25.0)
	Visit not reached	4 (1.0)	1 (0.3)
	Visit not scheduled	9 (2.3)	6 (1.6)
WEEK 42	Expected to Complete Questionnaires[d]	168 (43.3)	11 (3.0)
	Completed	152 (39.2)	10 (2.7)
	Compliance (% in those expected to complete questionnaires)[e]	152 (90.5)	10 (90.9)
	Not completed	16 (4.1)	1 (0.3)
	Not completed due to site staff error	2 (0.5)	0 (0.0)
	Subject in hospital or hospice	2 (0.5)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (0.3)
	Other	9 (2.3)	0 (0.0)
	With visit, no record	3 (0.8)	0 (0.0)
	Missing by Design[f]	220 (56.7)	353 (97.0)
	Discontinued due to adverse event	49 (12.6)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	20 (5.5)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	118 (30.4)	159 (43.7)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	92 (25.3)
	Subject died	1 (0.3)	0 (0.0)
	Visit not reached	13 (3.4)	3 (0.8)
	Visit not scheduled	11 (2.8)	9 (2.5)
WEEK 45	Expected to Complete Questionnaires[d]	151 (38.9)	14 (3.8)
	Completed	132 (34.0)	14 (3.8)
	Compliance (% in those expected to complete questionnaires)[e]	132 (87.4)	14 (100.0)
	Not completed	19 (4.9)	0 (0.0)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Subject refused for other reasons	3 (0.8)	0 (0.0)
	Other	12 (3.1)	0 (0.0)
	With visit, no record	3 (0.8)	0 (0.0)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-C30	N[c] = 388 n (%)	N[c] = 364 n (%)
	Missing by Design[f]	237 (61.1)	350 (96.2)
	Discontinued due to adverse event	51 (13.1)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	3 (0.8)	18 (4.9)
	Discontinued due to progressive disease	128 (33.0)	160 (44.0)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	92 (25.3)
	Subject died	1 (0.3)	0 (0.0)
	Visit not reached	18 (4.6)	5 (1.4)
	Visit not scheduled	12 (3.1)	2 (0.5)
WEEK 48	Expected to Complete Questionnaires[d]	140 (36.1)	8 (2.2)
	Completed	123 (31.7)	7 (1.9)
	Compliance (% in those expected to complete questionnaires)[e]	123 (87.9)	7 (87.5)
	Not completed	17 (4.4)	1 (0.3)
	Not completed due to site staff error	2 (0.5)	1 (0.3)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	11 (2.8)	0 (0.0)
	With visit, no record	3 (0.8)	0 (0.0)
	Missing by Design[f]	248 (63.9)	356 (97.8)
	Discontinued due to adverse event	54 (13.9)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	131 (33.8)	162 (44.5)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	26 (6.7)	6 (1.6)
	Visit not scheduled	9 (2.3)	5 (1.4)
WEEK 51	Expected to Complete Questionnaires[d]	124 (32.0)	12 (3.3)
	Completed	105 (27.1)	10 (2.7)
	Compliance (% in those expected to complete questionnaires)[e]	105 (84.7)	10 (83.3)
	Not completed	19 (4.9)	2 (0.5)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Subject refused for other reasons	2 (0.5)	0 (0.0)
	Other	13 (3.4)	1 (0.3)
	With visit, no record	3 (0.8)	1 (0.3)
	Missing by Design[f]	264 (68.0)	352 (96.7)
	Discontinued due to adverse event	57 (14.7)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	134 (34.5)	162 (44.5)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	91 (25.0)
	Subject died	2 (0.5)	0 (0.0)
	Visit not reached	39 (10.1)	6 (1.6)
	Visit not scheduled	4 (1.0)	2 (0.5)
WEEK 54	Expected to Complete Questionnaires[d]	114 (29.4)	6 (1.6)
	Completed	100 (25.8)	5 (1.4)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-C30	N[c] = 388 n (%)	N[c] = 364 n (%)
	Compliance (% in those expected to complete questionnaires)[e]	100 (87.7)	5 (83.3)
	Not completed	14 (3.6)	1 (0.3)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	10 (2.6)	1 (0.3)
	With visit, no record	2 (0.5)	0 (0.0)
	Missing by Design[f]	274 (70.6)	358 (98.4)
	Discontinued due to adverse event	59 (15.2)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	138 (35.6)	163 (44.8)
	Discontinued due to withdrawal by subject	14 (3.6)	21 (5.8)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	45 (11.6)	7 (1.9)
	Visit not scheduled	3 (0.8)	4 (1.1)
WEEK 57	Expected to Complete Questionnaires[d]	105 (27.1)	8 (2.2)
	Completed	94 (24.2)	7 (1.9)
	Compliance (% in those expected to complete questionnaires)[e]	94 (89.5)	7 (87.5)
	Not completed	11 (2.8)	1 (0.3)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	8 (2.1)	0 (0.0)
	With visit, no record	1 (0.3)	1 (0.3)
	Missing by Design[f]	283 (72.9)	356 (97.8)
	Discontinued due to adverse event	59 (15.2)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	141 (36.3)	162 (44.5)
	Discontinued due to withdrawal by subject	14 (3.6)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	50 (12.9)	7 (1.9)
	Visit not scheduled	4 (1.0)	2 (0.5)
WEEK 60	Expected to Complete Questionnaires[d]	93 (24.0)	8 (2.2)
	Completed	83 (21.4)	8 (2.2)
	Compliance (% in those expected to complete questionnaires)[e]	83 (89.2)	8 (100.0)
	Not completed	10 (2.6)	0 (0.0)
	Other	9 (2.3)	0 (0.0)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	295 (76.0)	356 (97.8)
	Discontinued due to adverse event	59 (15.2)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	146 (37.6)	163 (44.8)
	Discontinued due to withdrawal by subject	14 (3.6)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Subject died	1 (0.3)	0 (0.0)
	Visit not reached	55 (14.2)	7 (1.9)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-C30	N[c] = 388 n (%)	N[c] = 364 n (%)
	Visit not scheduled	5 (1.3)	1 (0.3)
WEEK 63	Expected to Complete Questionnaires[d]	79 (20.4)	6 (1.6)
	Completed	69 (17.8)	4 (1.1)
	Compliance (% in those expected to complete questionnaires)[e]	69 (87.3)	4 (66.7)
	Not completed	10 (2.6)	2 (0.5)
	Not completed due to site staff error	2 (0.5)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	7 (1.8)	2 (0.5)
	Missing by Design[f]	309 (79.6)	358 (98.4)
	Discontinued due to adverse event	60 (15.5)	27 (7.4)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	151 (38.9)	163 (44.8)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	59 (15.2)	9 (2.5)
	Visit not scheduled	9 (2.3)	1 (0.3)
WEEK 66	Expected to Complete Questionnaires[d]	73 (18.8)	3 (0.8)
	Completed	60 (15.5)	2 (0.5)
	Compliance (% in those expected to complete questionnaires)[e]	60 (82.2)	2 (66.7)
	Not completed	13 (3.4)	1 (0.3)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.3)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Subject did not complete due to side effects of treatment	1 (0.3)	0 (0.0)
	Subject refused for other reasons	2 (0.5)	0 (0.0)
	Other	8 (2.1)	0 (0.0)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	315 (81.2)	361 (99.2)
	Discontinued due to adverse event	60 (15.5)	27 (7.4)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	154 (39.7)	164 (45.1)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	65 (16.8)	9 (2.5)
	Visit not scheduled	6 (1.5)	2 (0.5)
WEEK 69	Expected to Complete Questionnaires[d]	70 (18.0)	4 (1.1)
	Completed	61 (15.7)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	61 (87.1)	1 (25.0)
	Not completed	9 (2.3)	3 (0.8)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	6 (1.5)	1 (0.3)
	With visit, no record	2 (0.5)	2 (0.5)
	Missing by Design[f]	318 (82.0)	360 (98.9)
	Discontinued due to adverse event	62 (16.0)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	155 (39.9)	164 (45.1)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-C30	N[c] = 388 n (%)	N[c] = 364 n (%)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	66 (17.0)	9 (2.5)
	Visit not scheduled	3 (0.8)	1 (0.3)
WEEK 72	Expected to Complete Questionnaires[d]	64 (16.5)	3 (0.8)
	Completed	58 (14.9)	2 (0.5)
	Compliance (% in those expected to complete questionnaires)[e]	58 (90.6)	2 (66.7)
	Not completed	6 (1.5)	1 (0.3)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Other	4 (1.0)	1 (0.3)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	324 (83.5)	361 (99.2)
	Discontinued due to adverse event	63 (16.2)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	156 (40.2)	166 (45.6)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	72 (18.6)	9 (2.5)
	Visit not scheduled	2 (0.5)	0 (0.0)
WEEK 75	Expected to Complete Questionnaires[d]	52 (13.4)	1 (0.3)
	Completed	48 (12.4)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	48 (92.3)	1 (100.0)
	Not completed	4 (1.0)	0 (0.0)
	Other	3 (0.8)	0 (0.0)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	336 (86.6)	363 (99.7)
	Discontinued due to adverse event	63 (16.2)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	157 (40.5)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	77 (19.8)	9 (2.5)
	Visit not scheduled	7 (1.8)	0 (0.0)
WEEK 78	Expected to Complete Questionnaires[d]	53 (13.7)	0 (0.0)
	Completed	49 (12.6)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	49 (92.5)	0 (0.0)
	Not completed	4 (1.0)	0 (0.0)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	2 (0.5)	0 (0.0)
	Missing by Design[f]	335 (86.3)	364 (100.0)
	Discontinued due to adverse event	63 (16.2)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	159 (41.0)	168 (46.2)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-C30	N[c] = 388 n (%)	N[c] = 364 n (%)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	80 (20.6)	9 (2.5)
	Visit not scheduled	1 (0.3)	1 (0.3)
WEEK 81	Expected to Complete Questionnaires[d]	46 (11.9)	1 (0.3)
	Completed	42 (10.8)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	42 (91.3)	1 (100.0)
	Not completed	4 (1.0)	0 (0.0)
	Other	3 (0.8)	0 (0.0)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	342 (88.1)	363 (99.7)
	Discontinued due to adverse event	64 (16.5)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	160 (41.2)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	84 (21.6)	9 (2.5)
	Visit not scheduled	2 (0.5)	0 (0.0)
WEEK 84	Expected to Complete Questionnaires[d]	36 (9.3)	1 (0.3)
	Completed	31 (8.0)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	31 (86.1)	1 (100.0)
	Not completed	5 (1.3)	0 (0.0)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Subject refused for other reasons	2 (0.5)	0 (0.0)
	Other	2 (0.5)	0 (0.0)
	Missing by Design[f]	352 (90.7)	363 (99.7)
	Discontinued due to adverse event	63 (16.2)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	162 (41.8)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	94 (24.2)	9 (2.5)
	Visit not scheduled	1 (0.3)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires[d]	28 (7.2)	1 (0.3)
	Completed	26 (6.7)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	26 (92.9)	1 (100.0)
	Not completed	2 (0.5)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	1 (0.3)	0 (0.0)
	Missing by Design[f]	360 (92.8)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	163 (42.0)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-C30	N[c] = 388 n (%)	N[c] = 364 n (%)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	98 (25.3)	9 (2.5)
	Visit not scheduled	2 (0.5)	0 (0.0)
WEEK 90	Expected to Complete Questionnaires[d]	25 (6.4)	0 (0.0)
	Completed	25 (6.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	25 (100.0)	0 (0.0)
	Missing by Design[f]	363 (93.6)	364 (100.0)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	164 (42.3)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	99 (25.5)	9 (2.5)
	Visit not scheduled	3 (0.8)	1 (0.3)
WEEK 93	Expected to Complete Questionnaires[d]	23 (5.9)	1 (0.3)
	Completed	23 (5.9)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	23 (100.0)	1 (100.0)
	Missing by Design[f]	365 (94.1)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	164 (42.3)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	104 (26.8)	9 (2.5)
WEEK 96	Expected to Complete Questionnaires[d]	14 (3.6)	1 (0.3)
	Completed	14 (3.6)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	14 (100.0)	1 (100.0)
	Missing by Design[f]	374 (96.4)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	110 (28.4)	9 (2.5)
	Visit not scheduled	1 (0.3)	0 (0.0)
WEEK 99	Expected to Complete Questionnaires[d]	12 (3.1)	1 (0.3)
	Completed	11 (2.8)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	11 (91.7)	1 (100.0)
	Not completed	1 (0.3)	0 (0.0)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	376 (96.9)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-C30	N[c] = 388 n (%)	N[c] = 364 n (%)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	114 (29.4)	9 (2.5)
WEEK 102	Expected to Complete Questionnaires[d]	10 (2.6)	0 (0.0)
	Completed	10 (2.6)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	10 (100.0)	0 (0.0)
	Missing by Design[f]	378 (97.4)	364 (100.0)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	116 (29.9)	9 (2.5)
	Visit not scheduled	0 (0.0)	1 (0.3)
WEEK 105	Expected to Complete Questionnaires[d]	6 (1.5)	1 (0.3)
	Completed	6 (1.5)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	6 (100.0)	1 (100.0)
	Missing by Design[f]	382 (98.5)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	119 (30.7)	9 (2.5)
WEEK 108	Expected to Complete Questionnaires[d]	5 (1.3)	0 (0.0)
	Completed	5 (1.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	5 (100.0)	0 (0.0)
	Missing by Design[f]	383 (98.7)	364 (100.0)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	120 (30.9)	9 (2.5)
	Visit not scheduled	0 (0.0)	1 (0.3)
WEEK 111	Expected to Complete Questionnaires[d]	2 (0.5)	1 (0.3)
	Completed	1 (0.3)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	1 (50.0)	1 (100.0)

Study: KEYNOTE 775[a]		**Pembrolizumab + Lenvatinib**	**TPC[b]**
Visit	**EORTC QLQ-C30**	**N[c] = 388 n (%)**	**N[c] = 364 n (%)**
	Not completed	1 (0.3)	0 (0.0)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	386 (99.5)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	123 (31.7)	9 (2.5)
WEEK 114	Expected to Complete Questionnaires[d]	2 (0.5)	0 (0.0)
	Completed	1 (0.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	1 (50.0)	0 (0.0)
	Not completed	1 (0.3)	0 (0.0)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	386 (99.5)	364 (100.0)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	123 (31.7)	10 (2.7)

a: Database Cutoff Date: 26OCT2020

b: Treatment of physician's choice of doxorubicin or paclitaxel

c: Number of participants: full-analysis-set population

d: Expected to complete questionnaire includes all participants who do not have missing data due to a missing by design reason.

e: Compliance is the proportion of participants who completed the PRO questionnaire among these who are expected to complete at each time point, excluding those missing by design. All the other categories are defined as the proportion of participants in the analysis population (N).

f: Missing by design includes: death, disease progression, other discontinuations (reasons may include unacceptable AEs, withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment), and translation not available.

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; TPC: Treatment of Physician's Choice

Rücklaufquoten des EORTC QLQ-EN24

Tabelle 4G-53: Gründe für das Fehlen von Werten im EORTC QLQ-EN24

Study: KEYNOTE 775[a]		**Pembrolizumab + Lenvatinib**	**TPC[b]**
Visit	**EORTC QLQ-EN24**	**N[c] = 388 n (%)**	**N[c] = 364 n (%)**
BASELINE	Expected to Complete Questionnaires[d]	386 (99.5)	363 (99.7)
	Completed	309 (79.6)	301 (82.7)
	Compliance (% in those expected to complete questionnaires)[e]	309 (80.1)	301 (82.9)
	Not completed	77 (19.8)	62 (17.0)
	Subject did not complete due to disease under study	1 (0.3)	1 (0.3)
	Not completed due to site staff error	3 (0.8)	6 (1.6)
	Physically unable to complete	1 (0.3)	2 (0.5)
	Subject refused for other reasons	2 (0.5)	1 (0.3)
	Other	10 (2.6)	7 (1.9)
	With visit, no record	60 (15.5)	45 (12.4)
	Missing by Design[f]	2 (0.5)	1 (0.3)
	Translation not available in subjects language	2 (0.5)	1 (0.3)
WEEK 3	Expected to Complete Questionnaires[d]	383 (98.7)	362 (99.5)
	Completed	298 (76.8)	277 (76.1)
	Compliance (% in those expected to complete questionnaires)[e]	298 (77.8)	277 (76.5)
	Not completed	85 (21.9)	85 (23.4)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.3)
	Not completed due to site staff error	3 (0.8)	5 (1.4)
	Subject in hospital or hospice	2 (0.5)	1 (0.3)
	Subject did not complete due to side effects of treatment	0 (0.0)	2 (0.5)
	Subject refused for other reasons	2 (0.5)	1 (0.3)
	Other	7 (1.8)	11 (3.0)
	With visit, no record	71 (18.3)	64 (17.6)
	Missing by Design[f]	5 (1.3)	2 (0.5)
	Translation not available in subjects language	2 (0.5)	1 (0.3)
	Visit not scheduled	3 (0.8)	1 (0.3)
WEEK 6	Expected to Complete Questionnaires[d]	368 (94.8)	348 (95.6)
	Completed	286 (73.7)	203 (55.8)
	Compliance (% in those expected to complete questionnaires)[e]	286 (77.7)	203 (58.3)
	Not completed	82 (21.1)	145 (39.8)
	Subject did not complete due to disease under study	1 (0.3)	1 (0.3)
	Not completed due to site staff error	3 (0.8)	4 (1.1)
	Subject in hospital or hospice	1 (0.3)	0 (0.0)
	Subject refused for other reasons	2 (0.5)	4 (1.1)
	Other	5 (1.3)	13 (3.6)
	With visit, no record	70 (18.0)	123 (33.8)
	Missing by Design[f]	20 (5.2)	16 (4.4)
	Discontinued due to adverse event	2 (0.5)	0 (0.0)
	Discontinued due to clinical progression	2 (0.5)	0 (0.0)
	Discontinued due to progressive disease	1 (0.3)	1 (0.3)
	Discontinued due to withdrawal by subject	2 (0.5)	1 (0.3)
	Translation not available in subjects language	3 (0.8)	2 (0.5)
	Subject died	1 (0.3)	3 (0.8)
	Visit not scheduled	9 (2.3)	9 (2.5)
WEEK 9	Expected to Complete Questionnaires[d]	348 (89.7)	319 (87.6)
	Completed	281 (72.4)	247 (67.9)
	Compliance (% in those expected to complete questionnaires)[e]	281 (80.7)	247 (77.4)
	Not completed	67 (17.3)	72 (19.8)
	Subject did not complete due to disease under study	2 (0.5)	3 (0.8)
	Not completed due to site staff error	2 (0.5)	6 (1.6)
	Subject did not complete due to side effects of treatment	1 (0.3)	0 (0.0)
	Subject refused for other reasons	2 (0.5)	9 (2.5)
	Other	8 (2.1)	8 (2.2)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-EN24	N[c] = 388 n (%)	N[c] = 364 n (%)
	With visit, no record	52 (13.4)	46 (12.6)
	Missing by Design[f]	40 (10.3)	45 (12.4)
	Discontinued due to adverse event	5 (1.3)	6 (1.6)
	Discontinued due to clinical progression	2 (0.5)	2 (0.5)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to progressive disease	2 (0.5)	10 (2.7)
	Discontinued due to withdrawal by subject	3 (0.8)	6 (1.6)
	Translation not available in subjects language	4 (1.0)	3 (0.8)
	Subject died	4 (1.0)	3 (0.8)
	Visit not scheduled	20 (5.2)	14 (3.8)
WEEK 12	Expected to Complete Questionnaires[d]	331 (85.3)	261 (71.7)
	Completed	257 (66.2)	190 (52.2)
	Compliance (% in those expected to complete questionnaires)[e]	257 (77.6)	190 (72.8)
	Not completed	74 (19.1)	71 (19.5)
	Subject did not complete due to disease under study	2 (0.5)	2 (0.5)
	Not completed due to site staff error	5 (1.3)	3 (0.8)
	Subject in hospital or hospice	2 (0.5)	0 (0.0)
	Physically unable to complete	0 (0.0)	1 (0.3)
	Subject did not complete due to side effects of treatment	1 (0.3)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	2 (0.5)
	Other	12 (3.1)	10 (2.7)
	With visit, no record	52 (13.4)	53 (14.6)
	Missing by Design[f]	57 (14.7)	103 (28.3)
	Discontinued due to adverse event	9 (2.3)	7 (1.9)
	Discontinued due to clinical progression	3 (0.8)	8 (2.2)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	0 (0.0)	3 (0.8)
	Discontinued due to progressive disease	10 (2.6)	61 (16.8)
	Discontinued due to withdrawal by subject	6 (1.5)	8 (2.2)
	Completed study treatment	0 (0.0)	1 (0.3)
	Translation not available in subjects language	2 (0.5)	3 (0.8)
	Subject died	2 (0.5)	1 (0.3)
	Visit not scheduled	25 (6.4)	9 (2.5)
WEEK 15	Expected to Complete Questionnaires[d]	307 (79.1)	230 (63.2)
	Completed	239 (61.6)	146 (40.1)
	Compliance (% in those expected to complete questionnaires)[e]	239 (77.9)	146 (63.5)
	Not completed	68 (17.5)	84 (23.1)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.3)
	Not completed due to site staff error	8 (2.1)	4 (1.1)
	Subject in hospital or hospice	2 (0.5)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.3)
	Subject refused for other reasons	4 (1.0)	7 (1.9)
	Other	8 (2.1)	9 (2.5)
	With visit, no record	46 (11.9)	62 (17.0)
	Missing by Design[f]	81 (20.9)	134 (36.8)
	Discontinued due to adverse event	14 (3.6)	11 (3.0)
	Discontinued due to clinical progression	4 (1.0)	13 (3.6)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	1 (0.3)	3 (0.8)
	Discontinued due to progressive disease	18 (4.6)	83 (22.8)
	Discontinued due to withdrawal by subject	8 (2.1)	8 (2.2)
	Completed study treatment	0 (0.0)	1 (0.3)
	Translation not available in subjects language	1 (0.3)	3 (0.8)
	Subject died	2 (0.5)	2 (0.5)
	Visit not scheduled	33 (8.5)	9 (2.5)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-EN24	N[c] = 388 n (%)	N[c] = 364 n (%)
WEEK 18	Expected to Complete Questionnaires[d]	291 (75.0)	199 (54.7)
	Completed	228 (58.8)	121 (33.2)
	Compliance (% in those expected to complete questionnaires)[e]	228 (78.4)	121 (60.8)
	Not completed	63 (16.2)	78 (21.4)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	4 (1.0)	7 (1.9)
	Subject in hospital or hospice	1 (0.3)	1 (0.3)
	Physically unable to complete	1 (0.3)	0 (0.0)
	Subject did not complete due to side effects of treatment	2 (0.5)	1 (0.3)
	Subject refused for other reasons	3 (0.8)	3 (0.8)
	Other	9 (2.3)	10 (2.7)
	With visit, no record	42 (10.8)	56 (15.4)
	Missing by Design[f]	97 (25.0)	165 (45.3)
	Discontinued due to adverse event	19 (4.9)	11 (3.0)
	Discontinued due to clinical progression	4 (1.0)	15 (4.1)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	1 (0.3)	5 (1.4)
	Discontinued due to progressive disease	31 (8.0)	98 (26.9)
	Discontinued due to withdrawal by subject	9 (2.3)	12 (3.3)
	Completed study treatment	0 (0.0)	6 (1.6)
	Translation not available in subjects language	2 (0.5)	1 (0.3)
	Subject died	4 (1.0)	2 (0.5)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	25 (6.4)	13 (3.6)
WEEK 21	Expected to Complete Questionnaires[d]	285 (73.5)	171 (47.0)
	Completed	212 (54.6)	113 (31.0)
	Compliance (% in those expected to complete questionnaires)[e]	212 (74.4)	113 (66.1)
	Not completed	73 (18.8)	58 (15.9)
	Not completed due to site staff error	6 (1.5)	4 (1.1)
	Subject in hospital or hospice	0 (0.0)	1 (0.3)
	Physically unable to complete	2 (0.5)	1 (0.3)
	Subject refused for other reasons	2 (0.5)	0 (0.0)
	Other	11 (2.8)	6 (1.6)
	With visit, no record	52 (13.4)	46 (12.6)
	Missing by Design[f]	103 (26.5)	193 (53.0)
	Discontinued due to adverse event	28 (7.2)	14 (3.8)
	Discontinued due to clinical progression	6 (1.5)	17 (4.7)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	2 (0.5)	6 (1.6)
	Discontinued due to progressive disease	38 (9.8)	115 (31.6)
	Discontinued due to withdrawal by subject	9 (2.3)	16 (4.4)
	Completed study treatment	0 (0.0)	13 (3.6)
	Translation not available in subjects language	1 (0.3)	0 (0.0)
	Subject died	0 (0.0)	1 (0.3)
	Visit not reached	1 (0.3)	0 (0.0)
	Visit not scheduled	18 (4.6)	9 (2.5)
WEEK 24	Expected to Complete Questionnaires[d]	261 (67.3)	120 (33.0)
	Completed	190 (49.0)	76 (20.9)
	Compliance (% in those expected to complete questionnaires)[e]	190 (72.8)	76 (63.3)
	Not completed	71 (18.3)	44 (12.1)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	4 (1.0)	1 (0.3)
	Subject in hospital or hospice	2 (0.5)	0 (0.0)
	Physically unable to complete	1 (0.3)	0 (0.0)

Study: KEYNOTE 775[a]		**Pembrolizumab + Lenvatinib**	**TPC[b]**
Visit	**EORTC QLQ-EN24**	**N[c] = 388 n (%)**	**N[c] = 364 n (%)**
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.3)
	Subject refused for other reasons	2 (0.5)	1 (0.3)
	Other	13 (3.4)	9 (2.5)
	With visit, no record	48 (12.4)	32 (8.8)
	Missing by Design[f]	127 (32.7)	244 (67.0)
	Discontinued due to adverse event	32 (8.2)	17 (4.7)
	Discontinued due to clinical progression	7 (1.8)	19 (5.2)
	Discontinued due to complete response	0 (0.0)	1 (0.3)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	2 (0.5)	11 (3.0)
	Discontinued due to progressive disease	49 (12.6)	131 (36.0)
	Discontinued due to withdrawal by subject	11 (2.8)	16 (4.4)
	Completed study treatment	0 (0.0)	30 (8.2)
	Translation not available in subjects language	1 (0.3)	0 (0.0)
	Subject died	2 (0.5)	2 (0.5)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	21 (5.4)	15 (4.1)
WEEK 27	Expected to Complete Questionnaires[d]	246 (63.4)	88 (24.2)
	Completed	181 (46.6)	47 (12.9)
	Compliance (% in those expected to complete questionnaires)[e]	181 (73.6)	47 (53.4)
	Not completed	65 (16.8)	41 (11.3)
	Subject did not complete due to disease under study	2 (0.5)	0 (0.0)
	Not completed due to site staff error	4 (1.0)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.3)
	Physically unable to complete	2 (0.5)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.3)
	Subject refused for other reasons	3 (0.8)	0 (0.0)
	Other	9 (2.3)	6 (1.6)
	With visit, no record	45 (11.6)	33 (9.1)
	Missing by Design[f]	142 (36.6)	276 (75.8)
	Discontinued due to adverse event	34 (8.8)	20 (5.5)
	Discontinued due to clinical progression	7 (1.8)	20 (5.5)
	Discontinued due to complete response	0 (0.0)	1 (0.3)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	2 (0.5)	13 (3.6)
	Discontinued due to progressive disease	65 (16.8)	139 (38.2)
	Discontinued due to withdrawal by subject	11 (2.8)	17 (4.7)
	Completed study treatment	0 (0.0)	44 (12.1)
	Translation not available in subjects language	3 (0.8)	0 (0.0)
	Subject died	2 (0.5)	3 (0.8)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	16 (4.1)	17 (4.7)
WEEK 30	Expected to Complete Questionnaires[d]	232 (59.8)	40 (11.0)
	Completed	177 (45.6)	24 (6.6)
	Compliance (% in those expected to complete questionnaires)[e]	177 (76.3)	24 (60.0)
	Not completed	55 (14.2)	16 (4.4)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.3)
	Not completed due to site staff error	2 (0.5)	3 (0.8)
	Subject in hospital or hospice	1 (0.3)	0 (0.0)
	Physically unable to complete	1 (0.3)	0 (0.0)
	Other	11 (2.8)	4 (1.1)
	With visit, no record	40 (10.3)	8 (2.2)
	Missing by Design[f]	156 (40.2)	324 (89.0)
	Discontinued due to adverse event	40 (10.3)	24 (6.6)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-EN24	N[c] = 388 n (%)	N[c] = 364 n (%)
	Discontinued due to clinical progression	8 (2.1)	20 (5.5)
	Discontinued due to complete response	0 (0.0)	2 (0.5)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	2 (0.5)	14 (3.8)
	Discontinued due to progressive disease	76 (19.6)	145 (39.8)
	Discontinued due to withdrawal by subject	13 (3.4)	17 (4.7)
	Completed study treatment	0 (0.0)	81 (22.3)
	Subject died	2 (0.5)	1 (0.3)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	13 (3.4)	18 (4.9)
WEEK 33	Expected to Complete Questionnaires[d]	211 (54.4)	38 (10.4)
	Completed	154 (39.7)	25 (6.9)
	Compliance (% in those expected to complete questionnaires)[e]	154 (73.0)	25 (65.8)
	Not completed	57 (14.7)	13 (3.6)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	3 (0.8)	2 (0.5)
	Physically unable to complete	2 (0.5)	0 (0.0)
	Subject did not complete due to side effects of treatment	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	3 (0.8)
	Other	12 (3.1)	2 (0.5)
	With visit, no record	37 (9.5)	6 (1.6)
	Missing by Design[f]	177 (45.6)	326 (89.6)
	Discontinued due to adverse event	44 (11.3)	24 (6.6)
	Discontinued due to clinical progression	8 (2.1)	20 (5.5)
	Discontinued due to complete response	0 (0.0)	2 (0.5)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	3 (0.8)	14 (3.8)
	Discontinued due to progressive disease	92 (23.7)	152 (41.8)
	Discontinued due to withdrawal by subject	13 (3.4)	19 (5.2)
	Completed study treatment	0 (0.0)	86 (23.6)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	15 (3.9)	7 (1.9)
WEEK 36	Expected to Complete Questionnaires[d]	206 (53.1)	25 (6.9)
	Completed	152 (39.2)	14 (3.8)
	Compliance (% in those expected to complete questionnaires)[e]	152 (73.8)	14 (56.0)
	Not completed	54 (13.9)	11 (3.0)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	0 (0.0)	1 (0.3)
	Physically unable to complete	2 (0.5)	0 (0.0)
	Subject refused for other reasons	2 (0.5)	3 (0.8)
	Other	9 (2.3)	1 (0.3)
	With visit, no record	40 (10.3)	6 (1.6)
	Missing by Design[f]	182 (46.9)	339 (93.1)
	Discontinued due to adverse event	47 (12.1)	25 (6.9)
	Discontinued due to clinical progression	9 (2.3)	20 (5.5)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	3 (0.8)	16 (4.4)
	Discontinued due to progressive disease	97 (25.0)	155 (42.6)
	Discontinued due to withdrawal by subject	13 (3.4)	19 (5.2)
	Completed study treatment	0 (0.0)	89 (24.5)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	10 (2.6)	10 (2.7)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-EN24	N[c] = 388 n (%)	N[c] = 364 n (%)
WEEK 39	Expected to Complete Questionnaires[d]	187 (48.2)	20 (5.5)
	Completed	139 (35.8)	15 (4.1)
	Compliance (% in those expected to complete questionnaires)[e]	139 (74.3)	15 (75.0)
	Not completed	48 (12.4)	5 (1.4)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	2 (0.5)	0 (0.0)
	Subject in hospital or hospice	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	2 (0.5)
	Other	9 (2.3)	2 (0.5)
	With visit, no record	34 (8.8)	1 (0.3)
	Missing by Design[f]	201 (51.8)	344 (94.5)
	Discontinued due to adverse event	49 (12.6)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	3 (0.8)	17 (4.7)
	Discontinued due to progressive disease	110 (28.4)	157 (43.1)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	91 (25.0)
	Visit not reached	4 (1.0)	1 (0.3)
	Visit not scheduled	11 (2.8)	6 (1.6)
WEEK 42	Expected to Complete Questionnaires[d]	167 (43.0)	11 (3.0)
	Completed	121 (31.2)	7 (1.9)
	Compliance (% in those expected to complete questionnaires)[e]	121 (72.5)	7 (63.6)
	Not completed	46 (11.9)	4 (1.1)
	Not completed due to site staff error	2 (0.5)	0 (0.0)
	Subject in hospital or hospice	2 (0.5)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (0.3)
	Other	9 (2.3)	1 (0.3)
	With visit, no record	33 (8.5)	2 (0.5)
	Missing by Design[f]	221 (57.0)	353 (97.0)
	Discontinued due to adverse event	49 (12.6)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	20 (5.5)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	118 (30.4)	159 (43.7)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	92 (25.3)
	Subject died	1 (0.3)	0 (0.0)
	Visit not reached	13 (3.4)	3 (0.8)
	Visit not scheduled	12 (3.1)	9 (2.5)
WEEK 45	Expected to Complete Questionnaires[d]	151 (38.9)	14 (3.8)
	Completed	104 (26.8)	12 (3.3)
	Compliance (% in those expected to complete questionnaires)[e]	104 (68.9)	12 (85.7)
	Not completed	47 (12.1)	2 (0.5)
	Subject refused for other reasons	3 (0.8)	0 (0.0)
	Other	11 (2.8)	0 (0.0)
	With visit, no record	33 (8.5)	2 (0.5)
	Missing by Design[f]	237 (61.1)	350 (96.2)
	Discontinued due to adverse event	51 (13.1)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-EN24	N[c] = 388 n (%)	N[c] = 364 n (%)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	3 (0.8)	18 (4.9)
	Discontinued due to progressive disease	128 (33.0)	160 (44.0)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	92 (25.3)
	Subject died	1 (0.3)	0 (0.0)
	Visit not reached	18 (4.6)	5 (1.4)
	Visit not scheduled	12 (3.1)	2 (0.5)
WEEK 48	Expected to Complete Questionnaires[d]	140 (36.1)	8 (2.2)
	Completed	93 (24.0)	5 (1.4)
	Compliance (% in those expected to complete questionnaires)[e]	93 (66.4)	5 (62.5)
	Not completed	47 (12.1)	3 (0.8)
	Not completed due to site staff error	2 (0.5)	1 (0.3)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	11 (2.8)	0 (0.0)
	With visit, no record	33 (8.5)	2 (0.5)
	Missing by Design[f]	248 (63.9)	356 (97.8)
	Discontinued due to adverse event	54 (13.9)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	131 (33.8)	162 (44.5)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	26 (6.7)	6 (1.6)
	Visit not scheduled	9 (2.3)	5 (1.4)
WEEK 51	Expected to Complete Questionnaires[d]	123 (31.7)	12 (3.3)
	Completed	78 (20.1)	9 (2.5)
	Compliance (% in those expected to complete questionnaires)[e]	78 (63.4)	9 (75.0)
	Not completed	45 (11.6)	3 (0.8)
	Subject refused for other reasons	2 (0.5)	0 (0.0)
	Other	13 (3.4)	1 (0.3)
	With visit, no record	30 (7.7)	2 (0.5)
	Missing by Design[f]	265 (68.3)	352 (96.7)
	Discontinued due to adverse event	57 (14.7)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	134 (34.5)	162 (44.5)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	91 (25.0)
	Subject died	2 (0.5)	0 (0.0)
	Visit not reached	39 (10.1)	6 (1.6)
	Visit not scheduled	5 (1.3)	2 (0.5)
WEEK 54	Expected to Complete Questionnaires[d]	114 (29.4)	6 (1.6)
	Completed	73 (18.8)	4 (1.1)
	Compliance (% in those expected to complete questionnaires)[e]	73 (64.0)	4 (66.7)
	Not completed	41 (10.6)	2 (0.5)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	10 (2.6)	1 (0.3)
	With visit, no record	30 (7.7)	1 (0.3)
	Missing by Design[f]	274 (70.6)	358 (98.4)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-EN24	N[c] = 388 n (%)	N[c] = 364 n (%)
	Discontinued due to adverse event	59 (15.2)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	138 (35.6)	163 (44.8)
	Discontinued due to withdrawal by subject	14 (3.6)	21 (5.8)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	45 (11.6)	7 (1.9)
	Visit not scheduled	3 (0.8)	4 (1.1)
WEEK 57	Expected to Complete Questionnaires[d]	104 (26.8)	8 (2.2)
	Completed	69 (17.8)	5 (1.4)
	Compliance (% in those expected to complete questionnaires)[e]	69 (66.3)	5 (62.5)
	Not completed	35 (9.0)	3 (0.8)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	8 (2.1)	0 (0.0)
	With visit, no record	26 (6.7)	3 (0.8)
	Missing by Design[f]	284 (73.2)	356 (97.8)
	Discontinued due to adverse event	59 (15.2)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	141 (36.3)	162 (44.5)
	Discontinued due to withdrawal by subject	14 (3.6)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	50 (12.9)	7 (1.9)
	Visit not scheduled	5 (1.3)	2 (0.5)
WEEK 60	Expected to Complete Questionnaires[d]	92 (23.7)	8 (2.2)
	Completed	59 (15.2)	6 (1.6)
	Compliance (% in those expected to complete questionnaires)[e]	59 (64.1)	6 (75.0)
	Not completed	33 (8.5)	2 (0.5)
	Other	8 (2.1)	0 (0.0)
	With visit, no record	25 (6.4)	2 (0.5)
	Missing by Design[f]	296 (76.3)	356 (97.8)
	Discontinued due to adverse event	59 (15.2)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	146 (37.6)	163 (44.8)
	Discontinued due to withdrawal by subject	14 (3.6)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Subject died	1 (0.3)	0 (0.0)
	Visit not reached	55 (14.2)	7 (1.9)
	Visit not scheduled	6 (1.5)	1 (0.3)
WEEK 63	Expected to Complete Questionnaires[d]	78 (20.1)	6 (1.6)
	Completed	45 (11.6)	3 (0.8)
	Compliance (% in those expected to complete questionnaires)[e]	45 (57.7)	3 (50.0)
	Not completed	33 (8.5)	3 (0.8)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	6 (1.5)	2 (0.5)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-EN24	N[c] = 388 n (%)	N[c] = 364 n (%)
	With visit, no record	25 (6.4)	1 (0.3)
	Missing by Design[f]	310 (79.9)	358 (98.4)
	Discontinued due to adverse event	60 (15.5)	27 (7.4)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	152 (39.2)	163 (44.8)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	59 (15.2)	9 (2.5)
	Visit not scheduled	9 (2.3)	1 (0.3)
WEEK 66	Expected to Complete Questionnaires[d]	73 (18.8)	3 (0.8)
	Completed	36 (9.3)	2 (0.5)
	Compliance (% in those expected to complete questionnaires)[e]	36 (49.3)	2 (66.7)
	Not completed	37 (9.5)	1 (0.3)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.3)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Subject refused for other reasons	2 (0.5)	0 (0.0)
	Other	8 (2.1)	0 (0.0)
	With visit, no record	26 (6.7)	0 (0.0)
	Missing by Design[f]	315 (81.2)	361 (99.2)
	Discontinued due to adverse event	60 (15.5)	27 (7.4)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	154 (39.7)	164 (45.1)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	65 (16.8)	9 (2.5)
	Visit not scheduled	6 (1.5)	2 (0.5)
WEEK 69	Expected to Complete Questionnaires[d]	69 (17.8)	4 (1.1)
	Completed	37 (9.5)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	37 (53.6)	0 (0.0)
	Not completed	32 (8.2)	4 (1.1)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	5 (1.3)	1 (0.3)
	With visit, no record	26 (6.7)	3 (0.8)
	Missing by Design[f]	319 (82.2)	360 (98.9)
	Discontinued due to adverse event	62 (16.0)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	155 (39.9)	164 (45.1)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	66 (17.0)	9 (2.5)
	Visit not scheduled	4 (1.0)	1 (0.3)
WEEK 72	Expected to Complete Questionnaires[d]	64 (16.5)	3 (0.8)
	Completed	33 (8.5)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	33 (51.6)	1 (33.3)
	Not completed	31 (8.0)	2 (0.5)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-EN24	N[c] = 388 n (%)	N[c] = 364 n (%)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Other	5 (1.3)	1 (0.3)
	With visit, no record	25 (6.4)	1 (0.3)
	Missing by Design[f]	324 (83.5)	361 (99.2)
	Discontinued due to adverse event	63 (16.2)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	156 (40.2)	166 (45.6)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	72 (18.6)	9 (2.5)
	Visit not scheduled	2 (0.5)	0 (0.0)
WEEK 75	Expected to Complete Questionnaires[d]	52 (13.4)	1 (0.3)
	Completed	27 (7.0)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	27 (51.9)	0 (0.0)
	Not completed	25 (6.4)	1 (0.3)
	Other	2 (0.5)	0 (0.0)
	With visit, no record	23 (5.9)	1 (0.3)
	Missing by Design[f]	336 (86.6)	363 (99.7)
	Discontinued due to adverse event	63 (16.2)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	157 (40.5)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	77 (19.8)	9 (2.5)
	Visit not scheduled	7 (1.8)	0 (0.0)
WEEK 78	Expected to Complete Questionnaires[d]	51 (13.1)	0 (0.0)
	Completed	26 (6.7)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	26 (51.0)	0 (0.0)
	Not completed	25 (6.4)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	2 (0.5)	0 (0.0)
	With visit, no record	22 (5.7)	0 (0.0)
	Missing by Design[f]	337 (86.9)	364 (100.0)
	Discontinued due to adverse event	63 (16.2)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	160 (41.2)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	80 (20.6)	9 (2.5)
	Visit not scheduled	2 (0.5)	1 (0.3)
WEEK 81	Expected to Complete Questionnaires[d]	44 (11.3)	1 (0.3)
	Completed	21 (5.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	21 (47.7)	0 (0.0)
	Not completed	23 (5.9)	1 (0.3)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-EN24	N[c] = 388 n (%)	N[c] = 364 n (%)
	Other	2 (0.5)	0 (0.0)
	With visit, no record	21 (5.4)	1 (0.3)
	Missing by Design[f]	344 (88.7)	363 (99.7)
	Discontinued due to adverse event	64 (16.5)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	160 (41.2)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	84 (21.6)	9 (2.5)
	Visit not scheduled	4 (1.0)	0 (0.0)
WEEK 84	Expected to Complete Questionnaires[d]	35 (9.0)	1 (0.3)
	Completed	13 (3.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	13 (37.1)	0 (0.0)
	Not completed	22 (5.7)	1 (0.3)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	1 (0.3)	0 (0.0)
	With visit, no record	19 (4.9)	1 (0.3)
	Missing by Design[f]	353 (91.0)	363 (99.7)
	Discontinued due to adverse event	63 (16.2)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	163 (42.0)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	94 (24.2)	9 (2.5)
	Visit not scheduled	1 (0.3)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires[d]	28 (7.2)	1 (0.3)
	Completed	9 (2.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	9 (32.1)	0 (0.0)
	Not completed	19 (4.9)	1 (0.3)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	1 (0.3)	0 (0.0)
	With visit, no record	17 (4.4)	1 (0.3)
	Missing by Design[f]	360 (92.8)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	163 (42.0)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	98 (25.3)	9 (2.5)
	Visit not scheduled	2 (0.5)	0 (0.0)
WEEK 90	Expected to Complete Questionnaires[d]	25 (6.4)	0 (0.0)
	Completed	10 (2.6)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	10 (40.0)	0 (0.0)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-EN24	N[c] = 388 n (%)	N[c] = 364 n (%)
	Not completed	15 (3.9)	0 (0.0)
	With visit, no record	15 (3.9)	0 (0.0)
	Missing by Design[f]	363 (93.6)	364 (100.0)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	164 (42.3)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	99 (25.5)	9 (2.5)
	Visit not scheduled	3 (0.8)	1 (0.3)
WEEK 93	Expected to Complete Questionnaires[d]	23 (5.9)	1 (0.3)
	Completed	9 (2.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	9 (39.1)	0 (0.0)
	Not completed	14 (3.6)	1 (0.3)
	With visit, no record	14 (3.6)	1 (0.3)
	Missing by Design[f]	365 (94.1)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	164 (42.3)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	104 (26.8)	9 (2.5)
WEEK 96	Expected to Complete Questionnaires[d]	13 (3.4)	1 (0.3)
	Completed	2 (0.5)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	2 (15.4)	0 (0.0)
	Not completed	11 (2.8)	1 (0.3)
	Other	1 (0.3)	0 (0.0)
	With visit, no record	10 (2.6)	1 (0.3)
	Missing by Design[f]	375 (96.6)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	110 (28.4)	9 (2.5)
	Visit not scheduled	2 (0.5)	0 (0.0)
WEEK 99	Expected to Complete Questionnaires[d]	12 (3.1)	1 (0.3)
	Completed	2 (0.5)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	2 (16.7)	0 (0.0)
	Not completed	10 (2.6)	1 (0.3)
	With visit, no record	10 (2.6)	1 (0.3)
	Missing by Design[f]	376 (96.9)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EORTC QLQ-EN24	N[c] = 388 n (%)	N[c] = 364 n (%)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	114 (29.4)	9 (2.5)
WEEK 102	Expected to Complete Questionnaires[d]	10 (2.6)	0 (0.0)
	Completed	3 (0.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	3 (30.0)	0 (0.0)
	Not completed	7 (1.8)	0 (0.0)
	With visit, no record	7 (1.8)	0 (0.0)
	Missing by Design[f]	378 (97.4)	364 (100.0)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	116 (29.9)	9 (2.5)
	Visit not scheduled	0 (0.0)	1 (0.3)
WEEK 105	Expected to Complete Questionnaires[d]	6 (1.5)	0 (0.0)
	Completed	1 (0.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	1 (16.7)	0 (0.0)
	Not completed	5 (1.3)	0 (0.0)
	With visit, no record	5 (1.3)	0 (0.0)
	Missing by Design[f]	382 (98.5)	364 (100.0)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	119 (30.7)	9 (2.5)
	Visit not scheduled	0 (0.0)	1 (0.3)
WEEK 108	Expected to Complete Questionnaires[d]	5 (1.3)	0 (0.0)
	Completed	1 (0.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	1 (20.0)	0 (0.0)
	Not completed	4 (1.0)	0 (0.0)
	With visit, no record	4 (1.0)	0 (0.0)
	Missing by Design[f]	383 (98.7)	364 (100.0)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)

Study: KEYNOTE 775[a]		**Pembrolizumab + Lenvatinib**	**TPC[b]**
Visit	**EORTC QLQ-EN24**	**N[c] = 388 n (%)**	**N[c] = 364 n (%)**
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	120 (30.9)	9 (2.5)
	Visit not scheduled	0 (0.0)	1 (0.3)
WEEK 111	Expected to Complete Questionnaires[d]	2 (0.5)	1 (0.3)
	Not completed	2 (0.5)	1 (0.3)
	With visit, no record	2 (0.5)	1 (0.3)
	Missing by Design[f]	386 (99.5)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	123 (31.7)	9 (2.5)
WEEK 114	Expected to Complete Questionnaires[d]	2 (0.5)	0 (0.0)
	Not completed	2 (0.5)	0 (0.0)
	With visit, no record	2 (0.5)	0 (0.0)
	Missing by Design[f]	386 (99.5)	364 (100.0)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	123 (31.7)	10 (2.7)

a: Database Cutoff Date: 26OCT2020

b: Treatment of physician's choice of doxorubicin or paclitaxel

c: Number of participants: full-analysis-set population

d: Expected to complete questionnaire includes all participants who do not have missing data due to a missing by design reason.

e: Compliance is the proportion of participants who completed the PRO questionnaire among these who are expected to complete at each time point, excluding those missing by design. All the other categories are defined as the proportion of participants in the analysis population (N).

f: Missing by design includes: death, disease progression, other discontinuations (reasons may include unacceptable AEs, withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment), and translation not available.

