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Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD Sharp & Dohme GmbH

Modul 4A

Erwachsene Patientinnen mit persistierendem, rezidivierendem oder metastasierendem Zervixkarzinom mit PD-L1-exprimierenden Tumoren (CPS ≥ 1)

Medizinischer Nutzen und
medizinischer Zusatznutzen,
Patientengruppen mit therapeutisch
bedeutsamem Zusatznutzen

Stand: 18.07.2022

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Anhang 4-G1: Rücklaufquoten des EORTC QLQ-C30, EORTC QLQ-CX24 und EQ-5D VAS (KEYNOTE 826)

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.2.2 die Rücklaufquoten des EORTC QLQ-C30, die Rücklaufquoten des EORTC QLQ-CX24 und die Rücklaufquoten des EQ-5D VAS dargestellt.

Alle Ergebnisse beziehen sich auf den zulassungsbegründeten Datenschnitt (03.05.2021).

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

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

Study: KEYNOTE-826[a]		**Pembrolizumab + chemotherapy**	**Chemotherapy**
Visit	**EORTC QLQ-C30**	**N[b] = 256 n (%)**	**N[b] = 264 n (%)**
Baseline	Expected to Complete Questionnaires[c]	255 (99.6)	262 (99.2)
	Completed	246 (96.1)	253 (95.8)
	Compliance (% in those expected to complete questionnaires)[d]	246 (96.5)	253 (96.6)
	Not completed	9 (3.5)	9 (3.4)
	Not completed due to site staff error	1 (0.4)	2 (0.8)
	Subject refused for other reasons	1 (0.4)	3 (1.1)
	Other	4 (1.6)	3 (1.1)
	With visit, no record	3 (1.2)	1 (0.4)
	Missing by Design[e]	1 (0.4)	2 (0.8)
	Translation not available in subjects language	1 (0.4)	2 (0.8)
Week 3	Expected to Complete Questionnaires[c]	241 (94.1)	250 (94.7)
	Completed	235 (91.8)	238 (90.2)
	Compliance (% in those expected to complete questionnaires)[d]	235 (97.5)	238 (95.2)
	Not completed	6 (2.3)	12 (4.5)
	Not completed due to site staff error	3 (1.2)	1 (0.4)
	Subject was physically unable to complete	0 (0.0)	1 (0.4)
	Subject refused for other reasons	1 (0.4)	1 (0.4)
	Other	2 (0.8)	9 (3.4)
	Missing by Design[e]	15 (5.9)	14 (5.3)
	Visit not scheduled	15 (5.9)	14 (5.3)
Week 6	Expected to Complete Questionnaires[c]	232 (90.6)	245 (92.8)
	Completed	224 (87.5)	230 (87.1)
	Compliance (% in those expected to complete questionnaires)[d]	224 (96.6)	230 (93.9)
	Not completed	8 (3.1)	15 (5.7)
	Not completed due to site staff error	2 (0.8)	1 (0.4)
	Subject in hospital or hospice	1 (0.4)	1 (0.4)
	Subject refused for other reasons	2 (0.8)	2 (0.8)
	Other	1 (0.4)	10 (3.8)
	With visit, no record	2 (0.8)	1 (0.4)
	Missing by Design[e]	24 (9.4)	19 (7.2)
	Discontinued due to adverse event	0 (0.0)	1 (0.4)
	Discontinued due to clinical progression	1 (0.4)	0 (0.0)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	1 (0.4)
	Visit not scheduled	21 (8.2)	17 (6.4)
Week 9	Expected to Complete Questionnaires[c]	226 (88.3)	232 (87.9)
	Completed	213 (83.2)	222 (84.1)
	Compliance (% in those expected to complete questionnaires)[d]	213 (94.2)	222 (95.7)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-C30	N[b] = 256 n (%)	N[b] = 264 n (%)
	Not completed	13 (5.1)	10 (3.8)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.8)
	Not completed due to site staff error	2 (0.8)	3 (1.1)
	Subject refused for other reasons	1 (0.4)	2 (0.8)
	Other	6 (2.3)	2 (0.8)
	With visit, no record	4 (1.6)	1 (0.4)
	Missing by Design[e]	30 (11.7)	32 (12.1)
	Discontinued due to adverse event	3 (1.2)	3 (1.1)
	Discontinued due to clinical progression	2 (0.8)	2 (0.8)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.4)
	Discontinued due to progressive disease	1 (0.4)	3 (1.1)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (0.4)
	Subject died	0 (0.0)	1 (0.4)
	Visit not scheduled	23 (9.0)	21 (8.0)
Week 12	Expected to Complete Questionnaires[c]	207 (80.9)	217 (82.2)
	Completed	200 (78.1)	206 (78.0)
	Compliance (% in those expected to complete questionnaires)[d]	200 (96.6)	206 (94.9)
	Not completed	7 (2.7)	11 (4.2)
	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)	3 (1.1)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	4 (1.6)	3 (1.1)
	With visit, no record	2 (0.8)	3 (1.1)
	Missing by Design[e]	49 (19.1)	47 (17.8)
	Discontinued due to adverse event	4 (1.6)	5 (1.9)
	Discontinued due to clinical progression	4 (1.6)	4 (1.5)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.4)
	Discontinued due to progressive disease	3 (1.2)	4 (1.5)
	Discontinued due to withdrawal by subject	1 (0.4)	2 (0.8)
	Subject died	1 (0.4)	2 (0.8)
	Visit not scheduled	35 (13.7)	29 (11.0)
Week 15	Expected to Complete Questionnaires[c]	204 (79.7)	204 (77.3)
	Completed	192 (75.0)	192 (72.7)
	Compliance (% in those expected to complete questionnaires)[d]	192 (94.1)	192 (94.1)
	Not completed	12 (4.7)	12 (4.5)
	Subject did not complete due to disease under study	2 (0.8)	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 was physically unable to complete	0 (0.0)	1 (0.4)
	Subject did not complete due to side effects of treatment	1 (0.4)	0 (0.0)
	Other	2 (0.8)	6 (2.3)
	With visit, no record	5 (2.0)	5 (1.9)
	Missing by Design[e]	52 (20.3)	60 (22.7)
	Discontinued due to adverse event	5 (2.0)	5 (1.9)
	Discontinued due to clinical progression	4 (1.6)	4 (1.5)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.4)
	Discontinued due to progressive disease	5 (2.0)	12 (4.5)
	Discontinued due to withdrawal by subject	1 (0.4)	3 (1.1)
	Subject died	1 (0.4)	1 (0.4)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-C30	N[b] = 256 n (%)	N[b] = 264 n (%)
	Visit not scheduled	35 (13.7)	34 (12.9)
Week 18	Expected to Complete Questionnaires[c]	205 (80.1)	195 (73.9)
	Completed	194 (75.8)	172 (65.2)
	Compliance (% in those expected to complete questionnaires)[d]	194 (94.6)	172 (88.2)
	Not completed	11 (4.3)	23 (8.7)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.8)
	Not completed due to site staff error	1 (0.4)	1 (0.4)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.4)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.4)
	Subject refused for other reasons	2 (0.8)	6 (2.3)
	Other	5 (2.0)	9 (3.4)
	With visit, no record	2 (0.8)	3 (1.1)
	Missing by Design[e]	51 (19.9)	69 (26.1)
	Discontinued due to adverse event	6 (2.3)	8 (3.0)
	Discontinued due to clinical progression	5 (2.0)	5 (1.9)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	2 (0.8)
	Discontinued due to progressive disease	5 (2.0)	14 (5.3)
	Discontinued due to withdrawal by subject	1 (0.4)	4 (1.5)
	Subject died	0 (0.0)	2 (0.8)
	Visit not scheduled	33 (12.9)	34 (12.9)
Week 21	Expected to Complete Questionnaires[c]	202 (78.9)	197 (74.6)
	Completed	188 (73.4)	173 (65.5)
	Compliance (% in those expected to complete questionnaires)[d]	188 (93.1)	173 (87.8)
	Not completed	14 (5.5)	24 (9.1)
	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)	3 (1.1)
	Subject was physically unable to complete	0 (0.0)	1 (0.4)
	Subject refused for other reasons	4 (1.6)	10 (3.8)
	Other	4 (1.6)	8 (3.0)
	With visit, no record	4 (1.6)	2 (0.8)
	Missing by Design[e]	54 (21.1)	67 (25.4)
	Discontinued due to adverse event	7 (2.7)	9 (3.4)
	Discontinued due to clinical progression	5 (2.0)	7 (2.7)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	10 (3.9)	25 (9.5)
	Discontinued due to withdrawal by subject	1 (0.4)	4 (1.5)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	0 (0.0)	1 (0.4)
	Visit not scheduled	29 (11.3)	18 (6.8)
Week 24	Expected to Complete Questionnaires[c]	198 (77.3)	178 (67.4)
	Completed	186 (72.7)	164 (62.1)
	Compliance (% in those expected to complete questionnaires)[d]	186 (93.9)	164 (92.1)
	Not completed	12 (4.7)	14 (5.3)
	Not completed due to site staff error	3 (1.2)	3 (1.1)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Subject was physically unable to complete	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.8)	2 (0.8)
	Other	2 (0.8)	6 (2.3)
	With visit, no record	4 (1.6)	2 (0.8)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-C30	N[b] = 256 n (%)	N[b] = 264 n (%)
	Missing by Design[e]	58 (22.7)	86 (32.6)
	Discontinued due to adverse event	10 (3.9)	9 (3.4)
	Discontinued due to clinical progression	6 (2.3)	8 (3.0)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	12 (4.7)	35 (13.3)
	Discontinued due to withdrawal by subject	1 (0.4)	6 (2.3)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	1 (0.4)
	Visit not scheduled	26 (10.2)	24 (9.1)
Week 27	Expected to Complete Questionnaires[c]	193 (75.4)	164 (62.1)
	Completed	184 (71.9)	144 (54.5)
	Compliance (% in those expected to complete questionnaires)[d]	184 (95.3)	144 (87.8)
	Not completed	9 (3.5)	20 (7.6)
	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)	4 (1.5)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	2 (0.8)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.4)
	Subject refused for other reasons	2 (0.8)	5 (1.9)
	Other	2 (0.8)	6 (2.3)
	With visit, no record	3 (1.2)	1 (0.4)
	Missing by Design[e]	63 (24.6)	100 (37.9)
	Discontinued due to adverse event	13 (5.1)	10 (3.8)
	Discontinued due to clinical progression	7 (2.7)	10 (3.8)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	19 (7.4)	38 (14.4)
	Discontinued due to withdrawal by subject	1 (0.4)	6 (2.3)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	0 (0.0)	2 (0.8)
	Visit not scheduled	21 (8.2)	31 (11.7)
Week 30	Expected to Complete Questionnaires[c]	191 (74.6)	160 (60.6)
	Completed	180 (70.3)	145 (54.9)
	Compliance (% in those expected to complete questionnaires)[d]	180 (94.2)	145 (90.6)
	Not completed	11 (4.3)	15 (5.7)
	Not completed due to site staff error	2 (0.8)	1 (0.4)
	Subject was physically unable to complete	0 (0.0)	2 (0.8)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.4)
	Subject refused for other reasons	1 (0.4)	1 (0.4)
	Other	6 (2.3)	9 (3.4)
	With visit, no record	2 (0.8)	1 (0.4)
	Missing by Design[e]	65 (25.4)	104 (39.4)
	Discontinued due to adverse event	15 (5.9)	12 (4.5)
	Discontinued due to clinical progression	7 (2.7)	11 (4.2)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	23 (9.0)	57 (21.6)
	Discontinued due to withdrawal by subject	2 (0.8)	8 (3.0)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	0 (0.0)
	Visit not scheduled	15 (5.9)	13 (4.9)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-C30	N[b] = 256 n (%)	N[b] = 264 n (%)
Week 33	Expected to Complete Questionnaires[c]	179 (69.9)	141 (53.4)
	Completed	164 (64.1)	120 (45.5)
	Compliance (% in those expected to complete questionnaires)[d]	164 (91.6)	120 (85.1)
	Not completed	15 (5.9)	21 (8.0)
	Not completed due to site staff error	1 (0.4)	2 (0.8)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	7 (2.7)	15 (5.7)
	With visit, no record	5 (2.0)	4 (1.5)
	Missing by Design[e]	77 (30.1)	123 (46.6)
	Discontinued due to adverse event	18 (7.0)	13 (4.9)