EORTC QLQ-EN24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer 24 items; PRO: Patient Reported Outcome; TPC: Treatment of Physician's Choice

Rücklaufquoten des EQ-5D VAS

Tabelle 4G-54: Gründe für das Fehlen von Werten im EQ-5D VAS

Study: KEYNOTE 775[a]		**Pembrolizumab + Lenvatinib**	**TPC[b]**
Visit	**EQ-5D VAS**	**N[c] = 388 n (%)**	**N[c] = 364 n (%)**
BASELINE	Expected to Complete Questionnaires[d]	386 (99.5)	363 (99.7)
	Completed	375 (96.6)	356 (97.8)
	Compliance (% in those expected to complete questionnaires)[e]	375 (97.2)	356 (98.1)
	Not completed	11 (2.8)	7 (1.9)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	1 (0.3)	5 (1.4)
	Subject refused for other reasons	1 (0.3)	1 (0.3)
	Other	6 (1.5)	1 (0.3)
	With visit, no record	2 (0.5)	0 (0.0)
	Missing by Design[f]	2 (0.5)	1 (0.3)
	Translation not available in subjects language	2 (0.5)	1 (0.3)
WEEK 3	Expected to Complete Questionnaires[d]	383 (98.7)	362 (99.5)
	Completed	358 (92.3)	328 (90.1)
	Compliance (% in those expected to complete questionnaires)[e]	358 (93.5)	328 (90.6)
	Not completed	25 (6.4)	34 (9.3)
	Not completed due to site staff error	3 (0.8)	4 (1.1)
	Subject in hospital or hospice	2 (0.5)	1 (0.3)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.3)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	4 (1.0)	6 (1.6)
	With visit, no record	15 (3.9)	22 (6.0)
	Missing by Design[f]	5 (1.3)	2 (0.5)
	Translation not available in subjects language	2 (0.5)	1 (0.3)
	Visit not scheduled	3 (0.8)	1 (0.3)
WEEK 6	Expected to Complete Questionnaires[d]	368 (94.8)	349 (95.9)
	Completed	340 (87.6)	244 (67.0)
	Compliance (% in those expected to complete questionnaires)[e]	340 (92.4)	244 (69.9)
	Not completed	28 (7.2)	105 (28.8)
	Subject did not complete due to disease under study	1 (0.3)	1 (0.3)
	Not completed due to site staff error	3 (0.8)	4 (1.1)
	Subject in hospital or hospice	1 (0.3)	0 (0.0)
	Subject refused for other reasons	2 (0.5)	4 (1.1)
	Other	3 (0.8)	5 (1.4)
	With visit, no record	18 (4.6)	91 (25.0)
	Missing by Design[f]	20 (5.2)	15 (4.1)
	Discontinued due to adverse event	2 (0.5)	0 (0.0)
	Discontinued due to clinical progression	1 (0.3)	0 (0.0)
	Discontinued due to progressive disease	1 (0.3)	0 (0.0)
	Discontinued due to withdrawal by subject	2 (0.5)	1 (0.3)
	Translation not available in subjects language	3 (0.8)	2 (0.5)
	Subject died	2 (0.5)	3 (0.8)
	Visit not scheduled	9 (2.3)	9 (2.5)
WEEK 9	Expected to Complete Questionnaires[d]	350 (90.2)	321 (88.2)
	Completed	333 (85.8)	291 (79.9)
	Compliance (% in those expected to complete questionnaires)[e]	333 (95.1)	291 (90.7)
	Not completed	17 (4.4)	30 (8.2)
	Subject did not complete due to disease under study	2 (0.5)	3 (0.8)
	Not completed due to site staff error	2 (0.5)	5 (1.4)
	Subject refused for other reasons	2 (0.5)	8 (2.2)
	Other	5 (1.3)	4 (1.1)
	With visit, no record	6 (1.5)	10 (2.7)
	Missing by Design[f]	38 (9.8)	43 (11.8)
	Discontinued due to adverse event	5 (1.3)	5 (1.4)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EQ-5D VAS	N[c] = 388 n (%)	N[c] = 364 n (%)
	Discontinued due to clinical progression	1 (0.3)	2 (0.5)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to progressive disease	2 (0.5)	10 (2.7)
	Discontinued due to withdrawal by subject	3 (0.8)	6 (1.6)
	Translation not available in subjects language	4 (1.0)	3 (0.8)
	Subject died	5 (1.3)	4 (1.1)
	Visit not scheduled	18 (4.6)	12 (3.3)
WEEK 12	Expected to Complete Questionnaires[d]	334 (86.1)	261 (71.7)
	Completed	310 (79.9)	228 (62.6)
	Compliance (% in those expected to complete questionnaires)[e]	310 (92.8)	228 (87.4)
	Not completed	24 (6.2)	33 (9.1)
	Subject did not complete due to disease under study	3 (0.8)	3 (0.8)
	Not completed due to site staff error	5 (1.3)	3 (0.8)
	Subject in hospital or hospice	2 (0.5)	0 (0.0)
	Subject did not complete due to side effects of treatment	1 (0.3)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	2 (0.5)
	Other	10 (2.6)	5 (1.4)
	With visit, no record	3 (0.8)	20 (5.5)
	Missing by Design[f]	54 (13.9)	103 (28.3)
	Discontinued due to adverse event	9 (2.3)	7 (1.9)
	Discontinued due to clinical progression	3 (0.8)	8 (2.2)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	0 (0.0)	3 (0.8)
	Discontinued due to progressive disease	10 (2.6)	61 (16.8)
	Discontinued due to withdrawal by subject	6 (1.5)	8 (2.2)
	Completed study treatment	0 (0.0)	1 (0.3)
	Translation not available in subjects language	2 (0.5)	3 (0.8)
	Subject died	2 (0.5)	1 (0.3)
	Visit not scheduled	22 (5.7)	9 (2.5)
WEEK 15	Expected to Complete Questionnaires[d]	308 (79.4)	233 (64.0)
	Completed	283 (72.9)	178 (48.9)
	Compliance (% in those expected to complete questionnaires)[e]	283 (91.9)	178 (76.4)
	Not completed	25 (6.4)	55 (15.1)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.3)
	Not completed due to site staff error	7 (1.8)	3 (0.8)
	Subject in hospital or hospice	2 (0.5)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.3)
	Subject refused for other reasons	5 (1.3)	7 (1.9)
	Other	8 (2.1)	4 (1.1)
	With visit, no record	3 (0.8)	39 (10.7)
	Missing by Design[f]	80 (20.6)	131 (36.0)
	Discontinued due to adverse event	13 (3.4)	11 (3.0)
	Discontinued due to clinical progression	4 (1.0)	13 (3.6)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	1 (0.3)	3 (0.8)
	Discontinued due to progressive disease	18 (4.6)	83 (22.8)
	Discontinued due to withdrawal by subject	8 (2.1)	8 (2.2)
	Completed study treatment	0 (0.0)	1 (0.3)
	Translation not available in subjects language	2 (0.5)	3 (0.8)
	Subject died	3 (0.8)	2 (0.5)
	Visit not scheduled	31 (8.0)	6 (1.6)
WEEK 18	Expected to Complete Questionnaires[d]	296 (76.3)	200 (54.9)
	Completed	277 (71.4)	142 (39.0)
	Compliance (% in those expected to complete questionnaires)[e]	277 (93.6)	142 (71.0)
	Not completed	19 (4.9)	58 (15.9)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EQ-5D VAS	N[c] = 388 n (%)	N[c] = 364 n (%)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	3 (0.8)	7 (1.9)
	Subject in hospital or hospice	1 (0.3)	1 (0.3)
	Physically unable to complete	1 (0.3)	0 (0.0)
	Subject did not complete due to side effects of treatment	2 (0.5)	1 (0.3)
	Subject refused for other reasons	3 (0.8)	2 (0.5)
	Other	8 (2.1)	7 (1.9)
	With visit, no record	0 (0.0)	40 (11.0)
	Missing by Design[f]	92 (23.7)	164 (45.1)
	Discontinued due to adverse event	19 (4.9)	11 (3.0)
	Discontinued due to clinical progression	4 (1.0)	15 (4.1)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	1 (0.3)	5 (1.4)
	Discontinued due to progressive disease	31 (8.0)	98 (26.9)
	Discontinued due to withdrawal by subject	9 (2.3)	12 (3.3)
	Completed study treatment	0 (0.0)	6 (1.6)
	Translation not available in subjects language	2 (0.5)	1 (0.3)
	Subject died	4 (1.0)	2 (0.5)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	20 (5.2)	12 (3.3)
WEEK 21	Expected to Complete Questionnaires[d]	285 (73.5)	172 (47.3)
	Completed	256 (66.0)	136 (37.4)
	Compliance (% in those expected to complete questionnaires)[e]	256 (89.8)	136 (79.1)
	Not completed	29 (7.5)	36 (9.9)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	5 (1.3)	4 (1.1)
	Subject in hospital or hospice	0 (0.0)	1 (0.3)
	Physically unable to complete	2 (0.5)	1 (0.3)
	Subject refused for other reasons	2 (0.5)	0 (0.0)
	Other	10 (2.6)	4 (1.1)
	With visit, no record	9 (2.3)	26 (7.1)
	Missing by Design[f]	103 (26.5)	192 (52.7)
	Discontinued due to adverse event	28 (7.2)	14 (3.8)
	Discontinued due to clinical progression	6 (1.5)	17 (4.7)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	2 (0.5)	6 (1.6)
	Discontinued due to progressive disease	38 (9.8)	115 (31.6)
	Discontinued due to withdrawal by subject	9 (2.3)	16 (4.4)
	Completed study treatment	0 (0.0)	13 (3.6)
	Translation not available in subjects language	1 (0.3)	0 (0.0)
	Subject died	0 (0.0)	1 (0.3)
	Visit not reached	1 (0.3)	0 (0.0)
	Visit not scheduled	18 (4.6)	8 (2.2)
WEEK 24	Expected to Complete Questionnaires[d]	261 (67.3)	121 (33.2)
	Completed	232 (59.8)	90 (24.7)
	Compliance (% in those expected to complete questionnaires)[e]	232 (88.9)	90 (74.4)
	Not completed	29 (7.5)	31 (8.5)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	3 (0.8)	1 (0.3)
	Subject in hospital or hospice	2 (0.5)	0 (0.0)
	Physically unable to complete	1 (0.3)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.3)
	Subject refused for other reasons	2 (0.5)	1 (0.3)
	Other	12 (3.1)	9 (2.5)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EQ-5D VAS	N[c] = 388 n (%)	N[c] = 364 n (%)
	With visit, no record	8 (2.1)	19 (5.2)
	Missing by Design[f]	127 (32.7)	243 (66.8)
	Discontinued due to adverse event	32 (8.2)	17 (4.7)
	Discontinued due to clinical progression	7 (1.8)	19 (5.2)
	Discontinued due to complete response	0 (0.0)	1 (0.3)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	2 (0.5)	11 (3.0)
	Discontinued due to progressive disease	49 (12.6)	131 (36.0)
	Discontinued due to withdrawal by subject	11 (2.8)	16 (4.4)
	Completed study treatment	0 (0.0)	29 (8.0)
	Translation not available in subjects language	1 (0.3)	0 (0.0)
	Subject died	2 (0.5)	2 (0.5)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	21 (5.4)	15 (4.1)
WEEK 27	Expected to Complete Questionnaires[d]	248 (63.9)	88 (24.2)
	Completed	222 (57.2)	61 (16.8)
	Compliance (% in those expected to complete questionnaires)[e]	222 (89.5)	61 (69.3)
	Not completed	26 (6.7)	27 (7.4)
	Subject did not complete due to disease under study	2 (0.5)	0 (0.0)
	Not completed due to site staff error	4 (1.0)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.3)
	Physically unable to complete	2 (0.5)	0 (0.0)
	Subject lost to follow-up/unable to contact	1 (0.3)	1 (0.3)
	Subject refused for other reasons	2 (0.5)	0 (0.0)
	Other	10 (2.6)	3 (0.8)
	With visit, no record	5 (1.3)	22 (6.0)
	Missing by Design[f]	140 (36.1)	276 (75.8)
	Discontinued due to adverse event	34 (8.8)	20 (5.5)
	Discontinued due to clinical progression	6 (1.5)	20 (5.5)
	Discontinued due to complete response	0 (0.0)	1 (0.3)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	2 (0.5)	13 (3.6)
	Discontinued due to progressive disease	65 (16.8)	139 (38.2)
	Discontinued due to withdrawal by subject	11 (2.8)	17 (4.7)
	Completed study treatment	0 (0.0)	44 (12.1)
	Translation not available in subjects language	3 (0.8)	0 (0.0)
	Subject died	2 (0.5)	3 (0.8)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	15 (3.9)	17 (4.7)
WEEK 30	Expected to Complete Questionnaires[d]	234 (60.3)	40 (11.0)
	Completed	214 (55.2)	27 (7.4)
	Compliance (% in those expected to complete questionnaires)[e]	214 (91.5)	27 (67.5)
	Not completed	20 (5.2)	13 (3.6)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.3)
	Not completed due to site staff error	2 (0.5)	3 (0.8)
	Subject in hospital or hospice	1 (0.3)	0 (0.0)
	Physically unable to complete	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	11 (2.8)	4 (1.1)
	With visit, no record	4 (1.0)	5 (1.4)
	Missing by Design[f]	154 (39.7)	324 (89.0)
	Discontinued due to adverse event	39 (10.1)	24 (6.6)
	Discontinued due to clinical progression	8 (2.1)	20 (5.5)
	Discontinued due to complete response	0 (0.0)	2 (0.5)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EQ-5D VAS	N[c] = 388 n (%)	N[c] = 364 n (%)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	2 (0.5)	14 (3.8)
	Discontinued due to progressive disease	76 (19.6)	145 (39.8)
	Discontinued due to withdrawal by subject	13 (3.4)	17 (4.7)
	Completed study treatment	0 (0.0)	81 (22.3)
	Subject died	2 (0.5)	1 (0.3)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	12 (3.1)	18 (4.9)
WEEK 33	Expected to Complete Questionnaires[d]	213 (54.9)	38 (10.4)
	Completed	190 (49.0)	28 (7.7)
	Compliance (% in those expected to complete questionnaires)[e]	190 (89.2)	28 (73.7)
	Not completed	23 (5.9)	10 (2.7)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	2 (0.5)	2 (0.5)
	Subject in hospital or hospice	0 (0.0)	1 (0.3)
	Physically unable to complete	2 (0.5)	0 (0.0)
	Subject did not complete due to side effects of treatment	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	3 (0.8)
	Other	12 (3.1)	2 (0.5)
	With visit, no record	4 (1.0)	2 (0.5)
	Missing by Design[f]	175 (45.1)	326 (89.6)
	Discontinued due to adverse event	43 (11.1)	24 (6.6)
	Discontinued due to clinical progression	8 (2.1)	20 (5.5)
	Discontinued due to complete response	0 (0.0)	2 (0.5)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	3 (0.8)	14 (3.8)
	Discontinued due to progressive disease	92 (23.7)	152 (41.8)
	Discontinued due to withdrawal by subject	13 (3.4)	19 (5.2)
	Completed study treatment	0 (0.0)	86 (23.6)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	14 (3.6)	7 (1.9)
WEEK 36	Expected to Complete Questionnaires[d]	207 (53.4)	25 (6.9)
	Completed	184 (47.4)	18 (4.9)
	Compliance (% in those expected to complete questionnaires)[e]	184 (88.9)	18 (72.0)
	Not completed	23 (5.9)	7 (1.9)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	0 (0.0)	1 (0.3)
	Physically unable to complete	2 (0.5)	0 (0.0)
	Subject refused for other reasons	3 (0.8)	3 (0.8)
	Other	9 (2.3)	1 (0.3)
	With visit, no record	8 (2.1)	2 (0.5)
	Missing by Design[f]	181 (46.6)	339 (93.1)
	Discontinued due to adverse event	47 (12.1)	25 (6.9)
	Discontinued due to clinical progression	9 (2.3)	20 (5.5)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	3 (0.8)	16 (4.4)
	Discontinued due to progressive disease	97 (25.0)	155 (42.6)
	Discontinued due to withdrawal by subject	13 (3.4)	19 (5.2)
	Completed study treatment	0 (0.0)	89 (24.5)
	Visit not reached	2 (0.5)	0 (0.0)
	Visit not scheduled	9 (2.3)	10 (2.7)
WEEK 39	Expected to Complete Questionnaires[d]	189 (48.7)	20 (5.5)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EQ-5D VAS	N[c] = 388 n (%)	N[c] = 364 n (%)
	Completed	171 (44.1)	16 (4.4)
	Compliance (% in those expected to complete questionnaires)[e]	171 (90.5)	16 (80.0)
	Not completed	18 (4.6)	4 (1.1)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Not completed due to site staff error	2 (0.5)	0 (0.0)
	Subject in hospital or hospice	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	2 (0.5)
	Other	9 (2.3)	2 (0.5)
	With visit, no record	4 (1.0)	0 (0.0)
	Missing by Design[f]	199 (51.3)	344 (94.5)
	Discontinued due to adverse event	49 (12.6)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	1 (0.3)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	3 (0.8)	17 (4.7)
	Discontinued due to progressive disease	110 (28.4)	157 (43.1)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	91 (25.0)
	Visit not reached	4 (1.0)	1 (0.3)
	Visit not scheduled	9 (2.3)	6 (1.6)
WEEK 42	Expected to Complete Questionnaires[d]	168 (43.3)	11 (3.0)
	Completed	152 (39.2)	10 (2.7)
	Compliance (% in those expected to complete questionnaires)[e]	152 (90.5)	10 (90.9)
	Not completed	16 (4.1)	1 (0.3)
	Not completed due to site staff error	2 (0.5)	0 (0.0)
	Subject in hospital or hospice	2 (0.5)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (0.3)
	Other	9 (2.3)	0 (0.0)
	With visit, no record	3 (0.8)	0 (0.0)
	Missing by Design[f]	220 (56.7)	353 (97.0)
	Discontinued due to adverse event	49 (12.6)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	20 (5.5)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	118 (30.4)	159 (43.7)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	92 (25.3)
	Subject died	1 (0.3)	0 (0.0)
	Visit not reached	13 (3.4)	3 (0.8)
	Visit not scheduled	11 (2.8)	9 (2.5)
WEEK 45	Expected to Complete Questionnaires[d]	151 (38.9)	14 (3.8)
	Completed	132 (34.0)	14 (3.8)
	Compliance (% in those expected to complete questionnaires)[e]	132 (87.4)	14 (100.0)
	Not completed	19 (4.9)	0 (0.0)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Subject refused for other reasons	3 (0.8)	0 (0.0)
	Other	12 (3.1)	0 (0.0)
	With visit, no record	3 (0.8)	0 (0.0)
	Missing by Design[f]	237 (61.1)	350 (96.2)
	Discontinued due to adverse event	51 (13.1)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)

Study: KEYNOTE 775[a]		**Pembrolizumab + Lenvatinib**	**TPC[b]**
Visit	**EQ-5D VAS**	**N[c] = 388 n (%)**	**N[c] = 364 n (%)**
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	3 (0.8)	18 (4.9)
	Discontinued due to progressive disease	128 (33.0)	160 (44.0)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	92 (25.3)
	Subject died	1 (0.3)	0 (0.0)
	Visit not reached	18 (4.6)	5 (1.4)
	Visit not scheduled	12 (3.1)	2 (0.5)
WEEK 48	Expected to Complete Questionnaires[d]	140 (36.1)	8 (2.2)
	Completed	123 (31.7)	7 (1.9)
	Compliance (% in those expected to complete questionnaires)[e]	123 (87.9)	7 (87.5)
	Not completed	17 (4.4)	1 (0.3)
	Not completed due to site staff error	2 (0.5)	1 (0.3)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	11 (2.8)	0 (0.0)
	With visit, no record	3 (0.8)	0 (0.0)
	Missing by Design[f]	248 (63.9)	356 (97.8)
	Discontinued due to adverse event	54 (13.9)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	131 (33.8)	162 (44.5)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	26 (6.7)	6 (1.6)
	Visit not scheduled	9 (2.3)	5 (1.4)
WEEK 51	Expected to Complete Questionnaires[d]	124 (32.0)	12 (3.3)
	Completed	106 (27.3)	10 (2.7)
	Compliance (% in those expected to complete questionnaires)[e]	106 (85.5)	10 (83.3)
	Not completed	18 (4.6)	2 (0.5)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Subject refused for other reasons	2 (0.5)	0 (0.0)
	Other	12 (3.1)	1 (0.3)
	With visit, no record	3 (0.8)	1 (0.3)
	Missing by Design[f]	264 (68.0)	352 (96.7)
	Discontinued due to adverse event	57 (14.7)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	134 (34.5)	162 (44.5)
	Discontinued due to withdrawal by subject	13 (3.4)	20 (5.5)
	Completed study treatment	0 (0.0)	91 (25.0)
	Subject died	2 (0.5)	0 (0.0)
	Visit not reached	39 (10.1)	6 (1.6)
	Visit not scheduled	4 (1.0)	2 (0.5)
WEEK 54	Expected to Complete Questionnaires[d]	114 (29.4)	6 (1.6)
	Completed	100 (25.8)	5 (1.4)
	Compliance (% in those expected to complete questionnaires)[e]	100 (87.7)	5 (83.3)
	Not completed	14 (3.6)	1 (0.3)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	10 (2.6)	1 (0.3)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EQ-5D VAS	N[c] = 388 n (%)	N[c] = 364 n (%)
	With visit, no record	2 (0.5)	0 (0.0)
	Missing by Design[f]	274 (70.6)	358 (98.4)
	Discontinued due to adverse event	59 (15.2)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	138 (35.6)	163 (44.8)
	Discontinued due to withdrawal by subject	14 (3.6)	21 (5.8)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	45 (11.6)	7 (1.9)
	Visit not scheduled	3 (0.8)	4 (1.1)
WEEK 57	Expected to Complete Questionnaires[d]	105 (27.1)	8 (2.2)
	Completed	94 (24.2)	7 (1.9)
	Compliance (% in those expected to complete questionnaires)[e]	94 (89.5)	7 (87.5)
	Not completed	11 (2.8)	1 (0.3)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	8 (2.1)	0 (0.0)
	With visit, no record	1 (0.3)	1 (0.3)
	Missing by Design[f]	283 (72.9)	356 (97.8)
	Discontinued due to adverse event	59 (15.2)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	141 (36.3)	162 (44.5)
	Discontinued due to withdrawal by subject	14 (3.6)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	50 (12.9)	7 (1.9)
	Visit not scheduled	4 (1.0)	2 (0.5)
WEEK 60	Expected to Complete Questionnaires[d]	93 (24.0)	8 (2.2)
	Completed	83 (21.4)	8 (2.2)
	Compliance (% in those expected to complete questionnaires)[e]	83 (89.2)	8 (100.0)
	Not completed	10 (2.6)	0 (0.0)
	Other	9 (2.3)	0 (0.0)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	295 (76.0)	356 (97.8)
	Discontinued due to adverse event	59 (15.2)	26 (7.1)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	146 (37.6)	163 (44.8)
	Discontinued due to withdrawal by subject	14 (3.6)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Subject died	1 (0.3)	0 (0.0)
	Visit not reached	55 (14.2)	7 (1.9)
	Visit not scheduled	5 (1.3)	1 (0.3)
WEEK 63	Expected to Complete Questionnaires[d]	79 (20.4)	6 (1.6)
	Completed	70 (18.0)	4 (1.1)
	Compliance (% in those expected to complete questionnaires)[e]	70 (88.6)	4 (66.7)
	Not completed	9 (2.3)	2 (0.5)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EQ-5D VAS	N[c] = 388 n (%)	N[c] = 364 n (%)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	7 (1.8)	2 (0.5)
	Missing by Design[f]	309 (79.6)	358 (98.4)
	Discontinued due to adverse event	60 (15.5)	27 (7.4)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	151 (38.9)	163 (44.8)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	59 (15.2)	9 (2.5)
	Visit not scheduled	9 (2.3)	1 (0.3)
WEEK 66	Expected to Complete Questionnaires[d]	73 (18.8)	3 (0.8)
	Completed	60 (15.5)	2 (0.5)
	Compliance (% in those expected to complete questionnaires)[e]	60 (82.2)	2 (66.7)
	Not completed	13 (3.4)	1 (0.3)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.3)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Subject did not complete due to side effects of treatment	1 (0.3)	0 (0.0)
	Subject refused for other reasons	2 (0.5)	0 (0.0)
	Other	8 (2.1)	0 (0.0)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	315 (81.2)	361 (99.2)
	Discontinued due to adverse event	60 (15.5)	27 (7.4)
	Discontinued due to clinical progression	10 (2.6)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	154 (39.7)	164 (45.1)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	65 (16.8)	9 (2.5)
	Visit not scheduled	6 (1.5)	2 (0.5)
WEEK 69	Expected to Complete Questionnaires[d]	70 (18.0)	4 (1.1)
	Completed	61 (15.7)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	61 (87.1)	1 (25.0)
	Not completed	9 (2.3)	3 (0.8)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	5 (1.3)	1 (0.3)
	With visit, no record	2 (0.5)	2 (0.5)
	Missing by Design[f]	318 (82.0)	360 (98.9)
	Discontinued due to adverse event	62 (16.0)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	155 (39.9)	164 (45.1)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	66 (17.0)	9 (2.5)
	Visit not scheduled	3 (0.8)	1 (0.3)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EQ-5D VAS	N[c] = 388 n (%)	N[c] = 364 n (%)
WEEK 72	Expected to Complete Questionnaires[d]	64 (16.5)	3 (0.8)
	Completed	58 (14.9)	2 (0.5)
	Compliance (% in those expected to complete questionnaires)[e]	58 (90.6)	2 (66.7)
	Not completed	6 (1.5)	1 (0.3)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Other	4 (1.0)	1 (0.3)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	324 (83.5)	361 (99.2)
	Discontinued due to adverse event	63 (16.2)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	1 (0.3)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	156 (40.2)	166 (45.6)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	72 (18.6)	9 (2.5)
	Visit not scheduled	2 (0.5)	0 (0.0)
WEEK 75	Expected to Complete Questionnaires[d]	52 (13.4)	1 (0.3)
	Completed	49 (12.6)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	49 (94.2)	1 (100.0)
	Not completed	3 (0.8)	0 (0.0)
	Other	2 (0.5)	0 (0.0)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	336 (86.6)	363 (99.7)
	Discontinued due to adverse event	63 (16.2)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	157 (40.5)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	77 (19.8)	9 (2.5)
	Visit not scheduled	7 (1.8)	0 (0.0)
WEEK 78	Expected to Complete Questionnaires[d]	53 (13.7)	0 (0.0)
	Completed	49 (12.6)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	49 (92.5)	0 (0.0)
	Not completed	4 (1.0)	0 (0.0)
	Subject did not complete due to disease under study	1 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	2 (0.5)	0 (0.0)
	Missing by Design[f]	335 (86.3)	364 (100.0)
	Discontinued due to adverse event	63 (16.2)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	159 (41.0)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	80 (20.6)	9 (2.5)
	Visit not scheduled	1 (0.3)	1 (0.3)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EQ-5D VAS	N[c] = 388 n (%)	N[c] = 364 n (%)
WEEK 81	Expected to Complete Questionnaires[d]	46 (11.9)	1 (0.3)
	Completed	42 (10.8)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	42 (91.3)	1 (100.0)
	Not completed	4 (1.0)	0 (0.0)
	Other	3 (0.8)	0 (0.0)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	342 (88.1)	363 (99.7)
	Discontinued due to adverse event	64 (16.5)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	160 (41.2)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	84 (21.6)	9 (2.5)
	Visit not scheduled	2 (0.5)	0 (0.0)
WEEK 84	Expected to Complete Questionnaires[d]	36 (9.3)	1 (0.3)
	Completed	32 (8.2)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	32 (88.9)	1 (100.0)
	Not completed	4 (1.0)	0 (0.0)
	Not completed due to site staff error	1 (0.3)	0 (0.0)
	Subject refused for other reasons	2 (0.5)	0 (0.0)
	Other	1 (0.3)	0 (0.0)
	Missing by Design[f]	352 (90.7)	363 (99.7)
	Discontinued due to adverse event	63 (16.2)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	162 (41.8)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	94 (24.2)	9 (2.5)
	Visit not scheduled	1 (0.3)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires[d]	28 (7.2)	1 (0.3)
	Completed	26 (6.7)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	26 (92.9)	1 (100.0)
	Not completed	2 (0.5)	0 (0.0)
	Subject refused for other reasons	1 (0.3)	0 (0.0)
	Other	1 (0.3)	0 (0.0)
	Missing by Design[f]	360 (92.8)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	163 (42.0)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	98 (25.3)	9 (2.5)
	Visit not scheduled	2 (0.5)	0 (0.0)
WEEK 90	Expected to Complete Questionnaires[d]	25 (6.4)	0 (0.0)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EQ-5D VAS	N[c] = 388 n (%)	N[c] = 364 n (%)
	Completed	25 (6.4)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	25 (100.0)	0 (0.0)
	Missing by Design[f]	363 (93.6)	364 (100.0)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	164 (42.3)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	99 (25.5)	9 (2.5)
	Visit not scheduled	3 (0.8)	1 (0.3)
WEEK 93	Expected to Complete Questionnaires[d]	23 (5.9)	1 (0.3)
	Completed	23 (5.9)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	23 (100.0)	1 (100.0)
	Missing by Design[f]	365 (94.1)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	164 (42.3)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	104 (26.8)	9 (2.5)
WEEK 96	Expected to Complete Questionnaires[d]	14 (3.6)	1 (0.3)
	Completed	14 (3.6)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	14 (100.0)	1 (100.0)
	Missing by Design[f]	374 (96.4)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	110 (28.4)	9 (2.5)
	Visit not scheduled	1 (0.3)	0 (0.0)
WEEK 99	Expected to Complete Questionnaires[d]	12 (3.1)	1 (0.3)
	Completed	11 (2.8)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	11 (91.7)	1 (100.0)
	Not completed	1 (0.3)	0 (0.0)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	376 (96.9)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EQ-5D VAS	N[c] = 388 n (%)	N[c] = 364 n (%)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	114 (29.4)	9 (2.5)
WEEK 102	Expected to Complete Questionnaires[d]	10 (2.6)	0 (0.0)
	Completed	10 (2.6)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	10 (100.0)	0 (0.0)
	Missing by Design[f]	378 (97.4)	364 (100.0)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	15 (3.9)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	116 (29.9)	9 (2.5)
	Visit not scheduled	0 (0.0)	1 (0.3)
WEEK 105	Expected to Complete Questionnaires[d]	6 (1.5)	1 (0.3)
	Completed	6 (1.5)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	6 (100.0)	1 (100.0)
	Missing by Design[f]	382 (98.5)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	119 (30.7)	9 (2.5)
WEEK 108	Expected to Complete Questionnaires[d]	5 (1.3)	0 (0.0)
	Completed	5 (1.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	5 (100.0)	0 (0.0)
	Missing by Design[f]	383 (98.7)	364 (100.0)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	120 (30.9)	9 (2.5)
	Visit not scheduled	0 (0.0)	1 (0.3)
WEEK 111	Expected to Complete Questionnaires[d]	2 (0.5)	1 (0.3)
	Completed	1 (0.3)	1 (0.3)
	Compliance (% in those expected to complete questionnaires)[e]	1 (50.0)	1 (100.0)
	Not completed	1 (0.3)	0 (0.0)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	386 (99.5)	363 (99.7)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)

Study: KEYNOTE 775[a]		Pembrolizumab + Lenvatinib	TPC[b]
Visit	EQ-5D VAS	N[c] = 388 n (%)	N[c] = 364 n (%)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	123 (31.7)	9 (2.5)
WEEK 114	Expected to Complete Questionnaires[d]	2 (0.5)	0 (0.0)
	Completed	1 (0.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[e]	1 (50.0)	0 (0.0)
	Not completed	1 (0.3)	0 (0.0)
	With visit, no record	1 (0.3)	0 (0.0)
	Missing by Design[f]	386 (99.5)	364 (100.0)
	Discontinued due to adverse event	65 (16.8)	27 (7.4)
	Discontinued due to clinical progression	11 (2.8)	21 (5.8)
	Discontinued due to complete response	2 (0.5)	3 (0.8)
	Discontinued due to non-study anti-cancer therapy	0 (0.0)	2 (0.5)
	Discontinued due to non-compliance with study drug	0 (0.0)	1 (0.3)
	Discontinued due to physician decision	4 (1.0)	18 (4.9)
	Discontinued due to progressive disease	165 (42.5)	168 (46.2)
	Discontinued due to withdrawal by subject	16 (4.1)	22 (6.0)
	Completed study treatment	0 (0.0)	92 (25.3)
	Visit not reached	123 (31.7)	10 (2.7)

a: Database Cutoff Date: 26OCT2020

b: Treatment of physician's choice of doxorubicin or paclitaxel

c: Number of participants: full-analysis-set population

d: Expected to complete questionnaire includes all participants who do not have missing data due to a missing by design reason.

e: Compliance is the proportion of participants who completed the PRO questionnaire among these who are expected to complete at each time point, excluding those missing by design. All the other categories are defined as the proportion of participants in the analysis population (N).

f: Missing by design includes: death, disease progression, other discontinuations (reasons may include unacceptable AEs, withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment), and translation not available.

EQ-5D VAS: European Quality of Life 5 Dimensions Visual Analog Scale; PRO: Patient Reported Outcome; TPC: Treatment of Physician's Choice

Tabelle 4G-55: Ergebnisse für die Endpunkte Krankheitssymptomatik und Gesundheitszustand – Änderung der Krankheitssymptomatik (EORTC QLQ-C30, EORTC QLQ-EN24) und des Gesundheitszustands (EQ-5D VAS) über den Beobachtungszeitraum insgesamt (MMRM) – aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]					Pembrolizumab + Lenvatinib vs. TPC[b]	
	N[c]	N[d]	Mean at Baseline (SD)[e]	Mean Change from Baseline (SE)[f]	Mean Difference[f] [95 %-CI]	Standardized Mean Difference[g] [95 %-CI]
EORTC QLQ-C30 Symptom Scales						
Fatigue						
Pembrolizumab + Lenvatinib	388	370	31.11 (22.53)	9.01 (0.84)	-3.02	-0.14
TPC[b]	364	350	34.10 (25.56)	12.03 (0.95)	[-5.41; -0.63]	[-0.26; -0.03]
Nausea and Vomiting						
Pembrolizumab + Lenvatinib	388	370	8.69 (17.45)	5.49 (0.73)	-2.58	-0.14
TPC[b]	364	350	9.29 (18.38)	8.07 (0.83)	[-4.66; -0.50]	[-0.24; -0.03]
Pain						
Pembrolizumab + Lenvatinib	388	370	29.05 (27.53)	6.20 (0.95)	1.85	-
TPC[b]	364	350	29.33 (28.57)	4.35 (1.06)	[-0.84; 4.53]	-
Dyspnea						
Pembrolizumab + Lenvatinib	388	370	15.59 (22.90)	2.05 (0.83)	-5.58	-0.27
TPC[b]	364	350	16.38 (23.90)	7.62 (0.92)	[-7.91; -3.24]	[-0.39; -0.16]
Insomnia						
Pembrolizumab + Lenvatinib	388	370	24.50 (27.44)	1.53 (0.99)	-2.79	-
TPC[b]	364	350	28.38 (28.11)	4.32 (1.11)	[-5.60; 0.02]	-
Appetite Loss						
Pembrolizumab + Lenvatinib	388	370	20.45 (27.64)	12.95 (1.07)	4.44	0.16
TPC[b]	364	350	21.24 (29.69)	8.51 (1.22)	[1.37; 7.51]	[0.05; 0.27]
Constipation						
Pembrolizumab + Lenvatinib	388	370	21.35 (28.47)	-1.23 (0.95)	-3.90	-0.16
TPC[b]	364	350	23.05 (30.94)	2.67 (1.07)	[-6.60; -1.20]	[-0.27; -0.05]
Diarrhea						
Pembrolizumab + Lenvatinib	388	370	6.94 (17.09)	11.15 (0.80)	5.77	0.25
TPC[b]	364	350	7.43 (17.54)	5.38 (0.94)	[3.44; 8.10]	[0.15; 0.35]
EORTC QLQ-EN24 Symptom Scales						
Lymphoedema						
Pembrolizumab + Lenvatinib	332	308	17.42 (26.38)	2.61 (1.00)	-6.60	-0.30
TPC[b]	319	297	16.67 (24.00)	9.21 (1.10)	[-9.37; -3.82]	[-0.43; -0.17]
Urological Symptoms						
Pembrolizumab + Lenvatinib	332	308	14.94 (17.95)	-0.93 (0.69)	-3.17	-0.21
TPC[b]	319	297	16.13 (19.40)	2.24 (0.75)	[-5.07; -1.27]	[-0.34; -0.09]
Gastrointestinal symptoms						
Pembrolizumab + Lenvatinib	332	308	12.64 (14.11)	3.24 (0.58)	0.43	-
TPC[b]	319	297	14.55 (14.65)	2.81 (0.65)	[-1.19; 2.05]	-
Poor Body Image						
Pembrolizumab + Lenvatinib	332	308	22.40 (28.24)	1.51 (1.28)	-11.73	-0.46
TPC[b]	319	297	24.80 (29.39)	13.23 (1.36)	[-15.23; -8.22]	[-0.59; -0.32]
Sexual/Vaginal Problems						

Pembrolizumab + Lenvatinib	80	28	26.98 (26.61)	2.36 (4.04)	-4.79	-
TPC[b]	58	30	31.11 (28.94)	7.15 (3.80)	[-13.80; 4.22]	-
Pain in Back and Pelvis						
Pembrolizumab + Lenvatinib	332	308	29.22 (29.68)	-0.69 (1.02)	-2.21	-
TPC[b]	319	297	31.76 (31.20)	1.52 (1.15)	[-5.09; 0.67]	-
Tingling/Numbness						
Pembrolizumab + Lenvatinib	332	308	30.84 (30.63)	-3.33 (1.12)	-7.15	-0.29
TPC[b]	319	297	27.05 (29.47)	3.81 (1.23)	[-10.27; -4.03]	[-0.41; -0.16]
Muscular Pain						
Pembrolizumab + Lenvatinib	332	308	23.16 (26.59)	8.69 (1.12)	6.37	0.24
TPC[b]	319	297	21.89 (27.87)	2.32 (1.25)	[3.22; 9.52]	[0.12; 0.36]
Hair Loss						
Pembrolizumab + Lenvatinib	332	308	15.37 (32.09)	-4.44 (1.25)	-58.03	-2.11
TPC[b]	319	297	17.28 (34.67)	53.60 (1.39)	[-61.54; -54.53]	[-2.23; -1.98]
Taste Change						
Pembrolizumab + Lenvatinib	332	308	11.47 (22.95)	14.31 (1.27)	-9.59	-0.34
TPC[b]	319	297	15.60 (26.56)	23.90 (1.41)	[-13.14; -6.04]	[-0.47; -0.22]
EQ-5D VAS						
EQ-5D VAS Score						
Pembrolizumab + Lenvatinib	388	375	73.70 (18.24)	-4.99 (0.70)	2.62	0.16
TPC[b]	364	356	73.53 (18.91)	-7.61 (0.76)	[0.67; 4.57]	[0.04; 0.27]

a: Database Cutoff Date: 26OCT2020

b: Treatment of physician's choice of doxorubicin or paclitaxel

c: Number of participants: full-analysis-set population

d: Number of participants with data available for analysis

e: Mean and SD at baseline are calculated based on number of subjects with data available for analysis.

f: MMRM of change from baseline with treatment, stratification factors MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation, time and baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed.

g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero

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; EQ-5D VAS: European Quality of Life 5 Dimensions Visual Analog Scale; MMR: Mismatch Repair; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; TPC: Treatment of Physician's Choice

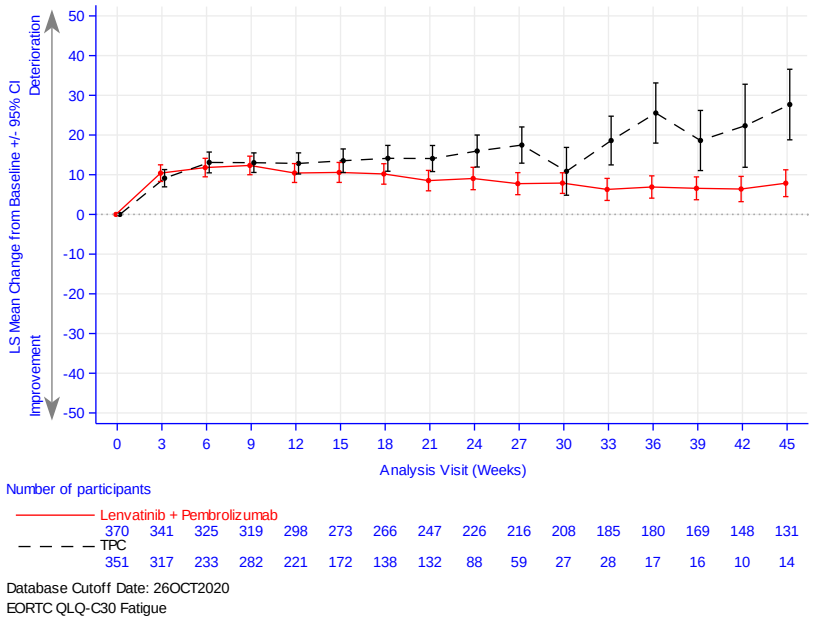

Abbildung 4G-46: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Erschöpfung zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ C30 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

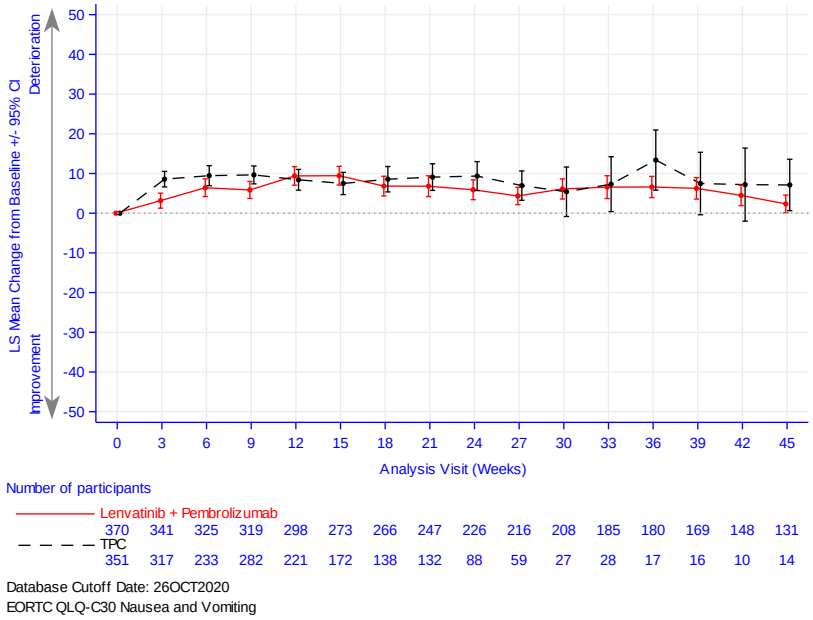

Abbildung 4G-47: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Übelkeit und Erbrechen zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ C30 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

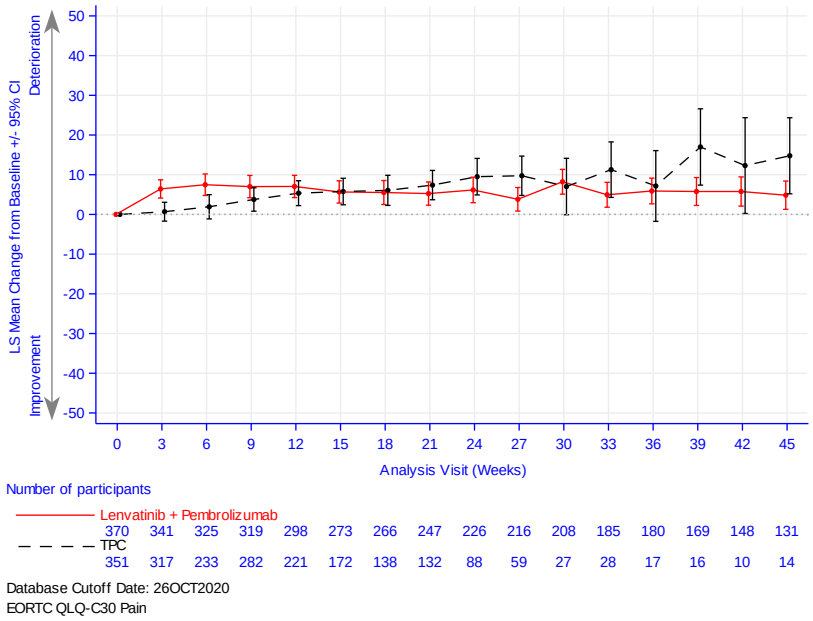

Abbildung 4G-48: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Schmerzen zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ C30 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

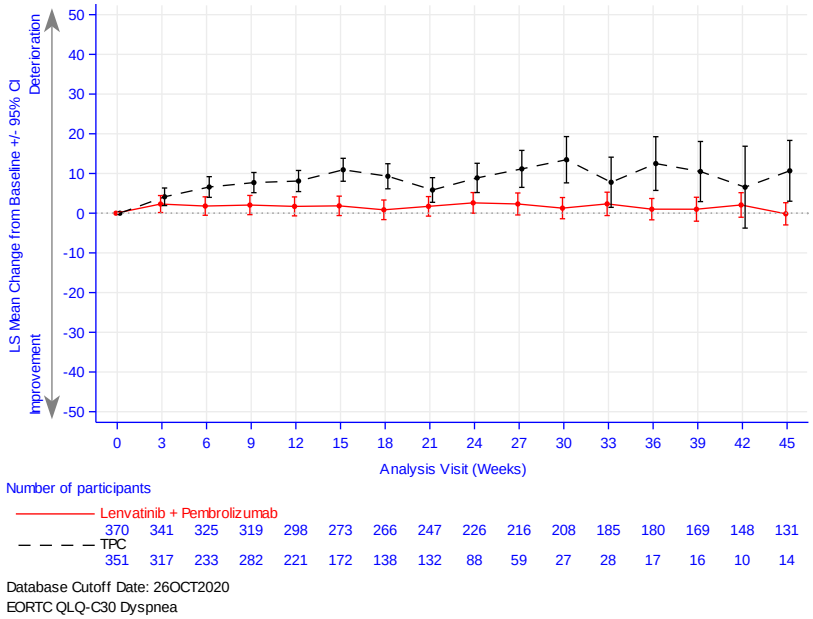

Abbildung 4G-49: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Dyspnoe zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ C30 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

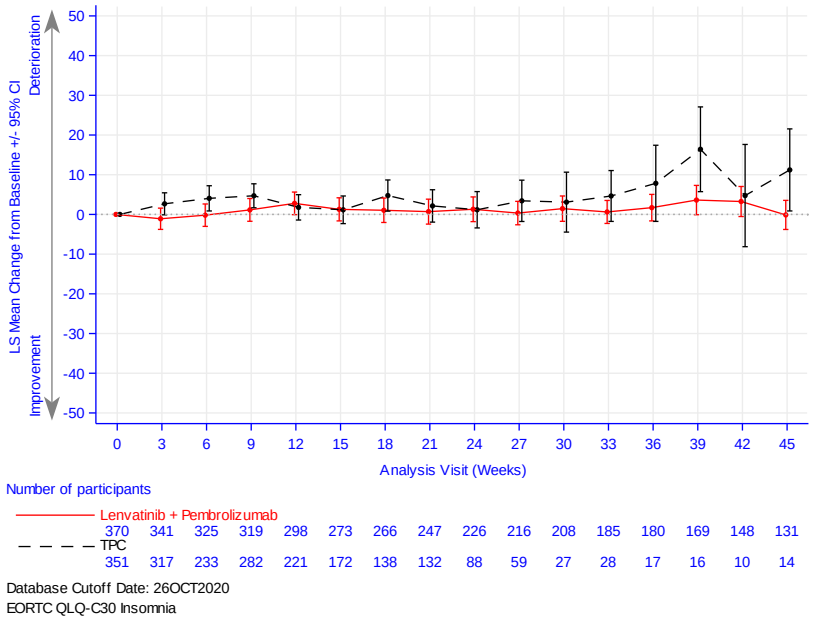

Abbildung 4G-50: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Schlaflosigkeit zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ C30 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

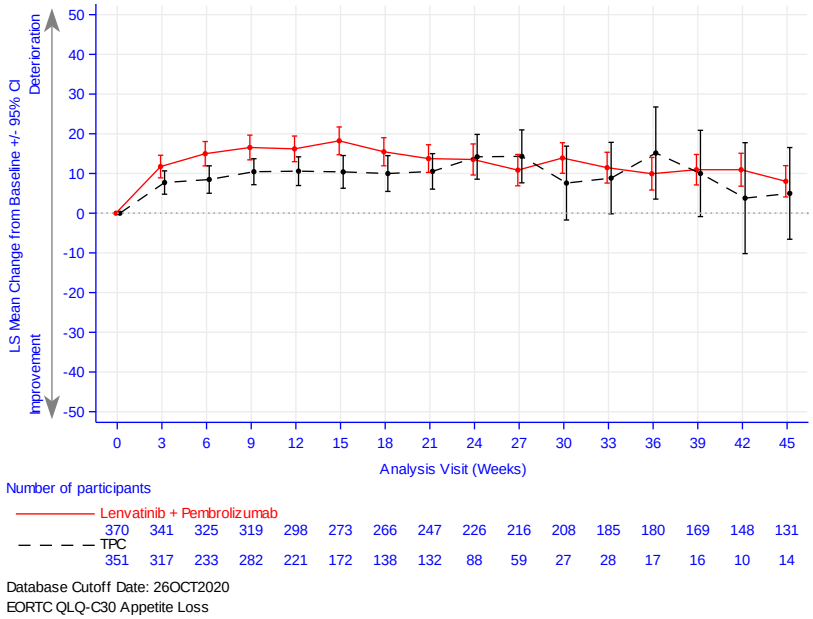

Abbildung 4G-51: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Appetitverlust zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ C30 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

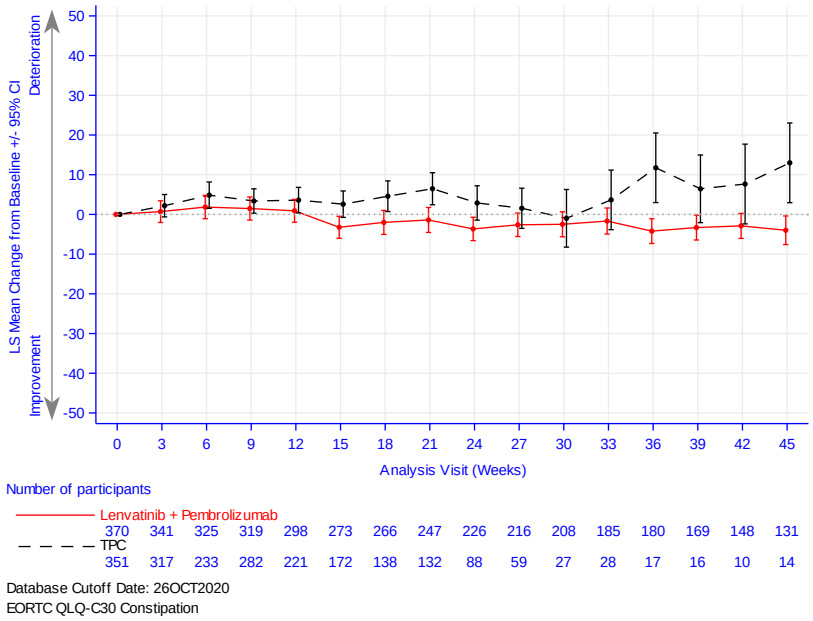

Abbildung 4G-52: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Verstopfung zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ C30 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

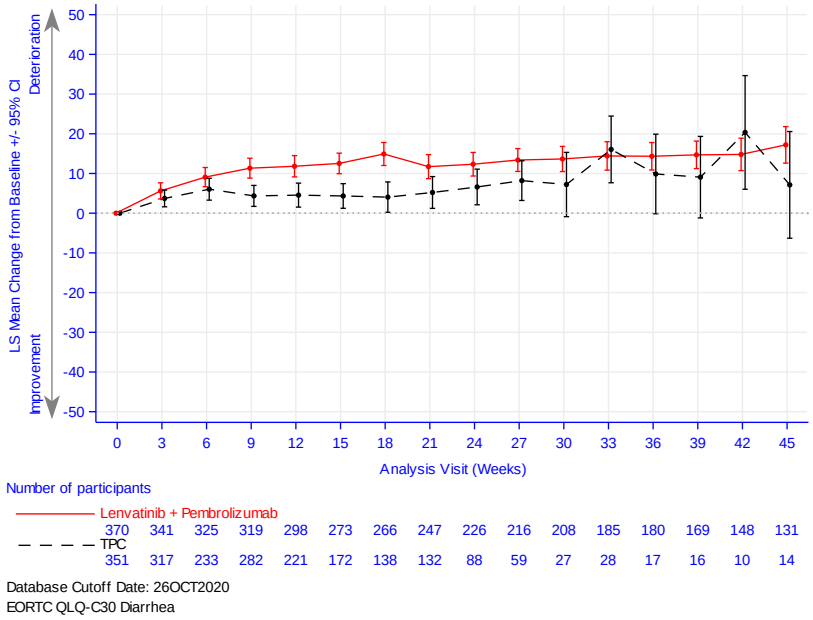

Abbildung 4G-53: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Diarrhö zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ C30 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

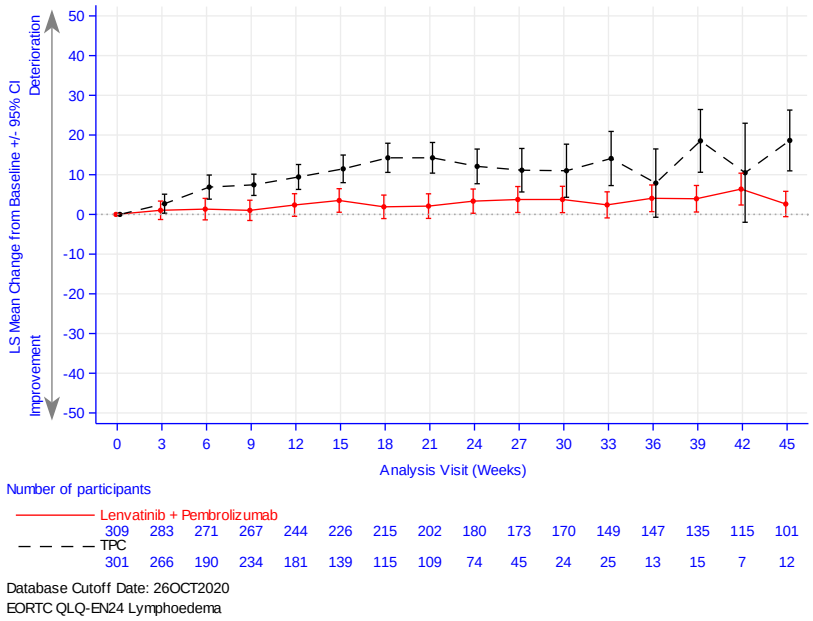

Abbildung 4G-54: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Lymphödem zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ EN24 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

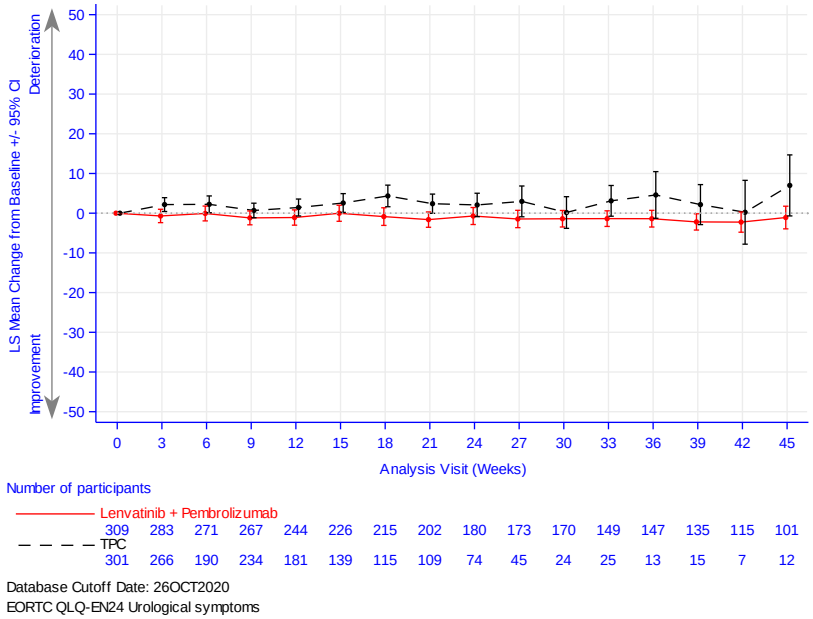

Abbildung 4G-55: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Urologische Beschwerden zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ EN24 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

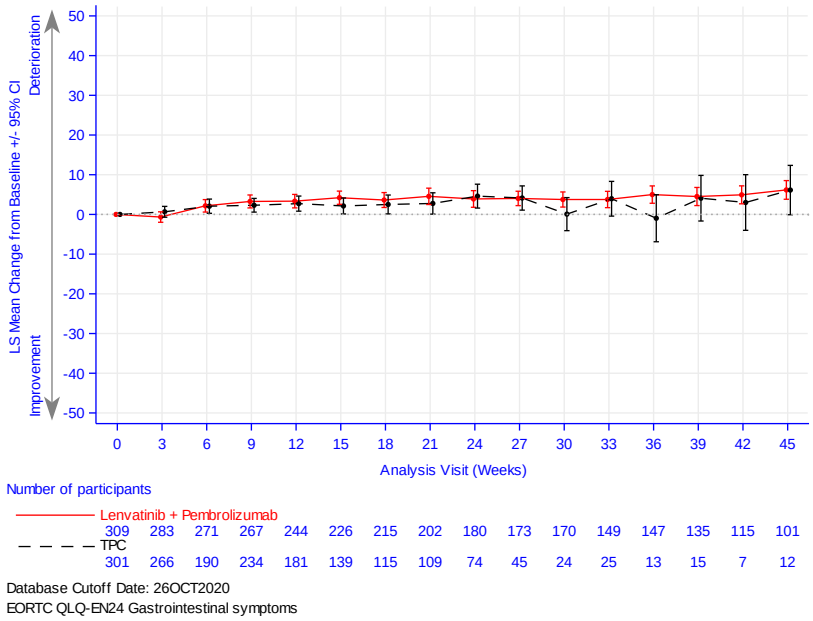

Abbildung 4G-56: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Gastrointestinale Beschwerden zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ EN24 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

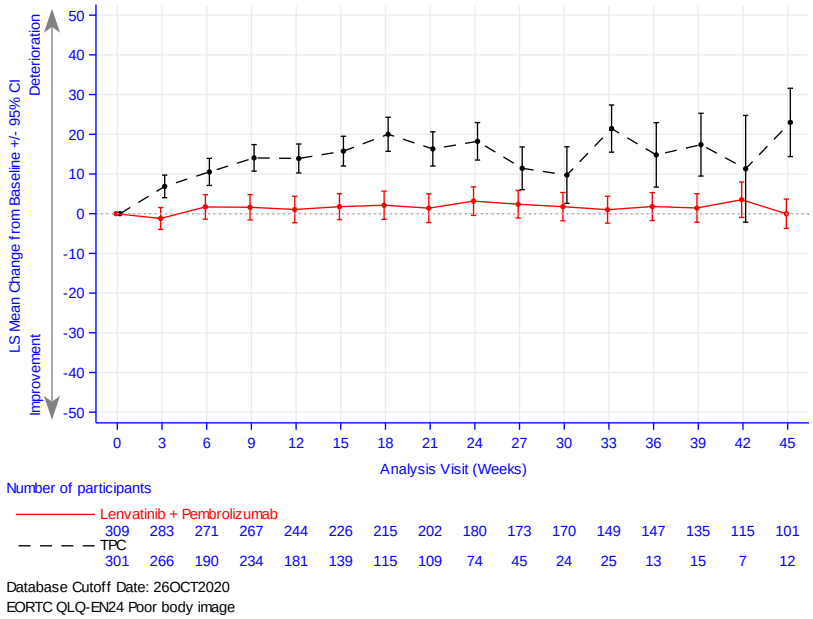

Abbildung 4G-57: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Negatives Körperbild zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ EN24 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

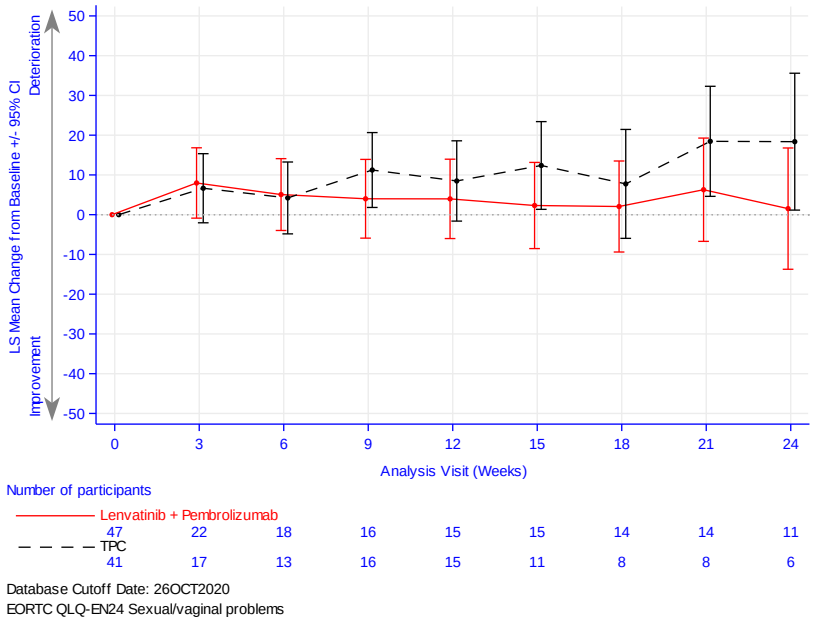

Abbildung 4G-58: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Sexuelle Probleme zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ EN24 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

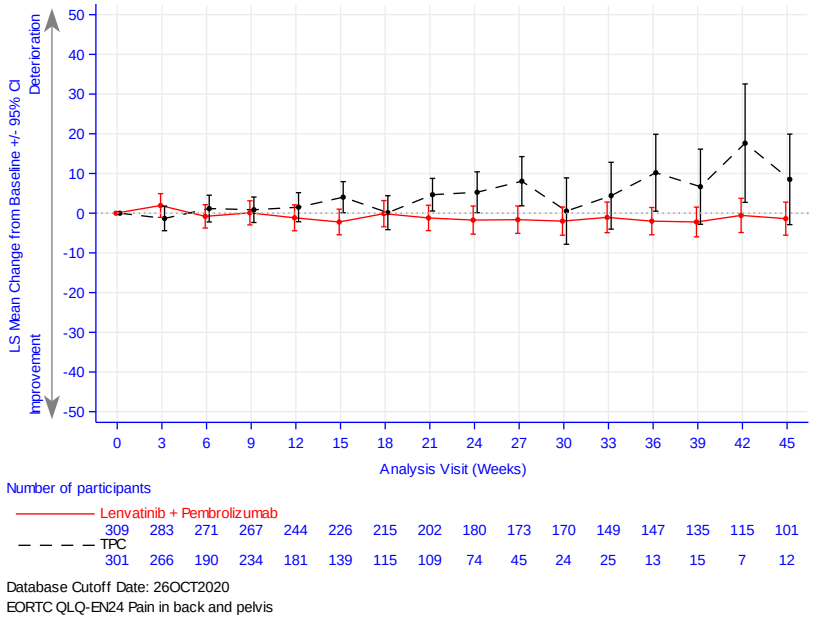

Abbildung 4G-59: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Rücken- und Beckenschmerzen zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ EN24 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

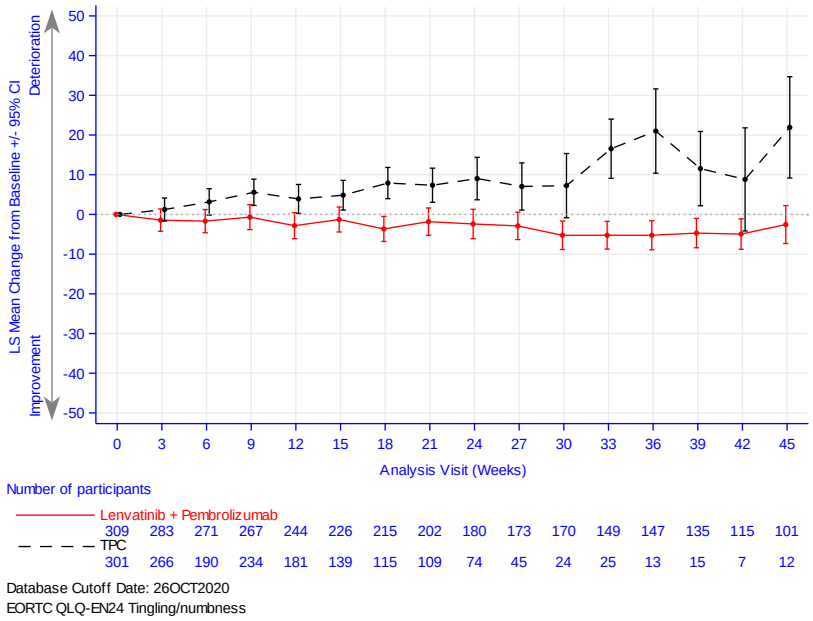

Abbildung 4G-60: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Kribbel-/Taubheitsgefühl zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ EN24 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

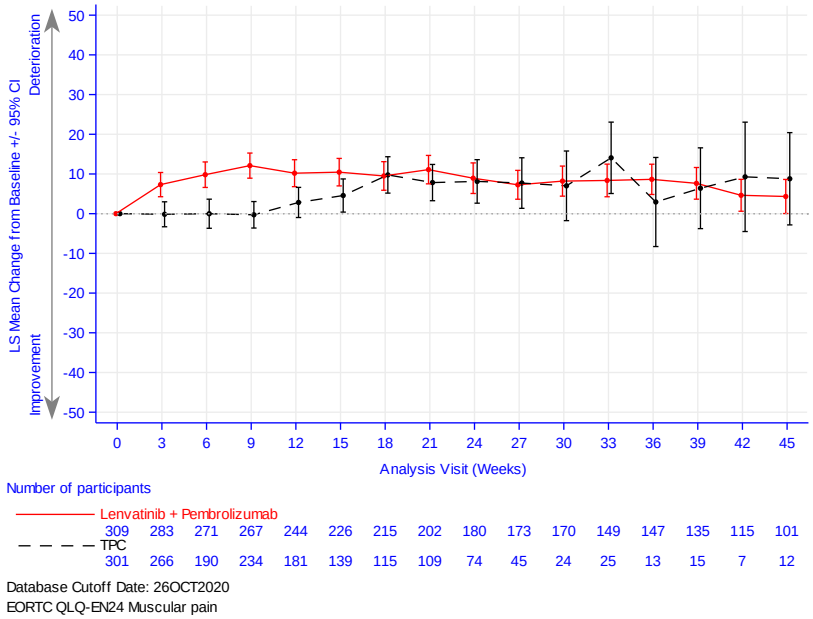

Abbildung 4G-61: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Muskulärer Schmerz zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ EN24 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

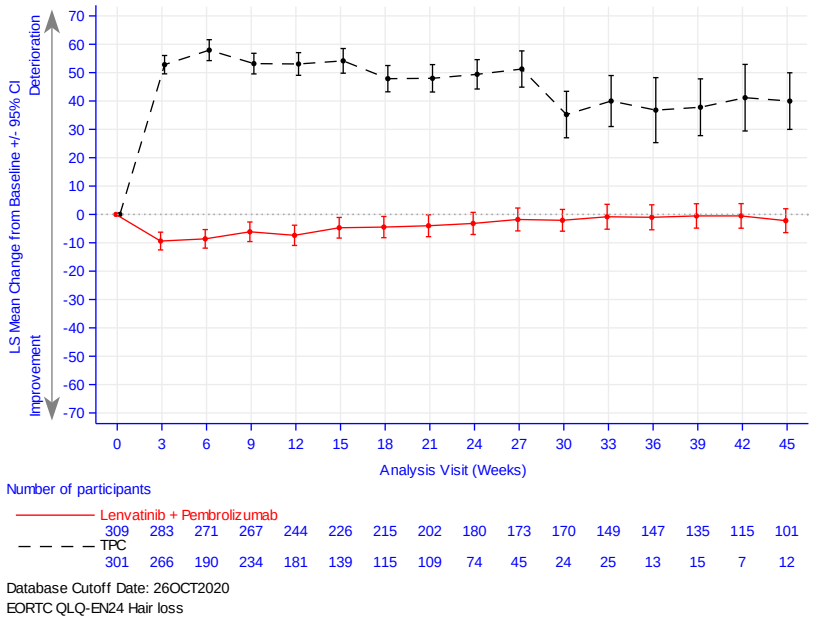

Abbildung 4G-62: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Haarausfall zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ EN24 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

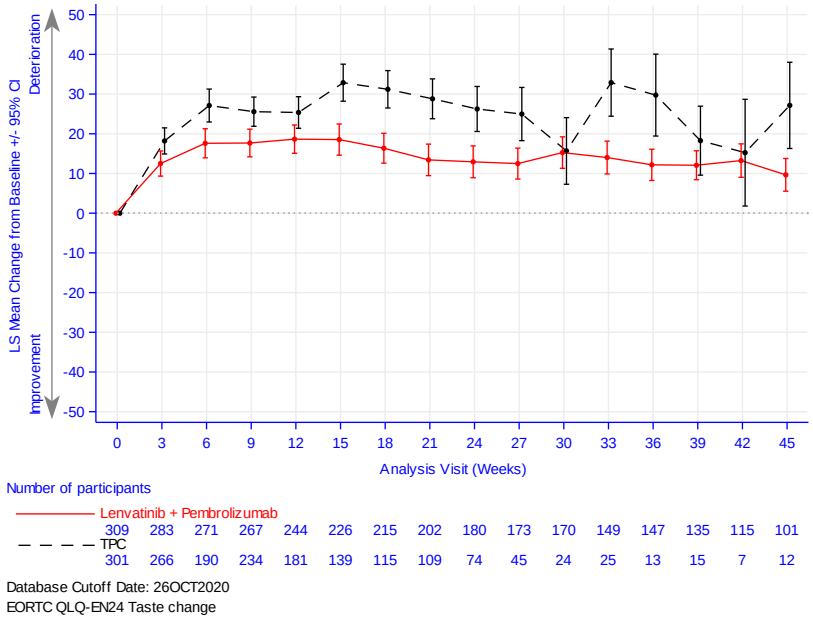

Abbildung 4G-63: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Symptomskala Geschmacksveränderung zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ EN24 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

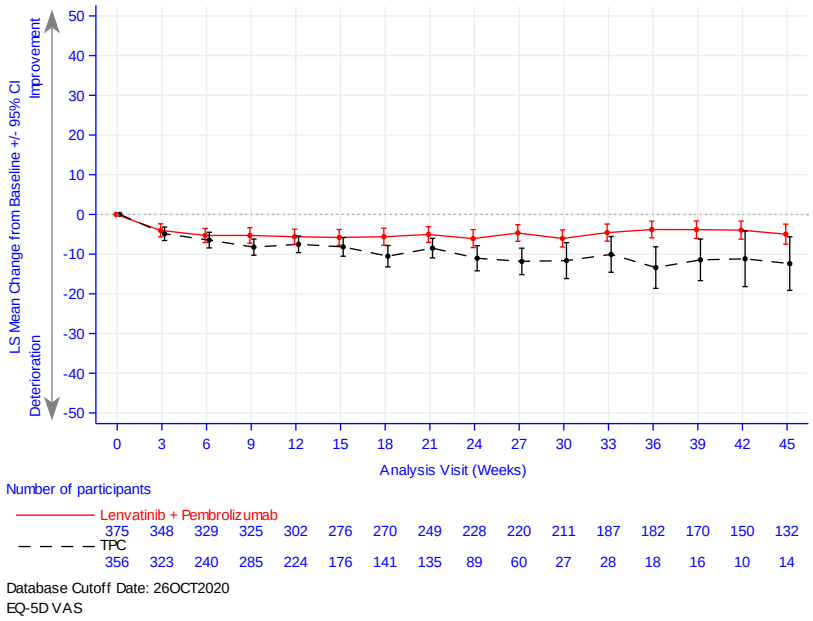

Abbildung 4G-64: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI des Gesundheitszustands zu den verschiedenen Erhebungszeitpunkten des EQ-5D VAS aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

Ergänzende Morbiditätsendpunkte

Progressionsfreies Überleben

Tabelle 4G-56: Ergebnisse für den Endpunkt Progressionsfreies Überleben aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib			TPC[b]			Pembrolizumab + Lenvatinib vs. TPC[b]	
	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]
Progression-Free Survival (BICR Primary Censoring Rule)	411	281 (68.4)	7.2 [5.7; 7.6]	416	286 (68.8)	3.8 [3.6; 4.2]	0.56 [0.47; 0.66]	< 0.001

a: Database Cutoff Date: 26OCT2020
b: Treatment of physician's choice of doxorubicin or paclitaxel
c: Number of participants: intention-to-treat population
d: From product-limit (Kaplan-Meier) method for censored data
e: 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
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
BICR: Blinded Independent Central Review; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; MMR: Mismatch Repair; TPC: Treatment of Physician's Choice

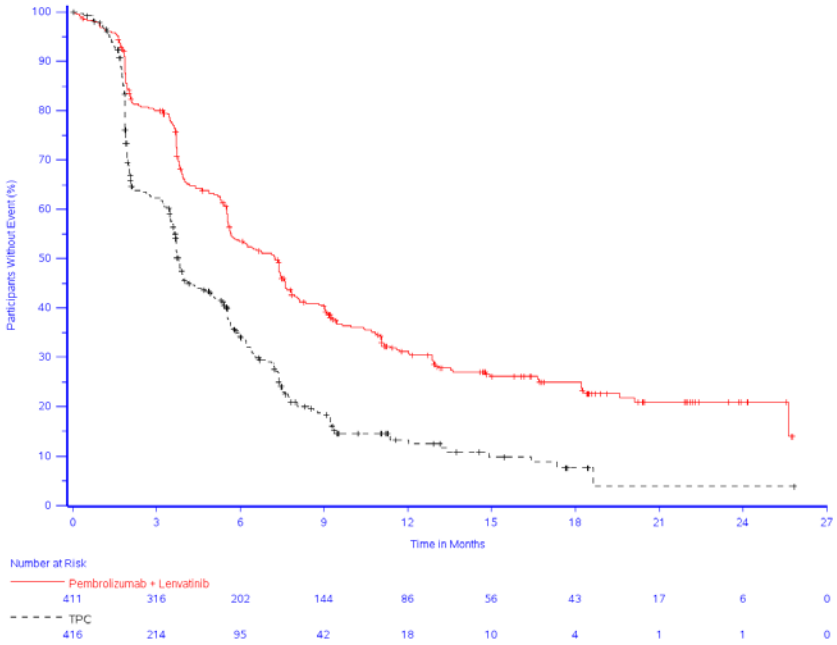

Abbildung 4G-65: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Progressionsfreies Überleben der Studie KEYNOTE 775

Objektive Ansprechrate

Tabelle 4G-57: Ergebnisse für den Endpunkt Progressionsfreies Überleben aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib		TPC[b]		Pembrolizumab + Lenvatinib vs. TPC[b]		
	N[c]	Participants with Event n (%)	N[c]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	Adjusted Difference[f] [95 %-CI]
Objective Response[g]	411	131 (31.9)	416	61 (14.7)	2.17 [1.66; 2.85]	< 0.001	17.21 [11.53; 22.87]

a: Database Cutoff Date: 26OCT2020

b: Treatment of physician's choice of doxorubicin or paclitaxel

c: Number of participants: intention-to-treat population

d: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is ≤ 1 % or ≥ 99 % in at least one cell, stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

e: Two-sided p-value based on Wald test

f: Miettinen and Nurminen method stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

g: Responses are based on BICR assessments per RECIST 1.1 with confirmation

BICR: Blinded Independent Central Review; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; MMR: Mismatch Repair; RECIST: Response Evaluation Criteria in Solid Tumors; TPC: Treatment of Physician's Choice

Anhang 4-G5.3: Gesundheitsbezogene Lebensqualität

Gesundheitsbezogene Lebensqualität

Tabelle 4G-58: Ergebnisse für den Endpunkt Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30, EORTC QLQ-EN24) über den Beobachtungszeitraum insgesamt (MMRM) – aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	N[c]	N[d]	Mean at Baseline (SD)[e]	Mean Change from Baseline (SE)[f]	Pembrolizumab + Lenvatinib vs. TPC[b]	
					Mean Difference[f] [95 %-CI]	Standardized Mean Difference[g] [95 %-CI]
EORTC QLQ-C30 Global Health Status/QoL						
Global Health Status/QoL						
Pembrolizumab + Lenvatinib	388	370	65.74 (21.87)	-6.58 (0.76)	1.45	-
TPC[b]	364	350	65.64 (22.72)	-8.03 (0.85)	[-0.69; 3.60]	-
EORTC QLQ-C30 Functional Scales						
Physical Functioning						
Pembrolizumab + Lenvatinib	388	370	78.68 (20.08)	-9.51 (0.76)	-0.27	-
TPC[b]	364	350	75.94 (20.90)	-9.24 (0.84)	[-2.41; 1.86]	-
Role Functioning						
Pembrolizumab + Lenvatinib	388	370	78.38 (25.46)	-11.67 (0.99)	0.24	-
TPC[b]	364	350	75.62 (27.83)	-11.92 (1.09)	[-2.53; 3.02]	-
Emotional Functioning						
Pembrolizumab + Lenvatinib	388	370	75.83 (19.85)	1.34 (0.76)	3.51	0.19
TPC[b]	364	350	73.48 (21.68)	-2.17 (0.83)	[1.38; 5.64]	[0.08; 0.31]
Cognitive Functioning						
Pembrolizumab + Lenvatinib	388	370	84.28 (19.59)	-3.56 (0.76)	1.68	-
TPC[b]	364	350	83.76 (18.43)	-5.23 (0.82)	[-0.44; 3.79]	-
Social Functioning						
Pembrolizumab + Lenvatinib	388	370	79.59 (23.80)	-6.99 (1.00)	3.27	0.14
TPC[b]	364	350	78.57 (25.10)	-10.26 (1.09)	[0.48; 6.05]	[0.02; 0.26]
EORTC QLQ-EN24 Functional Scales						
Sexual Interest						
Pembrolizumab + Lenvatinib	331	306	8.28 (17.61)	-3.45 (0.54)	0.79	-
TPC[b]	315	290	8.28 (17.11)	-4.24 (0.60)	[-0.72; 2.29]	-
Sexual Activity						
Pembrolizumab + Lenvatinib	331	302	7.40 (15.86)	-3.63 (0.45)	0.11	-
TPC[b]	315	289	5.88 (14.16)	-3.73 (0.50)	[-1.16; 1.37]	-
Sexual Enjoyment						
Pembrolizumab + Lenvatinib	80	29	47.13 (30.23)	-9.32 (3.83)	-3.45	-
TPC[b]	57	30	43.33 (29.23)	-5.87 (3.72)	[-11.66; 4.75]	-

a: Database Cutoff Date: 26OCT2020

b: Treatment of physician's choice of doxorubicin or paclitaxel

c: Number of participants: full-analysis-set population

d: Number of participants with data available for analysis

e: Mean and SD at baseline are calculated based on number of subjects with data available for analysis.

f: MMRM of change from baseline with treatment, stratification factors MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation, time and baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed.

g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero

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; MMR: Mismatch Repair; MMRM: Mixed-effect Model Repeated Measures; QoL: Quality of Life; SD: Standard Deviation; SE: Standard Error; TPC: Treatment of Physician's Choice

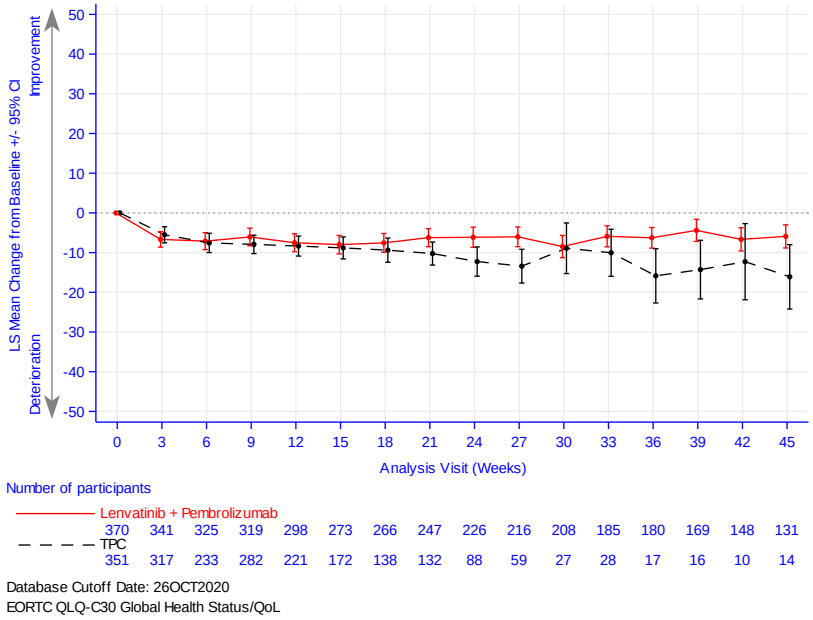

Abbildung 4G-66: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI für den Globalen Gesundheitsstatus zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ C30 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

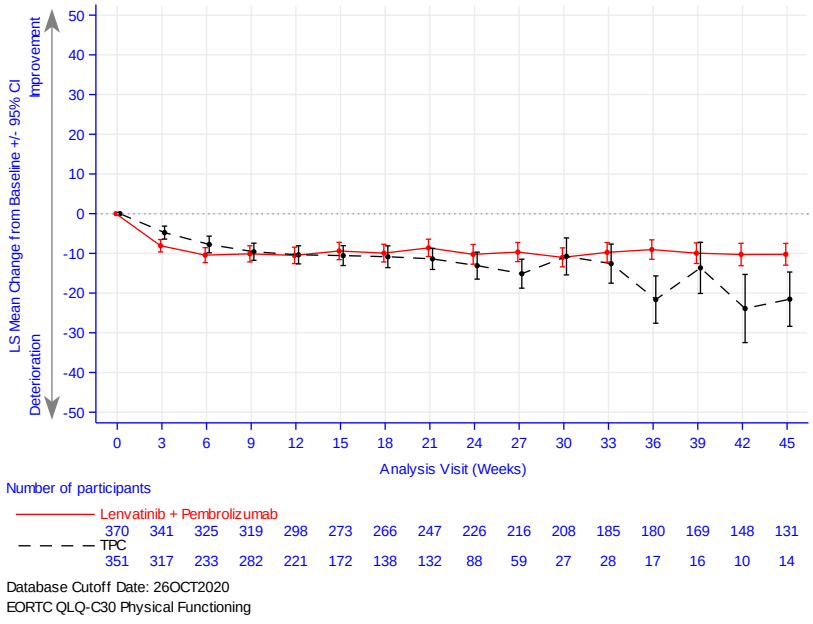

Abbildung 4G-67: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Funktionsskala Körperliche Funktion zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ C30 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

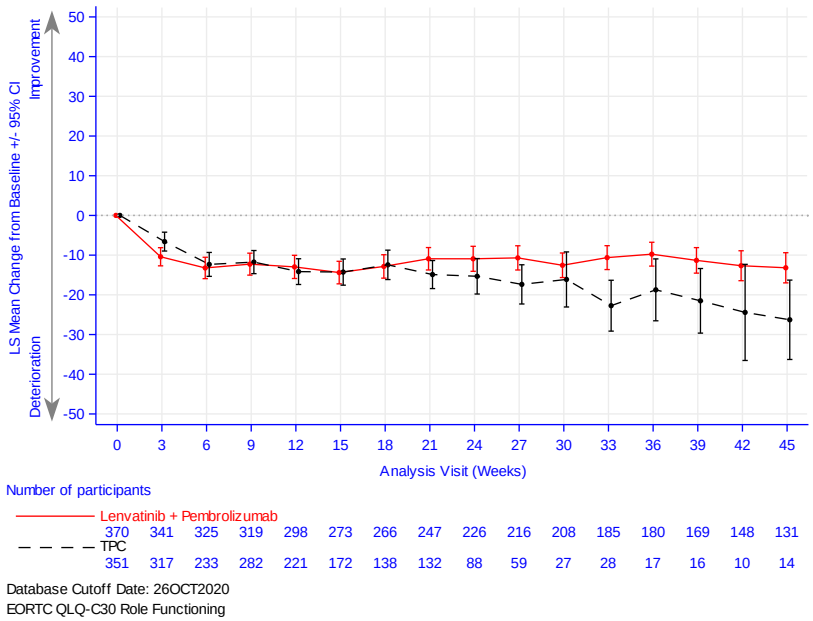

Abbildung 4G-68: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Funktionsskala Rollenfunktion zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ C30 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

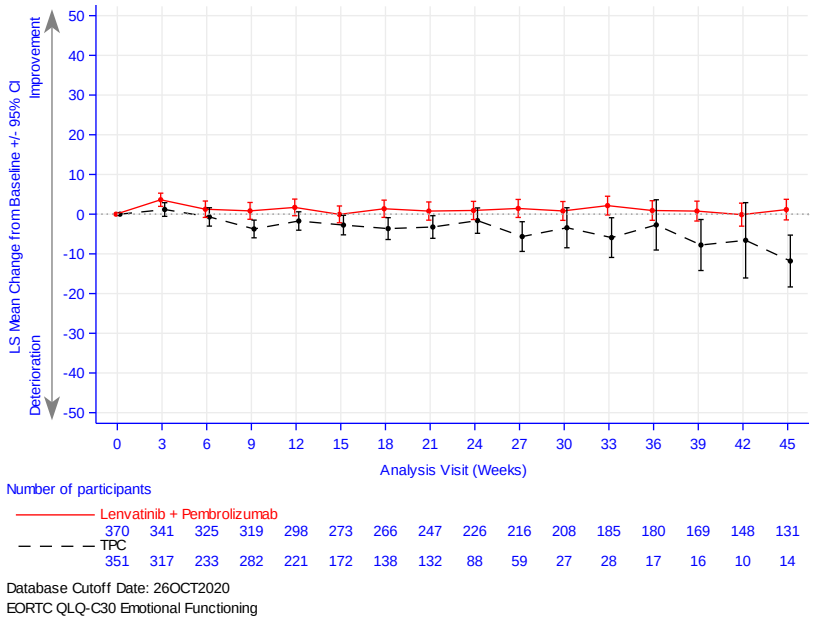

Abbildung 4G-69: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Funktionsskala Emotionale Funktion zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ C30 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

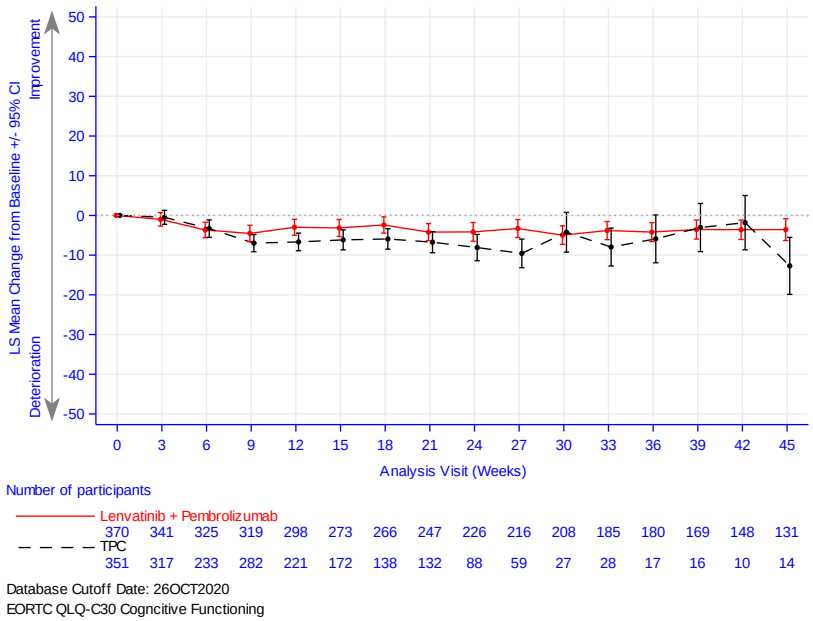

Abbildung 4G-70: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Funktionsskala Kognitive Funktion zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ C30 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

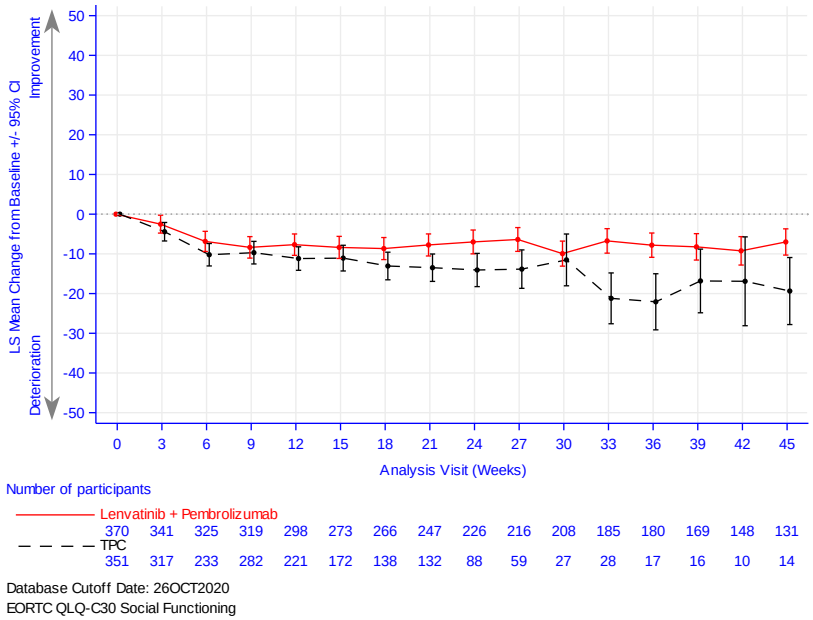

Abbildung 4G-71: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Funktionsskala Soziale Funktion zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ C30 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

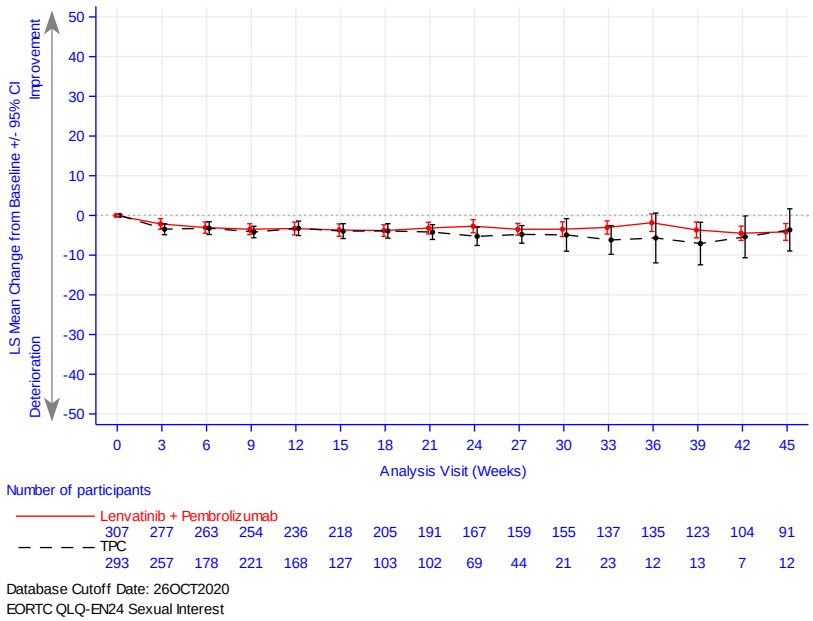

Abbildung 4G-72: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Funktionsskala Sexuelles Interesse zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ EN24 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

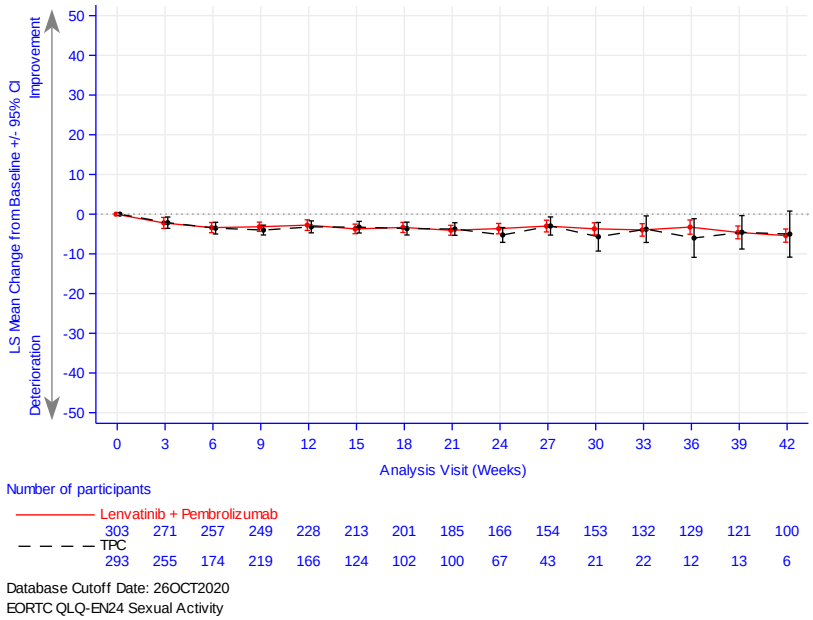

Abbildung 4G-73: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Funktionsskala Sexuelle Aktivität zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ EN24 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

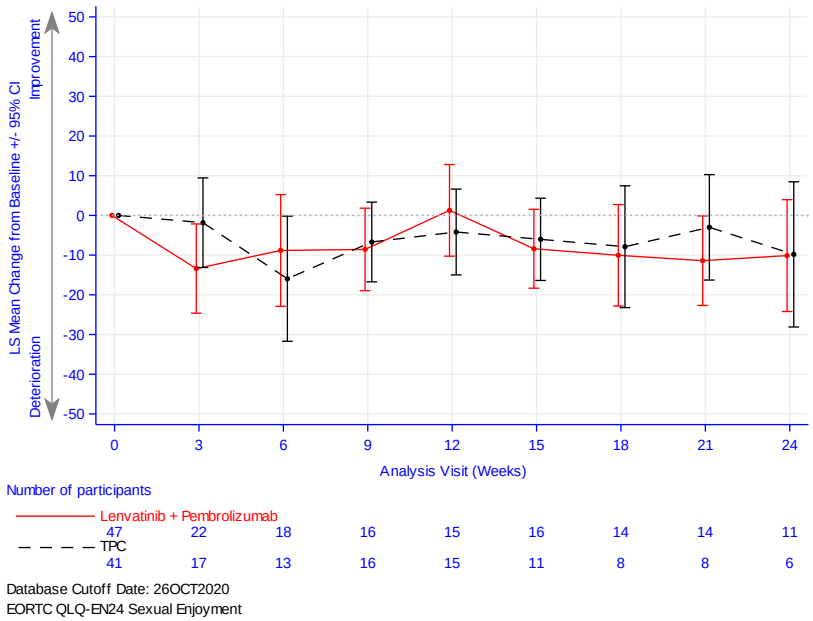

Abbildung 4G-74: Darstellung über den Studienverlauf: Mittlere Änderung zu Baseline +/- 95 % KI der Funktionsskala Sexueller Genuss zu den verschiedenen Erhebungszeitpunkten des EORTC QLQ EN24 aus der Studie KEYNOTE 775 mit dem zu bewertenden Arzneimittel