	Discontinued due to clinical progression	8 (3.1)	11 (4.2)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	4 (1.5)
	Discontinued due to progressive disease	33 (12.9)	62 (23.5)
	Discontinued due to withdrawal by subject	3 (1.2)	9 (3.4)
	Translation not available in subjects language	1 (0.4)	1 (0.4)
	Subject died	1 (0.4)	2 (0.8)
	Visit not scheduled	10 (3.9)	20 (7.6)
Week 36	Expected to Complete Questionnaires[c]	167 (65.2)	133 (50.4)
	Completed	155 (60.5)	115 (43.6)
	Compliance (% in those expected to complete questionnaires)[d]	155 (92.8)	115 (86.5)
	Not completed	12 (4.7)	18 (6.8)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	2 (0.8)	6 (2.3)
	Subject refused for other reasons	1 (0.4)	2 (0.8)
	Other	7 (2.7)	8 (3.0)
	With visit, no record	2 (0.8)	1 (0.4)
	Missing by Design[e]	89 (34.8)	131 (49.6)
	Discontinued due to adverse event	20 (7.8)	13 (4.9)
	Discontinued due to clinical progression	8 (3.1)	13 (4.9)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	4 (1.5)
	Discontinued due to progressive disease	42 (16.4)	75 (28.4)
	Discontinued due to withdrawal by subject	3 (1.2)	9 (3.4)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not scheduled	13 (5.1)	16 (6.1)
Week 39	Expected to Complete Questionnaires[c]	158 (61.7)	131 (49.6)
	Completed	150 (58.6)	118 (44.7)
	Compliance (% in those expected to complete questionnaires)[d]	150 (94.9)	118 (90.1)
	Not completed	8 (3.1)	13 (4.9)
	Not completed due to site staff error	2 (0.8)	5 (1.9)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	5 (2.0)	7 (2.7)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[e]	98 (38.3)	133 (50.4)
	Discontinued due to adverse event	21 (8.2)	14 (5.3)
	Discontinued due to clinical progression	8 (3.1)	14 (5.3)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-C30	N[b] = 256 n (%)	N[b] = 264 n (%)
	Discontinued due to physician decision	1 (0.4)	4 (1.5)
	Discontinued due to progressive disease	49 (19.1)	82 (31.1)
	Discontinued due to withdrawal by subject	3 (1.2)	10 (3.8)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not scheduled	12 (4.7)	8 (3.0)
Week 45	Expected to Complete Questionnaires[c]	150 (58.6)	119 (45.1)
	Completed	130 (50.8)	103 (39.0)
	Compliance (% in those expected to complete questionnaires)[d]	130 (86.7)	103 (86.6)
	Not completed	20 (7.8)	16 (6.1)
	Subject did not complete due to disease under study	1 (0.4)	1 (0.4)
	Not completed due to site staff error	3 (1.2)	4 (1.5)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Subject did not complete due to side effects of treatment	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.8)	3 (1.1)
	Other	5 (2.0)	4 (1.5)
	With visit, no record	8 (3.1)	3 (1.1)
	Missing by Design[e]	106 (41.4)	145 (54.9)
	Discontinued due to adverse event	21 (8.2)	15 (5.7)
	Discontinued due to clinical progression	8 (3.1)	14 (5.3)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	1 (0.4)	4 (1.5)
	Discontinued due to progressive disease	62 (24.2)	95 (36.0)
	Discontinued due to withdrawal by subject	4 (1.6)	11 (4.2)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not scheduled	6 (2.3)	5 (1.9)
Week 51	Expected to Complete Questionnaires[c]	137 (53.5)	103 (39.0)
	Completed	116 (45.3)	88 (33.3)
	Compliance (% in those expected to complete questionnaires)[d]	116 (84.7)	88 (85.4)
	Not completed	21 (8.2)	15 (5.7)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	6 (2.3)	1 (0.4)
	Subject refused for other reasons	2 (0.8)	2 (0.8)
	Other	8 (3.1)	3 (1.1)
	With visit, no record	5 (2.0)	8 (3.0)
	Missing by Design[e]	119 (46.5)	161 (61.0)
	Discontinued due to adverse event	24 (9.4)	16 (6.1)
	Discontinued due to clinical progression	8 (3.1)	16 (6.1)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	1 (0.4)	4 (1.5)
	Discontinued due to progressive disease	73 (28.5)	110 (41.7)
	Discontinued due to withdrawal by subject	5 (2.0)	11 (4.2)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	2 (0.8)	0 (0.0)
	Visit not scheduled	2 (0.8)	3 (1.1)
Week 57	Expected to Complete Questionnaires[c]	125 (48.8)	91 (34.5)
	Completed	111 (43.4)	79 (29.9)
	Compliance (% in those expected to complete questionnaires)[d]	111 (88.8)	79 (86.8)
	Not completed	14 (5.5)	12 (4.5)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.8)
	Not completed due to site staff error	1 (0.4)	2 (0.8)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-C30	N[b] = 256 n (%)	N[b] = 264 n (%)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	7 (2.7)	3 (1.1)
	With visit, no record	6 (2.3)	4 (1.5)
	Missing by Design[e]	131 (51.2)	173 (65.5)
	Discontinued due to adverse event	26 (10.2)	17 (6.4)
	Discontinued due to clinical progression	9 (3.5)	17 (6.4)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	2 (0.8)	4 (1.5)
	Discontinued due to progressive disease	78 (30.5)	119 (45.1)
	Discontinued due to withdrawal by subject	6 (2.3)	11 (4.2)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not scheduled	6 (2.3)	4 (1.5)
Week 63	Expected to Complete Questionnaires[c]	118 (46.1)	77 (29.2)
	Completed	103 (40.2)	66 (25.0)
	Compliance (% in those expected to complete questionnaires)[d]	103 (87.3)	66 (85.7)
	Not completed	15 (5.9)	11 (4.2)
	Not completed due to site staff error	3 (1.2)	2 (0.8)
	Subject refused for other reasons	1 (0.4)	1 (0.4)
	Other	4 (1.6)	0 (0.0)
	With visit, no record	7 (2.7)	8 (3.0)
	Missing by Design[e]	138 (53.9)	187 (70.8)
	Discontinued due to adverse event	27 (10.5)	17 (6.4)
	Discontinued due to clinical progression	9 (3.5)	18 (6.8)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	2 (0.8)	4 (1.5)
	Discontinued due to progressive disease	84 (32.8)	130 (49.2)
	Discontinued due to withdrawal by subject	7 (2.7)	12 (4.5)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not scheduled	5 (2.0)	5 (1.9)
Week 69	Expected to Complete Questionnaires[c]	114 (44.5)	71 (26.9)
	Completed	104 (40.6)	61 (23.1)
	Compliance (% in those expected to complete questionnaires)[d]	104 (91.2)	61 (85.9)
	Not completed	10 (3.9)	10 (3.8)
	Not completed due to site staff error	3 (1.2)	1 (0.4)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Subject was physically unable to complete	0 (0.0)	1 (0.4)
	Subject refused for other reasons	0 (0.0)	2 (0.8)
	Other	2 (0.8)	1 (0.4)
	With visit, no record	5 (2.0)	4 (1.5)
	Missing by Design[e]	142 (55.5)	193 (73.1)
	Discontinued due to adverse event	27 (10.5)	17 (6.4)
	Discontinued due to clinical progression	9 (3.5)	18 (6.8)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	2 (0.8)	4 (1.5)
	Discontinued due to progressive disease	89 (34.8)	136 (51.5)
	Discontinued due to withdrawal by subject	7 (2.7)	12 (4.5)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	0 (0.0)	1 (0.4)
	Visit not reached	1 (0.4)	0 (0.0)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-C30	N[b] = 256 n (%)	N[b] = 264 n (%)
	Visit not scheduled	3 (1.2)	4 (1.5)
Week 75	Expected to Complete Questionnaires[c]	100 (39.1)	63 (23.9)
	Completed	85 (33.2)	53 (20.1)
	Compliance (% in those expected to complete questionnaires)[d]	85 (85.0)	53 (84.1)
	Not completed	15 (5.9)	10 (3.8)
	Not completed due to site staff error	4 (1.6)	0 (0.0)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	2 (0.8)
	Other	1 (0.4)	1 (0.4)
	With visit, no record	9 (3.5)	7 (2.7)
	Missing by Design[e]	156 (60.9)	201 (76.1)
	Discontinued due to adverse event	28 (10.9)	18 (6.8)
	Discontinued due to clinical progression	9 (3.5)	18 (6.8)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	91 (35.5)	142 (53.8)
	Discontinued due to withdrawal by subject	7 (2.7)	14 (5.3)
	Translation not available in subjects language	2 (0.8)	0 (0.0)
	Visit not reached	11 (4.3)	3 (1.1)
	Visit not scheduled	2 (0.8)	1 (0.4)
Week 81	Expected to Complete Questionnaires[c]	91 (35.5)	49 (18.6)
	Completed	78 (30.5)	42 (15.9)
	Compliance (% in those expected to complete questionnaires)[d]	78 (85.7)	42 (85.7)
	Not completed	13 (5.1)	7 (2.7)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	2 (0.8)
	Other	1 (0.4)	1 (0.4)
	With visit, no record	10 (3.9)	4 (1.5)
	Missing by Design[e]	165 (64.5)	215 (81.4)
	Discontinued due to adverse event	27 (10.5)	18 (6.8)
	Discontinued due to clinical progression	9 (3.5)	18 (6.8)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	92 (35.9)	145 (54.9)
	Discontinued due to withdrawal by subject	7 (2.7)	17 (6.4)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	0 (0.0)
	Visit not reached	21 (8.2)	12 (4.5)
	Visit not scheduled	1 (0.4)	0 (0.0)
Week 87	Expected to Complete Questionnaires[c]	72 (28.1)	38 (14.4)
	Completed	63 (24.6)	29 (11.0)
	Compliance (% in those expected to complete questionnaires)[d]	63 (87.5)	29 (76.3)
	Not completed	9 (3.5)	9 (3.4)
	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)	2 (0.8)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	1 (0.4)	0 (0.0)
	With visit, no record	6 (2.3)	6 (2.3)
	Missing by Design[e]	184 (71.9)	226 (85.6)
	Discontinued due to adverse event	28 (10.9)	18 (6.8)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-C30	N[b] = 256 n (%)	N[b] = 264 n (%)
	Discontinued due to clinical progression	10 (3.9)	19 (7.2)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	95 (37.1)	149 (56.4)
	Discontinued due to withdrawal by subject	7 (2.7)	17 (6.4)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not reached	37 (14.5)	18 (6.8)
Week 93	Expected to Complete Questionnaires[c]	55 (21.5)	26 (9.8)
	Completed	43 (16.8)	17 (6.4)
	Compliance (% in those expected to complete questionnaires)[d]	43 (78.2)	17 (65.4)
	Not completed	12 (4.7)	9 (3.4)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	1 (0.4)	0 (0.0)
	With visit, no record	10 (3.9)	8 (3.0)
	Missing by Design[e]	201 (78.5)	238 (90.2)
	Discontinued due to adverse event	28 (10.9)	18 (6.8)
	Discontinued due to clinical progression	10 (3.9)	19 (7.2)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	98 (38.3)	151 (57.2)
	Discontinued due to withdrawal by subject	7 (2.7)	17 (6.4)
	Visit not reached	52 (20.3)	27 (10.2)
	Visit not scheduled	0 (0.0)	1 (0.4)
Week 99	Expected to Complete Questionnaires[c]	40 (15.6)	16 (6.1)
	Completed	32 (12.5)	10 (3.8)
	Compliance (% in those expected to complete questionnaires)[d]	32 (80.0)	10 (62.5)
	Not completed	8 (3.1)	6 (2.3)
	Not completed due to site staff error	0 (0.0)	2 (0.8)
	Other	2 (0.8)	0 (0.0)
	With visit, no record	6 (2.3)	4 (1.5)
	Missing by Design[e]	216 (84.4)	248 (93.9)
	Discontinued due to adverse event	28 (10.9)	18 (6.8)
	Discontinued due to clinical progression	10 (3.9)	19 (7.2)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	99 (38.7)	151 (57.2)
	Discontinued due to withdrawal by subject	7 (2.7)	17 (6.4)
	Visit not reached	65 (25.4)	37 (14.0)
	Visit not scheduled	1 (0.4)	1 (0.4)