Anhang 4-G5.4: Nebenwirkungen

Unerwünschte Ereignisse Gesamtraten

Tabelle 4G-59: Ergebnisse für den Endpunkt Unerwünschte Ereignisse Gesamtraten aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib			TPC[b]			Pembrolizumab + Lenvatinib vs. TPC[b]	
	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]
Adverse Events	406	405 (99.8)	0.6 [0.4; 0.7]	388	386 (99.5)	0.6 [0.4; 0.7]	1.09 [0.95; 1.25]	0.241
Serious Adverse Events	406	214 (52.7)	40.9 [30.0; 53.6]	388	118 (30.4)	Not reached [55.7; -]	1.67 [1.33; 2.09]	< 0.001
Severe Adverse Events (CTCAE-Grade 3-5)	406	361 (88.9)	5.1 [3.9; 6.3]	388	282 (72.7)	3.6 [2.3; 5.1]	1.07 [0.91; 1.25]	0.412
Adverse Events Leading to Treatment Discontinuation	406	134 (33.0)	Not reached [77.4; -]	388	31 (8.0)	Not reached [59.1; -]	2.81 [1.89; 4.20]	< 0.001

a: Database Cutoff Date: 26OCT2020
b: Treatment of physician's choice of doxorubicin or paclitaxel
c: Number of participants: all-participants-as-treated population
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)
CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; TPC: Treatment of Physician's Choice

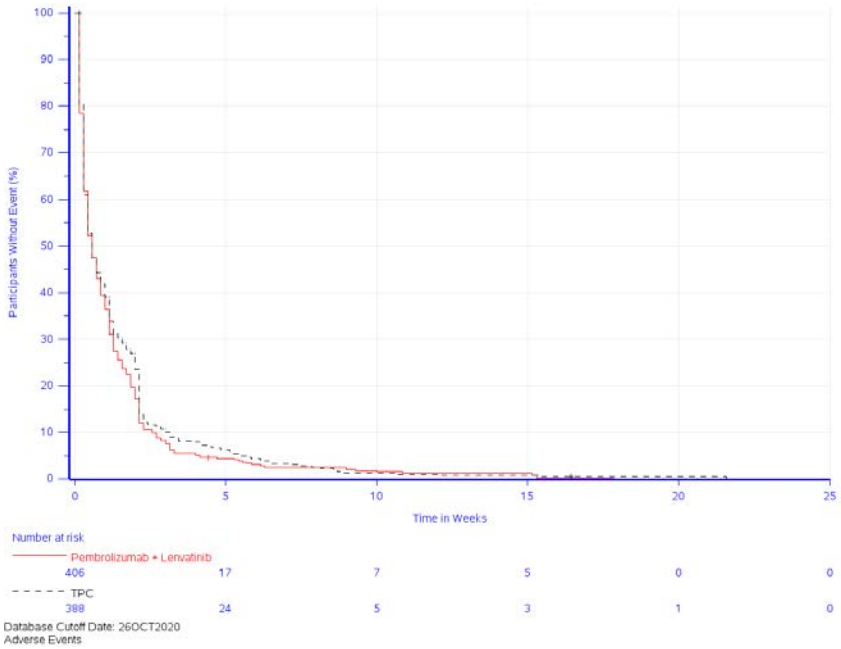

Abbildung 4G-75: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Unerwünschte Ereignisse gesamt der Studie KEYNOTE 775

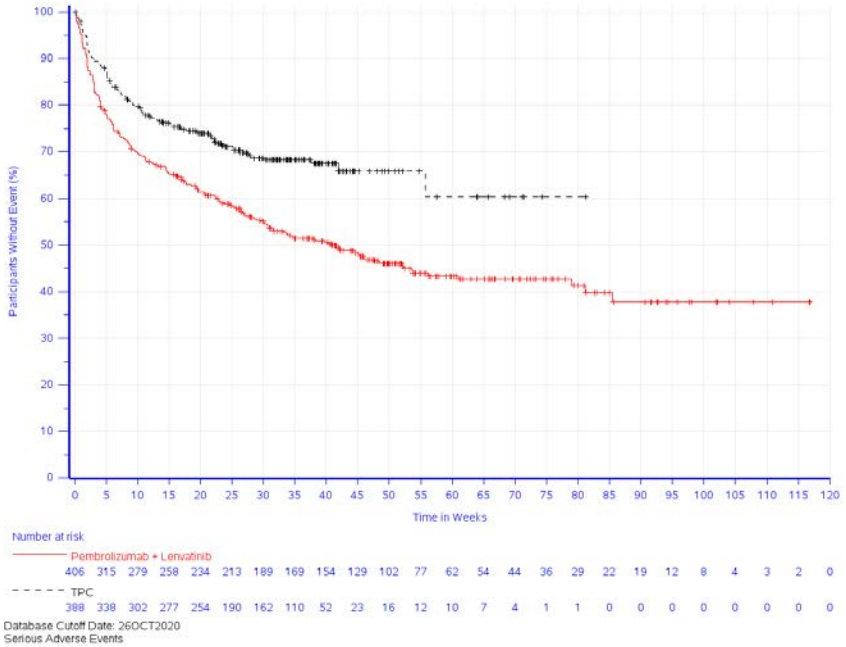

Abbildung 4G-76: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwerwiegende unerwünschte Ereignisse der Studie KEYNOTE 775

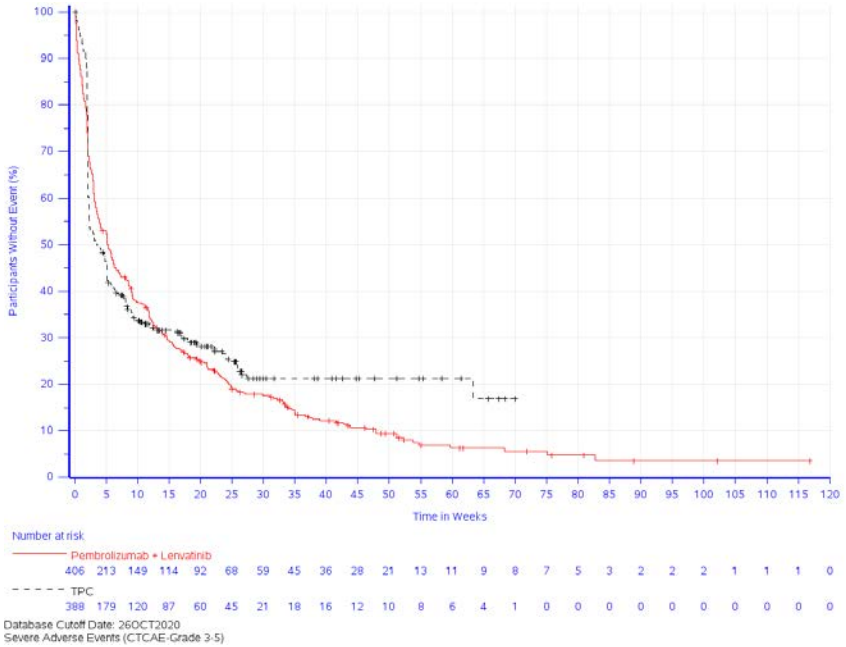

Abbildung 4G-77: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) der Studie KEYNOTE 775

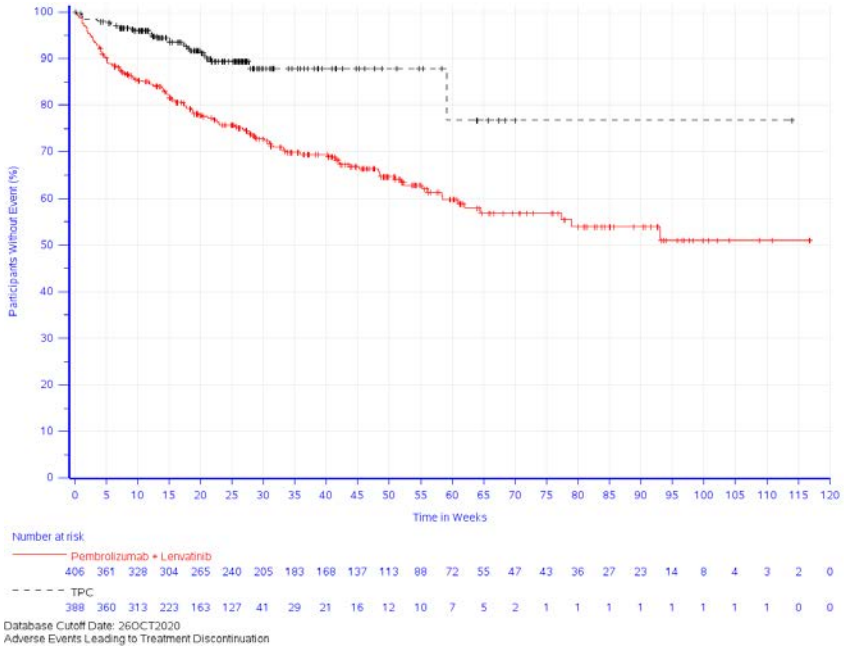

Abbildung 4G-78: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse der Studie KEYNOTE 775

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (gegliedert nach SOC und PT)

Tabelle 4G-60: Ergebnisse für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib (N[c]=406)**		**TPC[b] (N[c]=388)**		**Pembrolizumab + Lenvatinib vs. TPC[b]**		
Adverse Events by SOC and PT[d]	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**Adjusted p-Value[h]**
Blood and lymphatic system disorders	149 (36.7)	Not reached [57.1; -]	259 (66.8)	4.3 [2.4; 5.1]	0.30 [0.24; 0.37]	< 0.001	< 0.001
Anaemia	106 (26.1)	Not reached [-; -]	189 (48.7)	15.6 [12.1; -]	0.32 [0.25; 0.41]	< 0.001	< 0.001
Febrile neutropenia	2 (0.5)	Not reached [-; -]	23 (5.9)	Not reached [-; -]	0.06 [0.01; 0.27]	< 0.001	0.001
Leukopenia	28 (6.9)	Not reached [-; -]	51 (13.1)	Not reached [-; -]	0.42 [0.26; 0.67]	< 0.001	0.001
Lymphopenia	25 (6.2)	Not reached [-; -]	30 (7.7)	Not reached [-; -]	0.70 [0.41; 1.19]	0.183	0.274
Neutropenia	30 (7.4)	Not reached [-; -]	131 (33.8)	Not reached [-; -]	0.15 [0.10; 0.23]	< 0.001	< 0.001
Thrombocytopenia	44 (10.8)	Not reached [-; -]	26 (6.7)	Not reached [-; -]	1.30 [0.79; 2.13]	0.300	0.407
Cardiac disorders	50 (12.3)	Not reached [-; -]	45 (11.6)	Not reached [47.1; -]	0.63 [0.41; 0.97]	0.035	0.077
Tachycardia	10 (2.5)	Not reached [-; -]	11 (2.8)	Not reached [-; -]	0.60 [0.25; 1.47]	0.266	n.s.
Ear and labyrinth disorders	25 (6.2)	Not reached [-; -]	7 (1.8)	Not reached [59.6; -]	2.35 [0.99; 5.55]	0.052	0.095
Endocrine disorders	253 (62.3)	14.7 [12.0; 15.7]	9 (2.3)	Not reached [-; -]	34.47 [17.72; 67.04]	< 0.001	< 0.001
Hyperthyroidism	47 (11.6)	Not reached [-; -]	4 (1.0)	Not reached [-; -]	9.88 [3.55; 27.50]	< 0.001	< 0.001
Hypothyroidism	233 (57.4)	17.1 [15.0; 20.7]	3 (0.8)	Not reached [-; -]	88.69 [28.39; 277.08]	< 0.001	< 0.001
Eye disorders	43 (10.6)	Not reached [-; -]	21 (5.4)	Not reached [-; -]	1.17 [0.67; 2.03]	0.576	0.705
Vision blurred	10 (2.5)	Not reached [-; -]	6 (1.5)	Not reached [-; -]	1.24 [0.43; 3.53]	0.690	n.s.
Gastrointestinal disorders	355 (87.4)	2.9 [2.3; 3.3]	293 (75.5)	2.1 [1.3; 3.1]	1.03 [0.88; 1.21]	0.681	0.774
Abdominal distension	12 (3.0)	Not reached [-; -]	8 (2.1)	Not reached [-; -]	1.08 [0.43; 2.72]	0.864	0.881
Abdominal pain	83 (20.4)	Not reached [-; -]	53 (13.7)	Not reached [-; -]	1.05 [0.73; 1.50]	0.787	0.817
Abdominal pain lower	10 (2.5)	Not reached [-; -]	4 (1.0)	Not reached [-; -]	1.92 [0.59; 6.26]	0.279	0.383
Abdominal pain upper	53	Not reached	27	Not reached	1.50	0.094	0.165

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib (N[c]=406)		TPC[b] (N[c]=388)		Pembrolizumab + Lenvatinib vs. TPC[b]		
Adverse Events by SOC and PT[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	Adjusted p-Value[h]
	(13.1)	[-; -]	(7.0)	[-; -]	[0.93; 2.40]		
Colitis	16 (3.9)	Not reached [-; -]	1 (0.3)	Not reached [-; -]	7.62 [0.98; 59.41]	0.053	0.107
Constipation	105 (25.9)	Not reached [-; -]	96 (24.7)	Not reached [52.1; -]	0.80 [0.60; 1.06]	0.118	0.191
Diarrhoea	220 (54.2)	26.7 [20.0; 31.3]	78 (20.1)	Not reached [-; -]	2.51 [1.93; 3.25]	< 0.001	< 0.001
Dry mouth	40 (9.9)	Not reached [-; -]	11 (2.8)	Not reached [-; -]	3.14 [1.61; 6.15]	< 0.001	0.003
Dyspepsia	27 (6.7)	Not reached [-; -]	19 (4.9)	Not reached [-; -]	1.04 [0.57; 1.90]	0.897	0.897
Dysphagia	11 (2.7)	Not reached [-; -]	3 (0.8)	Not reached [-; -]	3.14 [0.87; 11.37]	0.081	0.149
Gastritis	21 (5.2)	Not reached [-; -]	2 (0.5)	Not reached [-; -]	6.47 [1.48; 28.27]	0.013	0.035
Gastrooesophageal reflux disease	28 (6.9)	Not reached [-; -]	8 (2.1)	Not reached [-; -]	2.17 [0.97; 4.88]	0.060	0.118
Haemorrhoids	23 (5.7)	Not reached [-; -]	7 (1.8)	Not reached [-; -]	2.10 [0.88; 5.01]	0.096	0.165
Nausea	201 (49.5)	31.6 [19.4; 48.4]	179 (46.1)	44.7 [13.9; -]	0.80 [0.65; 0.98]	0.031	0.072
Oral pain	20 (4.9)	Not reached [-; -]	3 (0.8)	Not reached [-; -]	5.33 [1.57; 18.07]	0.007	0.022
Stomatitis	78 (19.2)	Not reached [-; -]	47 (12.1)	Not reached [-; -]	1.34 [0.93; 1.94]	0.119	0.191
Toothache	13 (3.2)	Not reached [-; -]	5 (1.3)	Not reached [-; -]	1.53 [0.53; 4.46]	0.435	0.520
Vomiting	149 (36.7)	Not reached [60.3; -]	81 (20.9)	Not reached [-; -]	1.41 [1.07; 1.86]	0.014	0.036
General disorders and administration site conditions	306 (75.4)	4.9 [3.4; 6.7]	264 (68.0)	5.3 [3.3; 6.4]	0.98 [0.83; 1.16]	0.854	0.854
Asthenia	96 (23.6)	Not reached [-; -]	95 (24.5)	69.3 [54.4; -]	0.77 [0.58; 1.03]	0.078	n.s.
Chest pain	11 (2.7)	Not reached [-; -]	7 (1.8)	Not reached [-; -]	1.03 [0.38; 2.78]	0.960	n.s.
Chills	12 (3.0)	Not reached [-; -]	8 (2.1)	Not reached [-; -]	1.05 [0.41; 2.69]	0.915	n.s.
Fatigue	134 (33.0)	Not reached [-; -]	107 (27.6)	Not reached [-; -]	1.06 [0.82; 1.37]	0.684	n.s.
Malaise	25 (6.2)	Not reached [-; -]	19 (4.9)	Not reached [-; -]	0.90 [0.48; 1.68]	0.737	n.s.
Mucosal inflammation	49 (12.1)	Not reached [-; -]	38 (9.8)	Not reached [-; -]	1.07 [0.70; 1.65]	0.752	n.s.
Oedema	17 (4.2)	Not reached [-; -]	8 (2.1)	Not reached [-; -]	1.31 [0.55; 3.13]	0.546	n.s.
Oedema peripheral	49 (12.1)	Not reached [-; -]	36 (9.3)	Not reached [52.3; -]	0.72 [0.46; 1.15]	0.167	n.s.

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib (N[c]=406)		TPC[b] (N[c]=388)		Pembrolizumab + Lenvatinib vs. TPC[b]		
Adverse Events by SOC and PT[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	Adjusted p-Value[h]
Pain	12 (3.0)	Not reached [-; -]	6 (1.5)	Not reached [-; -]	1.27 [0.46; 3.50]	0.644	n.s.
Pyrexia	58 (14.3)	Not reached [-; -]	29 (7.5)	71.1 [-; -]	1.54 [0.97; 2.43]	0.065	n.s.
Hepatobiliary disorders	48 (11.8)	Not reached [-; -]	3 (0.8)	Not reached [-; -]	9.70 [2.99; 31.40]	< 0.001	< 0.001
Cholecystitis	10 (2.5)	Not reached [-; -]	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.016	0.040
Immune system disorders	17 (4.2)	Not reached [-; -]	6 (1.5)	Not reached [59.1; -]	1.93 [0.75; 5.00]	0.175	0.257
Infections and infestations	245 (60.3)	23.4 [18.3; 30.0]	147 (37.9)	30.1 [25.0; -]	1.24 [1.00; 1.53]	0.047	0.094
Cystitis	20 (4.9)	Not reached [-; -]	8 (2.1)	Not reached [-; -]	1.40 [0.59; 3.31]	0.443	0.522
Influenza	8 (2.0)	Not reached [-; -]	10 (2.6)	Not reached [-; -]	0.53 [0.20; 1.38]	0.191	0.278
Nasopharyngitis	14 (3.4)	Not reached [-; -]	24 (6.2)	Not reached [-; -]	0.31 [0.15; 0.63]	0.001	0.005
Pneumonia	12 (3.0)	Not reached [-; -]	7 (1.8)	Not reached [-; -]	0.84 [0.31; 2.30]	0.740	0.784
Sinusitis	10 (2.5)	Not reached [-; -]	4 (1.0)	Not reached [-; -]	1.25 [0.37; 4.26]	0.722	0.776
Skin infection	12 (3.0)	Not reached [-; -]	4 (1.0)	Not reached [-; -]	1.52 [0.46; 4.98]	0.490	0.559
Upper respiratory tract infection	19 (4.7)	Not reached [-; -]	17 (4.4)	79.3 [-; -]	0.58 [0.28; 1.18]	0.130	0.206
Urinary tract infection	104 (25.6)	Not reached [-; -]	39 (10.1)	Not reached [-; -]	1.98 [1.36; 2.88]	< 0.001	0.002
Injury, poisoning and procedural complications	48 (11.8)	Not reached [-; -]	21 (5.4)	Not reached [-; -]	1.28 [0.75; 2.18]	0.369	0.486
Fall	13 (3.2)	Not reached [-; -]	4 (1.0)	Not reached [-; -]	1.52 [0.47; 4.91]	0.485	n.s.
Investigations	306 (75.4)	9.0 [6.1; 10.4]	192 (49.5)	15.1 [11.0; 31.3]	1.35 [1.13; 1.62]	0.001	0.003
Alanine aminotransferase increased	86 (21.2)	Not reached [97.9; -]	20 (5.2)	Not reached [60.1; -]	3.07 [1.87; 5.04]	< 0.001	< 0.001
Amylase increased	29 (7.1)	Not reached [-; -]	5 (1.3)	Not reached [-; -]	4.02 [1.53; 10.55]	0.005	0.016
Aspartate aminotransferase increased	80 (19.7)	Not reached [-; -]	17 (4.4)	Not reached [-; -]	3.54 [2.08; 6.02]	< 0.001	< 0.001
Blood albumin decreased	11 (2.7)	Not reached [-; -]	6 (1.5)	Not reached [-; -]	1.47 [0.54; 4.03]	0.454	0.529
Blood alkaline phosphatase increased	50 (12.3)	Not reached [-; -]	15 (3.9)	Not reached [-; -]	2.42 [1.34; 4.36]	0.003	0.012
Blood bilirubin increased	22 (5.4)	Not reached [-; -]	7 (1.8)	Not reached [-; -]	1.75 [0.72; 4.21]	0.215	0.307

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib (N[c]=406)		TPC[b] (N[c]=388)		Pembrolizumab + Lenvatinib vs. TPC[b]		
Adverse Events by SOC and PT[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	Adjusted p-Value[h]
Blood cholesterol increased	34 (8.4)	Not reached [-; -]	7 (1.8)	Not reached [-; -]	3.22 [1.41; 7.36]	0.006	0.018
Blood creatine phosphokinase increased	17 (4.2)	Not reached [-; -]	2 (0.5)	Not reached [-; -]	5.73 [1.30; 25.29]	0.021	0.052
Blood creatinine increased	44 (10.8)	Not reached [-; -]	10 (2.6)	Not reached [-; -]	2.77 [1.37; 5.62]	0.005	0.016
Blood lactate dehydrogenase increased	19 (4.7)	Not reached [-; -]	12 (3.1)	Not reached [-; -]	1.20 [0.57; 2.51]	0.627	0.692
Blood thyroid stimulating hormone increased	52 (12.8)	Not reached [-; -]	1 (0.3)	Not reached [-; -]	41.32 [5.70; 299.54]	< 0.001	0.001
Blood triglycerides increased	13 (3.2)	Not reached [-; -]	8 (2.1)	Not reached [-; -]	1.18 [0.48; 2.91]	0.725	0.776
Electrocardiogram QT prolonged	16 (3.9)	Not reached [-; -]	8 (2.1)	Not reached [-; -]	1.15 [0.47; 2.78]	0.758	0.796
Gamma-glutamyltransferase increased	19 (4.7)	Not reached [-; -]	10 (2.6)	Not reached [-; -]	1.41 [0.65; 3.09]	0.386	0.481
Haemoglobin decreased	2 (0.5)	Not reached [-; -]	13 (3.4)	Not reached [-; -]	0.13 [0.03; 0.60]	0.008	0.024
Lipase increased	45 (11.1)	Not reached [-; -]	8 (2.1)	Not reached [-; -]	3.74 [1.73; 8.06]	< 0.001	0.003
Lymphocyte count decreased	17 (4.2)	Not reached [-; -]	23 (5.9)	Not reached [-; -]	0.55 [0.29; 1.05]	0.069	0.133
Neutrophil count decreased	22 (5.4)	Not reached [-; -]	94 (24.2)	Not reached [-; -]	0.17 [0.10; 0.27]	< 0.001	< 0.001
Platelet count decreased	50 (12.3)	Not reached [-; -]	22 (5.7)	Not reached [-; -]	2.04 [1.23; 3.38]	0.006	0.018
Weight decreased	138 (34.0)	Not reached [69.0; -]	22 (5.7)	Not reached [-; -]	5.05 [3.21; 7.95]	< 0.001	< 0.001
White blood cell count decreased	20 (4.9)	Not reached [-; -]	60 (15.5)	Not reached [-; -]	0.21 [0.12; 0.36]	< 0.001	< 0.001
Metabolism and nutrition disorders	290 (71.4)	10.1 [8.3; 14.4]	157 (40.5)	Not reached [22.1; -]	1.71 [1.40; 2.08]	< 0.001	< 0.001
Decreased appetite	182 (44.8)	53.0 [30.4; -]	82 (21.1)	Not reached [-; -]	1.98 [1.52; 2.58]	< 0.001	< 0.001
Dehydration	26 (6.4)	Not reached [-; -]	8 (2.1)	Not reached [-; -]	2.06 [0.91; 4.66]	0.084	0.150
Hypercalcaemia	16 (3.9)	Not reached [-; -]	4 (1.0)	Not reached [-; -]	1.95 [0.62; 6.19]	0.255	0.356
Hypercholesterolaemia	24 (5.9)	Not reached [-; -]	7 (1.8)	Not reached [-; -]	1.52 [0.63; 3.70]	0.351	0.451
Hyperglycaemia	38 (9.4)	Not reached [-; -]	19 (4.9)	Not reached [-; -]	1.23 [0.69; 2.18]	0.485	0.558
Hyperkalaemia	18 (4.4)	Not reached [-; -]	4 (1.0)	Not reached [-; -]	2.97 [0.98; 8.97]	0.054	0.108
Hypertriglyceridaemia	51 (12.6)	Not reached [-; -]	11 (2.8)	Not reached [-; -]	3.22 [1.66; 6.24]	< 0.001	0.002

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Adverse Events by SOC and PT[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	Adjusted p-Value[h]
Hyperuricaemia	10 (2.5)	Not reached [-; -]	4 (1.0)	Not reached [-; -]	1.18 [0.34; 4.13]	0.797	0.821
Hypoalbuminaemia	37 (9.1)	Not reached [-; -]	18 (4.6)	Not reached [-; -]	1.43 [0.80; 2.56]	0.226	0.319
Hypocalcaemia	15 (3.7)	Not reached [-; -]	13 (3.4)	Not reached [-; -]	0.58 [0.26; 1.31]	0.191	0.278
Hypokalaemia	53 (13.1)	Not reached [-; -]	26 (6.7)	Not reached [-; -]	1.50 [0.93; 2.42]	0.097	0.165
Hypomagnesaemia	72 (17.7)	Not reached [-; -]	26 (6.7)	Not reached [-; -]	1.80 [1.13; 2.85]	0.013	0.035
Hyponatraemia	36 (8.9)	Not reached [-; -]	18 (4.6)	Not reached [-; -]	1.28 [0.71; 2.29]	0.414	0.505
Hypophosphataemia	16 (3.9)	Not reached [-; -]	7 (1.8)	Not reached [-; -]	1.50 [0.60; 3.76]	0.384	0.481
Musculoskeletal and connective tissue disorders	234 (57.6)	13.1 [9.4; 20.4]	116 (29.9)	Not reached [42.4; -]	2.12 [1.69; 2.65]	< 0.001	< 0.001
Arthralgia	124 (30.5)	Not reached [90.3; -]	31 (8.0)	Not reached [-; -]	3.48 [2.34; 5.17]	< 0.001	< 0.001
Back pain	49 (12.1)	Not reached [-; -]	29 (7.5)	Not reached [-; -]	1.17 [0.73; 1.89]	0.512	0.577
Bone pain	10 (2.5)	Not reached [-; -]	11 (2.8)	Not reached [-; -]	0.71 [0.29; 1.70]	0.437	0.520
Flank pain	10 (2.5)	Not reached [-; -]	2 (0.5)	Not reached [-; -]	2.21 [0.45; 10.91]	0.332	0.440
Muscle spasms	15 (3.7)	Not reached [-; -]	8 (2.1)	Not reached [-; -]	1.45 [0.60; 3.48]	0.409	0.504
Muscular weakness	13 (3.2)	Not reached [-; -]	5 (1.3)	Not reached [-; -]	2.13 [0.75; 6.02]	0.155	0.240
Myalgia	72 (17.7)	Not reached [93.7; -]	19 (4.9)	Not reached [-; -]	3.05 [1.83; 5.09]	< 0.001	< 0.001
Pain in extremity	45 (11.1)	Not reached [-; -]	21 (5.4)	Not reached [-; -]	1.69 [1.00; 2.87]	0.049	0.104
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (3.0)	Not reached [-; -]	6 (1.5)	Not reached [-; -]	1.19 [0.42; 3.36]	0.739	0.774
Nervous system disorders	199 (49.0)	39.4 [22.7; 57.3]	139 (35.8)	29.1 [25.3; -]	1.21 [0.97; 1.51]	0.095	0.150
Dizziness	42 (10.3)	Not reached [-; -]	22 (5.7)	Not reached [-; -]	1.29 [0.75; 2.20]	0.353	0.451
Dysgeusia	40 (9.9)	Not reached [-; -]	27 (7.0)	Not reached [-; -]	1.10 [0.67; 1.81]	0.707	0.773
Headache	101 (24.9)	Not reached [-; -]	34 (8.8)	Not reached [-; -]	2.59 [1.75; 3.84]	< 0.001	< 0.001
Neuropathy peripheral	16 (3.9)	Not reached [-; -]	22 (5.7)	Not reached [-; -]	0.51 [0.26; 0.99]	0.045	0.098
Peripheral sensory neuropathy	8 (2.0)	Not reached [-; -]	17 (4.4)	Not reached [-; -]	0.30 [0.12; 0.73]	0.008	0.024

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib (N[c]=406)		TPC[b] (N[c]=388)		Pembrolizumab + Lenvatinib vs. TPC[b]		
Adverse Events by SOC and PT[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	Adjusted p-Value[h]
Tremor	13 (3.2)	Not reached [-; -]	1 (0.3)	Not reached [-; -]	9.41 [1.22; 72.72]	0.032	0.072
Psychiatric disorders	74 (18.2)	Not reached [-; -]	44 (11.3)	Not reached [-; -]	1.19 [0.81; 1.74]	0.375	0.486
Anxiety	13 (3.2)	Not reached [-; -]	11 (2.8)	Not reached [-; -]	0.63 [0.27; 1.47]	0.287	n.s.
Depression	18 (4.4)	Not reached [-; -]	6 (1.5)	Not reached [-; -]	2.10 [0.82; 5.37]	0.120	n.s.
Insomnia	33 (8.1)	Not reached [-; -]	20 (5.2)	Not reached [-; -]	1.17 [0.66; 2.07]	0.585	n.s.
Renal and urinary disorders	181 (44.6)	52.0 [42.0; 76.0]	46 (11.9)	Not reached [-; -]	3.49 [2.52; 4.85]	< 0.001	< 0.001
Acute kidney injury	20 (4.9)	Not reached [-; -]	5 (1.3)	Not reached [-; -]	2.48 [0.91; 6.78]	0.076	0.141
Dysuria	22 (5.4)	Not reached [-; -]	11 (2.8)	Not reached [-; -]	1.21 [0.57; 2.58]	0.619	0.690
Haematuria	18 (4.4)	Not reached [-; -]	11 (2.8)	Not reached [-; -]	1.06 [0.48; 2.31]	0.888	0.896
Pollakiuria	10 (2.5)	Not reached [-; -]	3 (0.8)	Not reached [-; -]	1.96 [0.51; 7.47]	0.326	0.437
Proteinuria	117 (28.8)	Not reached [-; -]	11 (2.8)	Not reached [-; -]	9.67 [5.20; 17.99]	< 0.001	< 0.001
Reproductive system and breast disorders	58 (14.3)	Not reached [-; -]	23 (5.9)	Not reached [-; -]	1.54 [0.93; 2.54]	0.095	0.150
Pelvic pain	13 (3.2)	Not reached [-; -]	8 (2.1)	Not reached [-; -]	0.90 [0.35; 2.29]	0.818	n.s.
Vaginal haemorrhage	22 (5.4)	Not reached [-; -]	12 (3.1)	Not reached [-; -]	0.99 [0.47; 2.10]	0.980	n.s.
Respiratory, thoracic and mediastinal disorders	210 (51.7)	30.6 [16.6; 45.4]	133 (34.3)	44.0 [42.4; 59.7]	1.48 [1.19; 1.85]	< 0.001	0.001
Cough	53 (13.1)	Not reached [-; -]	51 (13.1)	Not reached [49.9; -]	0.69 [0.46; 1.04]	0.073	0.138
Dysphonia	93 (22.9)	Not reached [-; -]	2 (0.5)	Not reached [-; -]	46.55 [11.46; 189.02]	< 0.001	< 0.001
Dyspnoea	46 (11.3)	Not reached [-; -]	42 (10.8)	69.3 [69.3; -]	0.70 [0.45; 1.09]	0.115	0.190
Epistaxis	32 (7.9)	Not reached [-; -]	10 (2.6)	Not reached [-; -]	2.30 [1.11; 4.74]	0.025	0.059
Oropharyngeal pain	22 (5.4)	Not reached [-; -]	9 (2.3)	Not reached [-; -]	1.78 [0.80; 3.93]	0.156	0.240
Pulmonary embolism	13 (3.2)	Not reached [-; -]	16 (4.1)	Not reached [-; -]	0.43 [0.20; 0.95]	0.036	0.080
Skin and subcutaneous tissue disorders	211 (52.0)	23.0 [16.3; 34.0]	158 (40.7)	38.1 [20.3; -]	1.04 [0.84; 1.28]	0.707	0.774
Alopecia	22 (5.4)	Not reached [-; -]	120 (30.9)	Not reached [-; -]	0.12 [0.07; 0.18]	< 0.001	< 0.001

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib (N[c]=406)		TPC[b] (N[c]=388)		Pembrolizumab + Lenvatinib vs. TPC[b]		
Adverse Events by SOC and PT[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	Adjusted p-Value[h]
Dry skin	28 (6.9)	Not reached [-; -]	11 (2.8)	Not reached [-; -]	1.79 [0.87; 3.66]	0.114	0.190
Erythema	12 (3.0)	Not reached [-; -]	4 (1.0)	Not reached [-; -]	2.28 [0.73; 7.14]	0.158	0.240
Nail discolouration	2 (0.5)	Not reached [-; -]	14 (3.6)	Not reached [-; -]	0.11 [0.03; 0.50]	0.004	0.014
Palmar-plantar erythrodysaesthesia syndrome	86 (21.2)	Not reached [-; -]	3 (0.8)	Not reached [-; -]	23.34 [7.37; 73.93]	< 0.001	< 0.001
Pruritus	42 (10.3)	Not reached [-; -]	12 (3.1)	Not reached [-; -]	2.33 [1.20; 4.52]	0.012	0.034
Rash	61 (15.0)	Not reached [99.3; -]	13 (3.4)	Not reached [-; -]	3.57 [1.95; 6.55]	< 0.001	< 0.001
Rash maculo-papular	15 (3.7)	Not reached [-; -]	2 (0.5)	Not reached [-; -]	5.32 [1.20; 23.55]	0.028	0.065
Vascular disorders	275 (67.7)	3.9 [3.0; 6.0]	71 (18.3)	Not reached [-; -]	5.10 [3.93; 6.64]	< 0.001	< 0.001
Deep vein thrombosis	8 (2.0)	Not reached [-; -]	14 (3.6)	Not reached [-; -]	0.41 [0.17; 1.01]	0.052	0.107
Hypertension	260 (64.0)	4.1 [3.1; 6.1]	20 (5.2)	Not reached [-; -]	17.79 [11.28; 28.06]	< 0.001	< 0.001
Hypotension	17 (4.2)	Not reached [-; -]	5 (1.3)	Not reached [-; -]	1.67 [0.58; 4.79]	0.342	0.448

a: Database Cutoff Date: 26OCT2020

b: Treatment of physician's choice of doxorubicin or paclitaxel

c: Number of participants: all-participants-as-treated population

d: A system organ class or 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 treatment groups

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

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

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

h: Adjusted p-values for treatment comparisons of adverse events at the SOC level were computed using the FDR procedure, and they were computed using the double FDR procedure (dFDR) for comparisons of adverse events at the PT level. Not significant (i.e., 'n.s.') is reported for PTs in a SOC when the SOC did not meet the threshold p-value criteria in the first step of the dFDR procedure. Adjusted p-values should be used for evaluating the results in order to reduce the number of false discoveries (i.e., statistical findings) when numerous statistical tests are performed

CI: Confidence Interval; FDR: False Discovery Rate; n.a.: not applicable (when estimation not possible); n.s.: non-significant (adjusted p-value ≥0.05); PT: Preferred Term; SOC: System Organ Class; TPC: Treatment of Physician's Choice

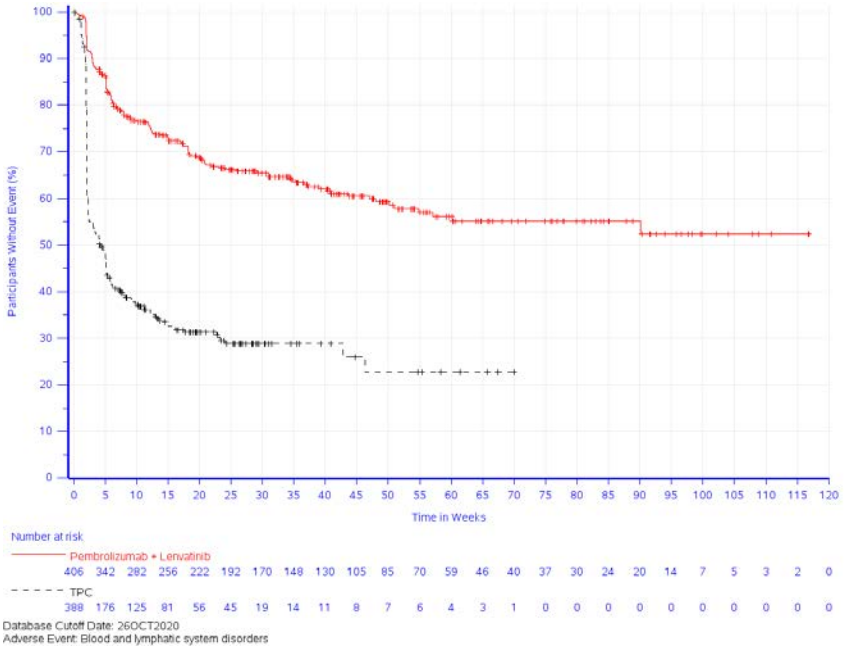

Abbildung 4G-79: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Erkrankungen des Blutes und des Lymphsystems für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

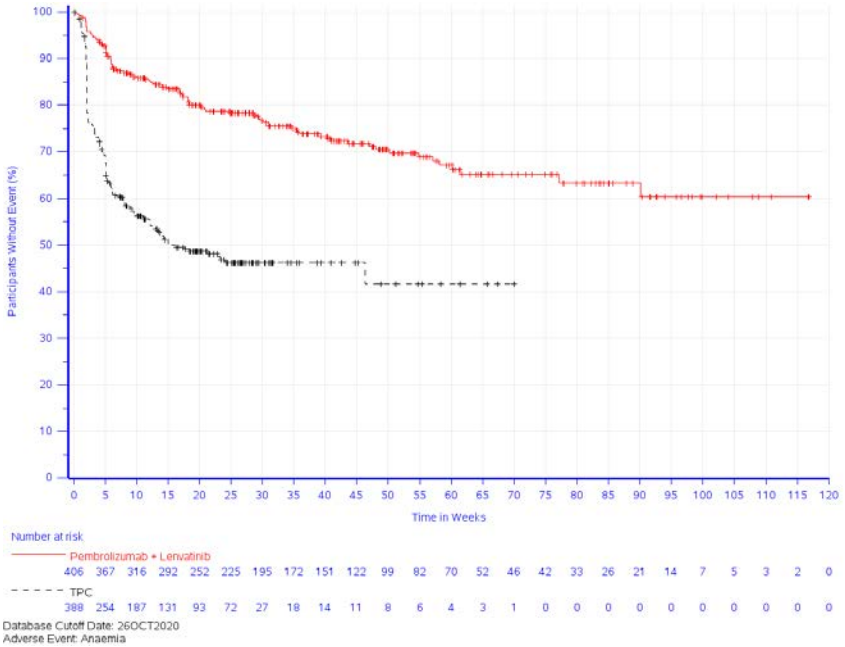

Abbildung 4G-80: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Anämie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

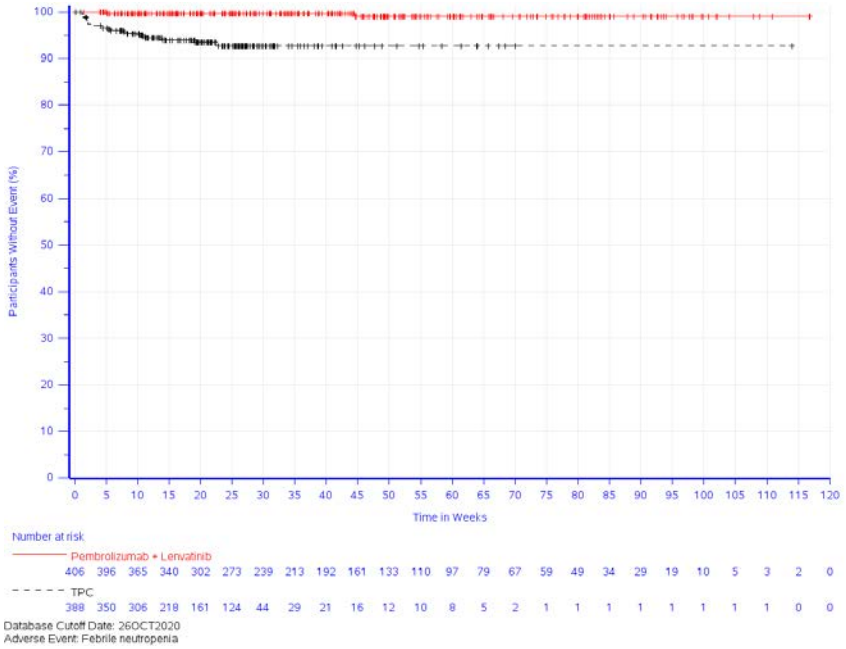

Abbildung 4G-81: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Febrile Neutropenie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

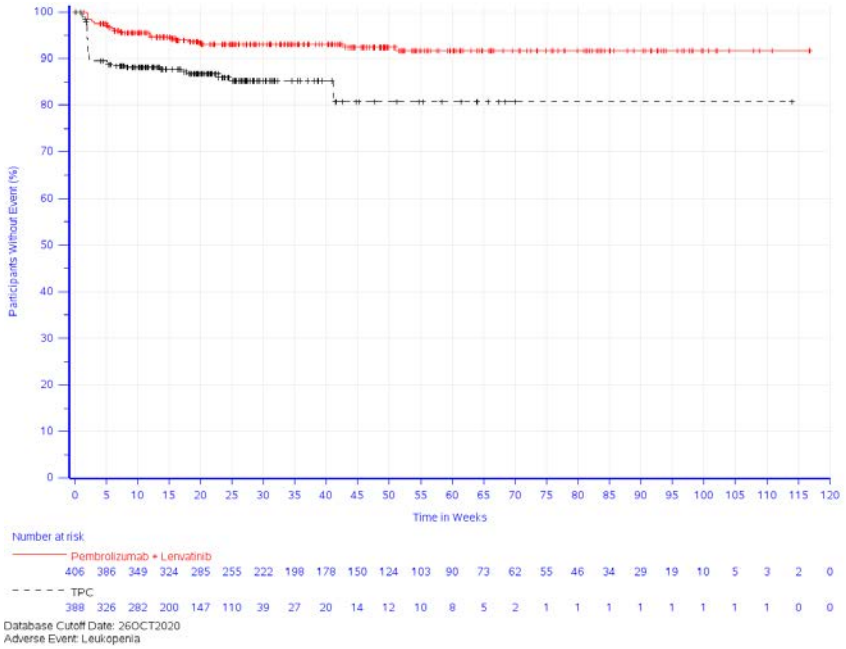

Abbildung 4G-82: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Leukopenie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

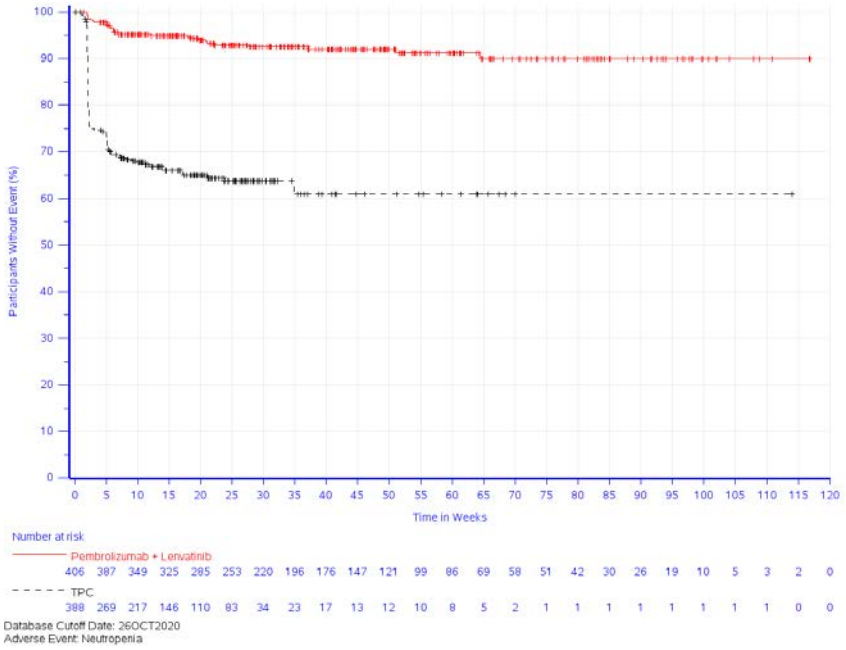

Abbildung 4G-83: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Neutropenie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

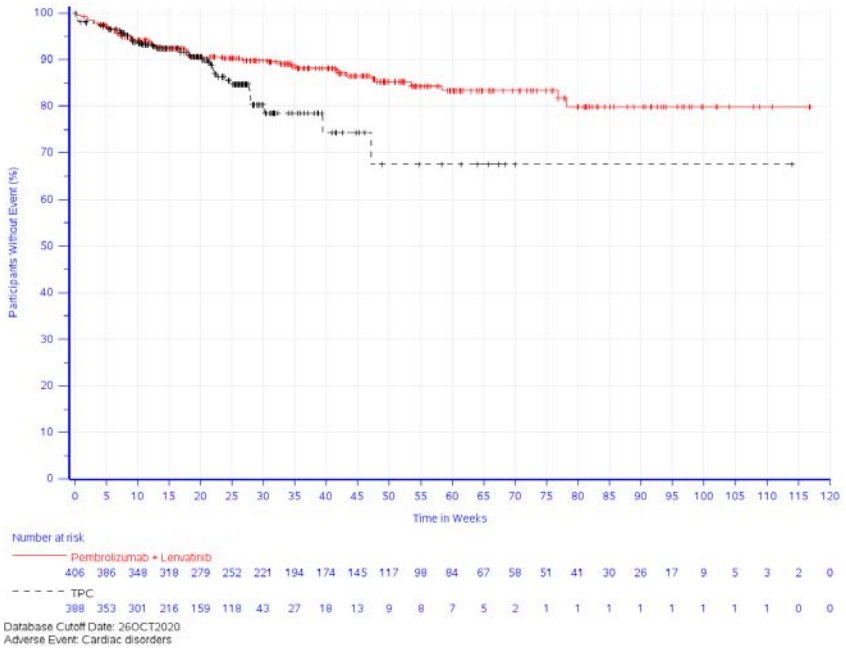

Abbildung 4G-84: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Herzerkrankungen für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

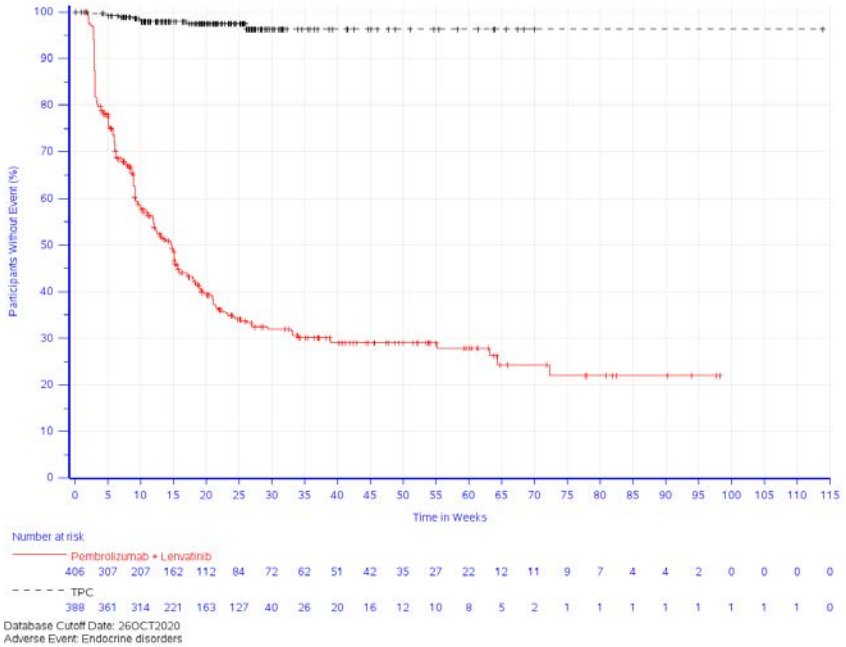

Abbildung 4G-85: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Endokrine Erkrankungen für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

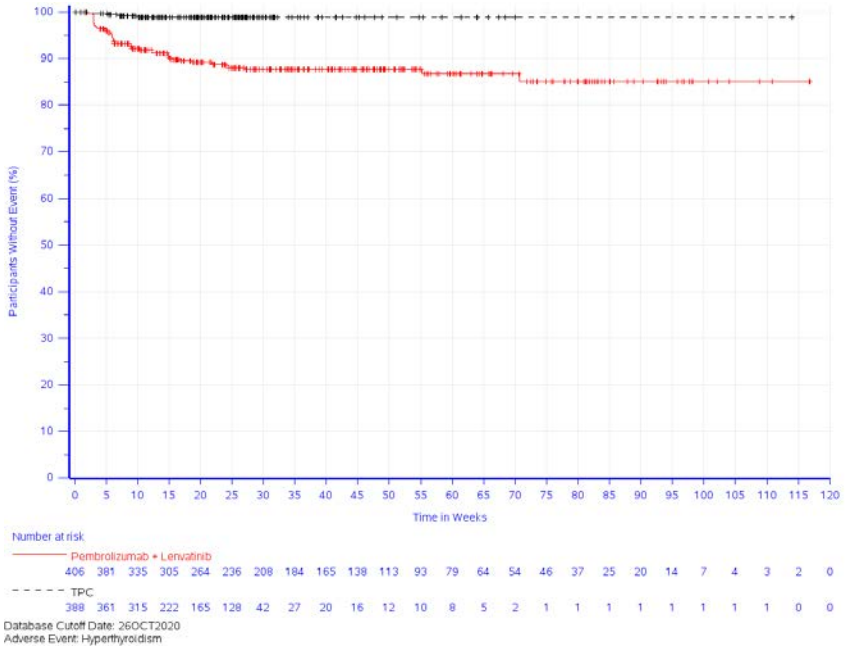

Abbildung 4G-86: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Hyperthyreose für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

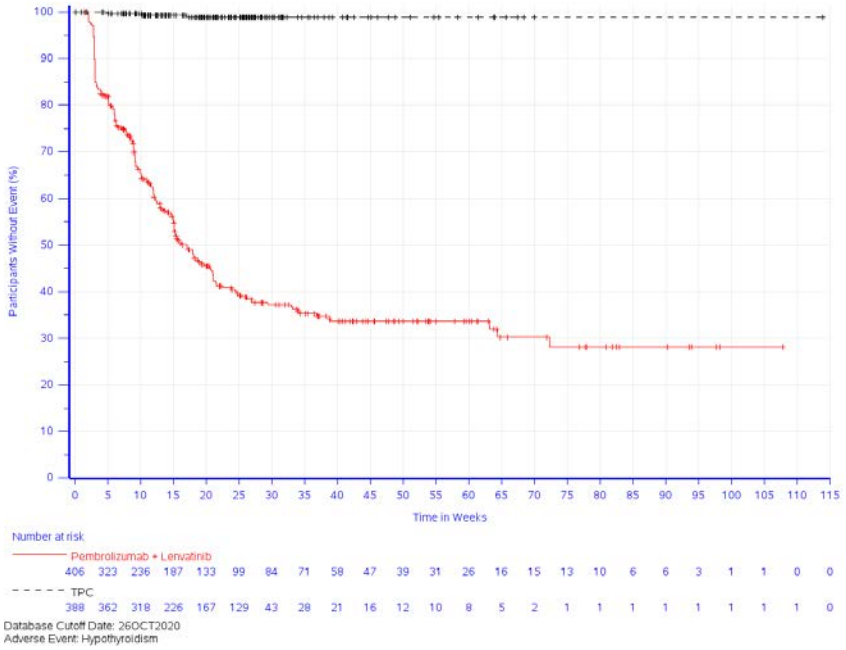

Abbildung 4G-87: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Hypothyreose für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

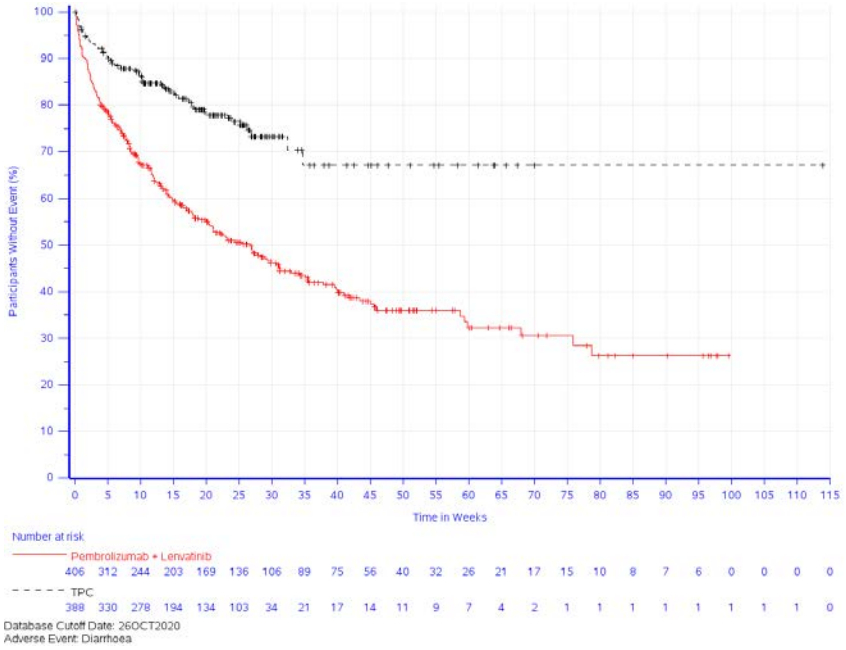

Abbildung 4G-88: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Diarrhö für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

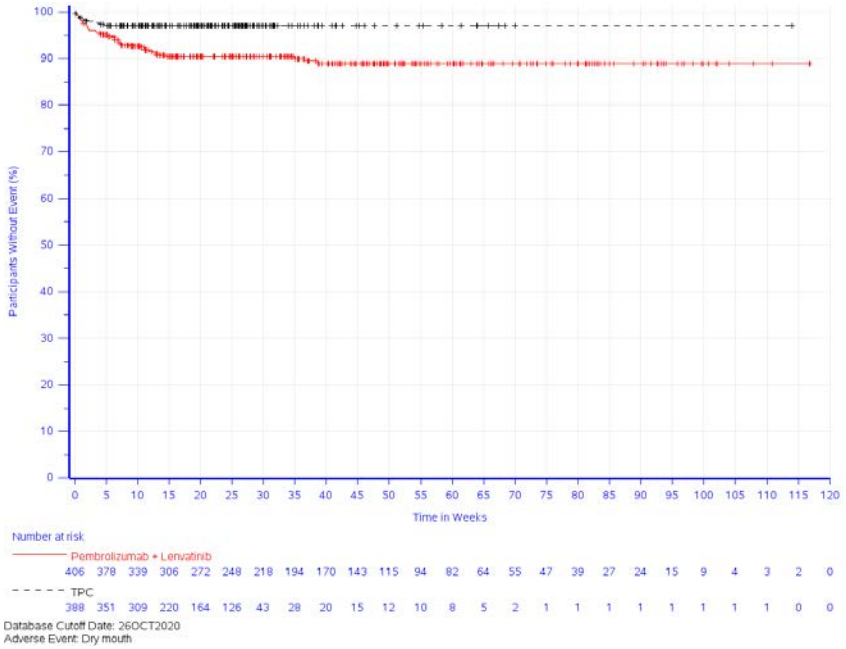

Abbildung 4G-89: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Mundtrockenheit für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

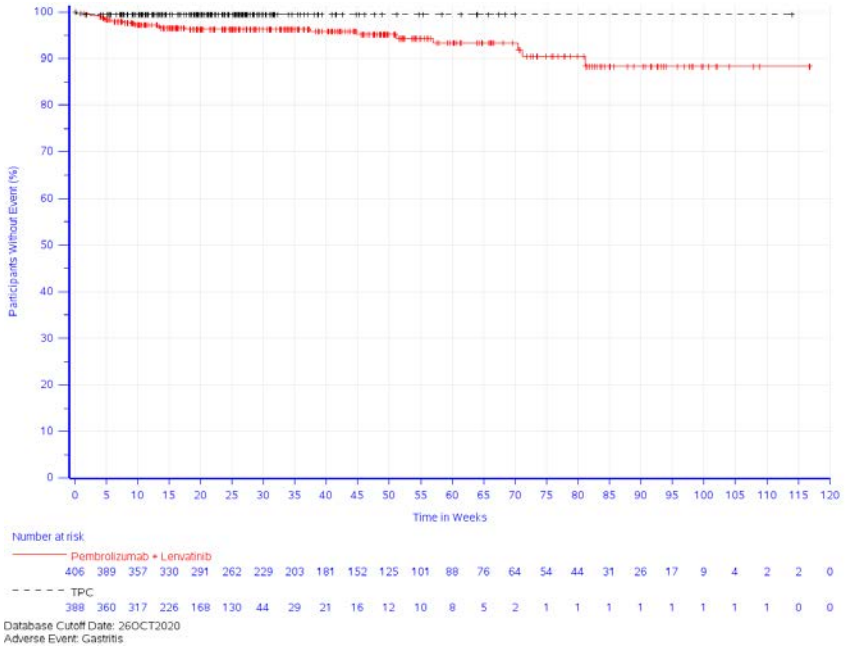

Abbildung 4G-90: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Gastritis SOC Gefäßerkrankungen für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

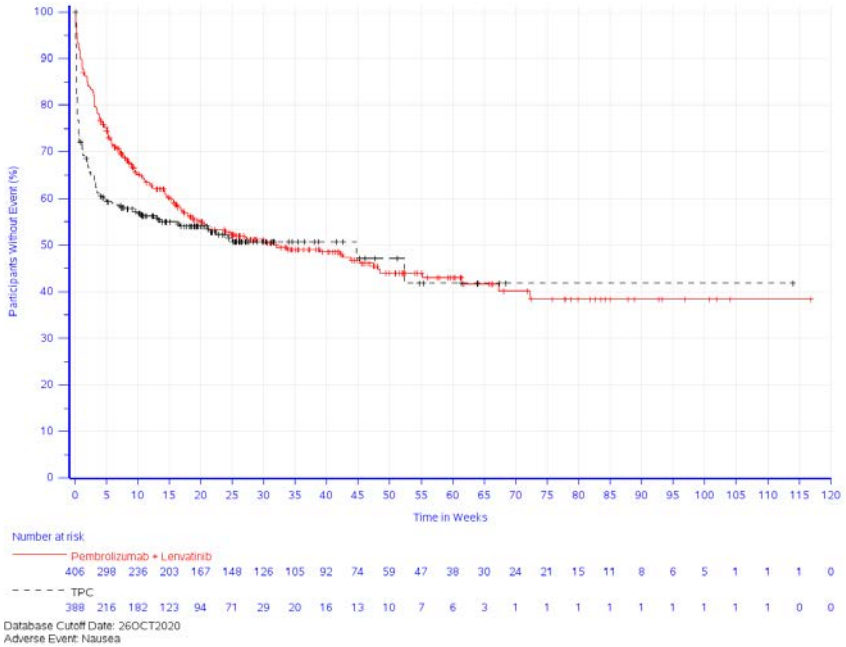

Abbildung 4G-91: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Übelkeit für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

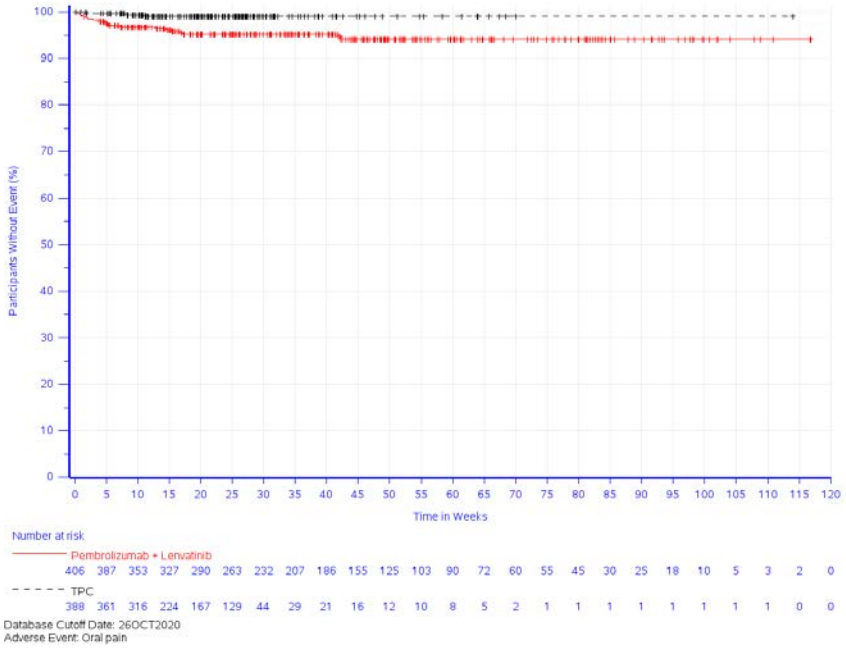

Abbildung 4G-92: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für PT Mundschmerzen für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

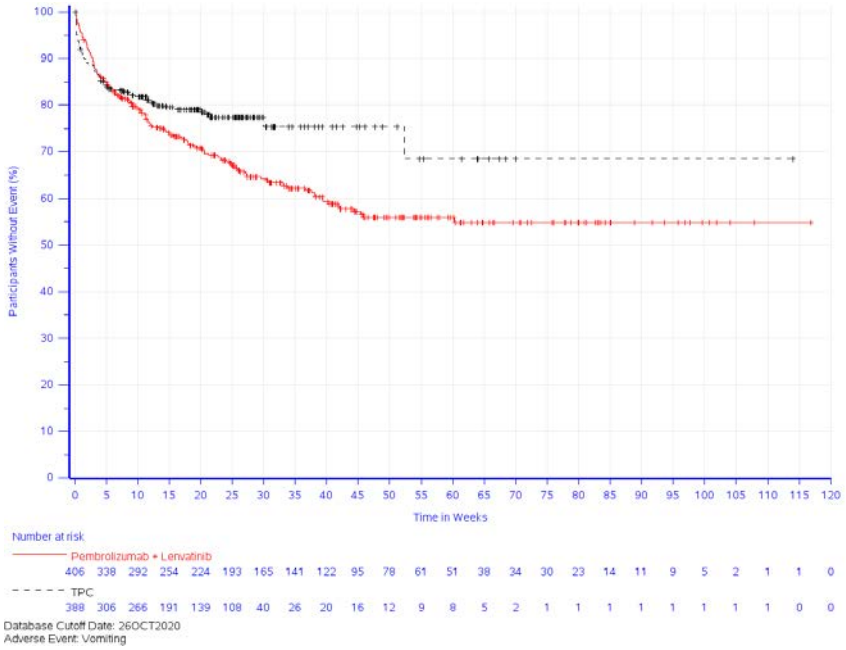

Abbildung 4G-93: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für PT Erbrechen für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

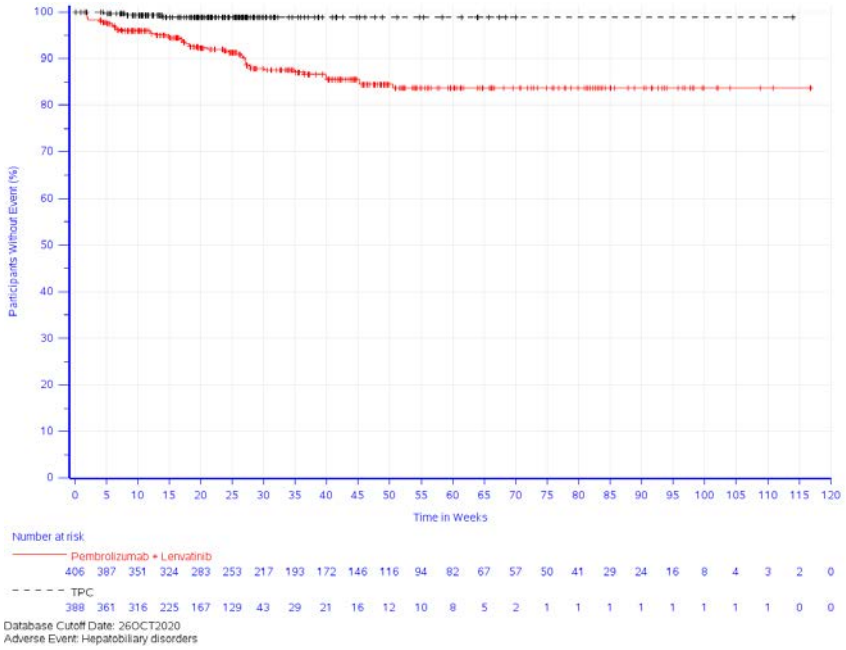

Abbildung 4G-94: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Leber- und Gallenerkrankungen für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

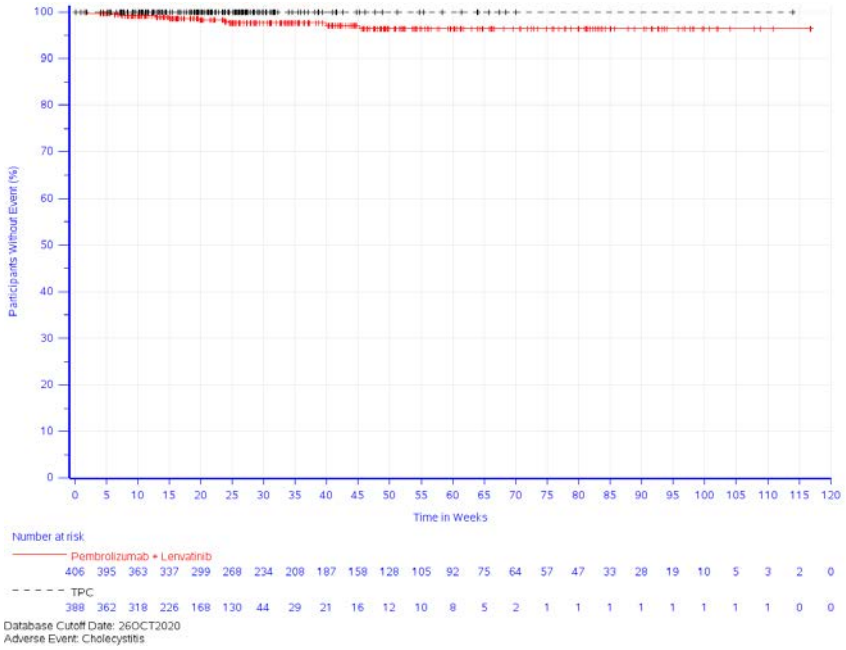

Abbildung 4G-95: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Cholecystitis für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

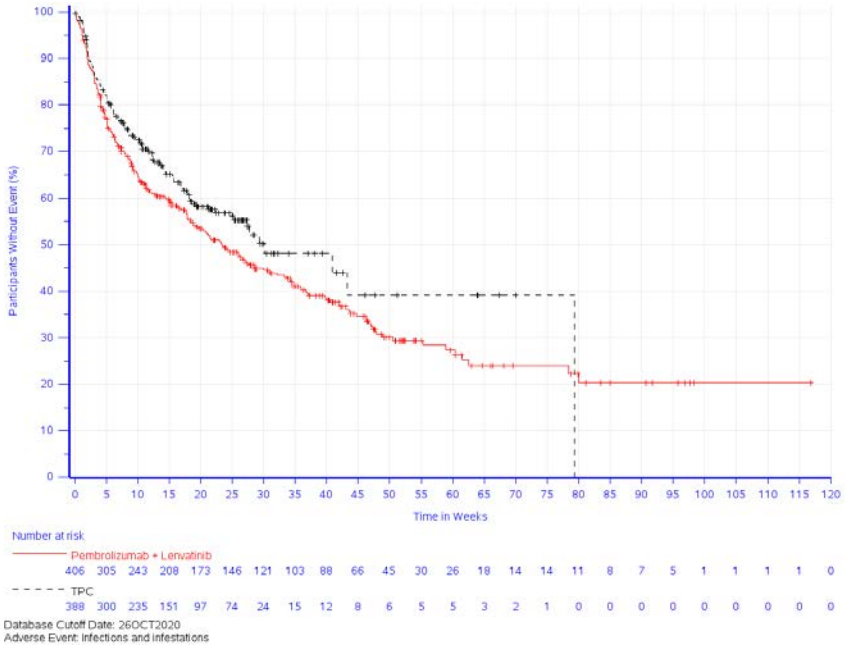

Abbildung 4G-96: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Infektionen und parasitäre Erkrankungen für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

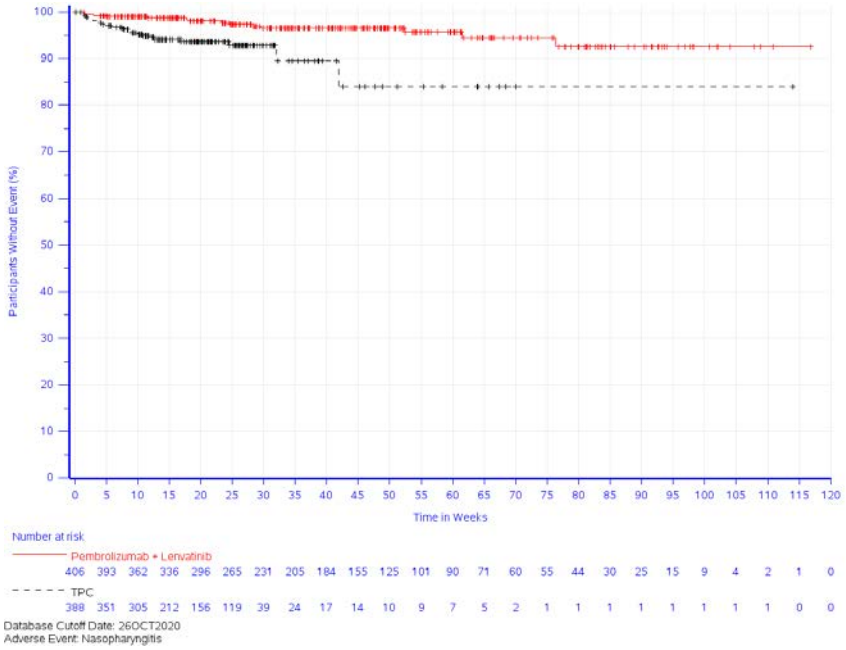

Abbildung 4G-97: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Nasopharyngitis für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

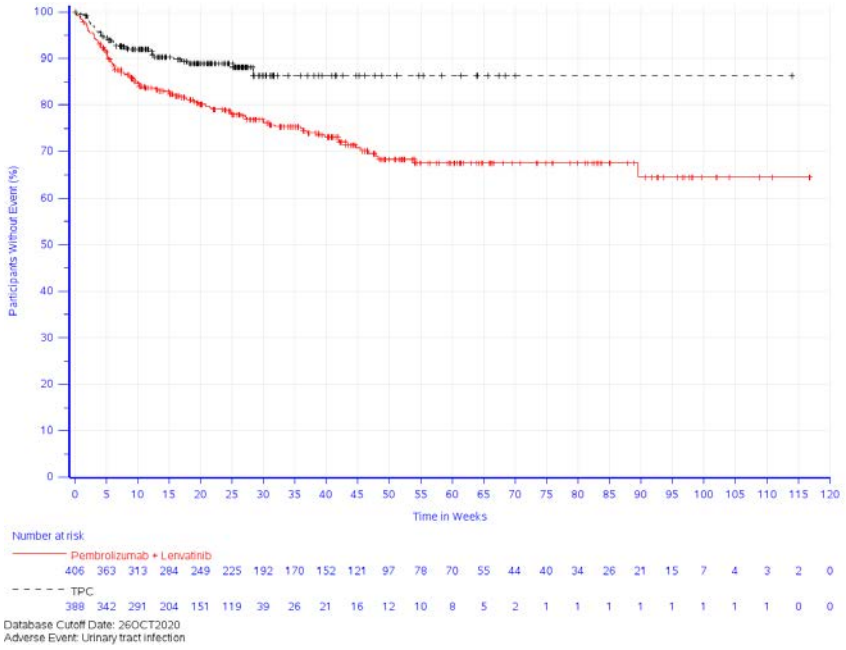

Abbildung 4G-98: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Harnwegsinfektion für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

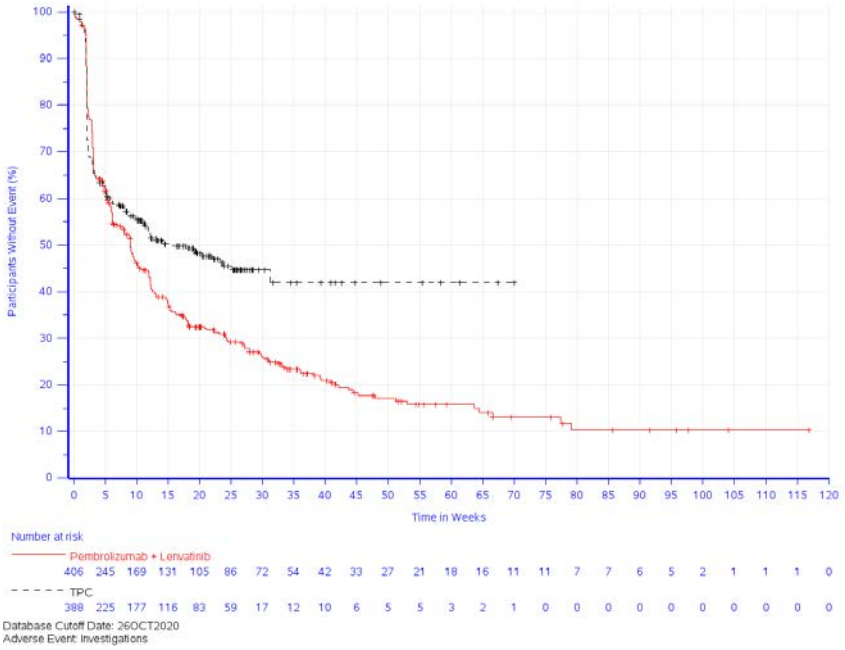

Abbildung 4G-99: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Untersuchungen für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

Abbildung 4G-100: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Alaninaminotransferase erhöht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

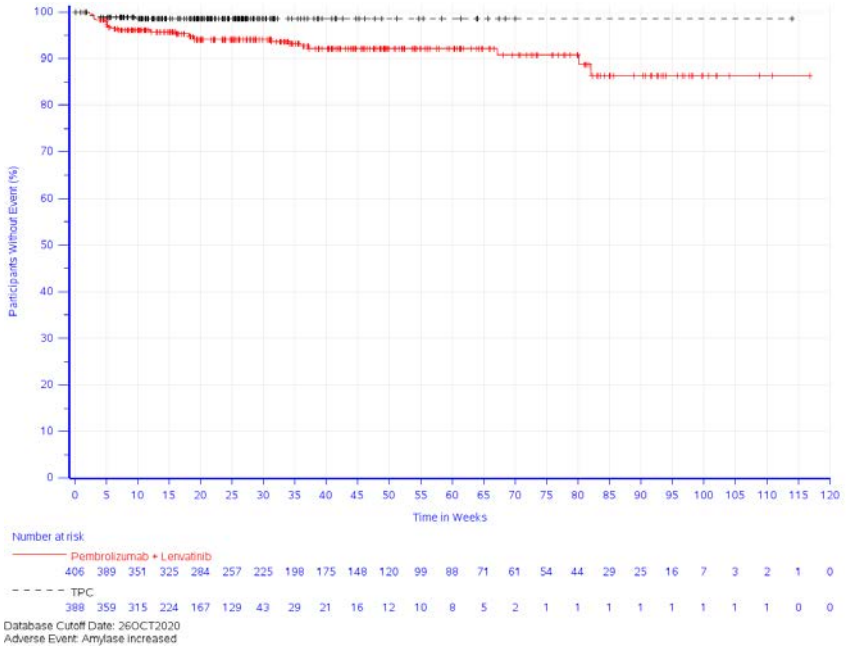

Abbildung 4G-101: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Amylase erhoeht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

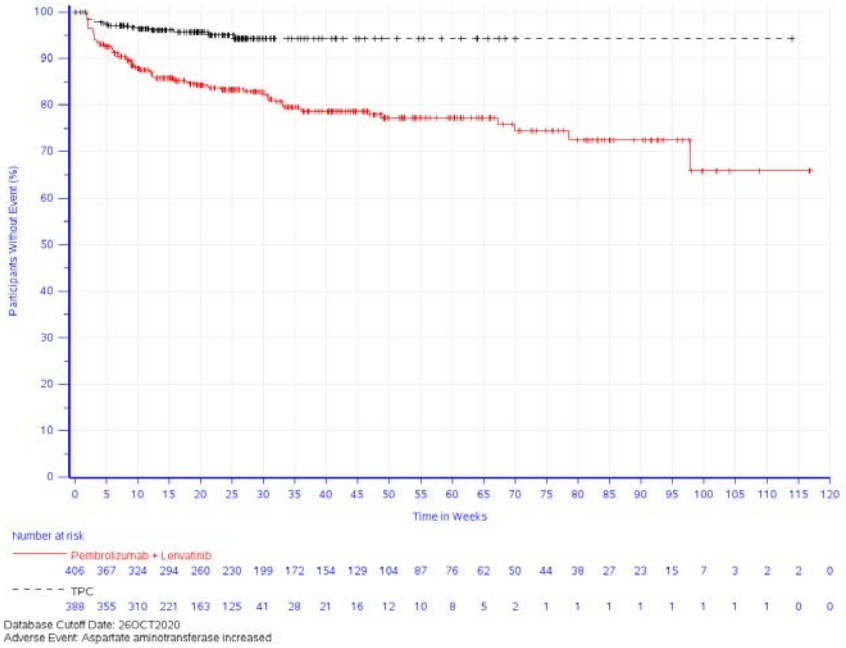

Abbildung 4G-102: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Aspartataminotransferase erhoeht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

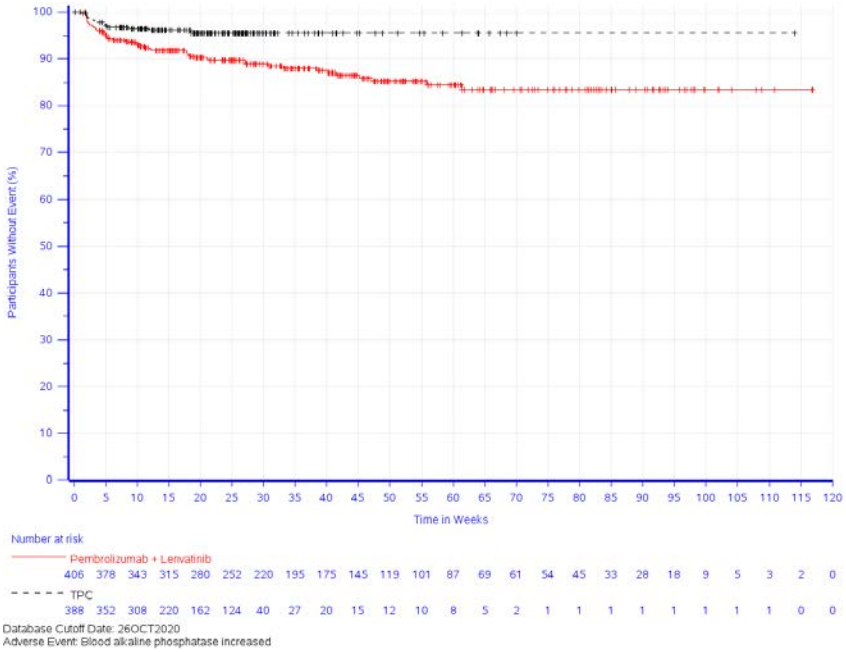

Abbildung 4G-103: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Alkalische Phosphatase im Blut erhoeht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

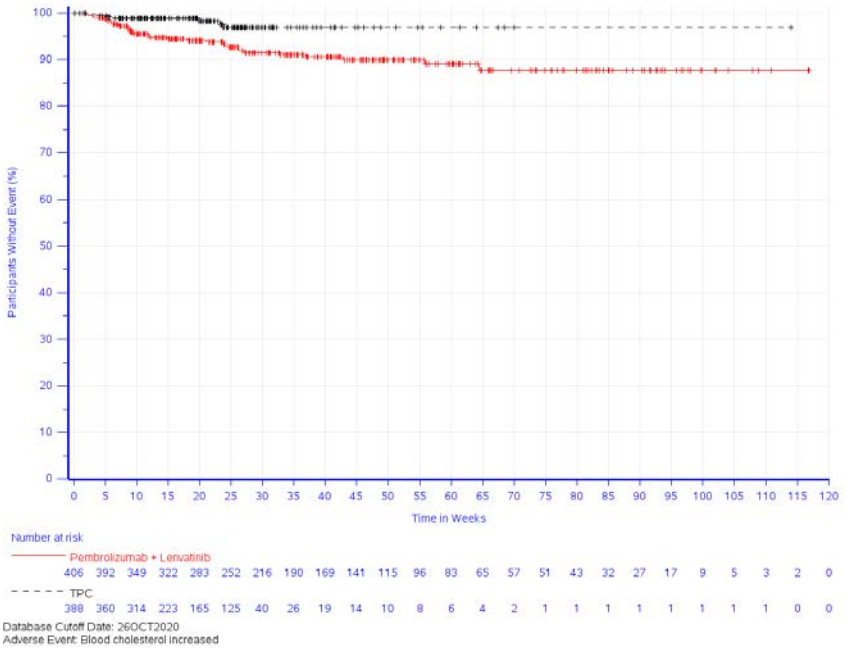

Abbildung 4G-104: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Cholesterin im Blut erhöht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

Abbildung 4G-105: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Kreatinphosphokinase im Blut erhoeht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

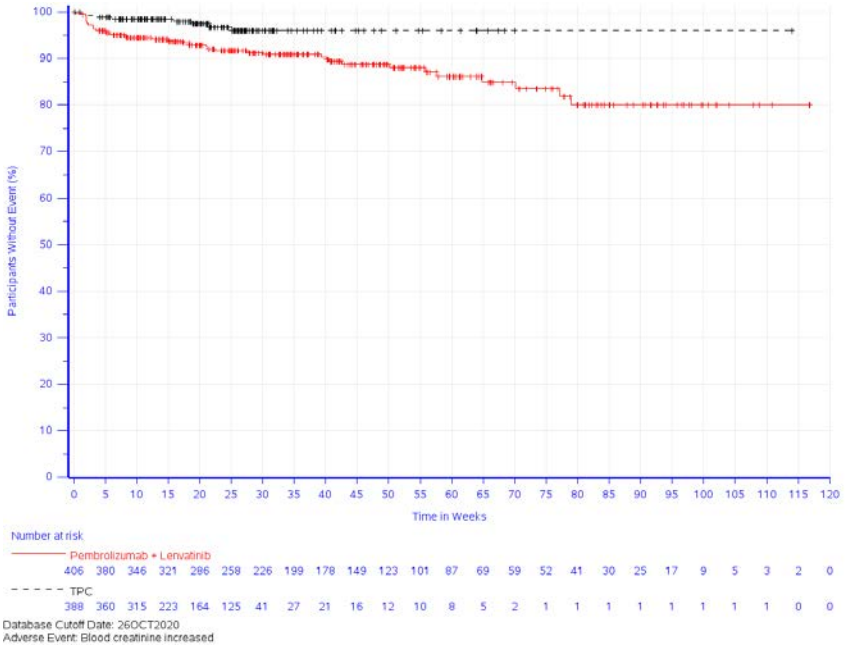

Abbildung 4G-106: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Kreatinin im Blut erhöht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

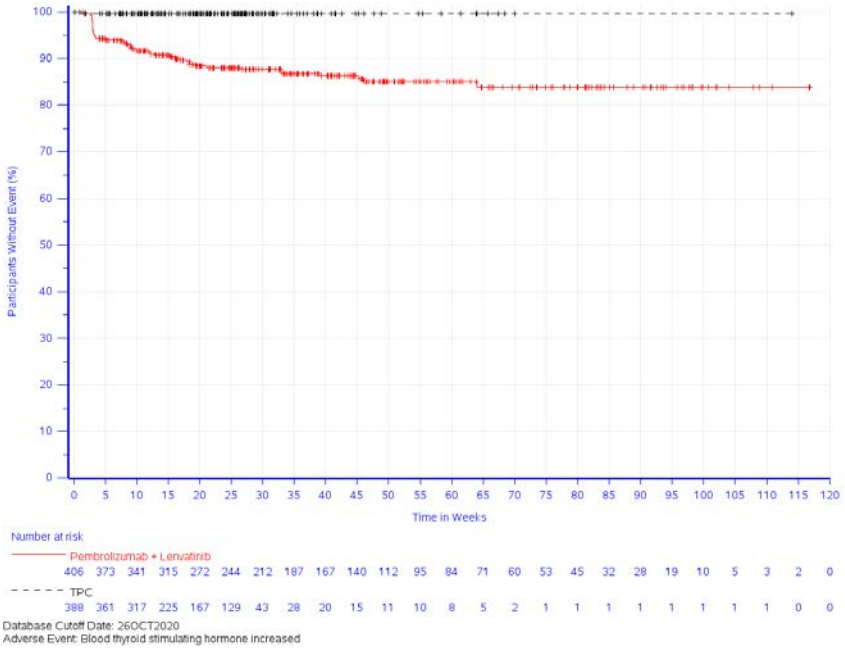

Abbildung 4G-107: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Schilddrüsenstimulierendes Hormon im Blut erhöht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

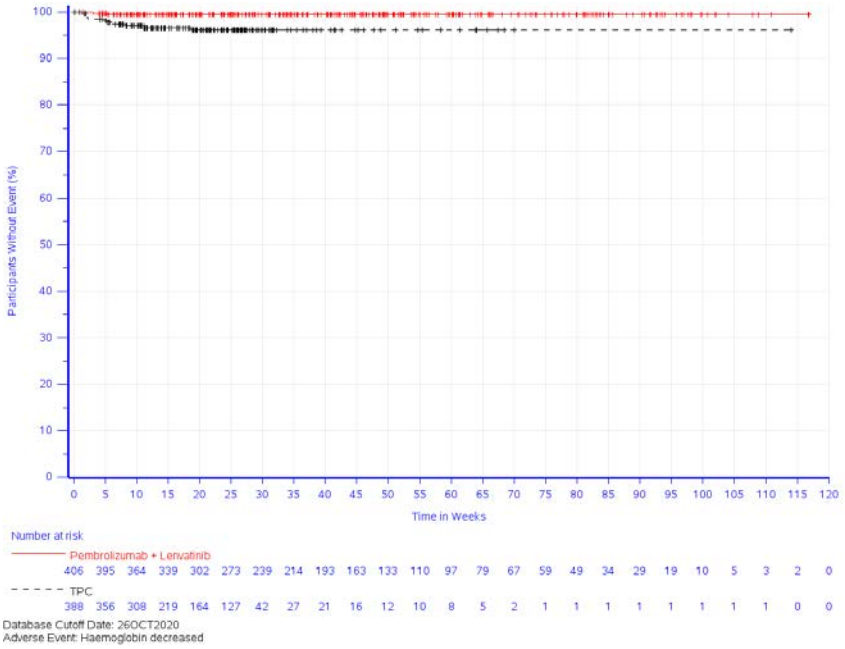

Abbildung 4G-108: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Hämoglobin erniedrigt für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

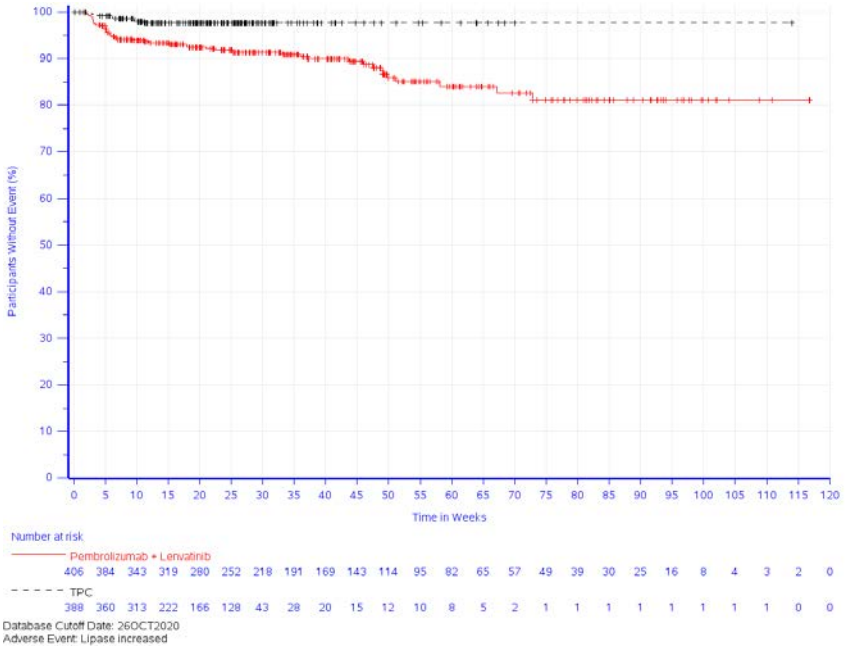

Abbildung 4G-109: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Lipase erhöht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

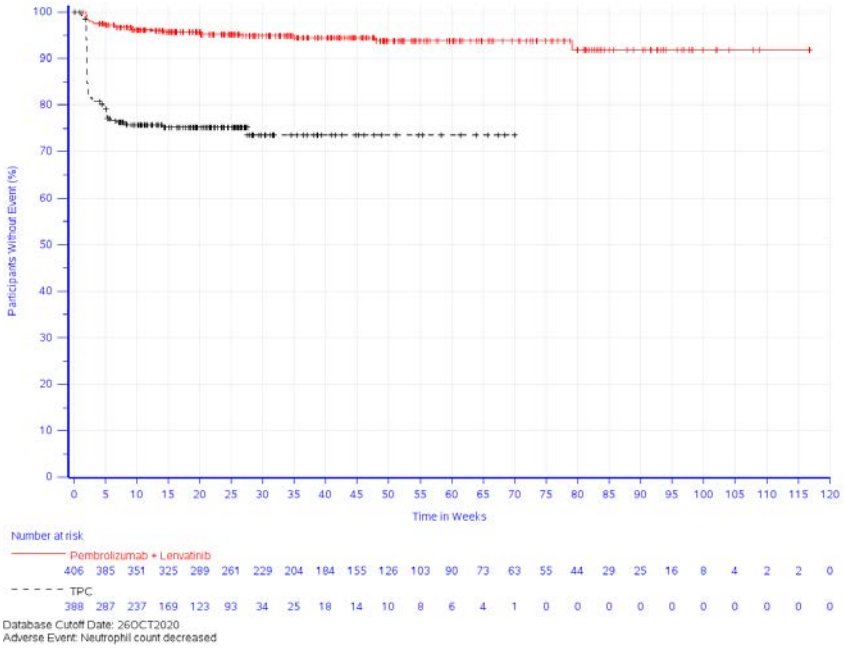

Abbildung 4G-110: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Neutrophilenzahl erniedrigt für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

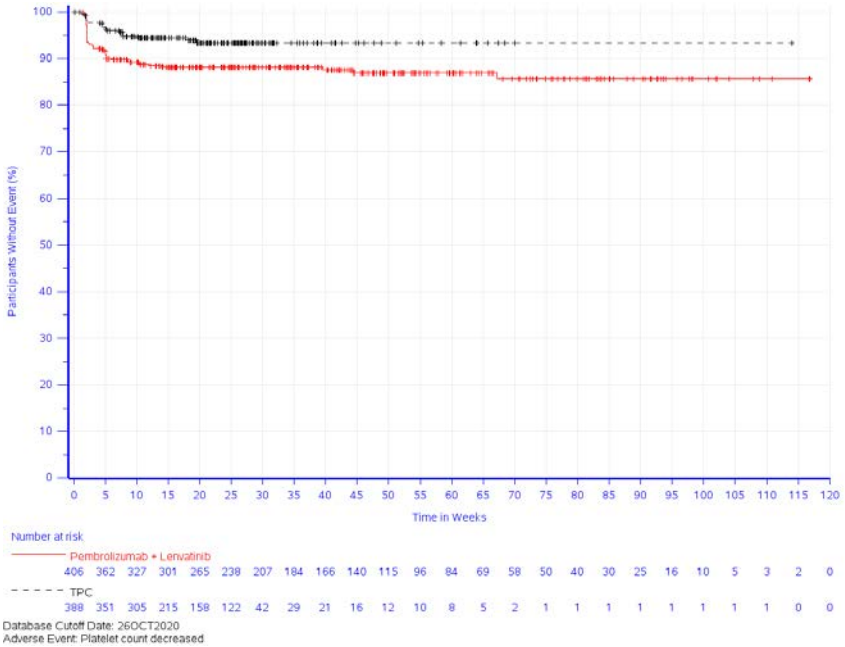

Abbildung 4G-111: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Thrombozytenzahl erniedrigt für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

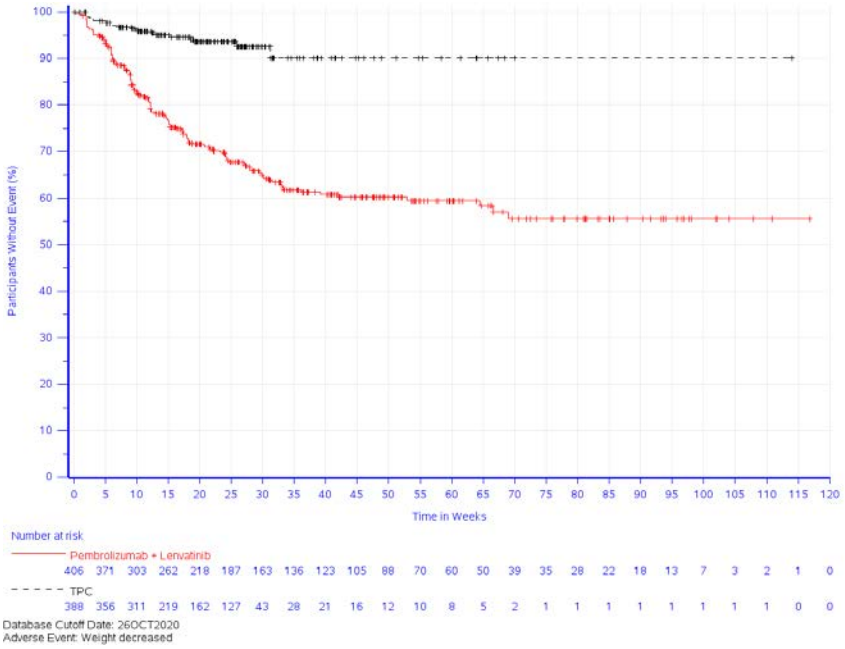

Abbildung 4G-112: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Gewicht erniedrigt für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

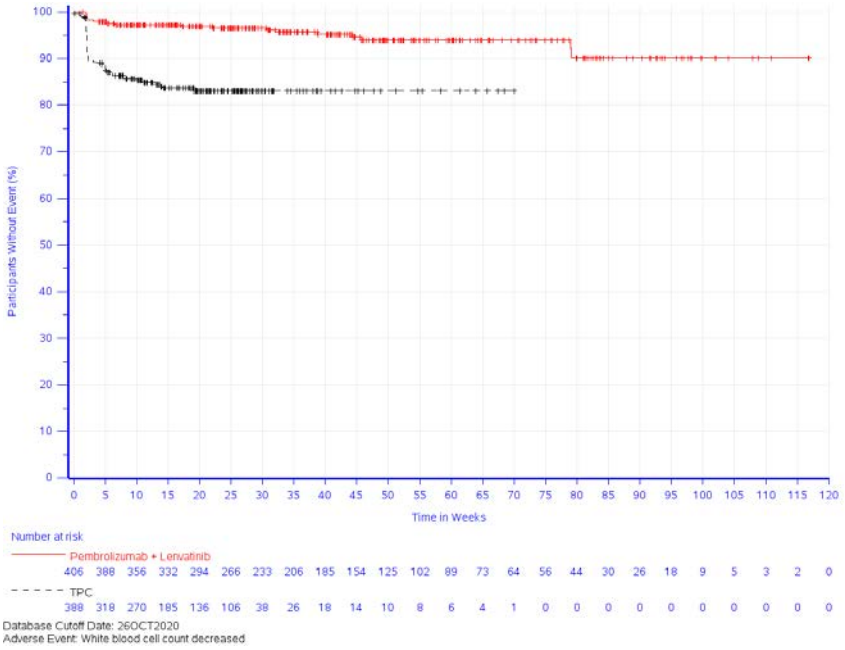

Abbildung 4G-113: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Leukozytenzahl erniedrigt für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