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

e: Missing by design includes: adverse event, death, discontinuation, translations not available, and no visit scheduled

CPS: Combined Positive Score; 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-CX24

Tabelle 4G-2: Gründe für das Fehlen von Werten im EORTC QLQ-CX24

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-CX24	N[b] = 256 n (%)	N[b] = 264 n (%)
Baseline	Expected to Complete Questionnaires[c]	255 (99.6)	262 (99.2)
	Completed	244 (95.3)	251 (95.1)
	Compliance (% in those expected to complete questionnaires)[d]	244 (95.7)	251 (95.8)
	Not completed	11 (4.3)	11 (4.2)
	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)	2 (0.8)
	Subject refused for other reasons	2 (0.8)	4 (1.5)
	Other	5 (2.0)	3 (1.1)
	With visit, no record	3 (1.2)	1 (0.4)
	Missing by Design[e]	1 (0.4)	2 (0.8)
	Translation not available in subjects language	1 (0.4)	2 (0.8)
Week 3	Expected to Complete Questionnaires[c]	241 (94.1)	250 (94.7)
	Completed	235 (91.8)	234 (88.6)
	Compliance (% in those expected to complete questionnaires)[d]	235 (97.5)	234 (93.6)
	Not completed	6 (2.3)	16 (6.1)
	Not completed due to site staff error	3 (1.2)	3 (1.1)
	Subject was physically unable to complete	0 (0.0)	1 (0.4)
	Subject refused for other reasons	1 (0.4)	2 (0.8)
	Other	2 (0.8)	10 (3.8)
	Missing by Design[e]	15 (5.9)	14 (5.3)
	Visit not scheduled	15 (5.9)	14 (5.3)
Week 6	Expected to Complete Questionnaires[c]	232 (90.6)	245 (92.8)
	Completed	223 (87.1)	228 (86.4)
	Compliance (% in those expected to complete questionnaires)[d]	223 (96.1)	228 (93.1)
	Not completed	9 (3.5)	17 (6.4)
	Not completed due to site staff error	3 (1.2)	1 (0.4)
	Subject in hospital or hospice	1 (0.4)	1 (0.4)
	Subject refused for other reasons	2 (0.8)	3 (1.1)
	Other	2 (0.8)	11 (4.2)
	With visit, no record	1 (0.4)	1 (0.4)
	Missing by Design[e]	24 (9.4)	19 (7.2)
	Discontinued due to adverse event	0 (0.0)	1 (0.4)
	Discontinued due to clinical progression	1 (0.4)	0 (0.0)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	1 (0.4)
	Visit not scheduled	21 (8.2)	17 (6.4)
Week 9	Expected to Complete Questionnaires[c]	226 (88.3)	232 (87.9)
	Completed	210 (82.0)	222 (84.1)
	Compliance (% in those expected to complete questionnaires)[d]	210 (92.9)	222 (95.7)
	Not completed	16 (6.3)	10 (3.8)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.8)
	Not completed due to site staff error	2 (0.8)	3 (1.1)
	Subject refused for other reasons	3 (1.2)	2 (0.8)
	Other	7 (2.7)	2 (0.8)
	With visit, no record	4 (1.6)	1 (0.4)
	Missing by Design[e]	30 (11.7)	32 (12.1)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-CX24	N[b] = 256 n (%)	N[b] = 264 n (%)
	Discontinued due to adverse event	3 (1.2)	3 (1.1)
	Discontinued due to clinical progression	2 (0.8)	2 (0.8)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.4)
	Discontinued due to progressive disease	1 (0.4)	3 (1.1)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (0.4)
	Subject died	0 (0.0)	1 (0.4)
	Visit not scheduled	23 (9.0)	21 (8.0)
Week 12	Expected to Complete Questionnaires[c]	207 (80.9)	217 (82.2)
	Completed	200 (78.1)	204 (77.3)
	Compliance (% in those expected to complete questionnaires)[d]	200 (96.6)	204 (94.0)
	Not completed	7 (2.7)	13 (4.9)
	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)	3 (1.1)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	4 (1.6)	4 (1.5)
	With visit, no record	2 (0.8)	4 (1.5)
	Missing by Design[e]	49 (19.1)	47 (17.8)
	Discontinued due to adverse event	4 (1.6)	5 (1.9)
	Discontinued due to clinical progression	4 (1.6)	4 (1.5)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.4)
	Discontinued due to progressive disease	3 (1.2)	4 (1.5)
	Discontinued due to withdrawal by subject	1 (0.4)	2 (0.8)
	Subject died	1 (0.4)	2 (0.8)
	Visit not scheduled	35 (13.7)	29 (11.0)
Week 15	Expected to Complete Questionnaires[c]	204 (79.7)	203 (76.9)
	Completed	191 (74.6)	190 (72.0)
	Compliance (% in those expected to complete questionnaires)[d]	191 (93.6)	190 (93.6)
	Not completed	13 (5.1)	13 (4.9)
	Subject did not complete due to disease under study	2 (0.8)	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 was physically unable to complete	0 (0.0)	1 (0.4)
	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	2 (0.8)	7 (2.7)
	With visit, no record	5 (2.0)	5 (1.9)
	Missing by Design[e]	52 (20.3)	61 (23.1)
	Discontinued due to adverse event	5 (2.0)	5 (1.9)
	Discontinued due to clinical progression	4 (1.6)	4 (1.5)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.4)
	Discontinued due to progressive disease	5 (2.0)	12 (4.5)
	Discontinued due to withdrawal by subject	1 (0.4)	3 (1.1)
	Subject died	1 (0.4)	1 (0.4)
	Visit not scheduled	35 (13.7)	35 (13.3)
Week 18	Expected to Complete Questionnaires[c]	205 (80.1)	195 (73.9)
	Completed	194 (75.8)	172 (65.2)
	Compliance (% in those expected to complete questionnaires)[d]	194 (94.6)	172 (88.2)
	Not completed	11 (4.3)	23 (8.7)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.8)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-CX24	N[b] = 256 n (%)	N[b] = 264 n (%)
	Not completed due to site staff error	1 (0.4)	1 (0.4)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.4)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.4)
	Subject refused for other reasons	2 (0.8)	6 (2.3)
	Other	5 (2.0)	9 (3.4)
	With visit, no record	2 (0.8)	3 (1.1)
	Missing by Design[e]	51 (19.9)	69 (26.1)
	Discontinued due to adverse event	6 (2.3)	8 (3.0)
	Discontinued due to clinical progression	5 (2.0)	5 (1.9)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	2 (0.8)
	Discontinued due to progressive disease	5 (2.0)	14 (5.3)
	Discontinued due to withdrawal by subject	1 (0.4)	4 (1.5)
	Subject died	0 (0.0)	2 (0.8)
	Visit not scheduled	33 (12.9)	34 (12.9)
Week 21	Expected to Complete Questionnaires[c]	202 (78.9)	197 (74.6)
	Completed	187 (73.0)	171 (64.8)
	Compliance (% in those expected to complete questionnaires)[d]	187 (92.6)	171 (86.8)
	Not completed	15 (5.9)	26 (9.8)
	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)	3 (1.1)
	Subject was physically unable to complete	0 (0.0)	1 (0.4)
	Subject refused for other reasons	4 (1.6)	12 (4.5)
	Other	5 (2.0)	8 (3.0)
	With visit, no record	4 (1.6)	2 (0.8)
	Missing by Design[e]	54 (21.1)	67 (25.4)
	Discontinued due to adverse event	7 (2.7)	9 (3.4)
	Discontinued due to clinical progression	5 (2.0)	7 (2.7)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	10 (3.9)	25 (9.5)
	Discontinued due to withdrawal by subject	1 (0.4)	4 (1.5)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	0 (0.0)	1 (0.4)
	Visit not scheduled	29 (11.3)	18 (6.8)
Week 24	Expected to Complete Questionnaires[c]	198 (77.3)	178 (67.4)
	Completed	186 (72.7)	164 (62.1)
	Compliance (% in those expected to complete questionnaires)[d]	186 (93.9)	164 (92.1)
	Not completed	12 (4.7)	14 (5.3)
	Not completed due to site staff error	3 (1.2)	3 (1.1)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Subject was physically unable to complete	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.8)	2 (0.8)
	Other	2 (0.8)	6 (2.3)
	With visit, no record	4 (1.6)	2 (0.8)
	Missing by Design[e]	58 (22.7)	86 (32.6)
	Discontinued due to adverse event	10 (3.9)	9 (3.4)
	Discontinued due to clinical progression	6 (2.3)	8 (3.0)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	12 (4.7)	35 (13.3)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-CX24	N[b] = 256 n (%)	N[b] = 264 n (%)
	Discontinued due to withdrawal by subject	1 (0.4)	6 (2.3)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	1 (0.4)
	Visit not scheduled	26 (10.2)	24 (9.1)
Week 27	Expected to Complete Questionnaires[c]	193 (75.4)	164 (62.1)
	Completed	182 (71.1)	144 (54.5)
	Compliance (% in those expected to complete questionnaires)[d]	182 (94.3)	144 (87.8)
	Not completed	11 (4.3)	20 (7.6)
	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)	4 (1.5)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	2 (0.8)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.4)
	Subject refused for other reasons	3 (1.2)	5 (1.9)
	Other	2 (0.8)	6 (2.3)
	With visit, no record	4 (1.6)	1 (0.4)
	Missing by Design[e]	63 (24.6)	100 (37.9)
	Discontinued due to adverse event	13 (5.1)	10 (3.8)
	Discontinued due to clinical progression	7 (2.7)	10 (3.8)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	19 (7.4)	38 (14.4)
	Discontinued due to withdrawal by subject	1 (0.4)	6 (2.3)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	0 (0.0)	2 (0.8)
	Visit not scheduled	21 (8.2)	31 (11.7)
Week 30	Expected to Complete Questionnaires[c]	191 (74.6)	160 (60.6)
	Completed	180 (70.3)	145 (54.9)
	Compliance (% in those expected to complete questionnaires)[d]	180 (94.2)	145 (90.6)
	Not completed	11 (4.3)	15 (5.7)
	Not completed due to site staff error	2 (0.8)	1 (0.4)
	Subject was physically unable to complete	0 (0.0)	2 (0.8)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.4)
	Subject refused for other reasons	1 (0.4)	1 (0.4)
	Other	6 (2.3)	8 (3.0)
	With visit, no record	2 (0.8)	2 (0.8)
	Missing by Design[e]	65 (25.4)	104 (39.4)
	Discontinued due to adverse event	15 (5.9)	12 (4.5)
	Discontinued due to clinical progression	7 (2.7)	11 (4.2)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	23 (9.0)	57 (21.6)
	Discontinued due to withdrawal by subject	2 (0.8)	8 (3.0)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	0 (0.0)
	Visit not scheduled	15 (5.9)	13 (4.9)
Week 33	Expected to Complete Questionnaires[c]	179 (69.9)	141 (53.4)
	Completed	164 (64.1)	120 (45.5)
	Compliance (% in those expected to complete questionnaires)[d]	164 (91.6)	120 (85.1)
	Not completed	15 (5.9)	21 (8.0)
	Not completed due to site staff error	1 (0.4)	2 (0.8)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-CX24	N[b] = 256 n (%)	N[b] = 264 n (%)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	7 (2.7)	14 (5.3)
	With visit, no record	5 (2.0)	5 (1.9)
	Missing by Design[e]	77 (30.1)	123 (46.6)
	Discontinued due to adverse event	18 (7.0)	13 (4.9)
	Discontinued due to clinical progression	8 (3.1)	11 (4.2)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	4 (1.5)
	Discontinued due to progressive disease	33 (12.9)	62 (23.5)
	Discontinued due to withdrawal by subject	3 (1.2)	9 (3.4)
	Translation not available in subjects language	1 (0.4)	1 (0.4)
	Subject died	1 (0.4)	2 (0.8)
	Visit not scheduled	10 (3.9)	20 (7.6)