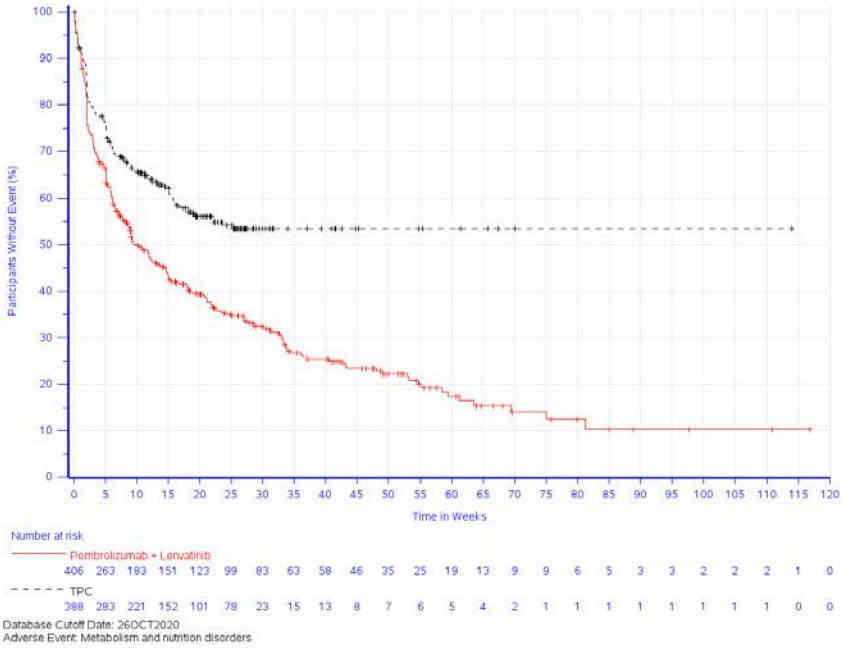

Abbildung 4G-114: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Stoffwechsel- und Ernährungsstörungen für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

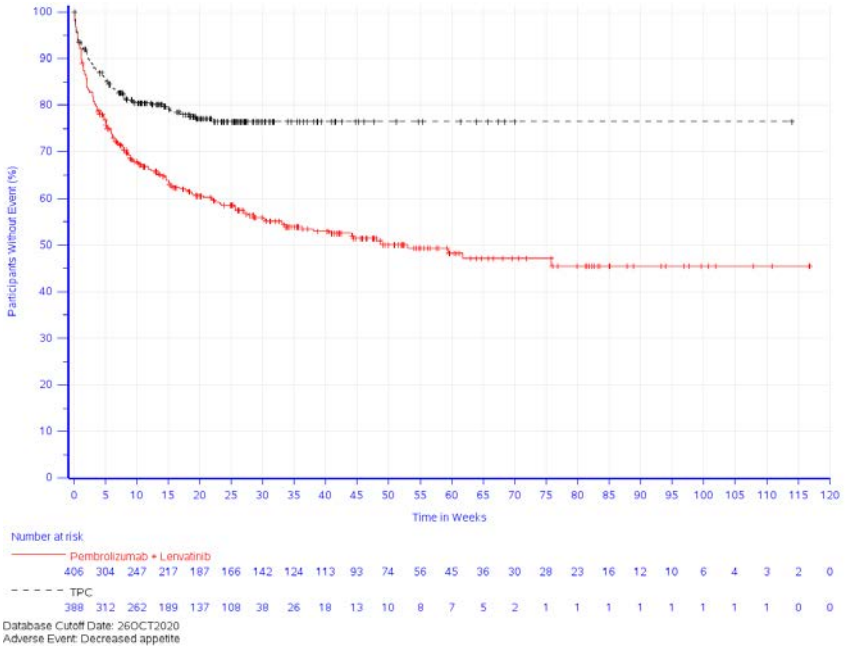

Abbildung 4G-115: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Appetit vermindert für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

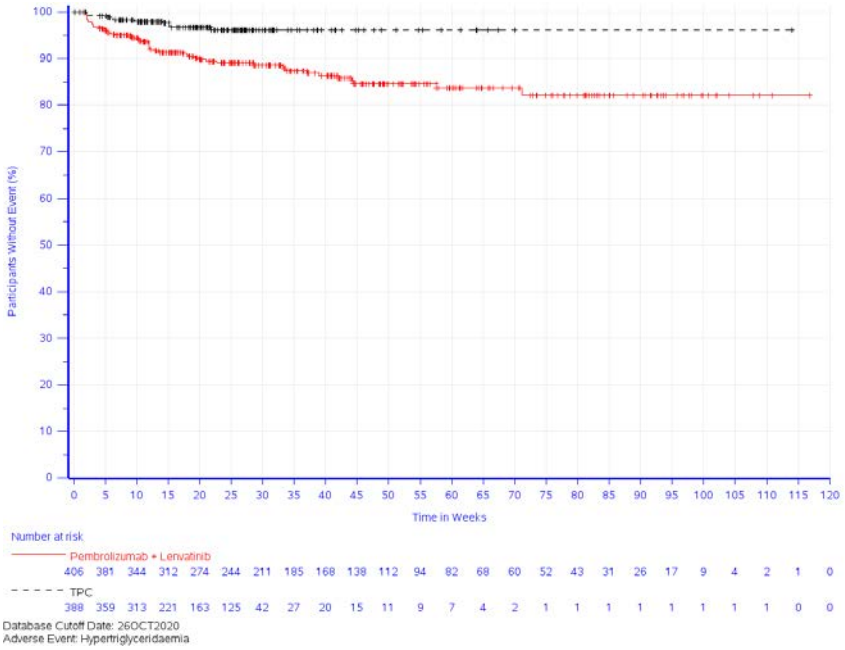

Abbildung 4G-116: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Hypertriglyzeridämie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

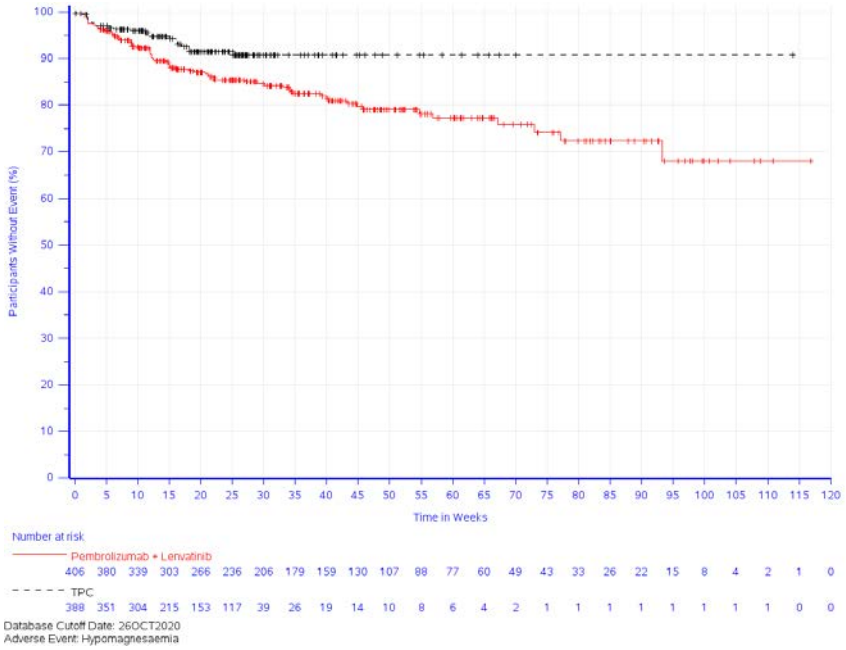

Abbildung 4G-117: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Hypomagnesiaemie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

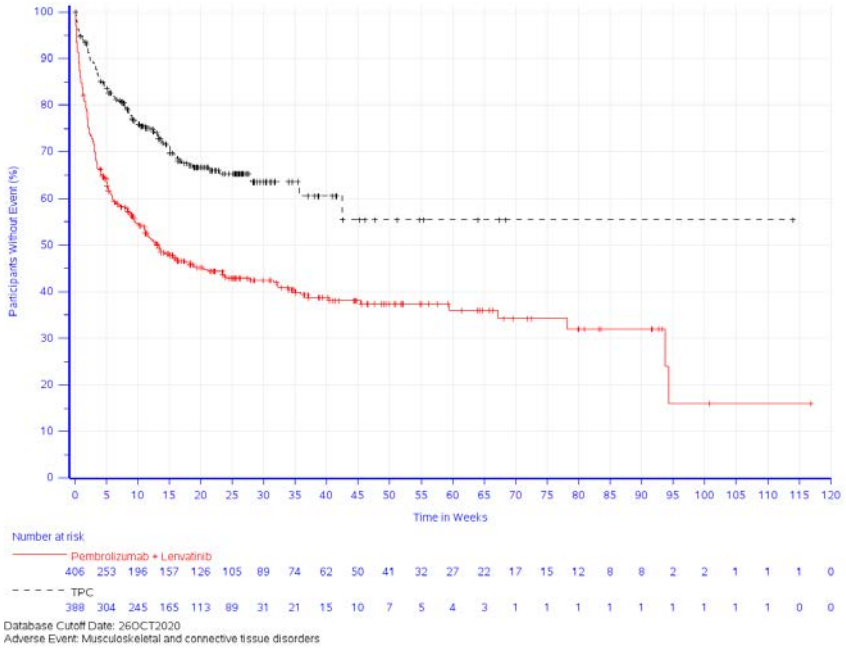

Abbildung 4G-118: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

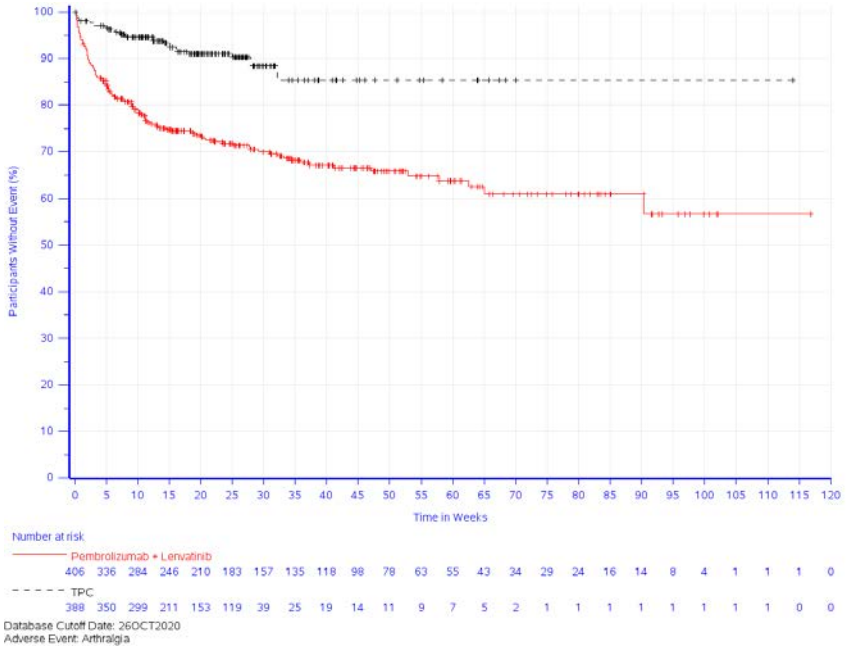

Abbildung 4G-119: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Arthralgie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

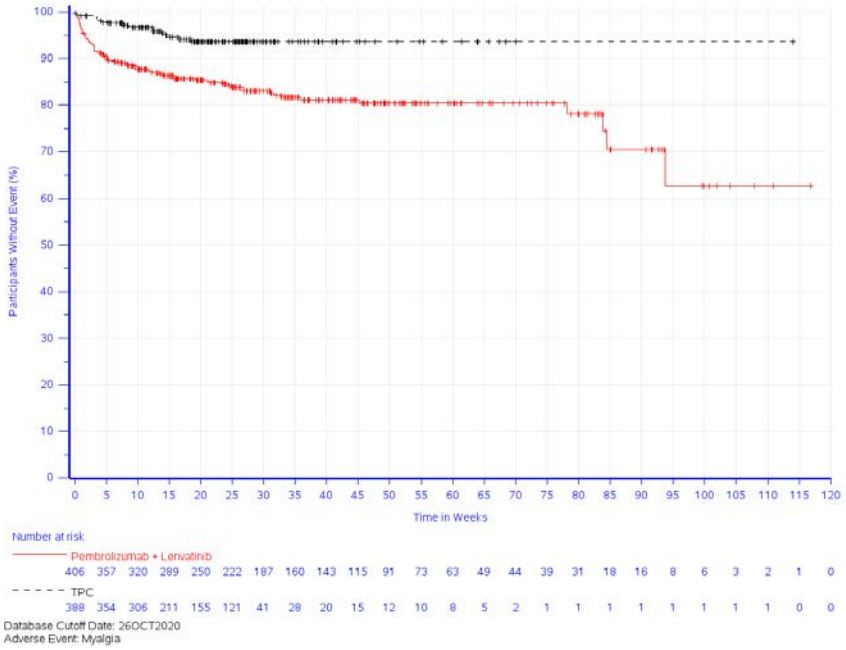

Abbildung 4G-120: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Myalgie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

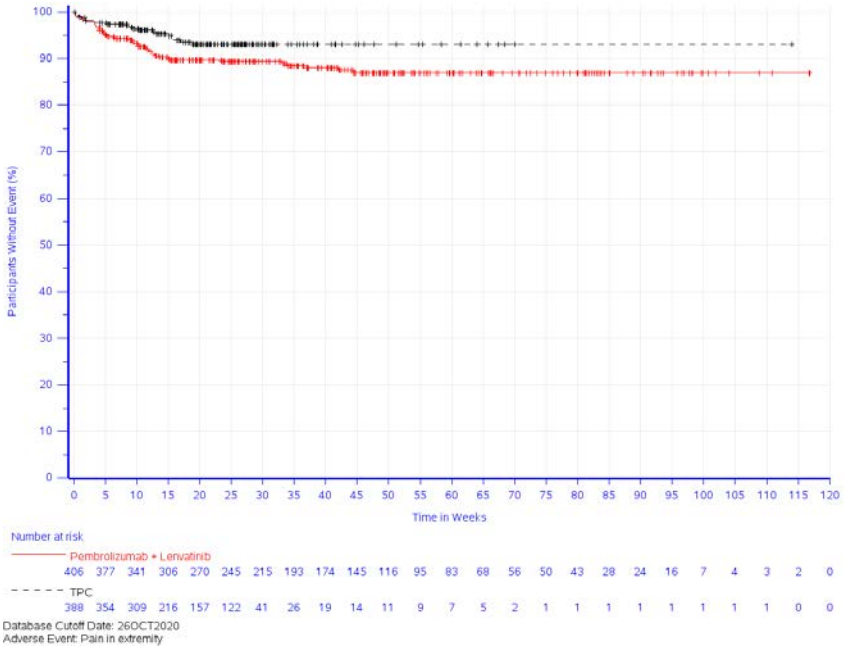

Abbildung 4G-121: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Schmerz in einer Extremitaet für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

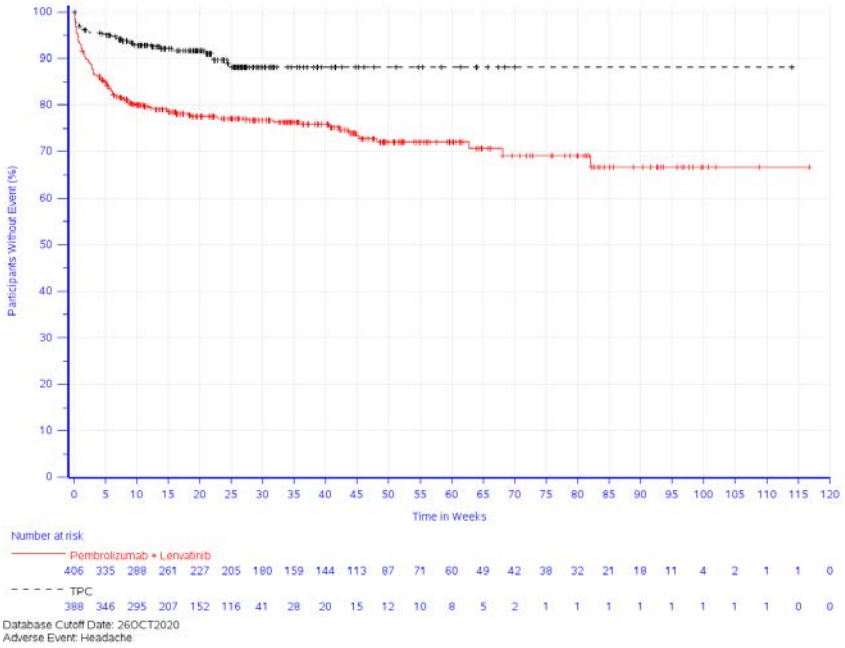

Abbildung 4G-122: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Kopfschmerzen für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

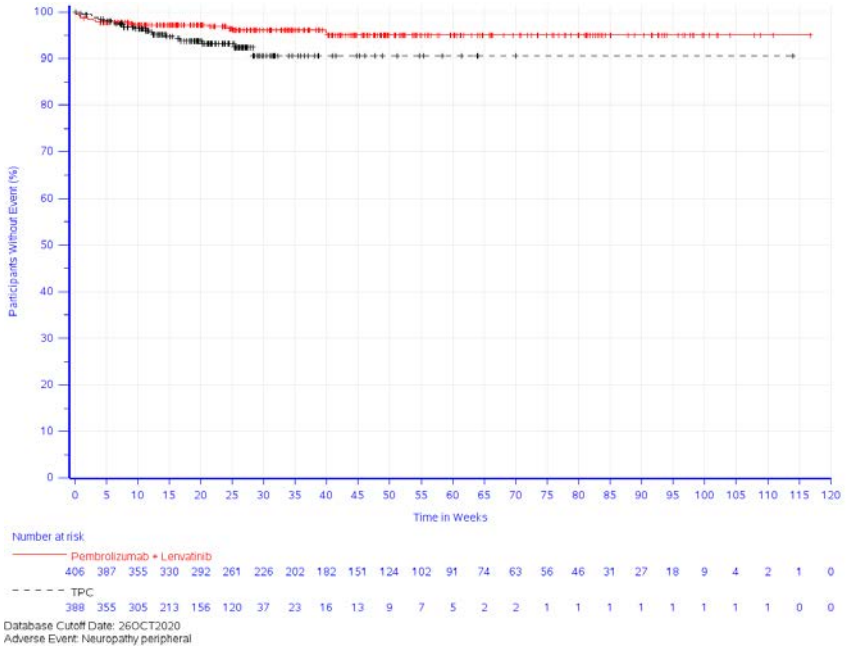

Abbildung 4G-123: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Periphere Neuropathie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

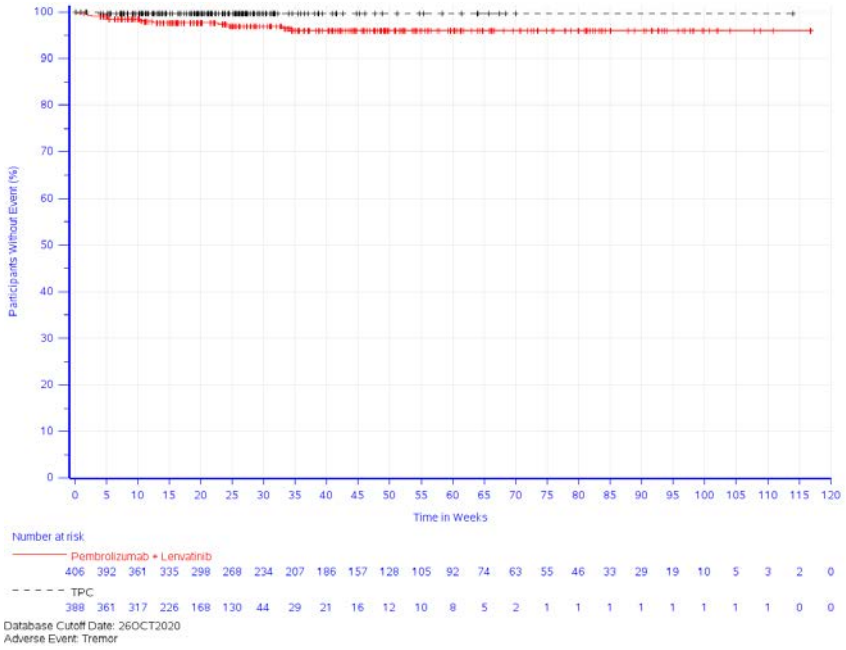

Abbildung 4G-124: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Tremor für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

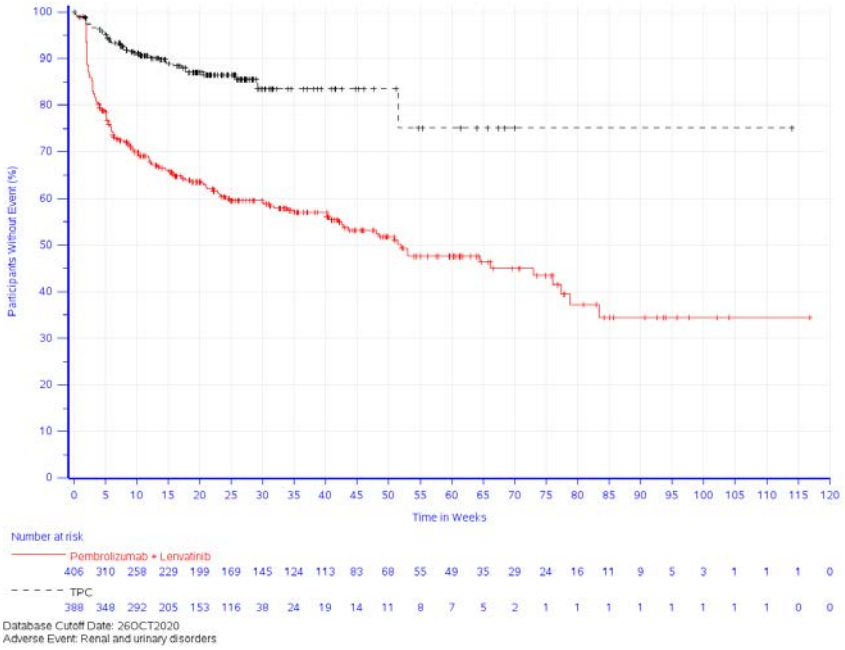

Abbildung 4G-125: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Erkrankungen der Nieren und Harnwege für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

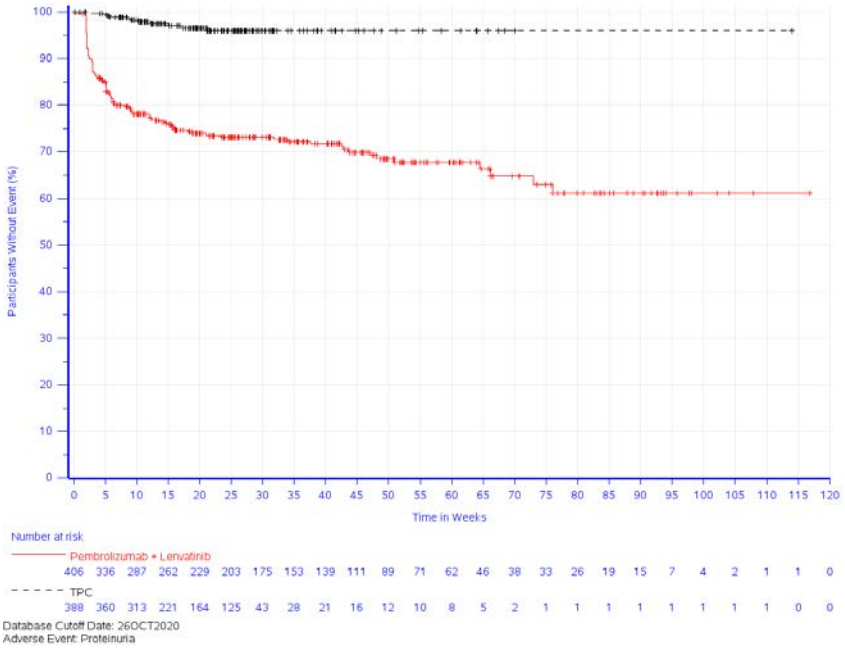

Abbildung 4G-126: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Proteinurie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

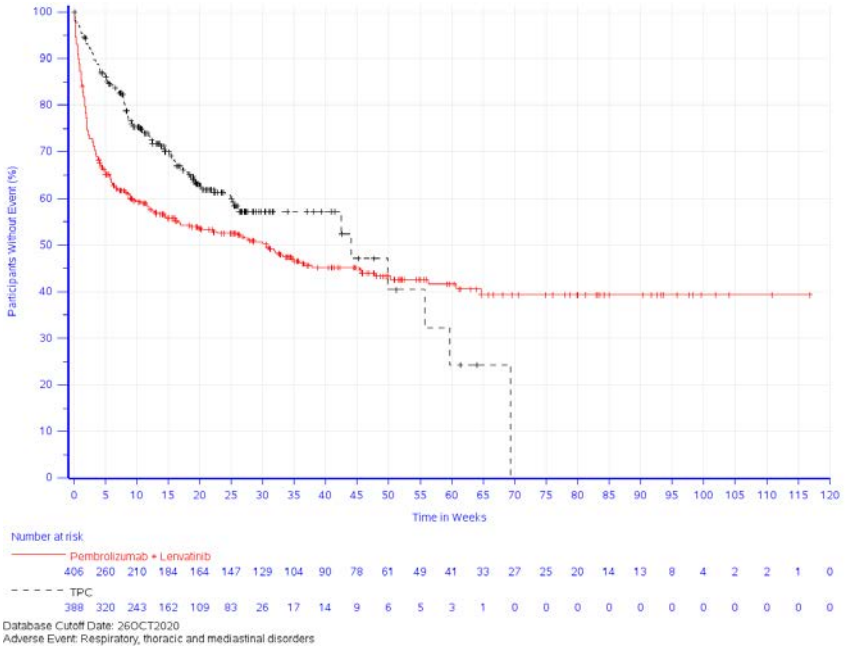

Abbildung 4G-127: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Erkrankungen der Atemwege, des Brustraums und Mediastinums für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

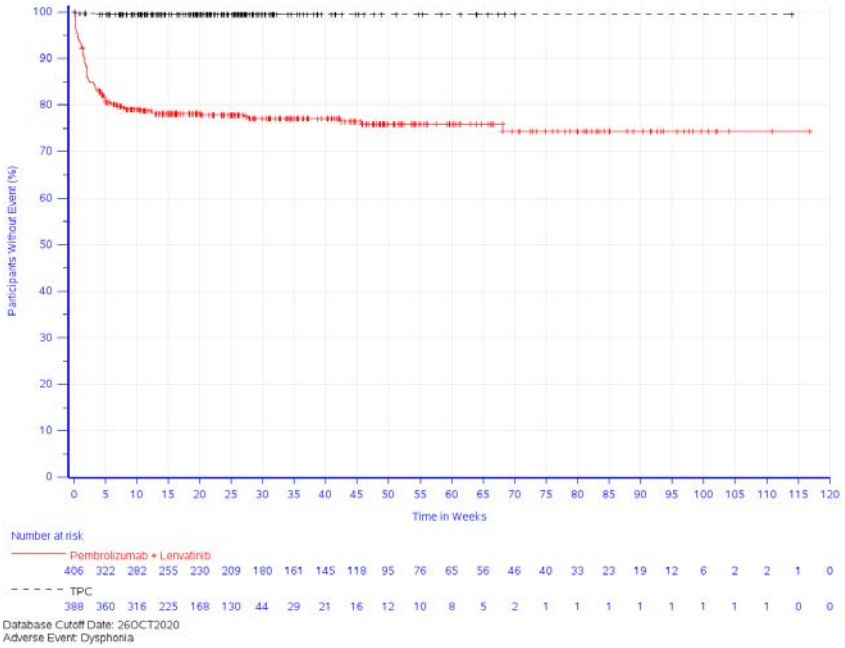

Abbildung 4G-128: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Dysponie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

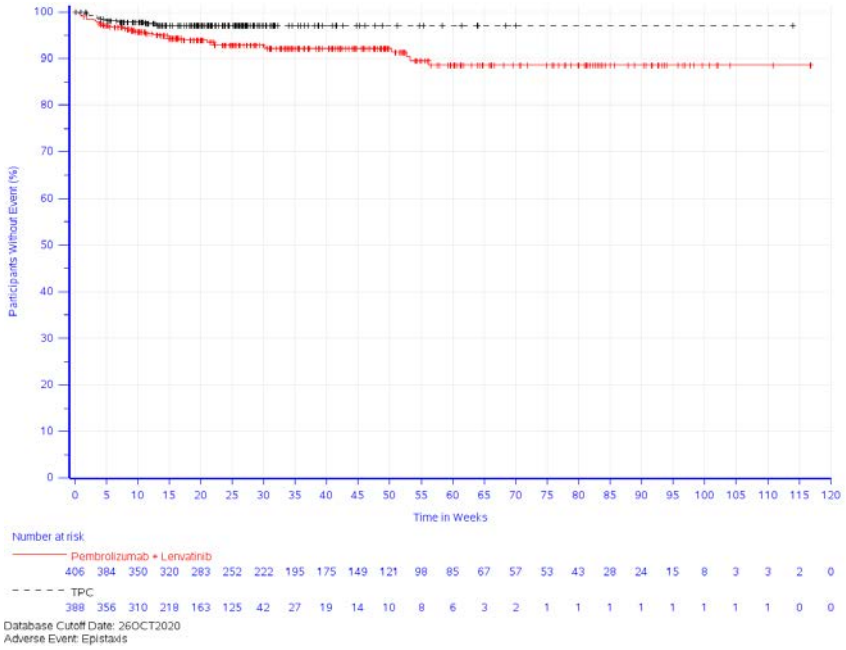

Abbildung 4G-129: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Epistaxis für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

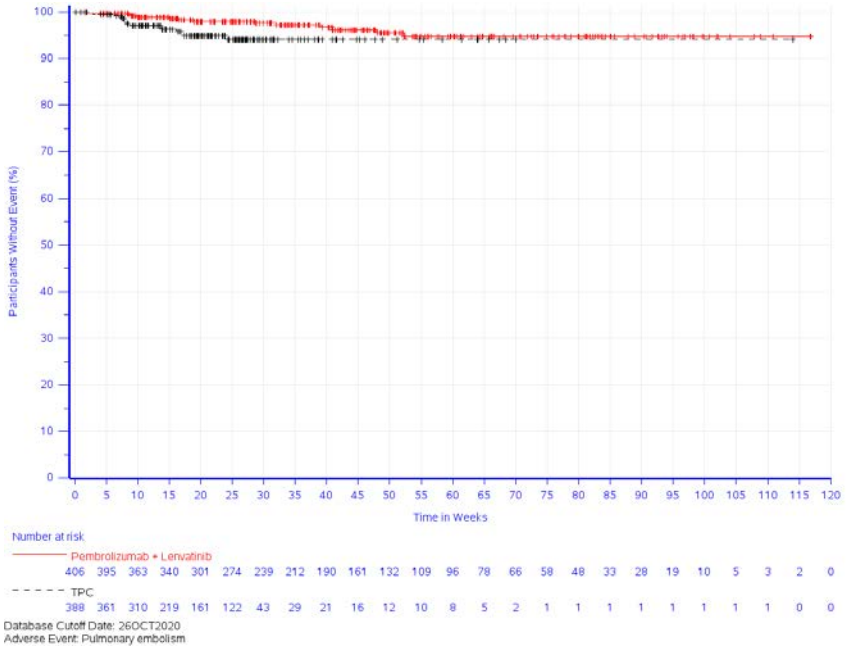

Abbildung 4G-130: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Lungenembolie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

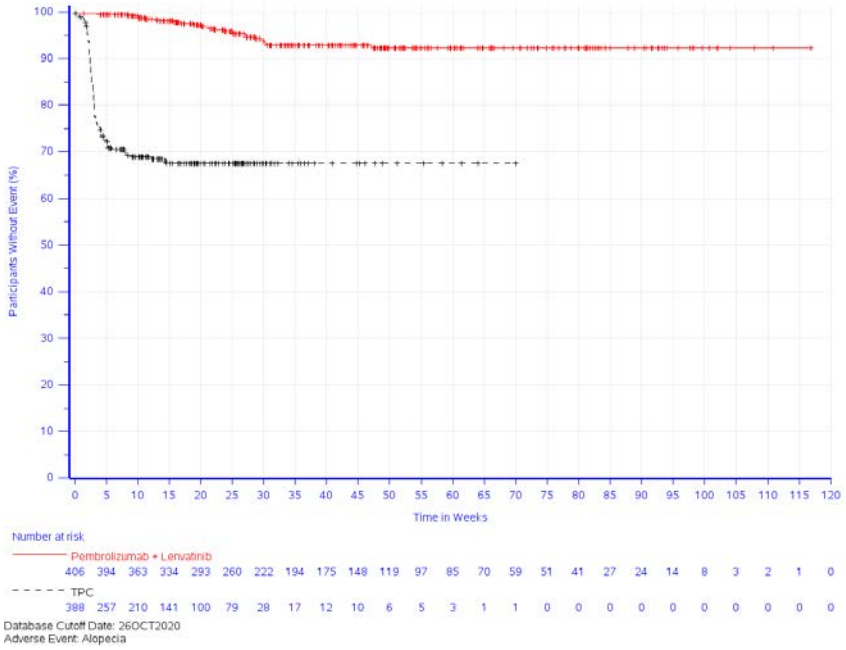

Abbildung 4G-131: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Alopezie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

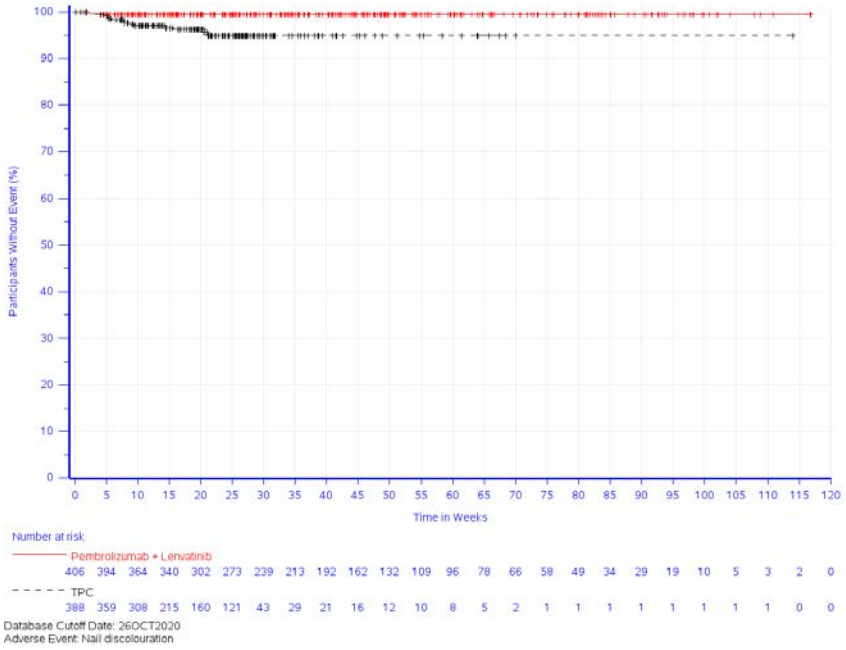

Abbildung 4G-132: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Nagelverfärbung für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

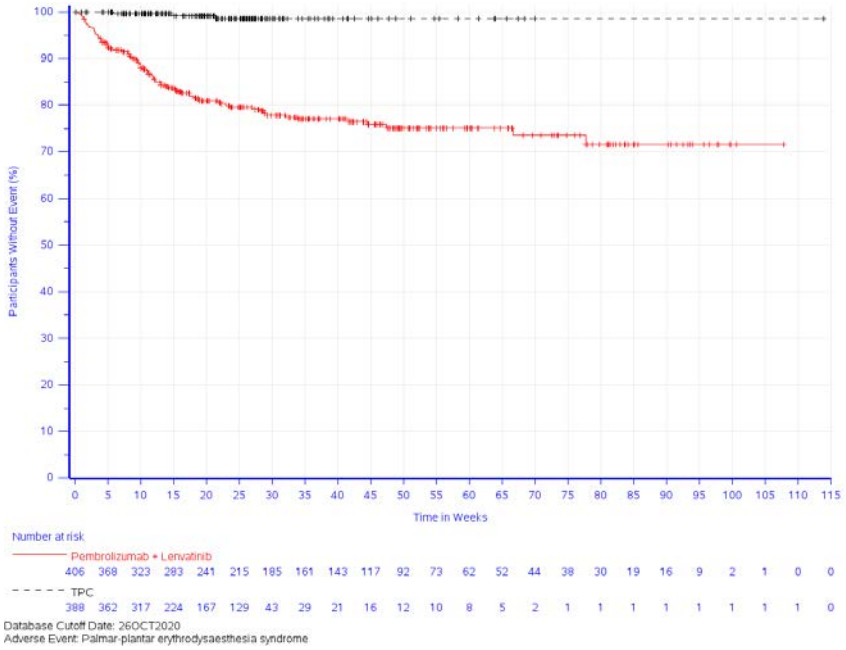

Abbildung 4G-133: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Palmar-plantares Erythrodysaesthesiesyndrom für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

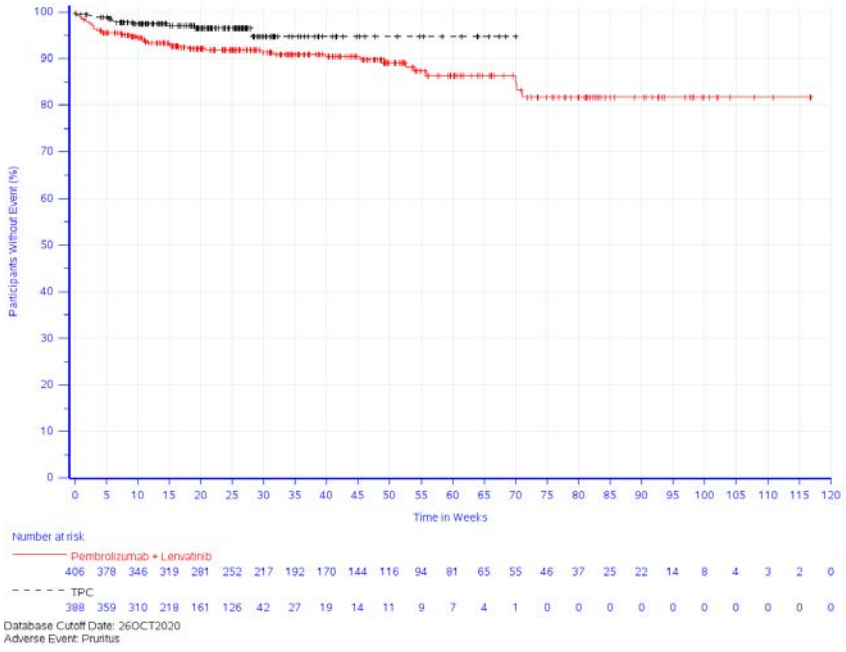

Abbildung 4G-134: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Juckreiz für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

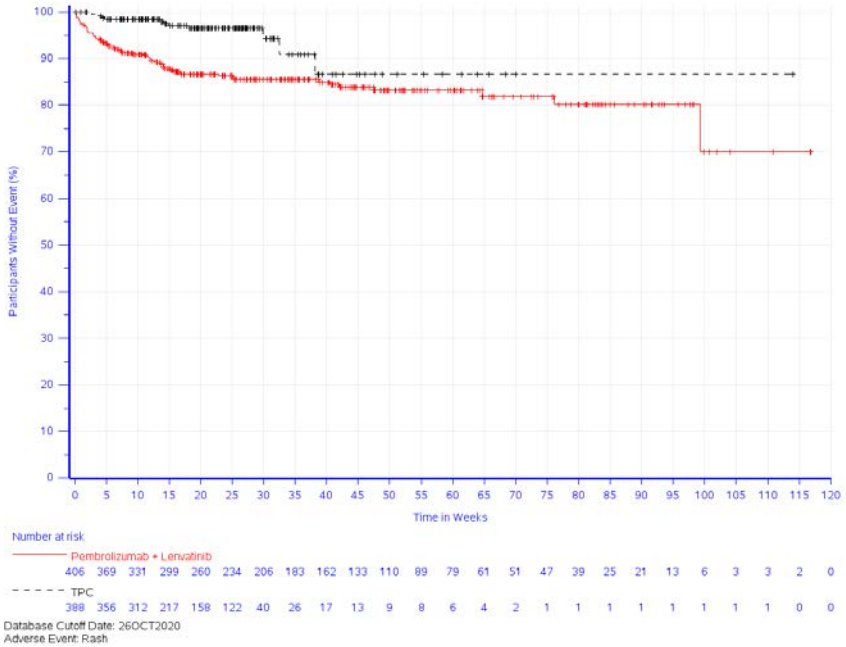

Abbildung 4G-135: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Ausschlag für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

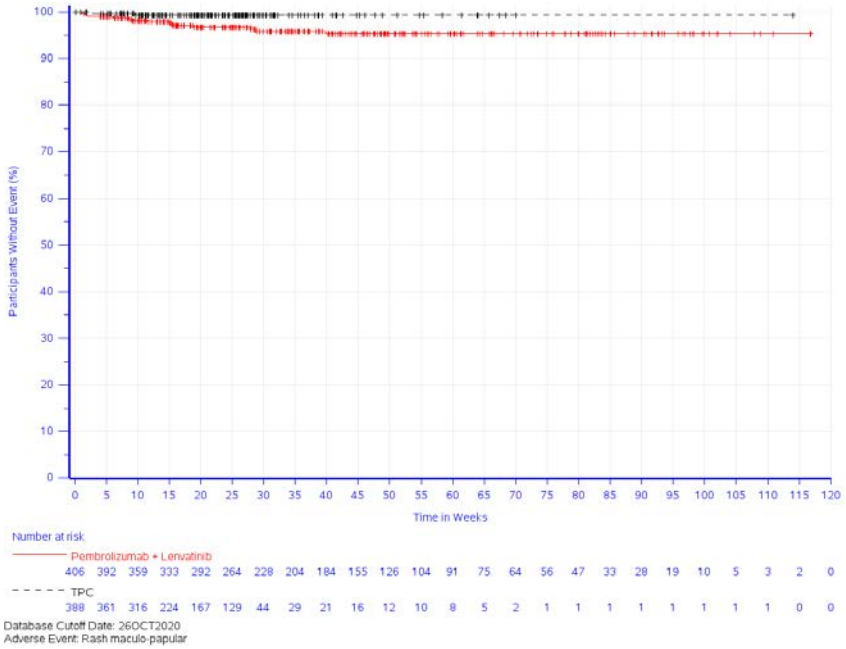

Abbildung 4G-136: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Ausschlag makulo-papuloes für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

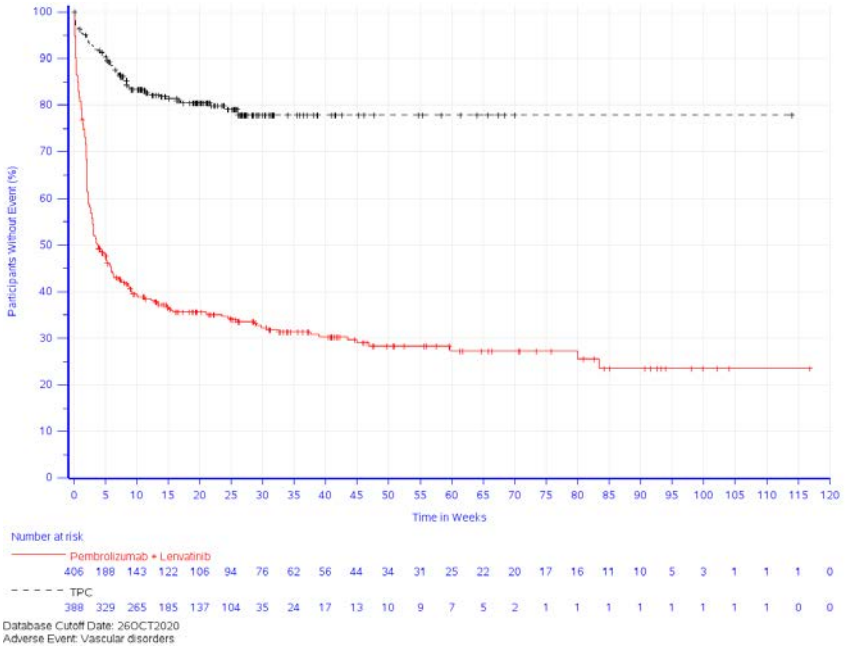

Abbildung 4G-137: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Gefäßerkrankungen für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

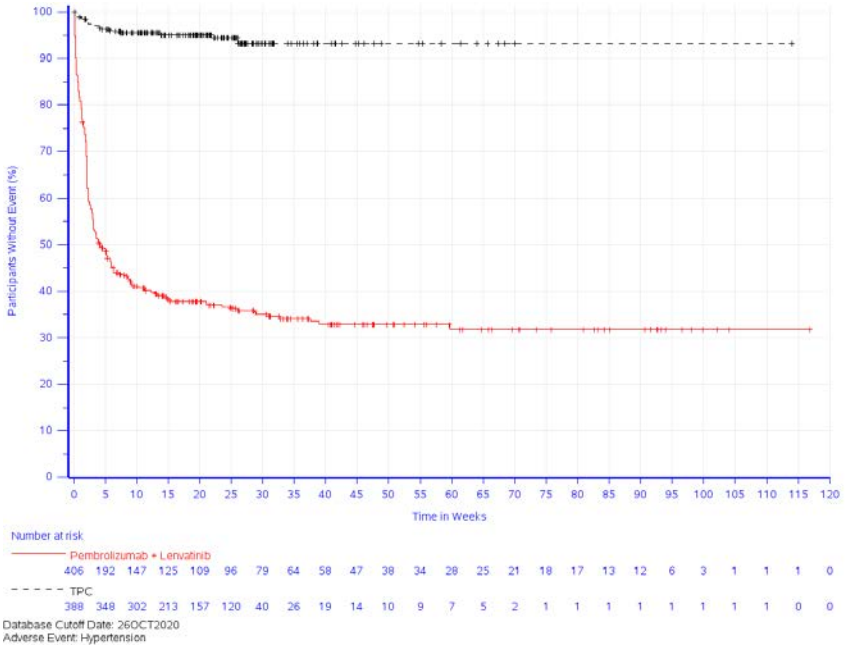

Abbildung 4G-138: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Hypertonie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) der Studie KEYNOTE 775

Schwerwiegende unerwünschte Ereignisse (gegliedert nach SOC und PT)

Tabelle 4G-61: Ergebnisse für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib (N[c]=406)**		**TPC[b] (N[c]=388)**		**Pembrolizumab + Lenvatinib vs. TPC[b]**		
Serious Adverse Events by SOC and PT[d]	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**Adjusted p-Value[h]**
Blood and lymphatic system disorders	7 (1.7)	Not reached [-; -]	30 (7.7)	Not reached [-; -]	0.20 [0.09; 0.45]	< 0.001	< 0.001
Febrile neutropenia	2 (0.5)	Not reached [-; -]	16 (4.1)	Not reached [-; -]	0.09 [0.02; 0.43]	0.002	0.003
Cardiac disorders	14 (3.4)	Not reached [-; -]	12 (3.1)	Not reached [-; -]	0.79 [0.35; 1.75]	0.554	0.554
Endocrine disorders	10 (2.5)	Not reached [-; -]	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.005	0.013
Gastrointestinal disorders	67 (16.5)	Not reached [-; -]	19 (4.9)	Not reached [-; -]	2.91 [1.74; 4.87]	< 0.001	< 0.001
Diarrhoea	10 (2.5)	Not reached [-; -]	3 (0.8)	Not reached [-; -]	2.71 [0.73; 10.02]	0.134	n.s.
General disorders and administration site conditions	24 (5.9)	Not reached [-; -]	15 (3.9)	Not reached [-; -]	1.42 [0.74; 2.72]	0.291	0.344
Hepatobiliary disorders	21 (5.2)	Not reached [-; -]	1 (0.3)	Not reached [-; -]	16.62 [2.23; 123.97]	0.006	0.013
Infections and infestations	57 (14.0)	Not reached [-; -]	28 (7.2)	Not reached [-; -]	1.66 [1.05; 2.63]	0.030	0.056
Urinary tract infection	13 (3.2)	Not reached [-; -]	2 (0.5)	Not reached [-; -]	5.04 [1.13; 22.58]	0.034	0.034
Metabolism and nutrition disorders	29 (7.1)	Not reached [-; -]	6 (1.5)	Not reached [-; -]	3.82 [1.57; 9.29]	0.003	0.010
Musculoskeletal and connective tissue disorders	10 (2.5)	Not reached [-; -]	2 (0.5)	Not reached [-; -]	3.87 [0.84; 17.91]	0.084	0.136
Nervous system disorders	16 (3.9)	Not reached [-; -]	8 (2.1)	Not reached [-; -]	1.83 [0.78; 4.27]	0.165	0.215
Renal and urinary disorders	15 (3.7)	Not reached [-; -]	7 (1.8)	Not reached [-; -]	1.54 [0.62; 3.87]	0.353	0.383
Respiratory, thoracic and mediastinal disorders	12 (3.0)	Not reached [-; -]	13 (3.4)	Not reached [-; -]	0.51 [0.22; 1.19]	0.122	0.176
Vascular disorders	24 (5.9)	Not reached [-; -]	3 (0.8)	Not reached [-; -]	7.01 [2.10; 23.39]	0.002	0.007
Hypertension	17 (4.2)	Not reached [-; -]	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	< 0.001

a: Database Cutoff Date: 26OCT2020

b: Treatment of physician's choice of doxorubicin or paclitaxel

c: Number of participants: all-participants-as-treated population

d: A system organ class or 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 treatment groups

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

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

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

h: Adjusted p-values for treatment comparisons of adverse events at the SOC level were computed using the FDR procedure, and they were computed using the double FDR procedure (dFDR) for comparisons of adverse events at the PT level. Not significant (i.e., 'n.s.') is reported

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib (N[c]=406)		TPC[b] (N[c]=388)		Pembrolizumab + Lenvatinib vs. TPC[b]		
Serious Adverse Events by SOC and PT[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	Adjusted p-Value[h]
for PTs in a SOC when the SOC did not meet the threshold p-value criteria in the first step of the dFDR procedure. Adjusted p-values should be used for evaluating the results in order to reduce the number of false discoveries (i.e., statistical findings) when numerous statistical tests are performed							
CI: Confidence Interval; FDR: False Discovery Rate; n.a.: not applicable (when estimation not possible); n.s.: non-significant (adjusted p-value ≥0.05); PT: Preferred Term; SOC: System Organ Class; TPC: Treatment of Physician's Choice							

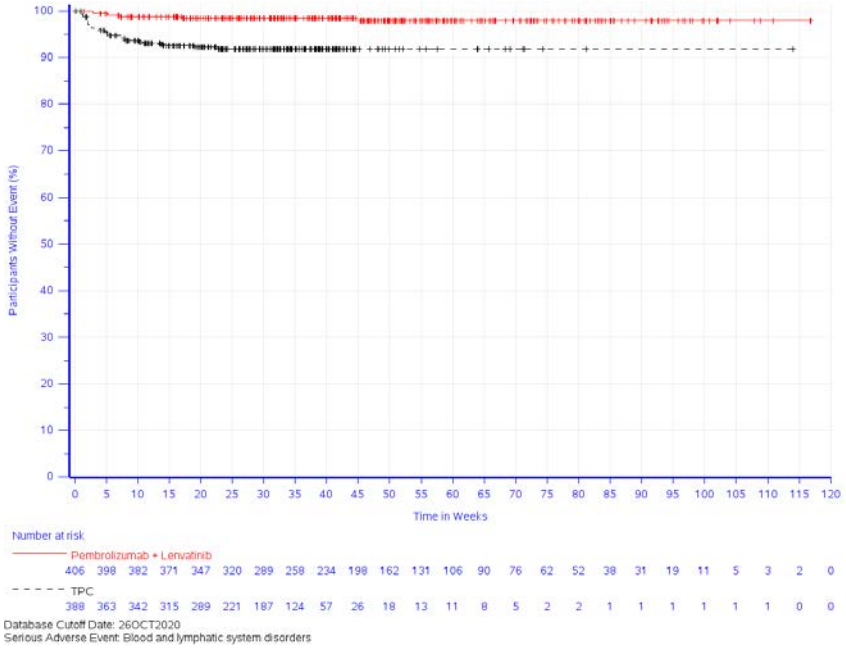

Abbildung 4G-139: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Erkrankungen des Blutes und des Lymphsystems für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) der Studie KEYNOTE 775

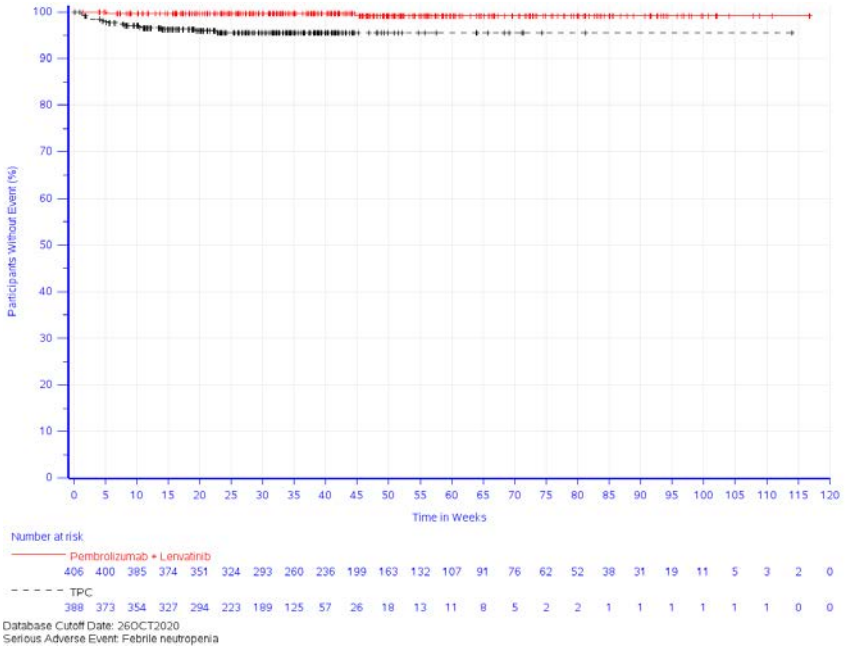

Abbildung 4G-140: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Febrile Neuropenie für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) der Studie KEYNOTE 775

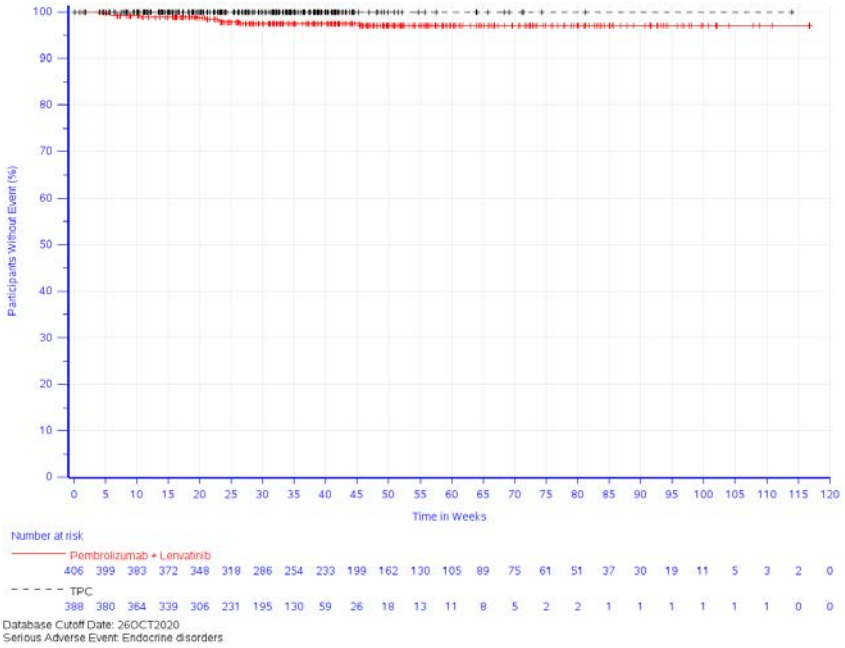

Abbildung 4G-141: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Endokrine Erkrankungen für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) der Studie KEYNOTE 775

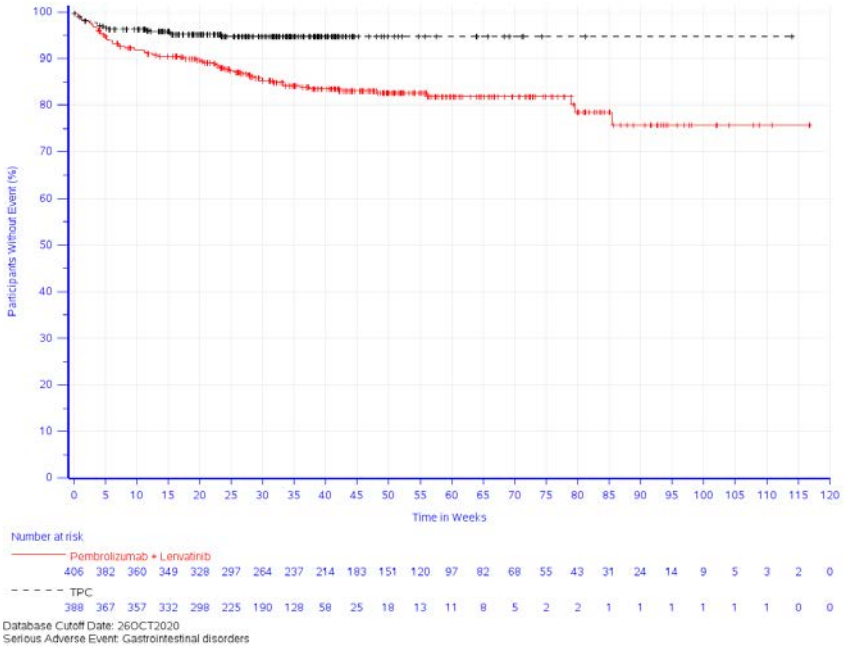

Abbildung 4G-142: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Erkrankungen des Gastrointestinaltrakts für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) der Studie KEYNOTE 775

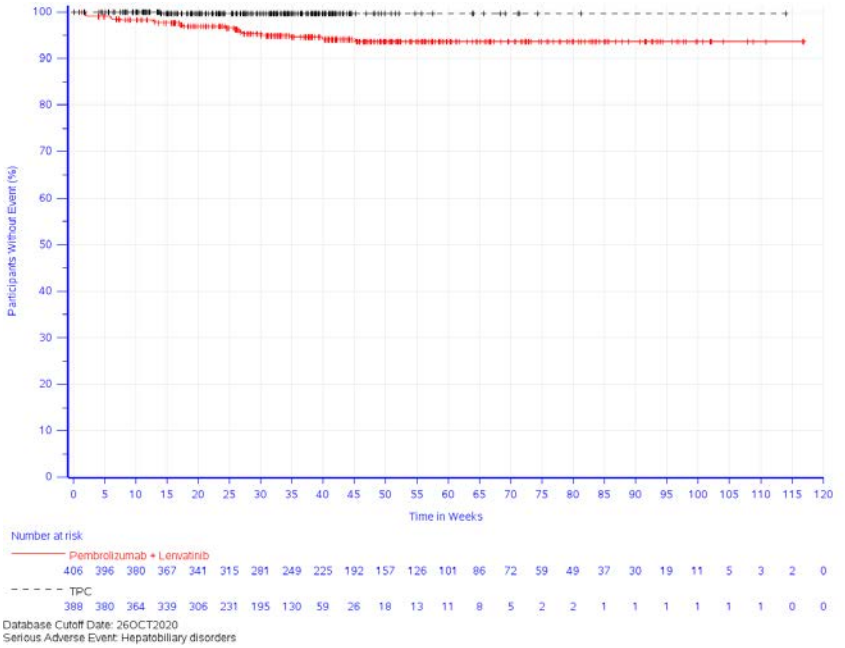

Abbildung 4G-143: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Leber- und Gallenerkrankungen für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) der Studie KEYNOTE 775

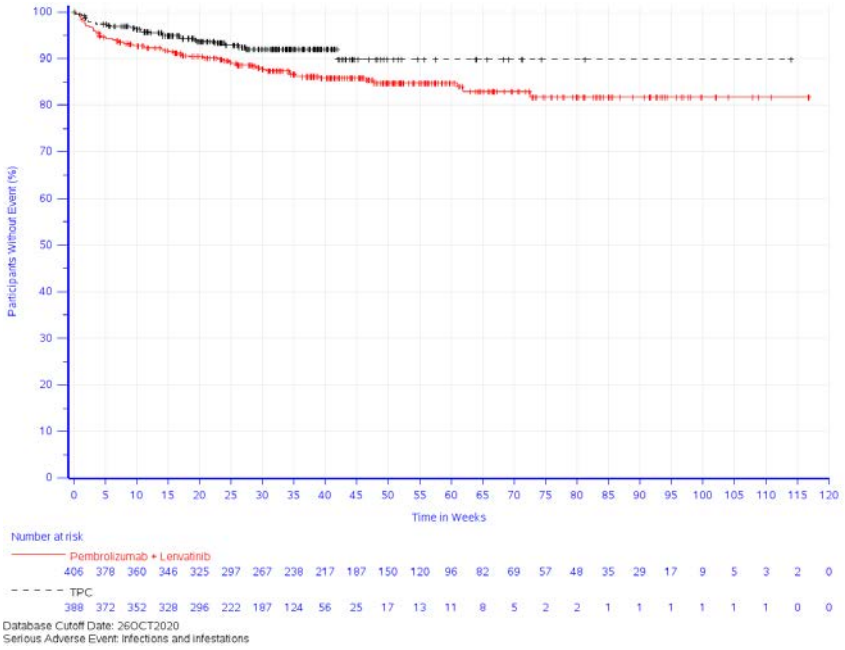

Abbildung 4G-144: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Infektionen und parasitäre Erkrankungen für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) der Studie KEYNOTE 775

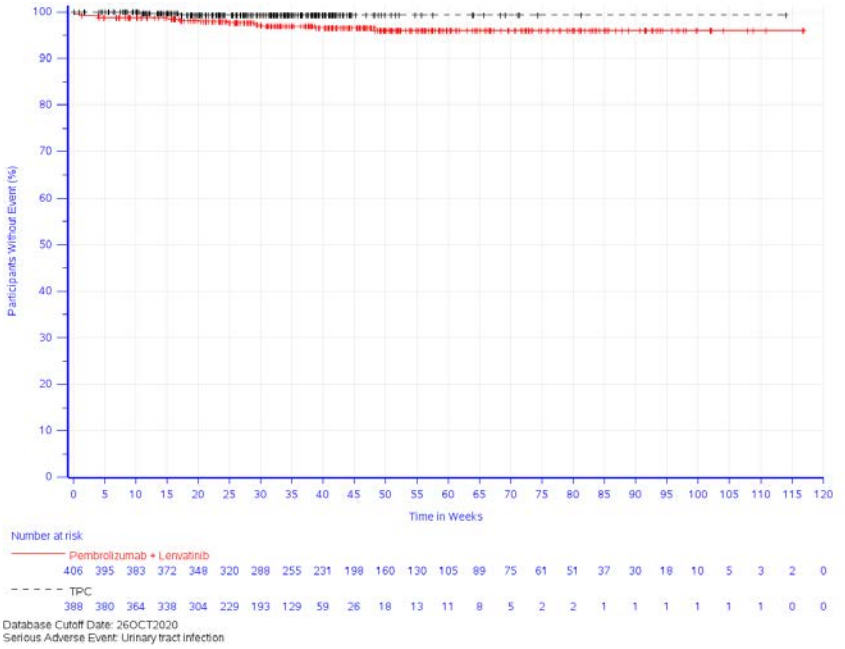

Abbildung 4G-145: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Harnwegsinfektion für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) der Studie KEYNOTE 775

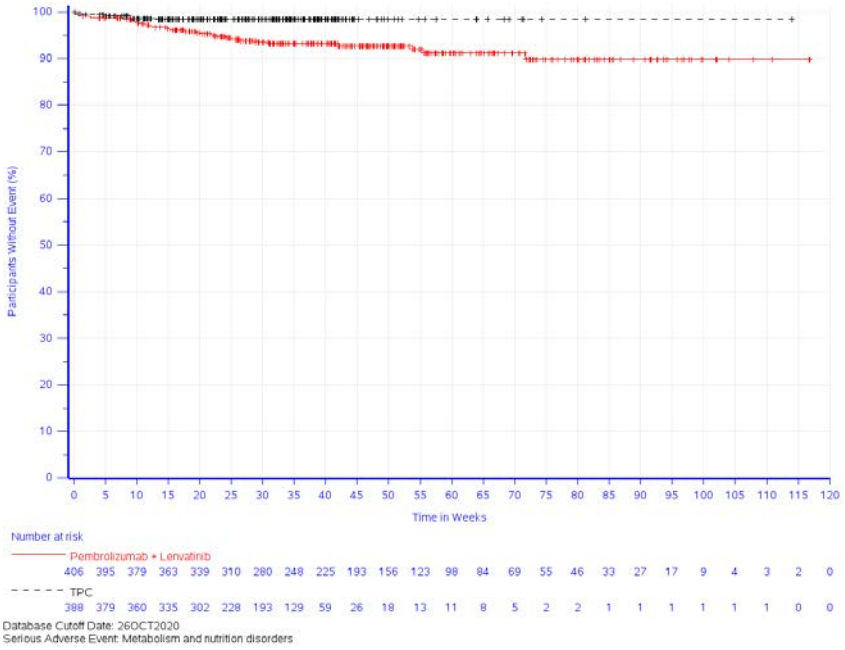

Abbildung 4G-146: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Stoffwechsel- und Ernährungsstörungen für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) der Studie KEYNOTE 775

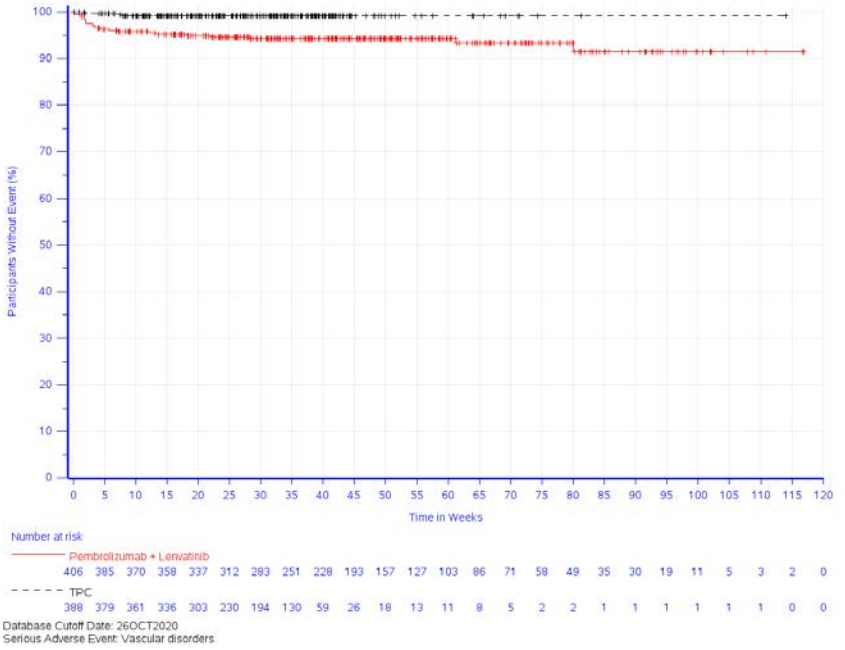

Abbildung 4G-147: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Gefäßerkrankungen für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) der Studie KEYNOTE 775

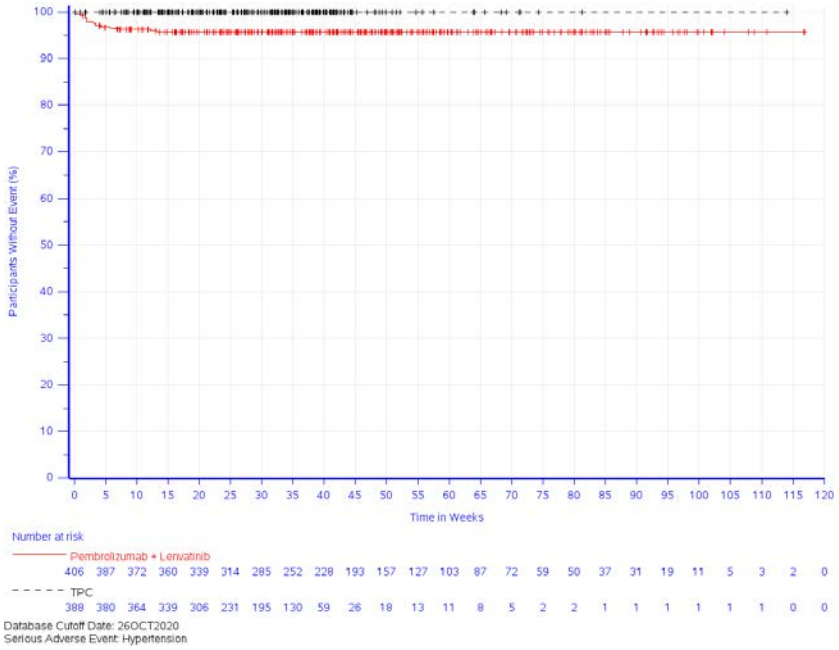

Abbildung 4G-148: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Hypertonie für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) der Studie KEYNOTE 775

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (gegliedert nach SOC und PT)

Tabelle 4G-62: Ergebnisse für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	**Pembrolizumab + Lenvatinib (N[c]=406)**		**TPC[b] (N[c]=388)**		**Pembrolizumab + Lenvatinib vs. TPC[b]**		
Severe Adverse Events (CTCAE-Grade 3-5) by SOC and PT[d]	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**Adjusted p-Value[h]**
Blood and lymphatic system disorders	45 (11.1)	Not reached [-; -]	159 (41.0)	Not reached [25.9; -]	0.18 [0.13; 0.26]	< 0.001	< 0.001
Anaemia	25 (6.2)	Not reached [-; -]	57 (14.7)	Not reached [-; -]	0.32 [0.20; 0.52]	< 0.001	< 0.001
Febrile neutropenia	2 (0.5)	Not reached [-; -]	22 (5.7)	Not reached [-; -]	0.06 [0.01; 0.28]	< 0.001	< 0.001
Leukopenia	0 (0.0)	Not reached [-; -]	31 (8.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	< 0.001
Lymphopenia	7 (1.7)	Not reached [-; -]	13 (3.4)	Not reached [-; -]	0.39 [0.15; 1.00]	0.049	0.069
Neutropenia	7 (1.7)	Not reached [-; -]	100 (25.8)	Not reached [-; -]	0.05 [0.02; 0.12]	< 0.001	< 0.001
Cardiac disorders	11 (2.7)	Not reached [-; -]	12 (3.1)	Not reached [-; -]	0.42 [0.17; 1.00]	0.050	0.062
Endocrine disorders	13 (3.2)	Not reached [-; -]	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.004	0.011
Gastrointestinal disorders	106 (26.1)	Not reached [85.4; -]	41 (10.6)	Not reached [-; -]	1.63 [1.12; 2.37]	0.010	0.014
Abdominal pain	10 (2.5)	Not reached [-; -]	5 (1.3)	Not reached [-; -]	1.42 [0.47; 4.28]	0.537	n.s.
Diarrhoea	31 (7.6)	Not reached [-; -]	8 (2.1)	Not reached [-; -]	1.83 [0.81; 4.15]	0.148	n.s.
Nausea	14 (3.4)	Not reached [-; -]	5 (1.3)	Not reached [-; -]	1.93 [0.68; 5.51]	0.219	n.s.
Vomiting	11 (2.7)	Not reached [-; -]	9 (2.3)	Not reached [-; -]	0.84 [0.34; 2.06]	0.700	n.s.
General disorders and administration site conditions	64 (15.8)	Not reached [-; -]	39 (10.1)	Not reached [-; -]	1.14 [0.76; 1.72]	0.526	0.563
Asthenia	24 (5.9)	Not reached [-; -]	15 (3.9)	Not reached [-; -]	0.91 [0.46; 1.82]	0.795	n.s.
Fatigue	21 (5.2)	Not reached [-; -]	12 (3.1)	Not reached [-; -]	1.29 [0.63; 2.66]	0.487	n.s.
Hepatobiliary disorders	27 (6.7)	Not reached [-; -]	1 (0.3)	Not reached [-; -]	13.95 [1.87; 103.91]	0.010	0.014
Infections and infestations	69 (17.0)	Not reached [-; -]	31 (8.0)	Not reached [-; -]	1.48 [0.95; 2.29]	0.080	0.093
Urinary tract infection	16 (3.9)	Not reached [-; -]	4 (1.0)	Not reached [-; -]	2.38 [0.77; 7.32]	0.131	n.s.
Investigations	133 (32.8)	Not reached [71.7; -]	114 (29.4)	82.1 [-; -]	0.71 [0.54; 0.92]	0.009	0.014
Alanine aminotransferase increased	19	Not reached	3	Not reached	3.64	0.041	0.062

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib (N[c]=406)		TPC[b] (N[c]=388)		Pembrolizumab + Lenvatinib vs. TPC[b]		
Severe Adverse Events (CTCAE-Grade 3-5) by SOC and PT[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	Adjusted p-Value[h]
	(4.7)	[-; -]	(0.8)	[-; -]	[1.05; 12.62]		
Amylase increased	11 (2.7)	Not reached [-; -]	2 (0.5)	Not reached [-; -]	3.77 [0.82; 17.38]	0.089	0.094
Aspartate aminotransferase increased	18 (4.4)	Not reached [-; -]	3 (0.8)	Not reached [-; -]	3.33 [0.96; 11.63]	0.059	0.077
Lipase increased	26 (6.4)	Not reached [-; -]	5 (1.3)	Not reached [-; -]	3.08 [1.15; 8.29]	0.026	0.045
Lymphocyte count decreased	7 (1.7)	Not reached [-; -]	14 (3.6)	Not reached [-; -]	0.43 [0.17; 1.06]	0.066	0.082
Neutrophil count decreased	10 (2.5)	Not reached [-; -]	83 (21.4)	82.1 [-; -]	0.08 [0.04; 0.15]	< 0.001	< 0.001
Platelet count decreased	11 (2.7)	Not reached [-; -]	3 (0.8)	Not reached [-; -]	3.07 [0.85; 11.14]	0.088	0.094
Weight decreased	42 (10.3)	Not reached [-; -]	1 (0.3)	Not reached [-; -]	16.29 [2.21; 119.86]	0.006	0.013
White blood cell count decreased	6 (1.5)	Not reached [-; -]	41 (10.6)	Not reached [-; -]	0.11 [0.05; 0.27]	< 0.001	< 0.001
Metabolism and nutrition disorders	97 (23.9)	Not reached [-; -]	27 (7.0)	Not reached [-; -]	2.44 [1.58; 3.77]	< 0.001	< 0.001
Decreased appetite	32 (7.9)	Not reached [-; -]	2 (0.5)	Not reached [-; -]	10.39 [2.47; 43.70]	0.001	0.004
Hypokalaemia	21 (5.2)	Not reached [-; -]	6 (1.5)	Not reached [-; -]	2.35 [0.93; 5.93]	0.070	0.082
Hyponatraemia	18 (4.4)	Not reached [-; -]	4 (1.0)	Not reached [-; -]	3.38 [1.14; 10.07]	0.029	0.046
Musculoskeletal and connective tissue disorders	30 (7.4)	Not reached [-; -]	5 (1.3)	Not reached [-; -]	3.65 [1.39; 9.57]	0.008	0.014
Nervous system disorders	14 (3.4)	Not reached [-; -]	11 (2.8)	Not reached [-; -]	0.92 [0.41; 2.06]	0.832	0.832
Renal and urinary disorders	47 (11.6)	Not reached [-; -]	12 (3.1)	Not reached [-; -]	2.54 [1.33; 4.87]	0.005	0.012
Acute kidney injury	12 (3.0)	Not reached [-; -]	4 (1.0)	Not reached [-; -]	1.84 [0.57; 5.91]	0.307	0.307
Proteinuria	22 (5.4)	Not reached [-; -]	1 (0.3)	Not reached [-; -]	16.16 [2.16; 120.89]	0.007	0.013
Respiratory, thoracic and mediastinal disorders	20 (4.9)	Not reached [-; -]	26 (6.7)	Not reached [-; -]	0.44 [0.23; 0.82]	0.009	0.014
Pulmonary embolism	11 (2.7)	Not reached [-; -]	13 (3.4)	Not reached [-; -]	0.45 [0.19; 1.07]	0.071	n.s.
Skin and subcutaneous tissue disorders	31 (7.6)	Not reached [-; -]	3 (0.8)	Not reached [-; -]	6.63 [2.01; 21.89]	0.002	0.007
Palmar-plantar erythrodysaesthesia syndrome	11 (2.7)	Not reached [-; -]	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.006	0.013
Vascular disorders	159 (39.2)	Not reached [68.3; -]	15 (3.9)	Not reached [63.3; -]	10.86 [6.38; 18.46]	< 0.001	< 0.001
Hypertension	154	Not reached	9	Not reached	17.49	< 0.001	< 0.001

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib (N[c]=406)		TPC[b] (N[c]=388)		Pembrolizumab + Lenvatinib vs. TPC[b]		
Severe Adverse Events (CTCAE-Grade 3-5) by SOC and PT[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	Adjusted p-Value[h]
	(37.9)	[73.0; -]	(2.3)	[63.3; -]	[8.92; 34.30]		

a: Database Cutoff Date: 26OCT2020

b: Treatment of physician's choice of doxorubicin or paclitaxel

c: Number of participants: all-participants-as-treated population

d: A system organ class or 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 treatment groups

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

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

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

h: Adjusted p-values for treatment comparisons of adverse events at the SOC level were computed using the FDR procedure, and they were computed using the double FDR procedure (dFDR) for comparisons of adverse events at the PT level. Not significant (i.e., 'n.s.') is reported for PTs in a SOC when the SOC did not meet the threshold p-value criteria in the first step of the dFDR procedure. Adjusted p-values should be used for evaluating the results in order to reduce the number of false discoveries (i.e., statistical findings) when numerous statistical tests are performed

CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; FDR: False Discovery Rate; n.a.: not applicable (when estimation not possible); n.s.: non-significant (adjusted p-value ≥0.05); PT: Preferred Term; SOC: System Organ Class; TPC: Treatment of Physician 's Choice

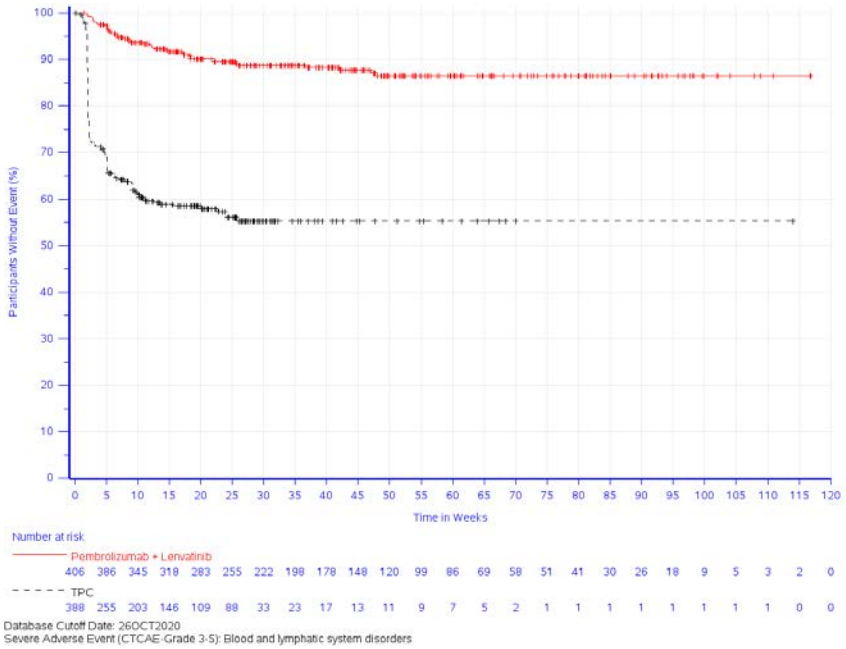

Abbildung 4G-149: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Erkrankungen des Blutes und des Lymphsystems für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

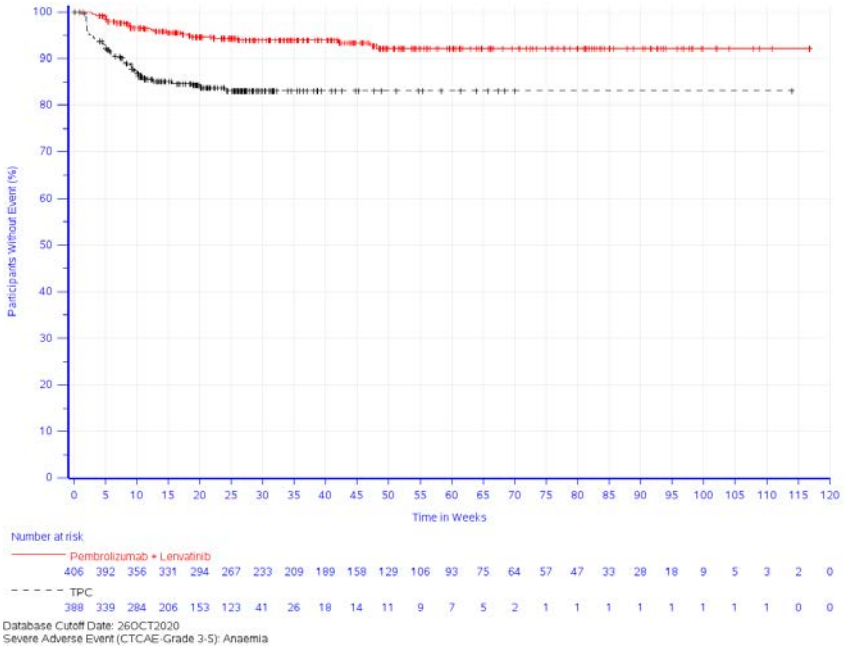

Abbildung 4G-150: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Anämie für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

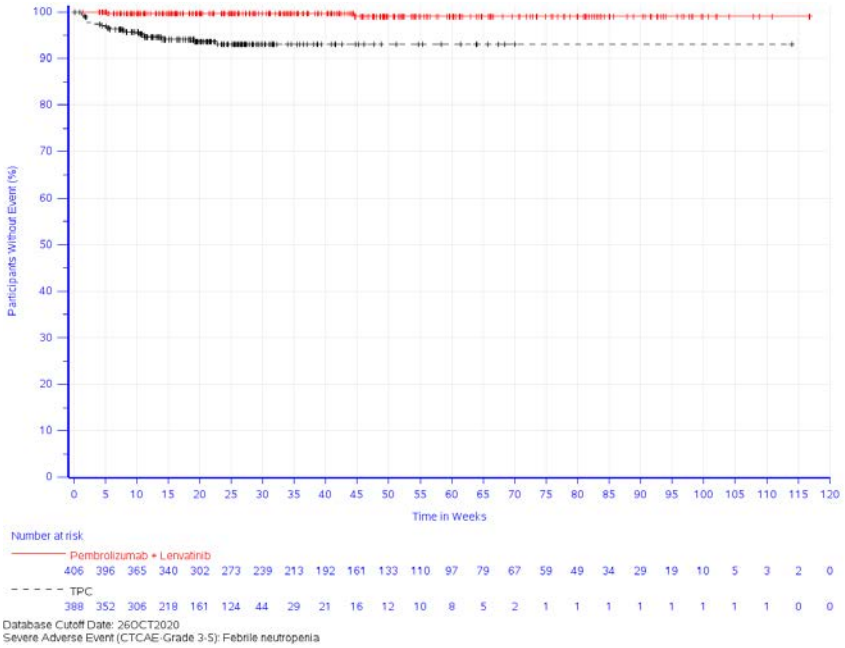

Abbildung 4G-151: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Febrile Neuropenie für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

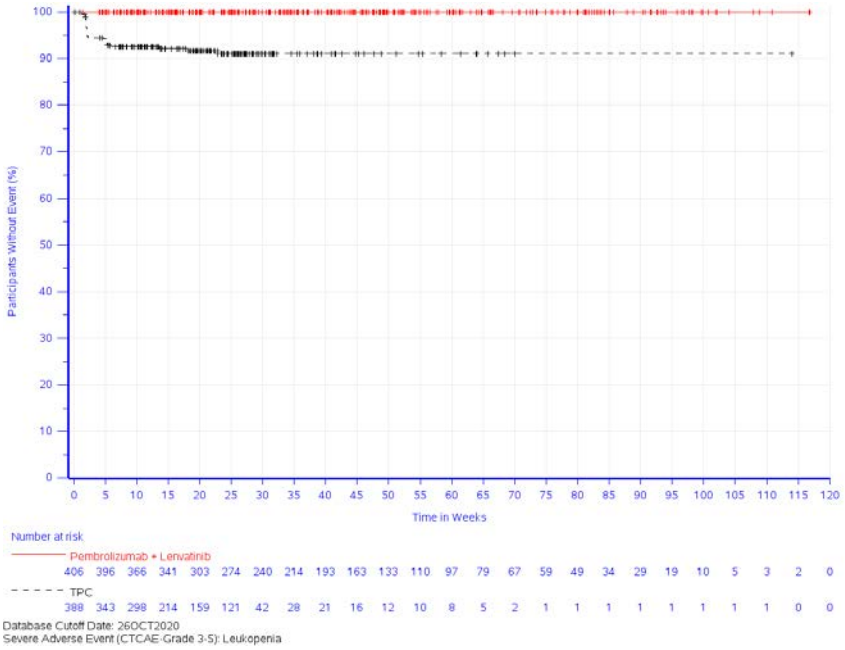

Abbildung 4G-152: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Leukopenie für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

Abbildung 4G-153: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Lymphopenie für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

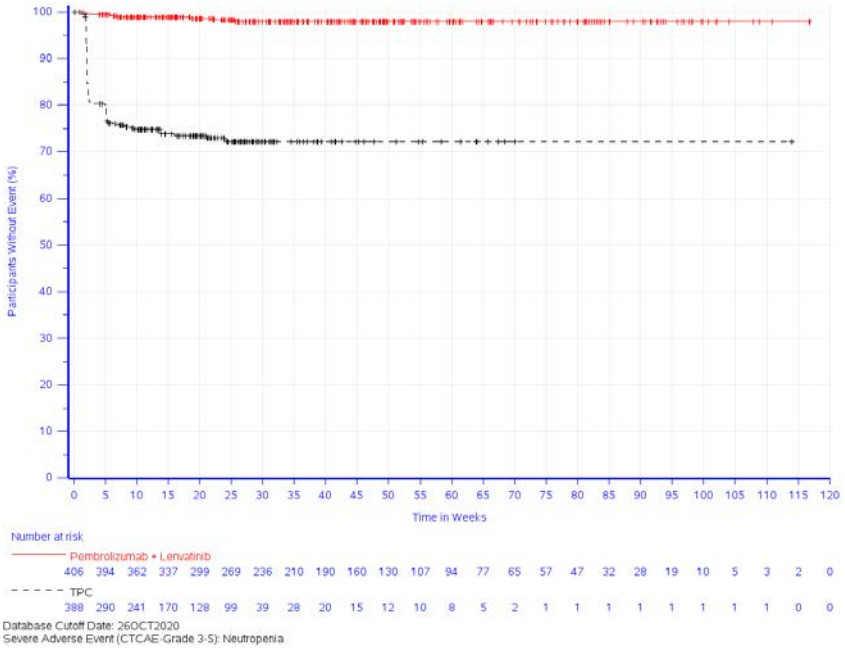

Abbildung 4G-154: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Neutropenie für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

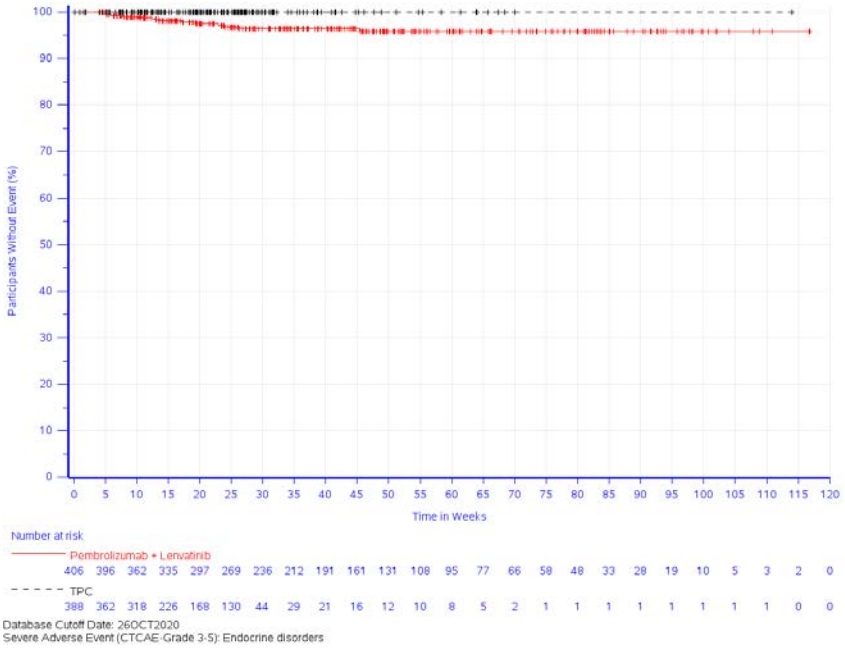

Abbildung 4G-155: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Endokrine Erkrankungen für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

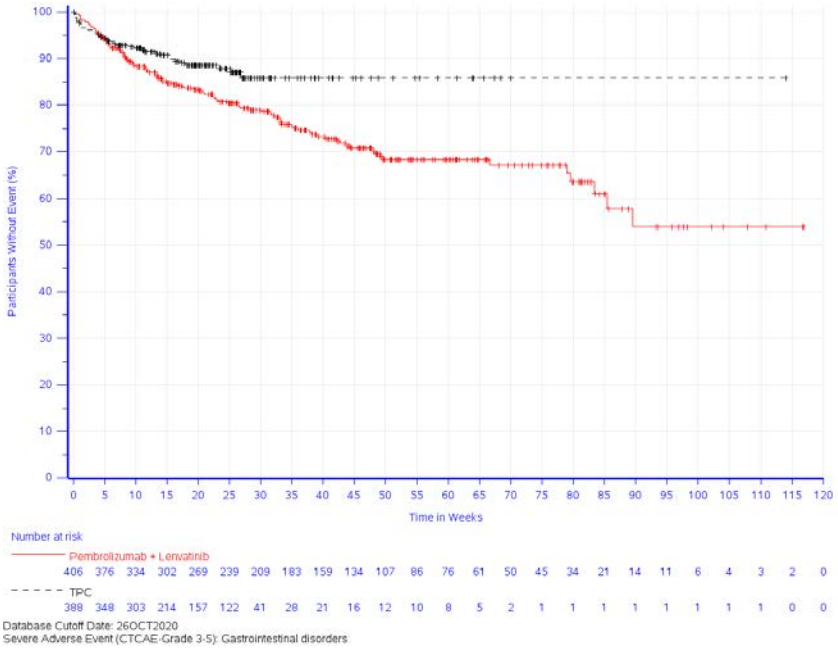

Abbildung 4G-156: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Erkrankungen des Gastrointestinaltrakts für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

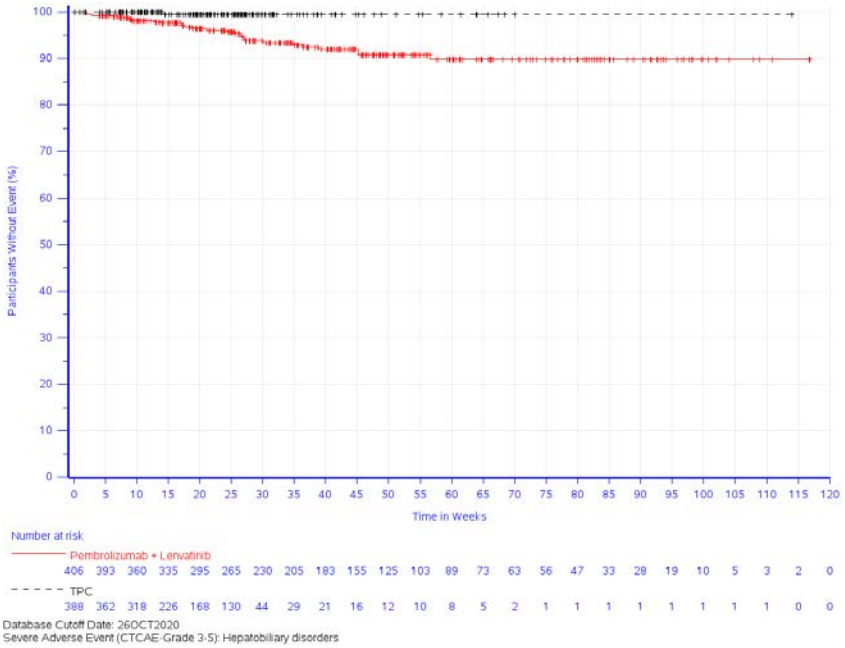

Abbildung 4G-157: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Leber- und Gallenerkrankungen für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

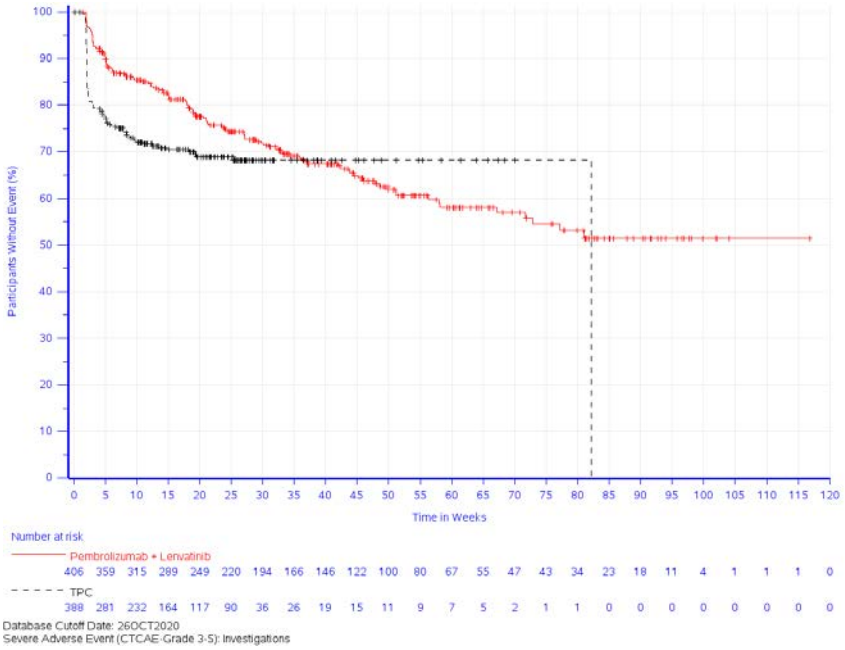

Abbildung 4G-158: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Untersuchungen für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

Abbildung 4G-159: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Alaninaminotransferase erhöht für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