Week 36	Expected to Complete Questionnaires[c]	167 (65.2)	133 (50.4)
	Completed	153 (59.8)	115 (43.6)
	Compliance (% in those expected to complete questionnaires)[d]	153 (91.6)	115 (86.5)
	Not completed	14 (5.5)	18 (6.8)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	2 (0.8)	6 (2.3)
	Subject refused for other reasons	1 (0.4)	2 (0.8)
	Other	9 (3.5)	8 (3.0)
	With visit, no record	2 (0.8)	1 (0.4)
	Missing by Design[e]	89 (34.8)	131 (49.6)
	Discontinued due to adverse event	20 (7.8)	13 (4.9)
	Discontinued due to clinical progression	8 (3.1)	13 (4.9)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	4 (1.5)
	Discontinued due to progressive disease	42 (16.4)	75 (28.4)
	Discontinued due to withdrawal by subject	3 (1.2)	9 (3.4)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not scheduled	13 (5.1)	16 (6.1)
Week 39	Expected to Complete Questionnaires[c]	158 (61.7)	131 (49.6)
	Completed	150 (58.6)	118 (44.7)
	Compliance (% in those expected to complete questionnaires)[d]	150 (94.9)	118 (90.1)
	Not completed	8 (3.1)	13 (4.9)
	Not completed due to site staff error	2 (0.8)	5 (1.9)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	5 (2.0)	7 (2.7)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[e]	98 (38.3)	133 (50.4)
	Discontinued due to adverse event	21 (8.2)	14 (5.3)
	Discontinued due to clinical progression	8 (3.1)	14 (5.3)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	1 (0.4)	4 (1.5)
	Discontinued due to progressive disease	49 (19.1)	82 (31.1)
	Discontinued due to withdrawal by subject	3 (1.2)	10 (3.8)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not scheduled	12 (4.7)	8 (3.0)
Week 45	Expected to Complete Questionnaires[c]	150 (58.6)	119 (45.1)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-CX24	N[b] = 256 n (%)	N[b] = 264 n (%)
	Completed	129 (50.4)	102 (38.6)
	Compliance (% in those expected to complete questionnaires)[d]	129 (86.0)	102 (85.7)
	Not completed	21 (8.2)	17 (6.4)
	Subject did not complete due to disease under study	1 (0.4)	1 (0.4)
	Not completed due to site staff error	3 (1.2)	4 (1.5)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Subject did not complete due to side effects of treatment	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.8)	3 (1.1)
	Other	6 (2.3)	5 (1.9)
	With visit, no record	8 (3.1)	3 (1.1)
	Missing by Design[e]	106 (41.4)	145 (54.9)
	Discontinued due to adverse event	21 (8.2)	15 (5.7)
	Discontinued due to clinical progression	8 (3.1)	14 (5.3)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	1 (0.4)	4 (1.5)
	Discontinued due to progressive disease	62 (24.2)	95 (36.0)
	Discontinued due to withdrawal by subject	4 (1.6)	11 (4.2)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not scheduled	6 (2.3)	5 (1.9)
Week 51	Expected to Complete Questionnaires[c]	137 (53.5)	103 (39.0)
	Completed	116 (45.3)	88 (33.3)
	Compliance (% in those expected to complete questionnaires)[d]	116 (84.7)	88 (85.4)
	Not completed	21 (8.2)	15 (5.7)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	6 (2.3)	1 (0.4)
	Subject refused for other reasons	2 (0.8)	2 (0.8)
	Other	8 (3.1)	3 (1.1)
	With visit, no record	5 (2.0)	8 (3.0)
	Missing by Design[e]	119 (46.5)	161 (61.0)
	Discontinued due to adverse event	24 (9.4)	16 (6.1)
	Discontinued due to clinical progression	8 (3.1)	16 (6.1)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	1 (0.4)	4 (1.5)
	Discontinued due to progressive disease	73 (28.5)	110 (41.7)
	Discontinued due to withdrawal by subject	5 (2.0)	11 (4.2)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	2 (0.8)	0 (0.0)
	Visit not scheduled	2 (0.8)	3 (1.1)
Week 57	Expected to Complete Questionnaires[c]	125 (48.8)	91 (34.5)
	Completed	111 (43.4)	79 (29.9)
	Compliance (% in those expected to complete questionnaires)[d]	111 (88.8)	79 (86.8)
	Not completed	14 (5.5)	12 (4.5)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.8)
	Not completed due to site staff error	1 (0.4)	2 (0.8)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	7 (2.7)	4 (1.5)
	With visit, no record	6 (2.3)	3 (1.1)
	Missing by Design[e]	131 (51.2)	173 (65.5)
	Discontinued due to adverse event	26 (10.2)	17 (6.4)
	Discontinued due to clinical progression	9 (3.5)	17 (6.4)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-CX24	N[b] = 256 n (%)	N[b] = 264 n (%)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	2 (0.8)	4 (1.5)
	Discontinued due to progressive disease	77 (30.1)	119 (45.1)
	Discontinued due to withdrawal by subject	6 (2.3)	11 (4.2)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	0 (0.0)
	Visit not scheduled	6 (2.3)	4 (1.5)
Week 63	Expected to Complete Questionnaires[c]	118 (46.1)	77 (29.2)
	Completed	103 (40.2)	65 (24.6)
	Compliance (% in those expected to complete questionnaires)[d]	103 (87.3)	65 (84.4)
	Not completed	15 (5.9)	12 (4.5)
	Not completed due to site staff error	3 (1.2)	2 (0.8)
	Subject refused for other reasons	1 (0.4)	1 (0.4)
	Other	4 (1.6)	0 (0.0)
	With visit, no record	7 (2.7)	9 (3.4)
	Missing by Design[e]	138 (53.9)	187 (70.8)
	Discontinued due to adverse event	27 (10.5)	17 (6.4)
	Discontinued due to clinical progression	9 (3.5)	18 (6.8)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	2 (0.8)	4 (1.5)
	Discontinued due to progressive disease	84 (32.8)	130 (49.2)
	Discontinued due to withdrawal by subject	7 (2.7)	12 (4.5)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not scheduled	5 (2.0)	5 (1.9)
Week 69	Expected to Complete Questionnaires[c]	114 (44.5)	71 (26.9)
	Completed	104 (40.6)	61 (23.1)
	Compliance (% in those expected to complete questionnaires)[d]	104 (91.2)	61 (85.9)
	Not completed	10 (3.9)	10 (3.8)
	Not completed due to site staff error	3 (1.2)	1 (0.4)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Subject was physically unable to complete	0 (0.0)	1 (0.4)
	Subject refused for other reasons	0 (0.0)	2 (0.8)
	Other	2 (0.8)	1 (0.4)
	With visit, no record	5 (2.0)	4 (1.5)
	Missing by Design[e]	142 (55.5)	193 (73.1)
	Discontinued due to adverse event	27 (10.5)	17 (6.4)
	Discontinued due to clinical progression	9 (3.5)	18 (6.8)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	2 (0.8)	4 (1.5)
	Discontinued due to progressive disease	89 (34.8)	136 (51.5)
	Discontinued due to withdrawal by subject	7 (2.7)	12 (4.5)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	0 (0.0)	1 (0.4)
	Visit not reached	1 (0.4)	0 (0.0)
	Visit not scheduled	3 (1.2)	4 (1.5)
Week 75	Expected to Complete Questionnaires[c]	100 (39.1)	63 (23.9)
	Completed	85 (33.2)	53 (20.1)
	Compliance (% in those expected to complete questionnaires)[d]	85 (85.0)	53 (84.1)
	Not completed	15 (5.9)	10 (3.8)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-CX24	N[b] = 256 n (%)	N[b] = 264 n (%)
	Not completed due to site staff error	4 (1.6)	0 (0.0)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	2 (0.8)
	Other	1 (0.4)	1 (0.4)
	With visit, no record	9 (3.5)	7 (2.7)
	Missing by Design[e]	156 (60.9)	201 (76.1)
	Discontinued due to adverse event	28 (10.9)	18 (6.8)
	Discontinued due to clinical progression	9 (3.5)	18 (6.8)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	91 (35.5)	142 (53.8)
	Discontinued due to withdrawal by subject	7 (2.7)	14 (5.3)
	Translation not available in subjects language	2 (0.8)	0 (0.0)
	Visit not reached	11 (4.3)	3 (1.1)
	Visit not scheduled	2 (0.8)	1 (0.4)
Week 81	Expected to Complete Questionnaires[c]	91 (35.5)	49 (18.6)
	Completed	78 (30.5)	42 (15.9)
	Compliance (% in those expected to complete questionnaires)[d]	78 (85.7)	42 (85.7)
	Not completed	13 (5.1)	7 (2.7)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	2 (0.8)
	Other	1 (0.4)	1 (0.4)
	With visit, no record	10 (3.9)	4 (1.5)
	Missing by Design[e]	165 (64.5)	215 (81.4)
	Discontinued due to adverse event	27 (10.5)	18 (6.8)
	Discontinued due to clinical progression	9 (3.5)	18 (6.8)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	92 (35.9)	145 (54.9)
	Discontinued due to withdrawal by subject	7 (2.7)	17 (6.4)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	0 (0.0)
	Visit not reached	21 (8.2)	12 (4.5)
	Visit not scheduled	1 (0.4)	0 (0.0)
Week 87	Expected to Complete Questionnaires[c]	72 (28.1)	38 (14.4)
	Completed	63 (24.6)	29 (11.0)
	Compliance (% in those expected to complete questionnaires)[d]	63 (87.5)	29 (76.3)
	Not completed	9 (3.5)	9 (3.4)
	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)	2 (0.8)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	1 (0.4)	0 (0.0)
	With visit, no record	6 (2.3)	6 (2.3)
	Missing by Design[e]	184 (71.9)	226 (85.6)
	Discontinued due to adverse event	28 (10.9)	18 (6.8)
	Discontinued due to clinical progression	10 (3.9)	19 (7.2)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	95 (37.1)	149 (56.4)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EORTC QLQ-CX24	N[b] = 256 n (%)	N[b] = 264 n (%)
	Discontinued due to withdrawal by subject	7 (2.7)	17 (6.4)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not reached	37 (14.5)	18 (6.8)
Week 93	Expected to Complete Questionnaires[c]	55 (21.5)	26 (9.8)
	Completed	43 (16.8)	17 (6.4)
	Compliance (% in those expected to complete questionnaires)[d]	43 (78.2)	17 (65.4)
	Not completed	12 (4.7)	9 (3.4)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	1 (0.4)	0 (0.0)
	With visit, no record	10 (3.9)	8 (3.0)
	Missing by Design[e]	201 (78.5)	238 (90.2)
	Discontinued due to adverse event	28 (10.9)	18 (6.8)
	Discontinued due to clinical progression	10 (3.9)	19 (7.2)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	98 (38.3)	151 (57.2)
	Discontinued due to withdrawal by subject	7 (2.7)	17 (6.4)
	Visit not reached	52 (20.3)	27 (10.2)
	Visit not scheduled	0 (0.0)	1 (0.4)
Week 99	Expected to Complete Questionnaires[c]	40 (15.6)	16 (6.1)
	Completed	32 (12.5)	10 (3.8)
	Compliance (% in those expected to complete questionnaires)[d]	32 (80.0)	10 (62.5)
	Not completed	8 (3.1)	6 (2.3)
	Not completed due to site staff error	0 (0.0)	2 (0.8)
	Other	2 (0.8)	0 (0.0)
	With visit, no record	6 (2.3)	4 (1.5)
	Missing by Design[e]	216 (84.4)	248 (93.9)
	Discontinued due to adverse event	28 (10.9)	18 (6.8)
	Discontinued due to clinical progression	10 (3.9)	19 (7.2)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	99 (38.7)	151 (57.2)
	Discontinued due to withdrawal by subject	7 (2.7)	17 (6.4)
	Visit not reached	65 (25.4)	37 (14.0)
	Visit not scheduled	1 (0.4)	1 (0.4)

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

e: Missing by design includes: adverse event, death, discontinuation, translations not available, and no visit scheduled

CPS: Combined Positive Score; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CX24

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

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

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EQ-5D VAS	N[b] = 256 n (%)	N[b] = 264 n (%)
Baseline	Expected to Complete Questionnaires[c]	255 (99.6)	262 (99.2)
	Completed	248 (96.9)	254 (96.2)
	Compliance (% in those expected to complete questionnaires)[d]	248 (97.3)	254 (96.9)
	Not completed	7 (2.7)	8 (3.0)
	Not completed due to site staff error	1 (0.4)	2 (0.8)
	Subject refused for other reasons	0 (0.0)	3 (1.1)
	Other	3 (1.2)	2 (0.8)
	With visit, no record	3 (1.2)	1 (0.4)
	Missing by Design[e]	1 (0.4)	2 (0.8)
	Translation not available in subjects language	1 (0.4)	2 (0.8)
Week 3	Expected to Complete Questionnaires[c]	241 (94.1)	250 (94.7)
	Completed	237 (92.6)	244 (92.4)
	Compliance (% in those expected to complete questionnaires)[d]	237 (98.3)	244 (97.6)
	Not completed	4 (1.6)	6 (2.3)
	Not completed due to site staff error	3 (1.2)	1 (0.4)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	1 (0.4)	4 (1.5)
	Missing by Design[e]	15 (5.9)	14 (5.3)
	Visit not scheduled	15 (5.9)	14 (5.3)
Week 6	Expected to Complete Questionnaires[c]	232 (90.6)	245 (92.8)
	Completed	224 (87.5)	233 (88.3)
	Compliance (% in those expected to complete questionnaires)[d]	224 (96.6)	233 (95.1)
	Not completed	8 (3.1)	12 (4.5)
	Not completed due to site staff error	2 (0.8)	1 (0.4)
	Subject in hospital or hospice	1 (0.4)	1 (0.4)
	Subject refused for other reasons	2 (0.8)	2 (0.8)
	Other	1 (0.4)	7 (2.7)
	With visit, no record	2 (0.8)	1 (0.4)
	Missing by Design[e]	24 (9.4)	19 (7.2)
	Discontinued due to adverse event	0 (0.0)	1 (0.4)
	Discontinued due to clinical progression	1 (0.4)	0 (0.0)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	1 (0.4)
	Visit not scheduled	21 (8.2)	17 (6.4)
Week 9	Expected to Complete Questionnaires[c]	226 (88.3)	232 (87.9)
	Completed	213 (83.2)	224 (84.8)
	Compliance (% in those expected to complete questionnaires)[d]	213 (94.2)	224 (96.6)
	Not completed	13 (5.1)	8 (3.0)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	2 (0.8)	3 (1.1)
	Subject refused for other reasons	1 (0.4)	1 (0.4)
	Other	6 (2.3)	2 (0.8)
	With visit, no record	4 (1.6)	1 (0.4)
	Missing by Design[e]	30 (11.7)	32 (12.1)
	Discontinued due to adverse event	3 (1.2)	3 (1.1)
	Discontinued due to clinical progression	2 (0.8)	2 (0.8)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.4)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EQ-5D VAS	N[b] = 256 n (%)	N[b] = 264 n (%)
	Discontinued due to progressive disease	1 (0.4)	3 (1.1)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (0.4)
	Subject died	0 (0.0)	1 (0.4)
	Visit not scheduled	23 (9.0)	21 (8.0)
Week 12	Expected to Complete Questionnaires[c]	207 (80.9)	217 (82.2)
	Completed	201 (78.5)	206 (78.0)
	Compliance (% in those expected to complete questionnaires)[d]	201 (97.1)	206 (94.9)
	Not completed	6 (2.3)	11 (4.2)
	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)	2 (0.8)
	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	3 (1.2)	3 (1.1)
	With visit, no record	2 (0.8)	3 (1.1)
	Missing by Design[e]	49 (19.1)	47 (17.8)
	Discontinued due to adverse event	4 (1.6)	5 (1.9)
	Discontinued due to clinical progression	4 (1.6)	4 (1.5)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.4)
	Discontinued due to progressive disease	3 (1.2)	4 (1.5)
	Discontinued due to withdrawal by subject	1 (0.4)	2 (0.8)
	Subject died	1 (0.4)	2 (0.8)
	Visit not scheduled	35 (13.7)	29 (11.0)
Week 15	Expected to Complete Questionnaires[c]	204 (79.7)	204 (77.3)
	Completed	192 (75.0)	192 (72.7)
	Compliance (% in those expected to complete questionnaires)[d]	192 (94.1)	192 (94.1)
	Not completed	12 (4.7)	12 (4.5)
	Subject did not complete due to disease under study	2 (0.8)	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 was physically unable to complete	0 (0.0)	1 (0.4)
	Subject did not complete due to side effects of treatment	1 (0.4)	0 (0.0)
	Other	2 (0.8)	6 (2.3)
	With visit, no record	5 (2.0)	5 (1.9)
	Missing by Design[e]	52 (20.3)	60 (22.7)
	Discontinued due to adverse event	5 (2.0)	5 (1.9)
	Discontinued due to clinical progression	4 (1.6)	4 (1.5)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.4)
	Discontinued due to progressive disease	5 (2.0)	12 (4.5)
	Discontinued due to withdrawal by subject	1 (0.4)	3 (1.1)
	Subject died	1 (0.4)	1 (0.4)
	Visit not scheduled	35 (13.7)	34 (12.9)
Week 18	Expected to Complete Questionnaires[c]	205 (80.1)	195 (73.9)
	Completed	195 (76.2)	175 (66.3)
	Compliance (% in those expected to complete questionnaires)[d]	195 (95.1)	175 (89.7)
	Not completed	10 (3.9)	20 (7.6)
	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)	1 (0.4)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.4)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.4)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EQ-5D VAS	N[b] = 256 n (%)	N[b] = 264 n (%)
	Subject refused for other reasons	2 (0.8)	5 (1.9)
	Other	4 (1.6)	8 (3.0)
	With visit, no record	2 (0.8)	3 (1.1)
	Missing by Design[e]	51 (19.9)	69 (26.1)
	Discontinued due to adverse event	6 (2.3)	8 (3.0)
	Discontinued due to clinical progression	5 (2.0)	5 (1.9)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	2 (0.8)
	Discontinued due to progressive disease	5 (2.0)	14 (5.3)
	Discontinued due to withdrawal by subject	1 (0.4)	4 (1.5)
	Subject died	0 (0.0)	2 (0.8)
	Visit not scheduled	33 (12.9)	34 (12.9)
Week 21	Expected to Complete Questionnaires[c]	202 (78.9)	197 (74.6)
	Completed	189 (73.8)	173 (65.5)
	Compliance (% in those expected to complete questionnaires)[d]	189 (93.6)	173 (87.8)
	Not completed	13 (5.1)	24 (9.1)
	Not completed due to site staff error	1 (0.4)	3 (1.1)
	Subject was physically unable to complete	0 (0.0)	1 (0.4)
	Subject refused for other reasons	3 (1.2)	10 (3.8)
	Other	5 (2.0)	8 (3.0)
	With visit, no record	4 (1.6)	2 (0.8)
	Missing by Design[e]	54 (21.1)	67 (25.4)
	Discontinued due to adverse event	7 (2.7)	9 (3.4)
	Discontinued due to clinical progression	5 (2.0)	7 (2.7)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	10 (3.9)	25 (9.5)
	Discontinued due to withdrawal by subject	1 (0.4)	4 (1.5)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	0 (0.0)	1 (0.4)
	Visit not scheduled	29 (11.3)	18 (6.8)
Week 24	Expected to Complete Questionnaires[c]	198 (77.3)	178 (67.4)
	Completed	187 (73.0)	165 (62.5)
	Compliance (% in those expected to complete questionnaires)[d]	187 (94.4)	165 (92.7)
	Not completed	11 (4.3)	13 (4.9)
	Not completed due to site staff error	2 (0.8)	3 (1.1)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Subject was physically unable to complete	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	2 (0.8)
	Other	3 (1.2)	5 (1.9)
	With visit, no record	4 (1.6)	2 (0.8)
	Missing by Design[e]	58 (22.7)	86 (32.6)
	Discontinued due to adverse event	10 (3.9)	9 (3.4)
	Discontinued due to clinical progression	6 (2.3)	8 (3.0)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	12 (4.7)	35 (13.3)
	Discontinued due to withdrawal by subject	1 (0.4)	6 (2.3)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	1 (0.4)
	Visit not scheduled	26 (10.2)	24 (9.1)
Week 27	Expected to Complete Questionnaires[c]	193 (75.4)	164 (62.1)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EQ-5D VAS	N[b] = 256 n (%)	N[b] = 264 n (%)
	Completed	184 (71.9)	146 (55.3)
	Compliance (% in those expected to complete questionnaires)[d]	184 (95.3)	146 (89.0)
	Not completed	9 (3.5)	18 (6.8)
	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)	3 (1.1)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	2 (0.8)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.4)
	Subject refused for other reasons	2 (0.8)	4 (1.5)
	Other	2 (0.8)	6 (2.3)
	With visit, no record	3 (1.2)	1 (0.4)
	Missing by Design[e]	63 (24.6)	100 (37.9)
	Discontinued due to adverse event	12 (4.7)	10 (3.8)
	Discontinued due to clinical progression	7 (2.7)	10 (3.8)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	19 (7.4)	38 (14.4)
	Discontinued due to withdrawal by subject	1 (0.4)	6 (2.3)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	2 (0.8)
	Visit not scheduled	21 (8.2)	31 (11.7)
Week 30	Expected to Complete Questionnaires[c]	191 (74.6)	160 (60.6)
	Completed	181 (70.7)	145 (54.9)
	Compliance (% in those expected to complete questionnaires)[d]	181 (94.8)	145 (90.6)
	Not completed	10 (3.9)	15 (5.7)
	Not completed due to site staff error	1 (0.4)	1 (0.4)
	Subject was physically unable to complete	0 (0.0)	2 (0.8)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.4)
	Subject refused for other reasons	2 (0.8)	1 (0.4)
	Other	6 (2.3)	8 (3.0)
	With visit, no record	1 (0.4)	2 (0.8)
	Missing by Design[e]	65 (25.4)	104 (39.4)
	Discontinued due to adverse event	15 (5.9)	12 (4.5)
	Discontinued due to clinical progression	7 (2.7)	11 (4.2)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	3 (1.1)
	Discontinued due to progressive disease	23 (9.0)	57 (21.6)
	Discontinued due to withdrawal by subject	2 (0.8)	8 (3.0)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	0 (0.0)
	Visit not scheduled	15 (5.9)	13 (4.9)
Week 33	Expected to Complete Questionnaires[c]	179 (69.9)	141 (53.4)
	Completed	165 (64.5)	120 (45.5)
	Compliance (% in those expected to complete questionnaires)[d]	165 (92.2)	120 (85.1)
	Not completed	14 (5.5)	21 (8.0)
	Not completed due to site staff error	0 (0.0)	2 (0.8)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	0 (0.0)
	Other	7 (2.7)	15 (5.7)
	With visit, no record	5 (2.0)	4 (1.5)
	Missing by Design[e]	77 (30.1)	123 (46.6)
	Discontinued due to adverse event	18 (7.0)	13 (4.9)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EQ-5D VAS	N[b] = 256 n (%)	N[b] = 264 n (%)
	Discontinued due to clinical progression	8 (3.1)	11 (4.2)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	4 (1.5)
	Discontinued due to progressive disease	33 (12.9)	62 (23.5)
	Discontinued due to withdrawal by subject	3 (1.2)	9 (3.4)
	Translation not available in subjects language	1 (0.4)	1 (0.4)
	Subject died	1 (0.4)	2 (0.8)
	Visit not scheduled	10 (3.9)	20 (7.6)
Week 36	Expected to Complete Questionnaires[c]	167 (65.2)	133 (50.4)
	Completed	155 (60.5)	115 (43.6)
	Compliance (% in those expected to complete questionnaires)[d]	155 (92.8)	115 (86.5)
	Not completed	12 (4.7)	18 (6.8)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.8)
	Not completed due to site staff error	3 (1.2)	5 (1.9)
	Subject refused for other reasons	1 (0.4)	2 (0.8)
	Other	5 (2.0)	8 (3.0)
	With visit, no record	3 (1.2)	1 (0.4)
	Missing by Design[e]	89 (34.8)	131 (49.6)
	Discontinued due to adverse event	20 (7.8)	13 (4.9)
	Discontinued due to clinical progression	8 (3.1)	13 (4.9)
	Discontinued due to complete response	1 (0.4)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	4 (1.5)
	Discontinued due to progressive disease	42 (16.4)	75 (28.4)
	Discontinued due to withdrawal by subject	3 (1.2)	9 (3.4)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not scheduled	13 (5.1)	16 (6.1)
Week 39	Expected to Complete Questionnaires[c]	158 (61.7)	131 (49.6)
	Completed	152 (59.4)	118 (44.7)
	Compliance (% in those expected to complete questionnaires)[d]	152 (96.2)	118 (90.1)
	Not completed	6 (2.3)	13 (4.9)
	Not completed due to site staff error	2 (0.8)	5 (1.9)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	3 (1.2)	7 (2.7)
	With visit, no record	1 (0.4)	0 (0.0)
	Missing by Design[e]	98 (38.3)	133 (50.4)
	Discontinued due to adverse event	21 (8.2)	14 (5.3)
	Discontinued due to clinical progression	8 (3.1)	14 (5.3)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	1 (0.4)	4 (1.5)
	Discontinued due to progressive disease	49 (19.1)	82 (31.1)
	Discontinued due to withdrawal by subject	3 (1.2)	10 (3.8)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not scheduled	12 (4.7)	8 (3.0)
Week 45	Expected to Complete Questionnaires[c]	150 (58.6)	119 (45.1)
	Completed	130 (50.8)	103 (39.0)
	Compliance (% in those expected to complete questionnaires)[d]	130 (86.7)	103 (86.6)
	Not completed	20 (7.8)	16 (6.1)
	Subject did not complete due to disease under study	1 (0.4)	1 (0.4)
	Not completed due to site staff error	3 (1.2)	4 (1.5)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EQ-5D VAS	N[b] = 256 n (%)	N[b] = 264 n (%)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Subject did not complete due to side effects of treatment	1 (0.4)	0 (0.0)
	Subject refused for other reasons	2 (0.8)	3 (1.1)
	Other	5 (2.0)	4 (1.5)
	With visit, no record	8 (3.1)	3 (1.1)
	Missing by Design[e]	106 (41.4)	145 (54.9)
	Discontinued due to adverse event	21 (8.2)	15 (5.7)
	Discontinued due to clinical progression	8 (3.1)	14 (5.3)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	1 (0.4)	4 (1.5)
	Discontinued due to progressive disease	62 (24.2)	95 (36.0)
	Discontinued due to withdrawal by subject	4 (1.6)	11 (4.2)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not scheduled	6 (2.3)	5 (1.9)
Week 51	Expected to Complete Questionnaires[c]	137 (53.5)	103 (39.0)
	Completed	116 (45.3)	88 (33.3)
	Compliance (% in those expected to complete questionnaires)[d]	116 (84.7)	88 (85.4)
	Not completed	21 (8.2)	15 (5.7)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.4)
	Not completed due to site staff error	6 (2.3)	1 (0.4)
	Subject refused for other reasons	2 (0.8)	2 (0.8)
	Other	8 (3.1)	3 (1.1)
	With visit, no record	5 (2.0)	8 (3.0)
	Missing by Design[e]	119 (46.5)	161 (61.0)
	Discontinued due to adverse event	24 (9.4)	16 (6.1)
	Discontinued due to clinical progression	8 (3.1)	16 (6.1)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	1 (0.4)	4 (1.5)
	Discontinued due to progressive disease	73 (28.5)	110 (41.7)
	Discontinued due to withdrawal by subject	5 (2.0)	11 (4.2)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	2 (0.8)	0 (0.0)
	Visit not scheduled	2 (0.8)	3 (1.1)
Week 57	Expected to Complete Questionnaires[c]	125 (48.8)	91 (34.5)
	Completed	112 (43.8)	79 (29.9)
	Compliance (% in those expected to complete questionnaires)[d]	112 (89.6)	79 (86.8)
	Not completed	13 (5.1)	12 (4.5)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.8)
	Not completed due to site staff error	1 (0.4)	2 (0.8)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	7 (2.7)	4 (1.5)
	With visit, no record	5 (2.0)	3 (1.1)
	Missing by Design[e]	131 (51.2)	173 (65.5)
	Discontinued due to adverse event	26 (10.2)	17 (6.4)
	Discontinued due to clinical progression	9 (3.5)	17 (6.4)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	2 (0.8)	4 (1.5)
	Discontinued due to progressive disease	77 (30.1)	119 (45.1)
	Discontinued due to withdrawal by subject	6 (2.3)	11 (4.2)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EQ-5D VAS	N[b] = 256 n (%)	N[b] = 264 n (%)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	1 (0.4)	0 (0.0)
	Visit not scheduled	6 (2.3)	4 (1.5)
Week 63	Expected to Complete Questionnaires[c]	118 (46.1)	77 (29.2)
	Completed	104 (40.6)	66 (25.0)
	Compliance (% in those expected to complete questionnaires)[d]	104 (88.1)	66 (85.7)
	Not completed	14 (5.5)	11 (4.2)
	Not completed due to site staff error	3 (1.2)	2 (0.8)
	Subject refused for other reasons	1 (0.4)	1 (0.4)
	Other	4 (1.6)	0 (0.0)
	With visit, no record	6 (2.3)	8 (3.0)
	Missing by Design[e]	138 (53.9)	187 (70.8)
	Discontinued due to adverse event	27 (10.5)	17 (6.4)
	Discontinued due to clinical progression	9 (3.5)	18 (6.8)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	2 (0.8)	4 (1.5)
	Discontinued due to progressive disease	84 (32.8)	130 (49.2)
	Discontinued due to withdrawal by subject	7 (2.7)	12 (4.5)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not scheduled	5 (2.0)	5 (1.9)
Week 69	Expected to Complete Questionnaires[c]	114 (44.5)	71 (26.9)
	Completed	105 (41.0)	61 (23.1)
	Compliance (% in those expected to complete questionnaires)[d]	105 (92.1)	61 (85.9)
	Not completed	9 (3.5)	10 (3.8)
	Not completed due to site staff error	2 (0.8)	1 (0.4)
	Subject in hospital or hospice	0 (0.0)	1 (0.4)
	Subject was physically unable to complete	0 (0.0)	1 (0.4)
	Subject refused for other reasons	0 (0.0)	2 (0.8)
	Other	2 (0.8)	1 (0.4)
	With visit, no record	5 (2.0)	4 (1.5)
	Missing by Design[e]	142 (55.5)	193 (73.1)
	Discontinued due to adverse event	27 (10.5)	17 (6.4)
	Discontinued due to clinical progression	9 (3.5)	18 (6.8)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	2 (0.8)	4 (1.5)
	Discontinued due to progressive disease	89 (34.8)	136 (51.5)
	Discontinued due to withdrawal by subject	7 (2.7)	12 (4.5)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Subject died	0 (0.0)	1 (0.4)
	Visit not reached	1 (0.4)	0 (0.0)
	Visit not scheduled	3 (1.2)	4 (1.5)
Week 75	Expected to Complete Questionnaires[c]	100 (39.1)	63 (23.9)
	Completed	85 (33.2)	53 (20.1)
	Compliance (% in those expected to complete questionnaires)[d]	85 (85.0)	53 (84.1)
	Not completed	15 (5.9)	10 (3.8)
	Not completed due to site staff error	4 (1.6)	0 (0.0)
	Subject in hospital or hospice	1 (0.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	2 (0.8)
	Other	1 (0.4)	1 (0.4)
	With visit, no record	9 (3.5)	7 (2.7)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EQ-5D VAS	N[b] = 256 n (%)	N[b] = 264 n (%)
	Missing by Design[e]	156 (60.9)	201 (76.1)
	Discontinued due to adverse event	28 (10.9)	18 (6.8)
	Discontinued due to clinical progression	9 (3.5)	18 (6.8)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	91 (35.5)	142 (53.8)
	Discontinued due to withdrawal by subject	7 (2.7)	14 (5.3)
	Translation not available in subjects language	2 (0.8)	0 (0.0)
	Visit not reached	11 (4.3)	3 (1.1)
	Visit not scheduled	2 (0.8)	1 (0.4)
Week 81	Expected to Complete Questionnaires[c]	91 (35.5)	49 (18.6)
	Completed	79 (30.9)	42 (15.9)
	Compliance (% in those expected to complete questionnaires)[d]	79 (86.8)	42 (85.7)
	Not completed	12 (4.7)	7 (2.7)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	1 (0.4)	2 (0.8)
	Other	1 (0.4)	1 (0.4)
	With visit, no record	9 (3.5)	4 (1.5)
	Missing by Design[e]	165 (64.5)	215 (81.4)
	Discontinued due to adverse event	28 (10.9)	18 (6.8)
	Discontinued due to clinical progression	9 (3.5)	18 (6.8)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	92 (35.9)	145 (54.9)
	Discontinued due to withdrawal by subject	7 (2.7)	17 (6.4)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not reached	21 (8.2)	12 (4.5)
	Visit not scheduled	1 (0.4)	0 (0.0)
Week 87	Expected to Complete Questionnaires[c]	72 (28.1)	38 (14.4)
	Completed	63 (24.6)	29 (11.0)
	Compliance (% in those expected to complete questionnaires)[d]	63 (87.5)	29 (76.3)
	Not completed	9 (3.5)	9 (3.4)
	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)	2 (0.8)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	1 (0.4)	0 (0.0)
	With visit, no record	6 (2.3)	6 (2.3)
	Missing by Design[e]	184 (71.9)	226 (85.6)
	Discontinued due to adverse event	28 (10.9)	18 (6.8)
	Discontinued due to clinical progression	10 (3.9)	19 (7.2)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	95 (37.1)	149 (56.4)
	Discontinued due to withdrawal by subject	7 (2.7)	17 (6.4)
	Translation not available in subjects language	1 (0.4)	0 (0.0)
	Visit not reached	37 (14.5)	18 (6.8)
Week 93	Expected to Complete Questionnaires[c]	55 (21.5)	26 (9.8)
	Completed	43 (16.8)	17 (6.4)
	Compliance (% in those expected to complete questionnaires)[d]	43 (78.2)	17 (65.4)