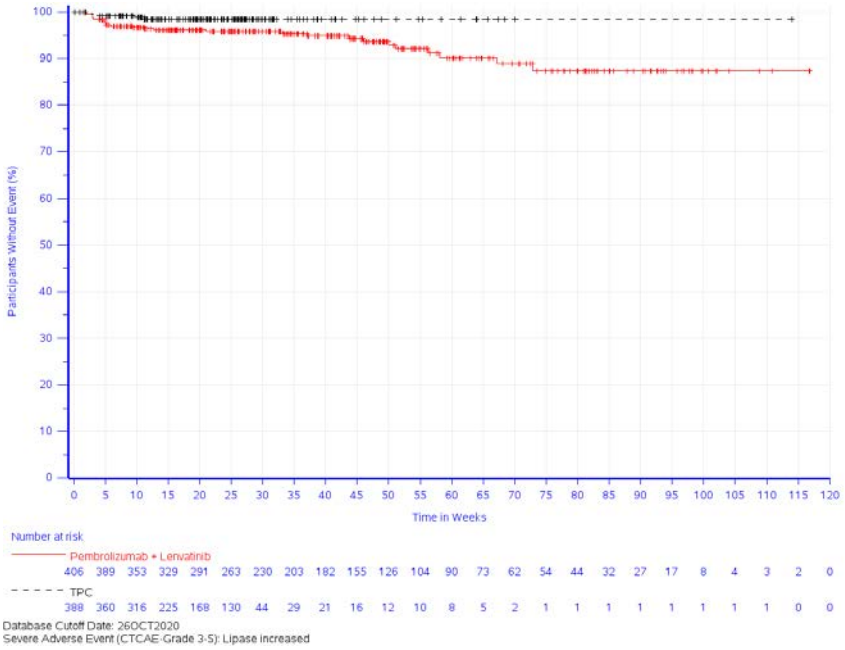

Abbildung 4G-160: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Lipase erhöht für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

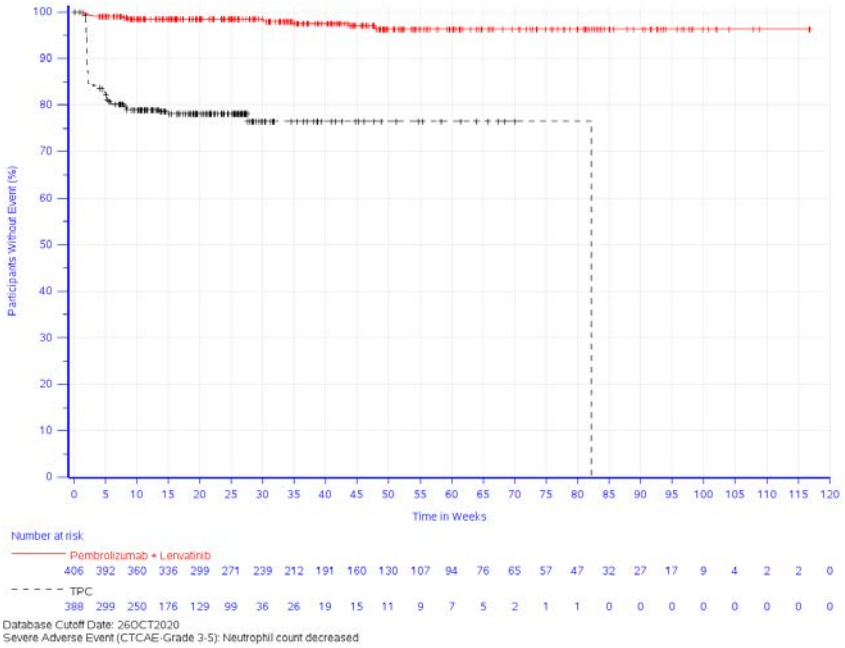

Abbildung 4G-161: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Neutrophilenzahl erniedrigt für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

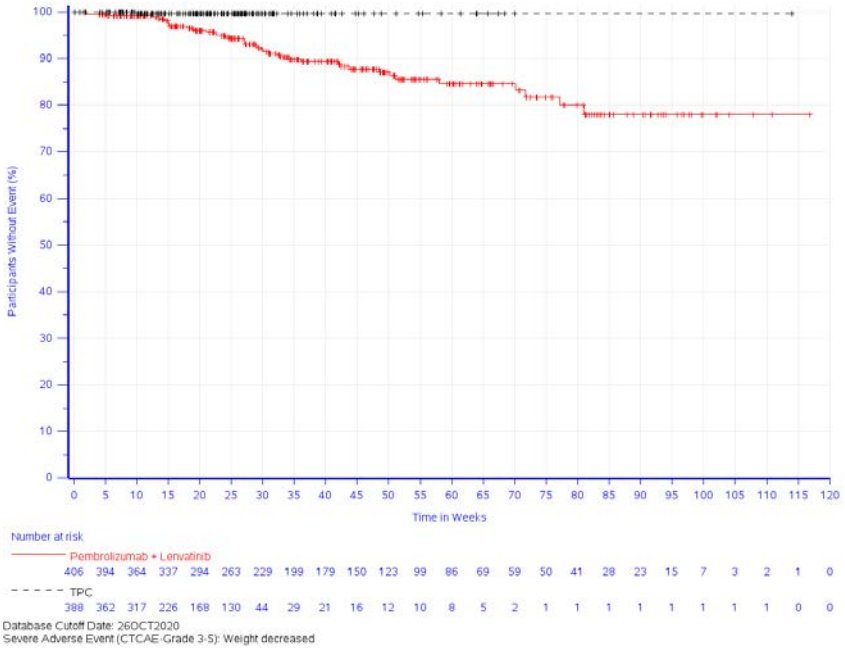

Abbildung 4G-162: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Gewicht erniedrigt für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

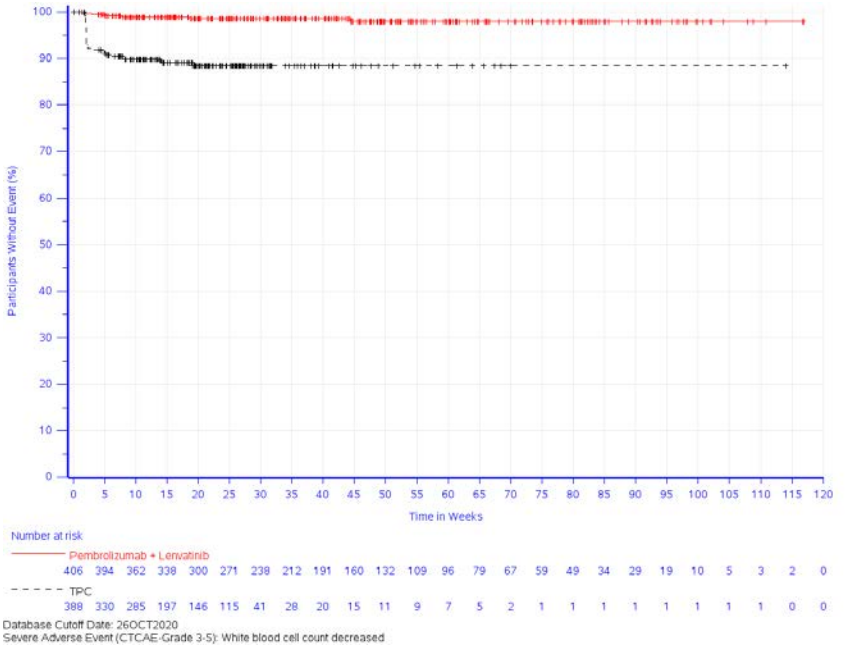

Abbildung 4G-163: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Leukozytenzahl erniedrigt für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

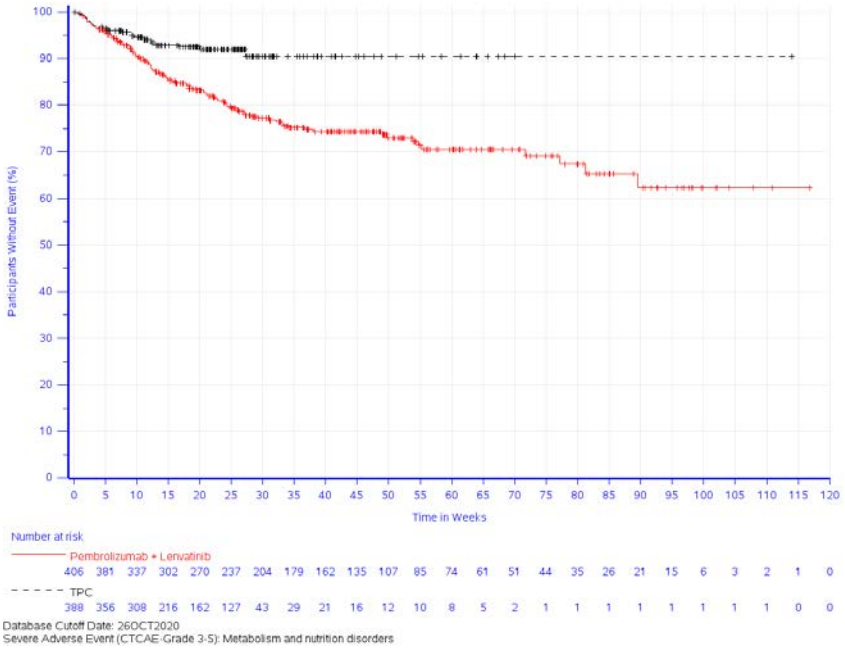

Abbildung 4G-164: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Stoffwechsel- und Ernährungsstörungen für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

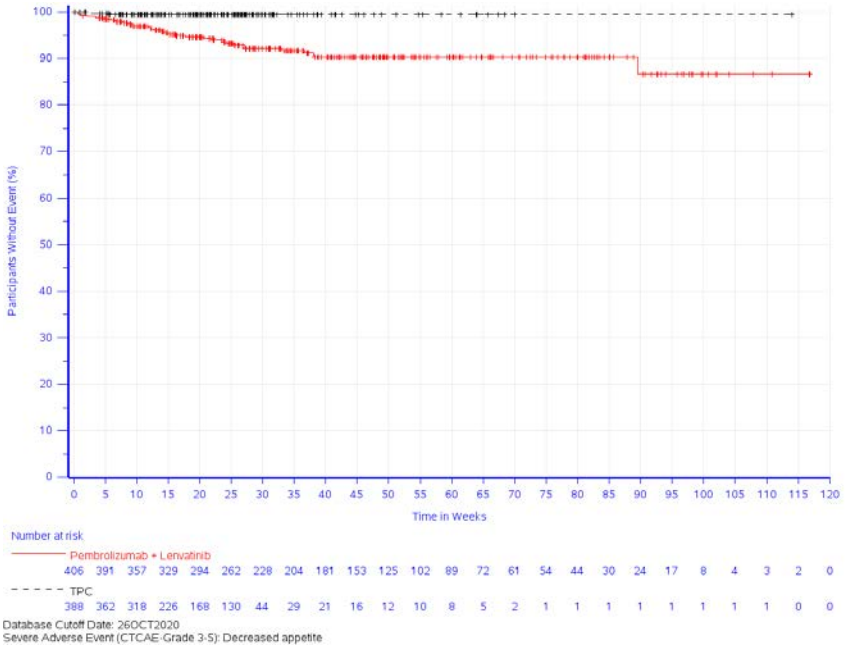

Abbildung 4G-165: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Appetit vermindert für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

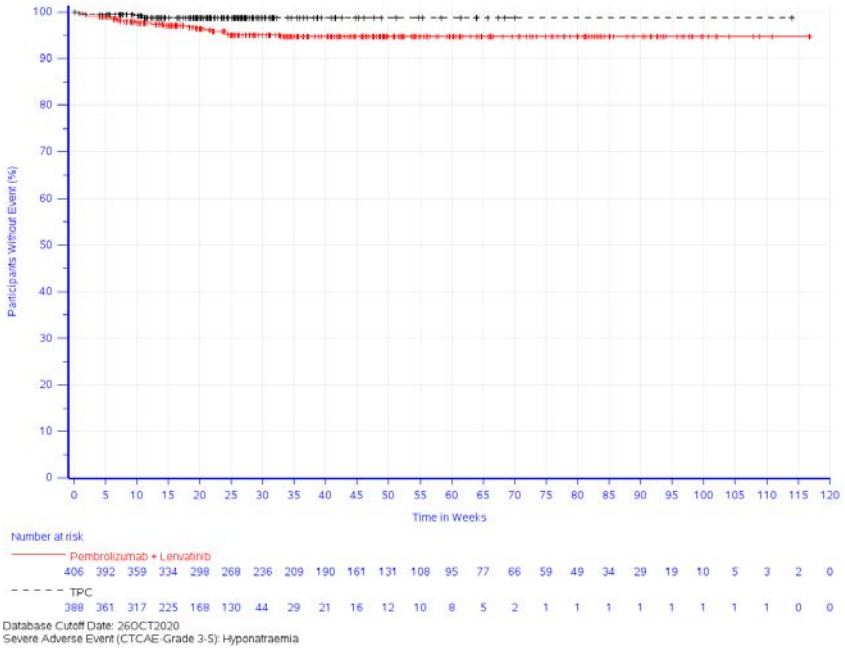

Abbildung 4G-166: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Hyponatriämie für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

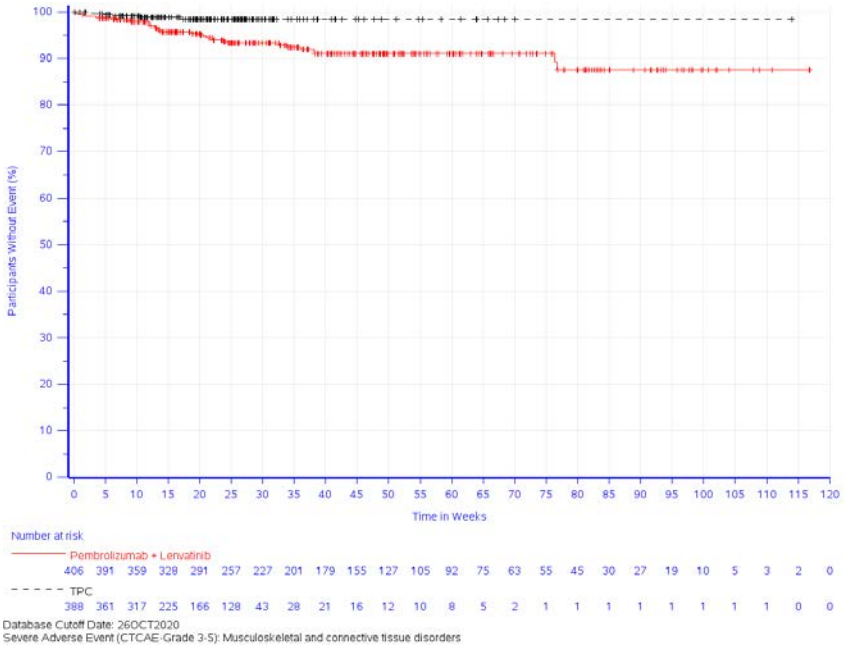

Abbildung 4G-167: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

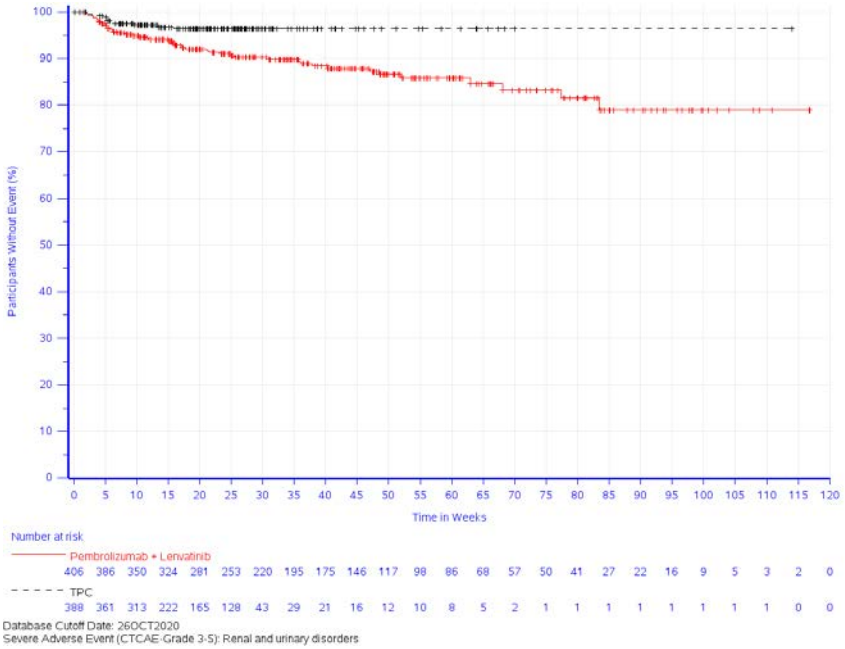

Abbildung 4G-168: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Erkrankungen der Nieren und Harnwege für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

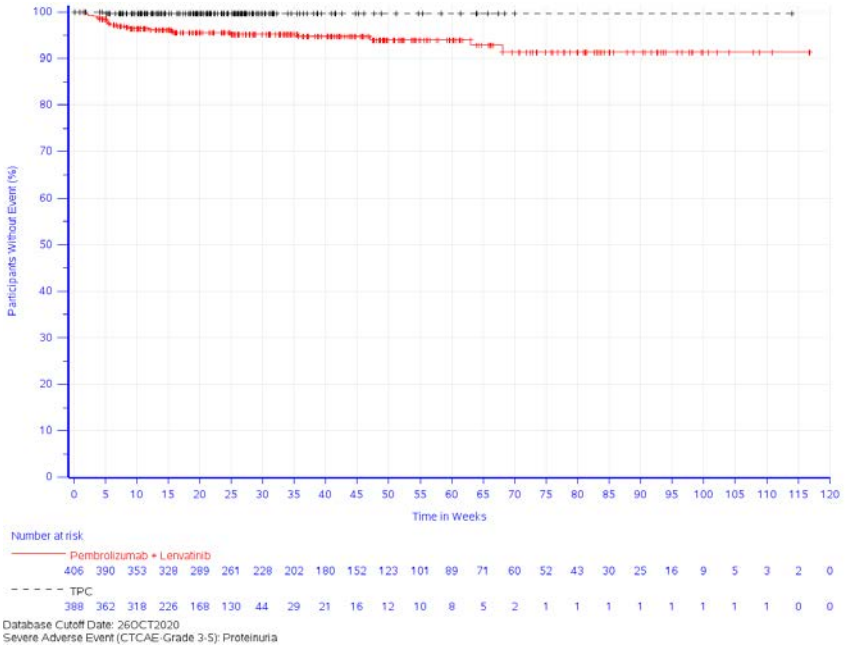

Abbildung 4G-169: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Proteinurie für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

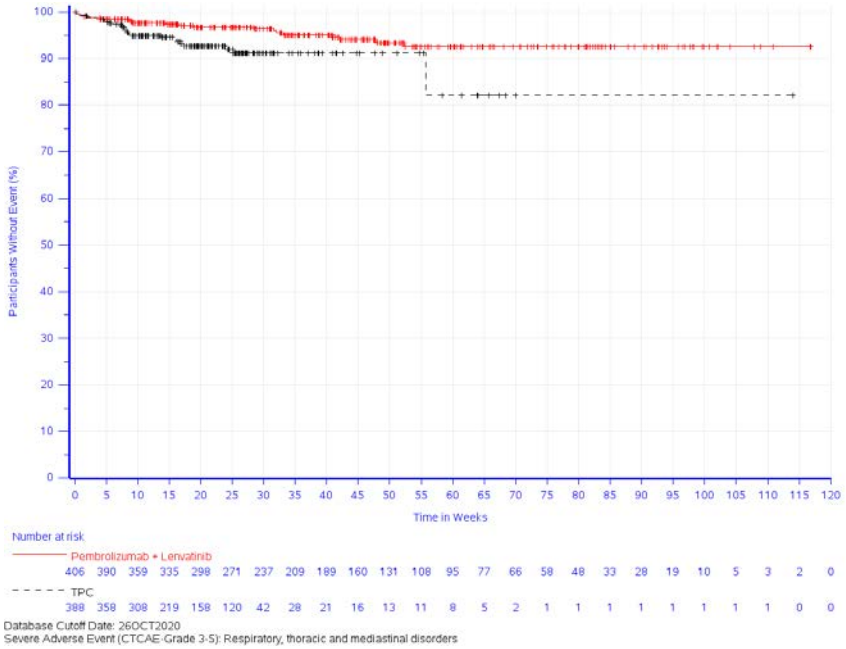

Abbildung 4G-170: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Erkrankungen der Atemwege, des Brustraums und Mediastinums für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

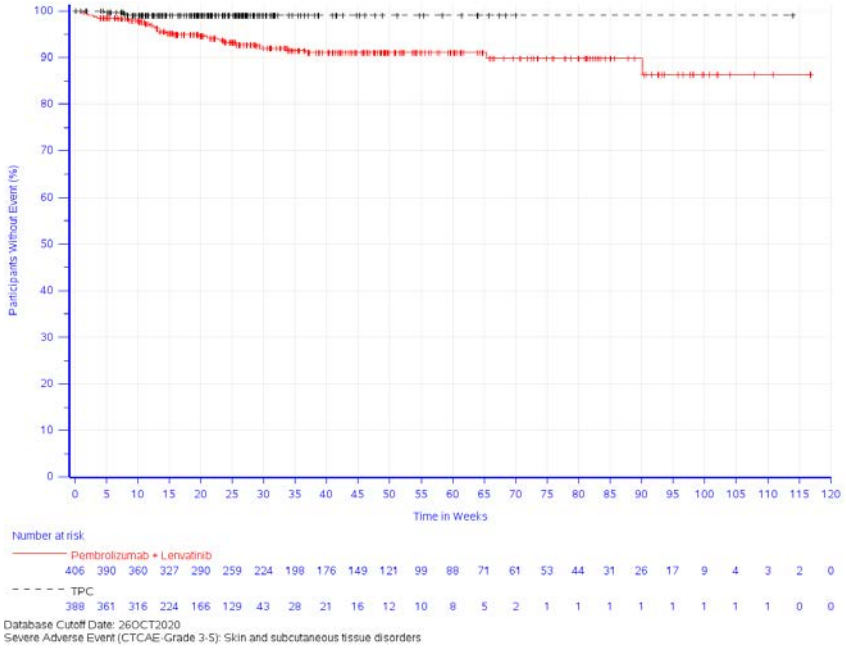

Abbildung 4G-171: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Erkrankungen der Haut und des Unterhautzellgewebes für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

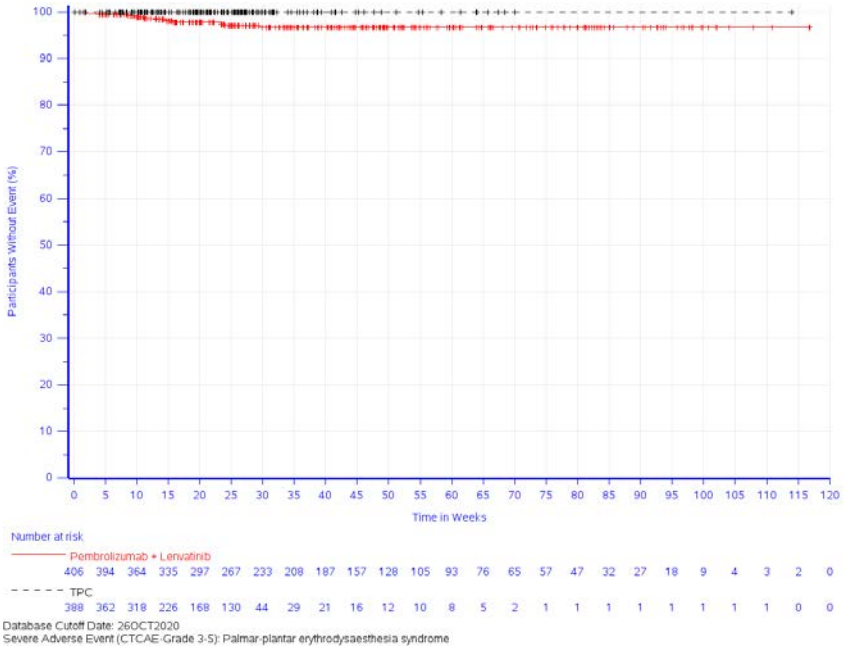

Abbildung 4G-172: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Palmar-plantares Erythrodysaesthesiesyndrom für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

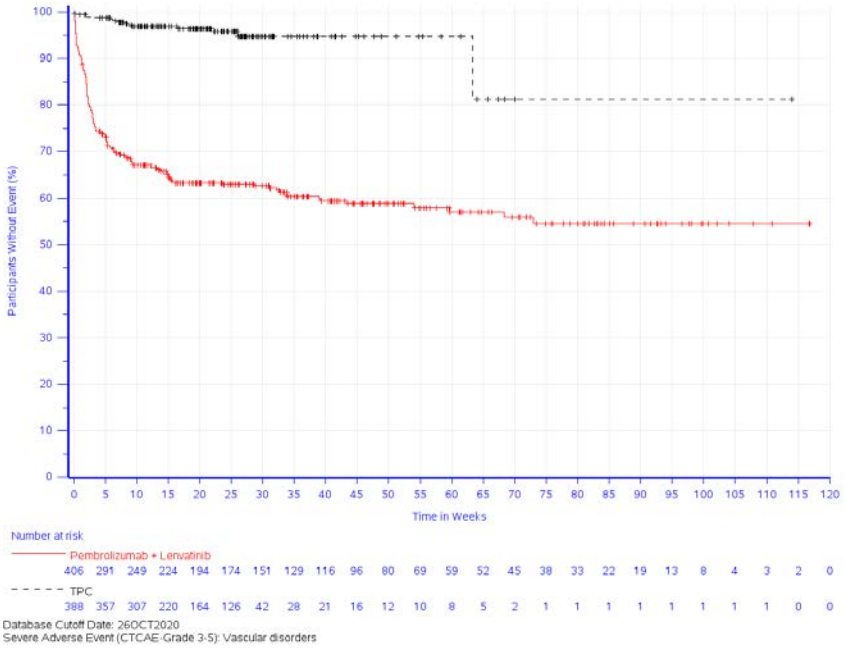

Abbildung 4G-173: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für die SOC Gefäßerkrankungen für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

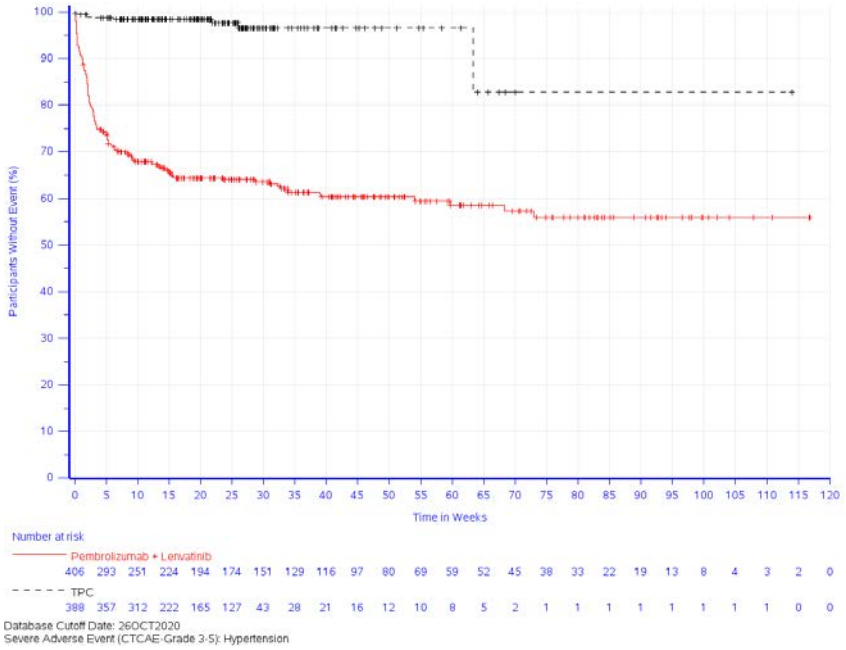

Abbildung 4G-174: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den PT Hypertonie für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) der Studie KEYNOTE 775

Therapieabbruch wegen unerwünschter Ereignisse (gegliedert nach SOC und PT)

Tabelle 4G-63: Ergebnisse für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse (SOC und PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	**Participants with Event n(%)**	
Adverse Events Leading to Treatment Discontinuation by SOC and PT[c]	**Pembrolizumab + Lenvatinib (N^d=406)**	**TPC[b] (N^d=388)**
Participants with one or more adverse events	134 (33.0)	31 (8.0)
Blood and lymphatic system disorders	3 (0.7)	2 (0.5)
Anaemia	1 (0.2)	1 (0.3)
Febrile neutropenia	1 (0.2)	0 (0.0)
Leukopenia	0 (0.0)	1 (0.3)
Neutropenia	0 (0.0)	1 (0.3)
Thrombocytopenia	0 (0.0)	1 (0.3)
Thrombotic microangiopathy	1 (0.2)	0 (0.0)
Cardiac disorders	7 (1.7)	5 (1.3)
Acute coronary syndrome	1 (0.2)	0 (0.0)
Acute myocardial infarction	1 (0.2)	0 (0.0)
Atrial fibrillation	1 (0.2)	0 (0.0)
Cardiac failure	0 (0.0)	1 (0.3)
Cardiotoxicity	0 (0.0)	1 (0.3)
Left ventricular dysfunction	0 (0.0)	1 (0.3)
Myocardial infarction	1 (0.2)	0 (0.0)
Myocarditis	1 (0.2)	0 (0.0)
Right ventricular dysfunction	1 (0.2)	0 (0.0)
Sinus tachycardia	0 (0.0)	1 (0.3)
Toxic cardiomyopathy	0 (0.0)	1 (0.3)
Ventricular fibrillation	1 (0.2)	0 (0.0)
Endocrine disorders	1 (0.2)	0 (0.0)
Hypothyroidism	1 (0.2)	0 (0.0)
Eye disorders	2 (0.5)	0 (0.0)
Iridocyclitis	1 (0.2)	0 (0.0)
Macular ischaemia	1 (0.2)	0 (0.0)
Retinopathy	1 (0.2)	0 (0.0)
Gastrointestinal disorders	37 (9.1)	4 (1.0)
Abdominal pain	3 (0.7)	0 (0.0)
Ascites	1 (0.2)	1 (0.3)
Colitis	3 (0.7)	0 (0.0)
Colonic fistula	0 (0.0)	1 (0.3)
Diarrhoea	7 (1.7)	1 (0.3)
Dyspepsia	1 (0.2)	0 (0.0)
Enterocolitis	1 (0.2)	0 (0.0)
Gastrointestinal perforation	2 (0.5)	0 (0.0)
Gastrointestinal toxicity	0 (0.0)	1 (0.3)
Ileus	1 (0.2)	0 (0.0)
Intestinal fistula	1 (0.2)	0 (0.0)
Intestinal obstruction	4 (1.0)	0 (0.0)
Intestinal perforation	3 (0.7)	0 (0.0)
Large intestine perforation	2 (0.5)	0 (0.0)
Lower gastrointestinal haemorrhage	2 (0.5)	0 (0.0)
Lower gastrointestinal perforation	1 (0.2)	0 (0.0)
Mechanical ileus	1 (0.2)	0 (0.0)
Nausea	2 (0.5)	0 (0.0)
Pancreatitis acute	1 (0.2)	0 (0.0)
Rectal perforation	1 (0.2)	0 (0.0)
Stomatitis	1 (0.2)	0 (0.0)
Vomiting	4 (1.0)	0 (0.0)
General disorders and administration site conditions	15 (3.7)	8 (2.1)
Asthenia	7 (1.7)	1 (0.3)
Chest discomfort	0 (0.0)	1 (0.3)

Study: KEYNOTE 775[a]	Participants with Event n(%)	
Adverse Events Leading to Treatment Discontinuation by SOC and PT[c]	**Pembrolizumab + Lenvatinib (N[d]=406)**	**TPC[b] (N[d]=388)**
Chills	1 (0.2)	0 (0.0)
Death	3 (0.7)	1 (0.3)
Fatigue	1 (0.2)	2 (0.5)
General physical health deterioration	1 (0.2)	0 (0.0)
Mucosal inflammation	1 (0.2)	1 (0.3)
Multiple organ dysfunction syndrome	1 (0.2)	2 (0.5)
Perforated ulcer	1 (0.2)	0 (0.0)
Pyrexia	1 (0.2)	0 (0.0)
Hepatobiliary disorders	8 (2.0)	0 (0.0)
Biliary obstruction	1 (0.2)	0 (0.0)
Cholangitis	1 (0.2)	0 (0.0)
Hepatic function abnormal	1 (0.2)	0 (0.0)
Hepatitis	1 (0.2)	0 (0.0)
Hepatotoxicity	1 (0.2)	0 (0.0)
Immune-mediated hepatitis	3 (0.7)	0 (0.0)
Immune system disorders	2 (0.5)	1 (0.3)
Anaphylactic reaction	1 (0.2)	0 (0.0)
Drug hypersensitivity	0 (0.0)	1 (0.3)
Hypersensitivity	1 (0.2)	0 (0.0)
Infections and infestations	10 (2.5)	2 (0.5)
Appendicitis perforated	1 (0.2)	0 (0.0)
Encephalitis	1 (0.2)	0 (0.0)
Meningitis bacterial	1 (0.2)	0 (0.0)
Peritonitis	2 (0.5)	0 (0.0)
Pneumonia	1 (0.2)	1 (0.3)
Postoperative wound infection	1 (0.2)	0 (0.0)
Psoas abscess	1 (0.2)	0 (0.0)
Sepsis	1 (0.2)	1 (0.3)
Urosepsis	1 (0.2)	0 (0.0)
Injury, poisoning and procedural complications	1 (0.2)	0 (0.0)
Wound dehiscence	1 (0.2)	0 (0.0)
Investigations	17 (4.2)	2 (0.5)
Alanine aminotransferase increased	4 (1.0)	0 (0.0)
Aspartate aminotransferase increased	3 (0.7)	0 (0.0)
Blood alkaline phosphatase increased	2 (0.5)	0 (0.0)
Blood bilirubin increased	1 (0.2)	0 (0.0)
Blood creatine phosphokinase increased	1 (0.2)	0 (0.0)
Blood creatinine increased	1 (0.2)	0 (0.0)
Gamma-glutamyltransferase increased	1 (0.2)	0 (0.0)
Hepatic enzyme increased	1 (0.2)	0 (0.0)
Lipase increased	2 (0.5)	0 (0.0)
Neutrophil count decreased	1 (0.2)	1 (0.3)
Transaminases increased	1 (0.2)	0 (0.0)
Troponin increased	0 (0.0)	1 (0.3)
Weight decreased	6 (1.5)	0 (0.0)
Metabolism and nutrition disorders	11 (2.7)	2 (0.5)
Decreased appetite	7 (1.7)	0 (0.0)
Dehydration	0 (0.0)	1 (0.3)
Hyperglycaemia	1 (0.2)	0 (0.0)
Hypokalaemia	1 (0.2)	1 (0.3)
Hypomagnesaemia	1 (0.2)	0 (0.0)
Hyponatraemia	1 (0.2)	0 (0.0)
Type 1 diabetes mellitus	1 (0.2)	0 (0.0)
Musculoskeletal and connective tissue disorders	4 (1.0)	0 (0.0)
Arthritis	1 (0.2)	0 (0.0)
Musculoskeletal pain	1 (0.2)	0 (0.0)
Myalgia	1 (0.2)	0 (0.0)
Myositis	1 (0.2)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.7)	0 (0.0)

Study: KEYNOTE 775[a]	**Participants with Event n(%)**	
Adverse Events Leading to Treatment Discontinuation by SOC and PT[c]	**Pembrolizumab + Lenvatinib (N[d]=406)**	**TPC[b] (N[d]=388)**
Cutaneous T-cell lymphoma	1 (0.2)	0 (0.0)
Myelodysplastic syndrome	1 (0.2)	0 (0.0)
Plasma cell myeloma	1 (0.2)	0 (0.0)
Nervous system disorders	14 (3.4)	4 (1.0)
Cerebral haemorrhage	2 (0.5)	0 (0.0)
Cerebral infarction	1 (0.2)	0 (0.0)
Cerebrovascular accident	2 (0.5)	2 (0.5)
Dizziness	1 (0.2)	0 (0.0)
Dysgeusia	1 (0.2)	0 (0.0)
Encephalitis autoimmune	1 (0.2)	0 (0.0)
Haemorrhage intracranial	1 (0.2)	0 (0.0)
Haemorrhagic stroke	1 (0.2)	0 (0.0)
Hypertensive encephalopathy	1 (0.2)	0 (0.0)
Myasthenia gravis	1 (0.2)	0 (0.0)
Neuropathy peripheral	0 (0.0)	1 (0.3)
Optic neuritis	1 (0.2)	0 (0.0)
Paraesthesia	0 (0.0)	1 (0.3)
Transient ischaemic attack	1 (0.2)	0 (0.0)
Psychiatric disorders	1 (0.2)	0 (0.0)
Depression	1 (0.2)	0 (0.0)
Renal and urinary disorders	13 (3.2)	1 (0.3)
Acute kidney injury	3 (0.7)	0 (0.0)
Autoimmune nephritis	1 (0.2)	0 (0.0)
Chronic kidney disease	2 (0.5)	0 (0.0)
Proteinuria	5 (1.2)	0 (0.0)
Renal failure	1 (0.2)	1 (0.3)
Urogenital fistula	1 (0.2)	0 (0.0)
Reproductive system and breast disorders	3 (0.7)	0 (0.0)
Female genital tract fistula	2 (0.5)	0 (0.0)
Vaginal haemorrhage	1 (0.2)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	9 (2.2)	4 (1.0)
Aspiration	1 (0.2)	1 (0.3)
Dyspnoea	1 (0.2)	2 (0.5)
Dyspnoea exertional	0 (0.0)	1 (0.3)
Pneumonitis	3 (0.7)	0 (0.0)
Pulmonary embolism	3 (0.7)	0 (0.0)
Respiratory failure	1 (0.2)	0 (0.0)
Skin and subcutaneous tissue disorders	5 (1.2)	3 (0.8)
Cold sweat	0 (0.0)	1 (0.3)
Lichen planus	0 (0.0)	1 (0.3)
Nail discolouration	0 (0.0)	1 (0.3)
Palmar-plantar erythrodysaesthesia syndrome	2 (0.5)	0 (0.0)
Pruritus	1 (0.2)	0 (0.0)
Rash maculo-papular	1 (0.2)	0 (0.0)
Skin disorder	1 (0.2)	0 (0.0)
Stevens-Johnson syndrome	1 (0.2)	0 (0.0)
Vascular disorders	13 (3.2)	1 (0.3)
Aortic thrombosis	1 (0.2)	0 (0.0)
Embolism venous	1 (0.2)	0 (0.0)
Hypertension	8 (2.0)	0 (0.0)
Hypotension	3 (0.7)	1 (0.3)

a: Database Cutoff Date: 26OCT2020
b: Treatment of physician's choice of doxorubicin or paclitaxel
c: A SOC or specific adverse event appears on this report only if its incidence is > 0% in one or more treatment groups
d: Number of participants: all-participants-as-treated population
PT: Preferred Term; SOC: System Organ Class; TPC: Treatment of Physician's Choice

Immunvermittelte unerwünschte Ereignisse (AEOSI)

Tabelle 4G-64: Ergebnisse für den Endpunkt Immunvermittelte unerwünschte Ereignisse (AEOSI) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib			TPC[b]			Pembrolizumab + Lenvatinib vs. TPC[b]	
	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]
Serious AEOSI	406	41 (10.1)	Not reached [-; -]	388	1 (0.3)	Not reached [-; -]	29.55 [4.05; 215.69]	< 0.001
Severe AEOSI (CTCAE-Grade 3-5)	406	53 (13.1)	Not reached [-; -]	388	1 (0.3)	Not reached [-; -]	29.93 [4.11; 217.76]	< 0.001

a: Database Cutoff Date: 26OCT2020
b: Treatment of physician's choice of doxorubicin or paclitaxel
c: Number of participants: all-participants-as-treated population
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)
AEOSI: Adverse Events of Special Interest; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; TPC: Treatment of Physician's Choice

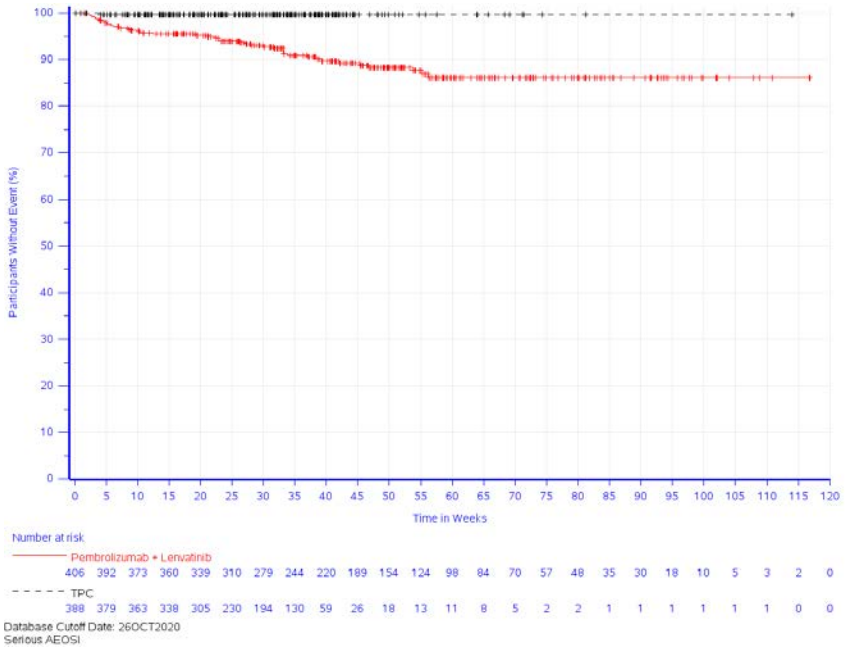

Abbildung 4G-175: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwerwiegende AEOSI der Studie KEYNOTE 775

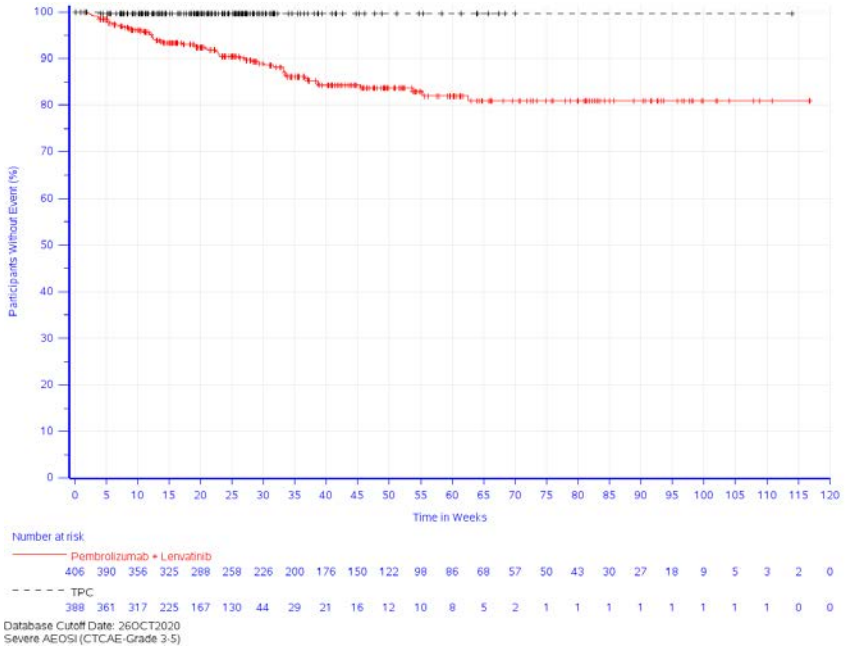

Abbildung 4G-176: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwere AEOSI (CTCAE-Grad 3-5) der Studie KEYNOTE 775

Klinisch signifikante unerwünschte Ereignisse (CSAE)

Tabelle 4G-65: Ergebnisse für den Endpunkt CSAE aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 775[a]	Pembrolizumab + Lenvatinib			TPC[b]			Pembrolizumab + Lenvatinib vs. TPC[b]	
	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]
Serious CSAE	406	80 (19.7)	Not reached [-; -]	388	27 (7.0)	Not reached [-; -]	2.51 [1.61; 3.90]	< 0.001
Severe CSAE (CTCAE-Grade 3-5)	406	218 (53.7)	27.1 [16.6; 42.1]	388	49 (12.6)	Not reached [63.3; -]	4.54 [3.32; 6.21]	< 0.001

a: Database Cutoff Date: 26OCT2020
b: Treatment of physician's choice of doxorubicin or paclitaxel
c: Number of participants: all-participants-as-treated population
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)
CI: Confidence Interval; CSAE: Clinically Significant Adverse Event; CTCAE: Common Terminology Criteria for Adverse Events; TPC: Treatment of Physician's Choice

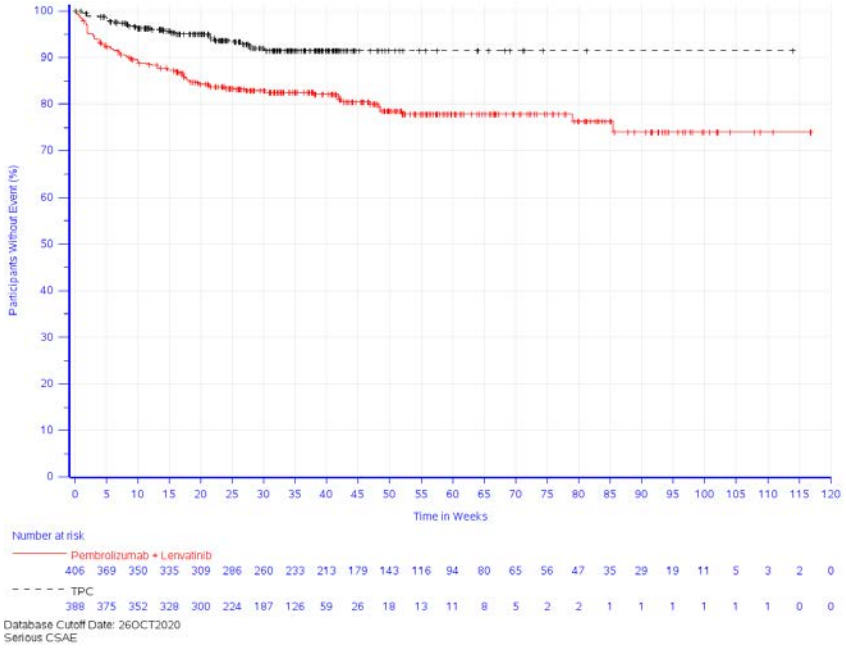

Abbildung 4G-177: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwerwiegende CSAE der Studie KEYNOTE 775

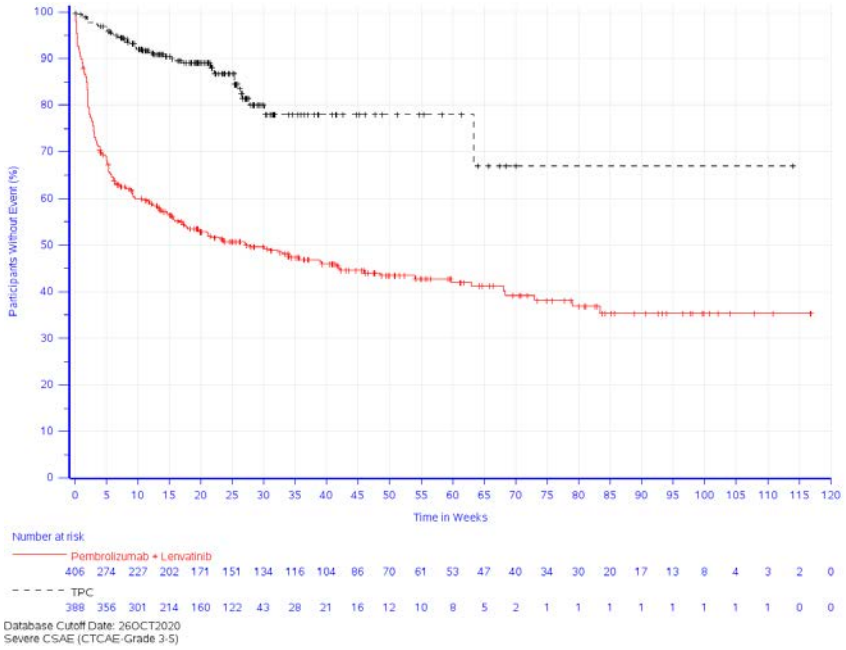

Abbildung 4G-178: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwere CSAE (CTCAE-Grad 3-5) der Studie KEYNOTE 775