Study: KEYNOTE-826[a]		Pembrolizumab + chemotherapy	Chemotherapy
Visit	EQ-5D VAS	N[b] = 256 n (%)	N[b] = 264 n (%)
	Not completed	12 (4.7)	9 (3.4)
	Not completed due to site staff error	1 (0.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (0.4)
	Other	1 (0.4)	0 (0.0)
	With visit, no record	10 (3.9)	8 (3.0)
	Missing by Design[e]	201 (78.5)	238 (90.2)
	Discontinued due to adverse event	28 (10.9)	18 (6.8)
	Discontinued due to clinical progression	10 (3.9)	19 (7.2)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	98 (38.3)	151 (57.2)
	Discontinued due to withdrawal by subject	7 (2.7)	17 (6.4)
	Visit not reached	52 (20.3)	27 (10.2)
	Visit not scheduled	0 (0.0)	1 (0.4)
Week 99	Expected to Complete Questionnaires[c]	40 (15.6)	16 (6.1)
	Completed	33 (12.9)	10 (3.8)
	Compliance (% in those expected to complete questionnaires)[d]	33 (82.5)	10 (62.5)
	Not completed	7 (2.7)	6 (2.3)
	Not completed due to site staff error	0 (0.0)	2 (0.8)
	Other	1 (0.4)	0 (0.0)
	With visit, no record	6 (2.3)	4 (1.5)
	Missing by Design[e]	216 (84.4)	248 (93.9)
	Discontinued due to adverse event	28 (10.9)	18 (6.8)
	Discontinued due to clinical progression	10 (3.9)	19 (7.2)
	Discontinued due to complete response	2 (0.8)	1 (0.4)
	Discontinued due to excluded medication	1 (0.4)	0 (0.0)
	Discontinued due to physician decision	3 (1.2)	4 (1.5)
	Discontinued due to progressive disease	99 (38.7)	151 (57.2)
	Discontinued due to withdrawal by subject	7 (2.7)	17 (6.4)
	Visit not reached	65 (25.4)	37 (14.0)
	Visit not scheduled	1 (0.4)	1 (0.4)

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

e: Missing by design includes: adverse event, death, discontinuation, translations not available, and no visit scheduled

CPS: Combined Positive Score; EQ-5D: European Quality of Life 5 Dimensions; VAS: Visual Analog Scale

Anhang 4-G2: Kaplan-Meier-Kurven der Subgruppen mit signifikantem Interaktionstest (p < 0,05) (KEYNOTE 826)

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.2.2 die Kaplan-Meier-Kurven der Subgruppenanalysen, für die ein signifikanter Interaktionstest (p < 0,05) vorliegt, dargestellt.

Alle Ergebnisse beziehen sich auf den zulassungsbegründeten Datenschnitt (03.05.2021).

Morbidität

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30: Symptomskala Verstopfung

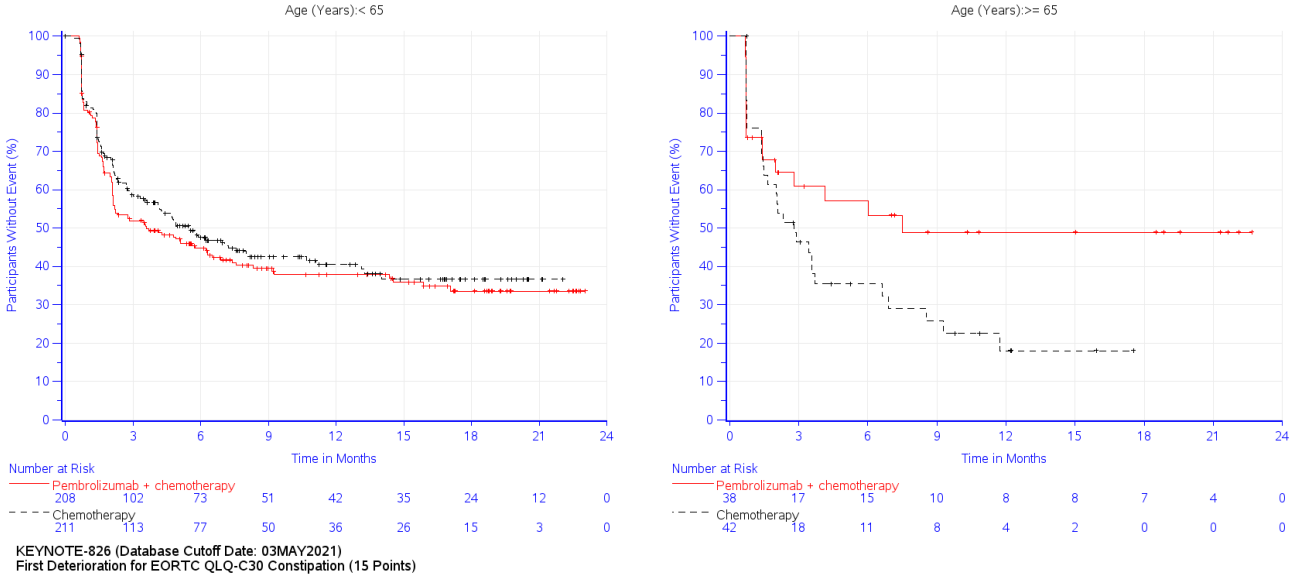

Abbildung 4G-1: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter (Jahre) (< 65 vs. ≥ 65) für die Symptomskala Verstopfung des EORTC QLQ-C30 der Studie KEYNOTE 826

EORTC QLQ-CX24: Symptomskala Symptomerleben

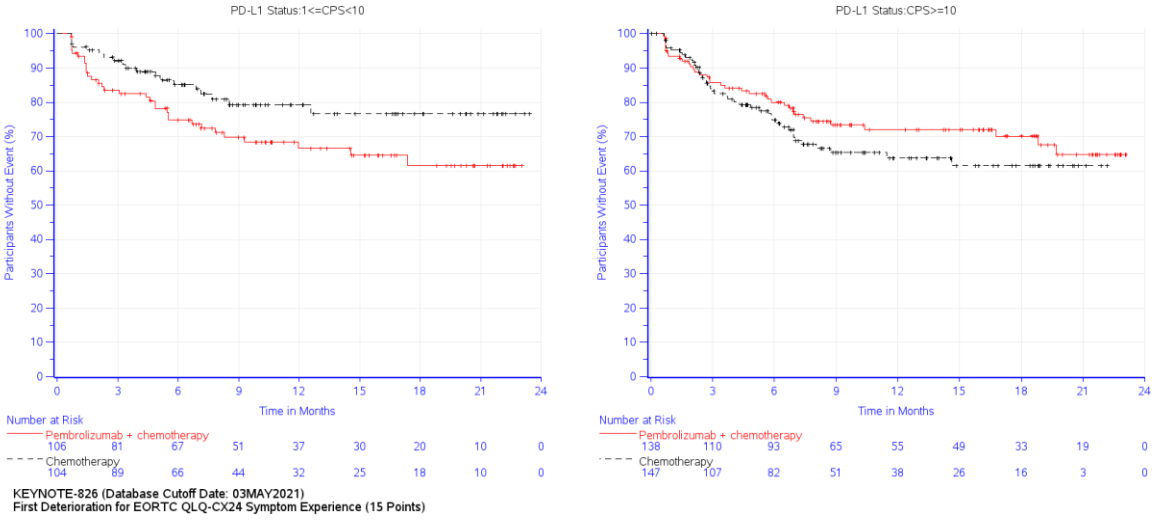

Abbildung 4G-2: Kaplan-Meier-Kurve für die Subgruppenanalyse nach PD-L1 Status (1 ≤ CPS < 10 vs. CPS ≥ 10) für die Symptomskala Symptomerleben des EORTC QLQ-CX24 der Studie KEYNOTE 826

EORTC QLQ-CX24: Symptomskala Lymphödem

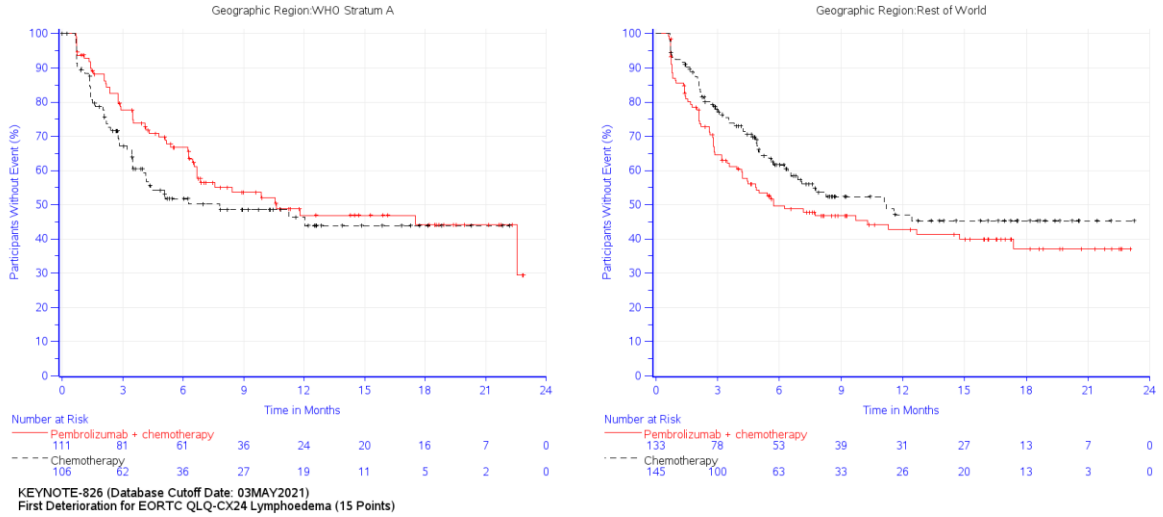

Abbildung 4G-3: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region (WHO Stratum A vs. Rest der Welt) für die Symptomskala Lymphödem des EORTC QLQ-CX24 der Studie KEYNOTE 826

EORTC QLQ-CX24: Symptomskala Periphere Neuropathie

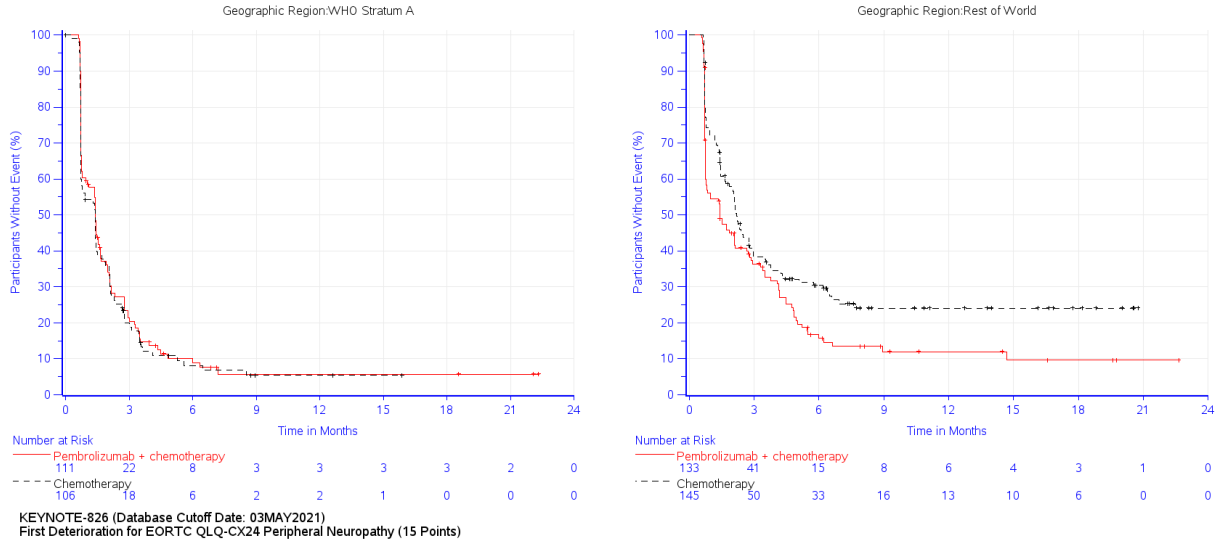

Abbildung 4G-4: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region (WHO Stratum A vs. Rest der Welt) für die Symptomskala Periphere Neuropathie des EORTC QLQ-CX24 der Studie KEYNOTE 826

EORTC QLQ-CX24: Symptomskala Menopausale Symptome

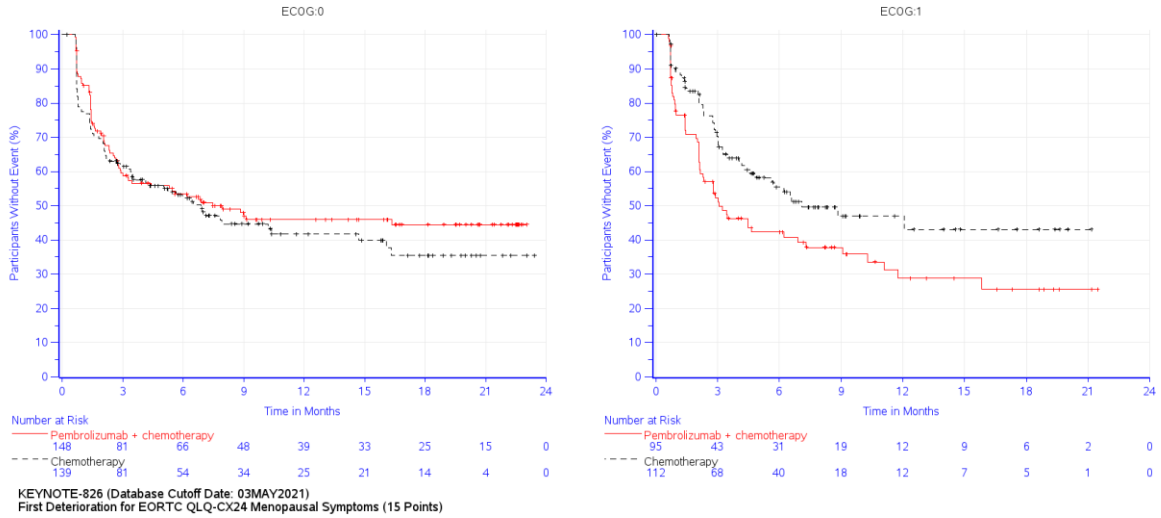

Abbildung 4G-5: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus (0 vs. 1) für die Symptomskala Menopausale Symptome des EORTC QLQ-CX24 der Studie KEYNOTE 826

EQ-5D VAS

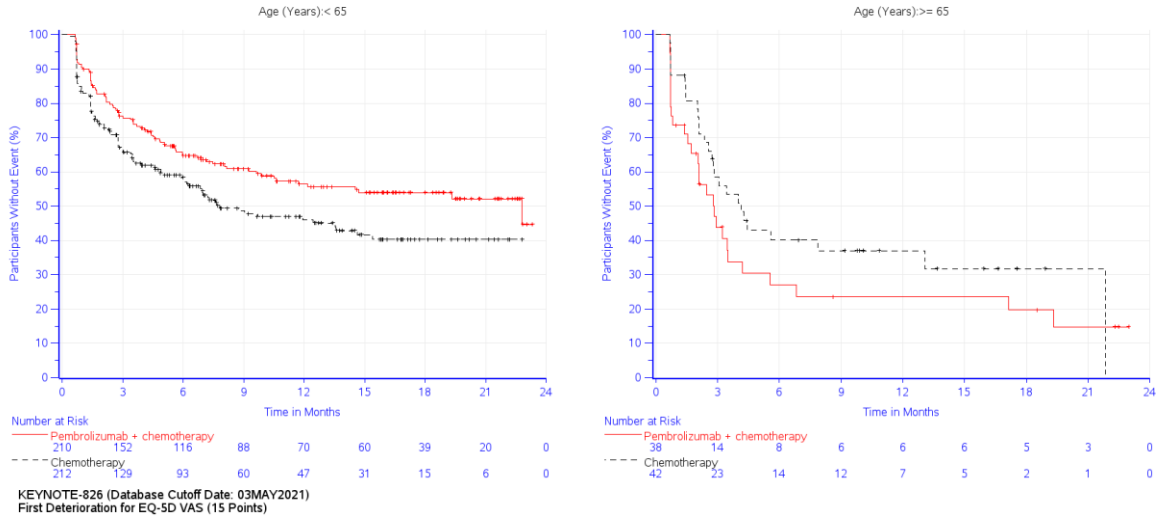

Abbildung 4G-6: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter (Jahre) (< 65 vs. ≥ 65) für den Gesundheitszustand: EQ-5D VAS der Studie KEYNOTE 826

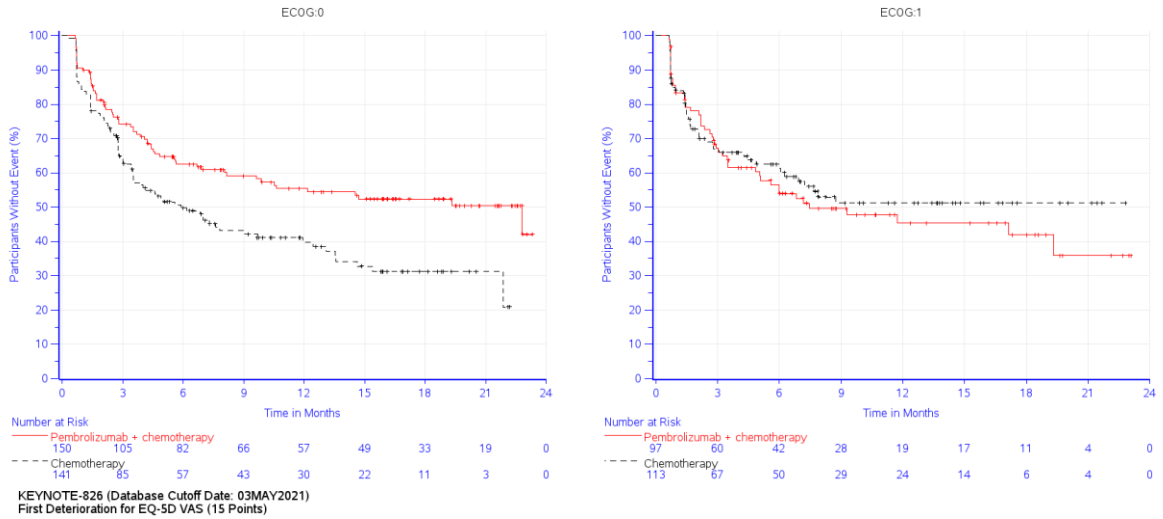

Abbildung 4G-7: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus (0 vs. 1) für den Gesundheitszustand: EQ-5D VAS der Studie KEYNOTE 826

Gesundheitsbezogene Lebensqualität

Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30: Gesundheitsbezogene Lebensqualität anhand des Globaler Gesundheitsstatus

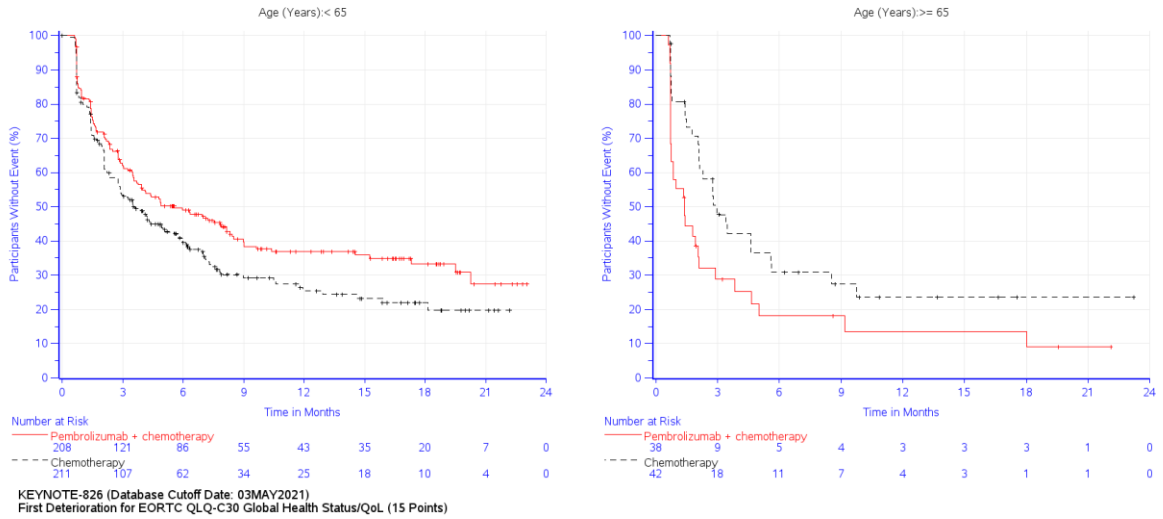

Abbildung 4G-8: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter (Jahre) (< 65 vs. ≥ 65) für den Endpunkt Gesundheitsbezogene Lebensqualität anhand des Globalen Gesundheitsstatus des EORTC QLQ-C30 der Studie KEYNOTE 826

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

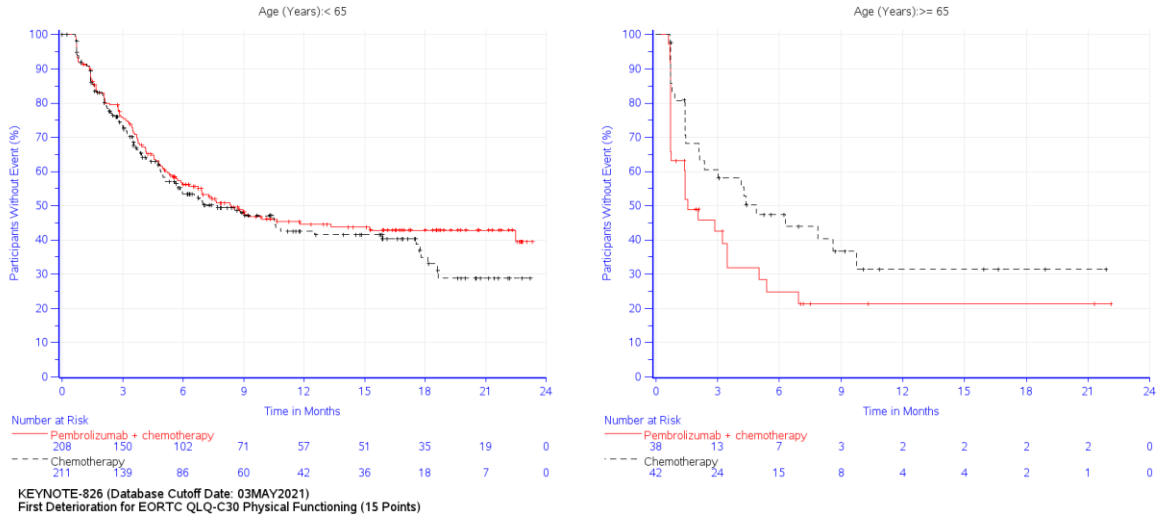

Abbildung 4G-9: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter (Jahre) (< 65 vs. ≥ 65) für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 der Studie KEYNOTE 826

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

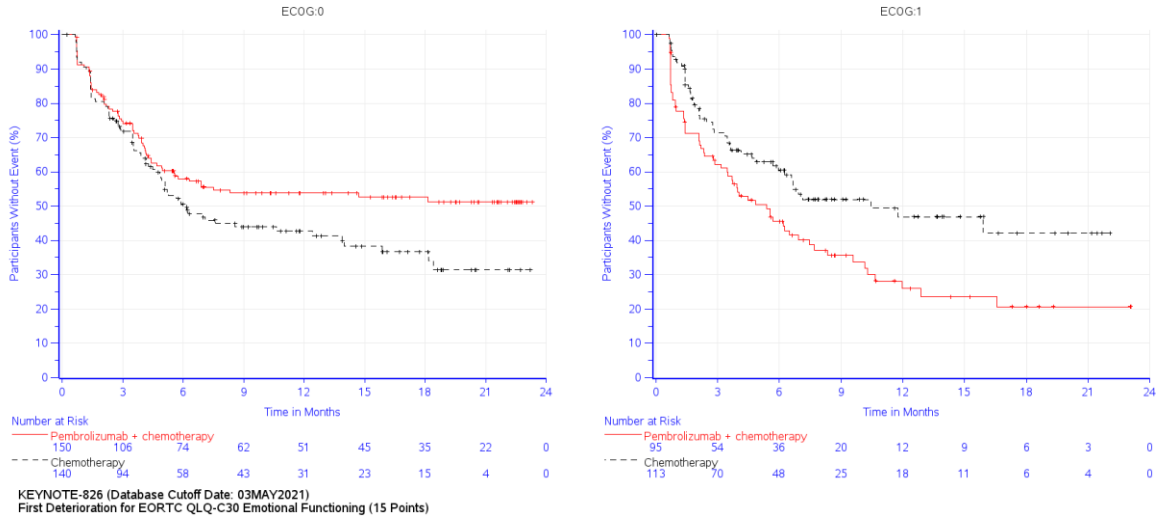

Abbildung 4G-10: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus (0 vs. 1) für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 der Studie KEYNOTE 826

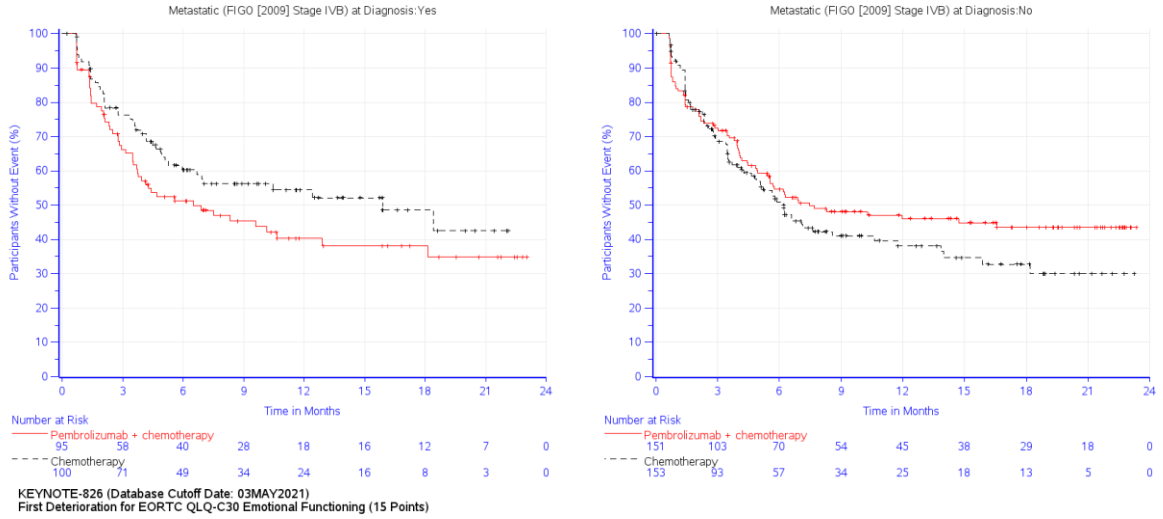

Abbildung 4G-11: Kaplan-Meier-Kurve für die Subgruppenanalyse nach FIGO (2009) Stadium IVB zum Zeitpunkt der Diagnose (Ja vs. Nein) für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 der Studie KEYNOTE 826

EORTC QLQ-CX24: Funktionsskala Sexuelle / vaginale Funktionsfähigkeit

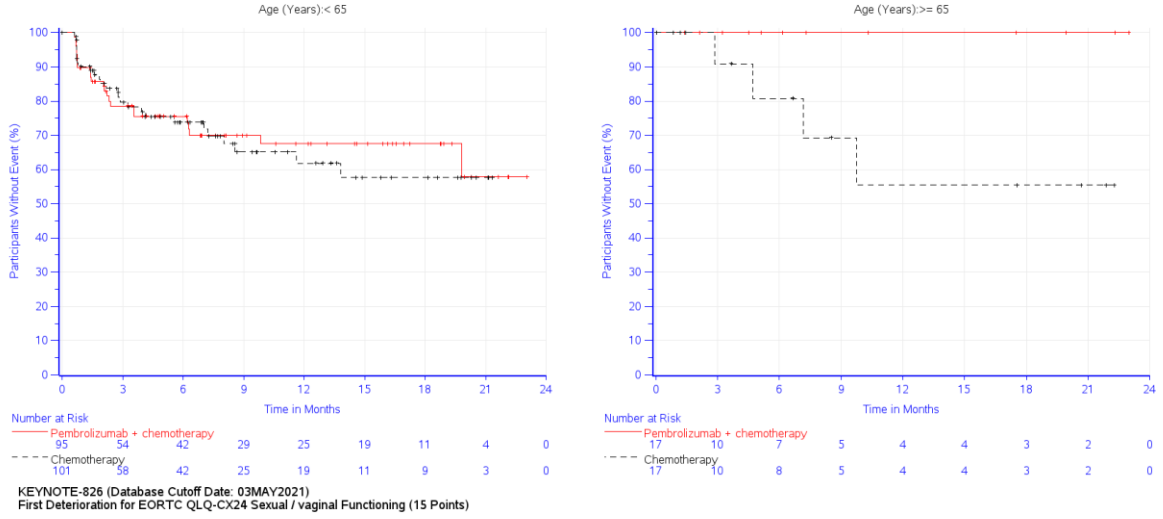

Abbildung 4G-12: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter (Jahre) (< 65 vs. ≥ 65) für die Funktionsskala Sexuelle / vaginale Funktionsfähigkeit des EORTC QLQ-CX24 der Studie KEYNOTE 826

EORTC QLQ-CX24: Funktionsskala Körperbild

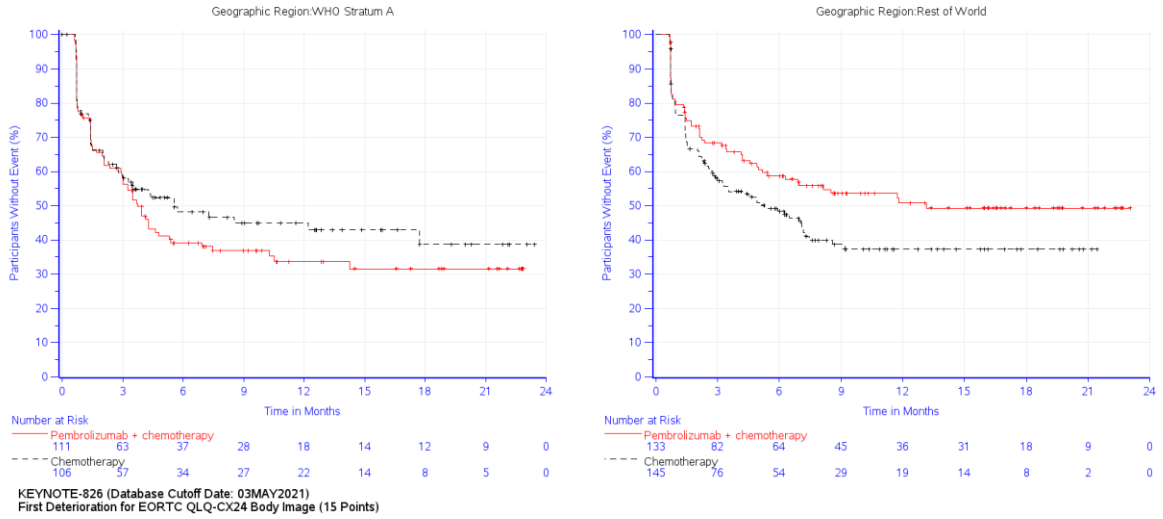

Abbildung 4G-13: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region (WHO Stratum A vs. Rest der Welt) für die Funktionsskala Körperbild des EORTC QLQ-CX24 der Studie KEYNOTE 826

Nebenwirkungen

Unerwünschte Ereignisse gesamt (SOC und PT)

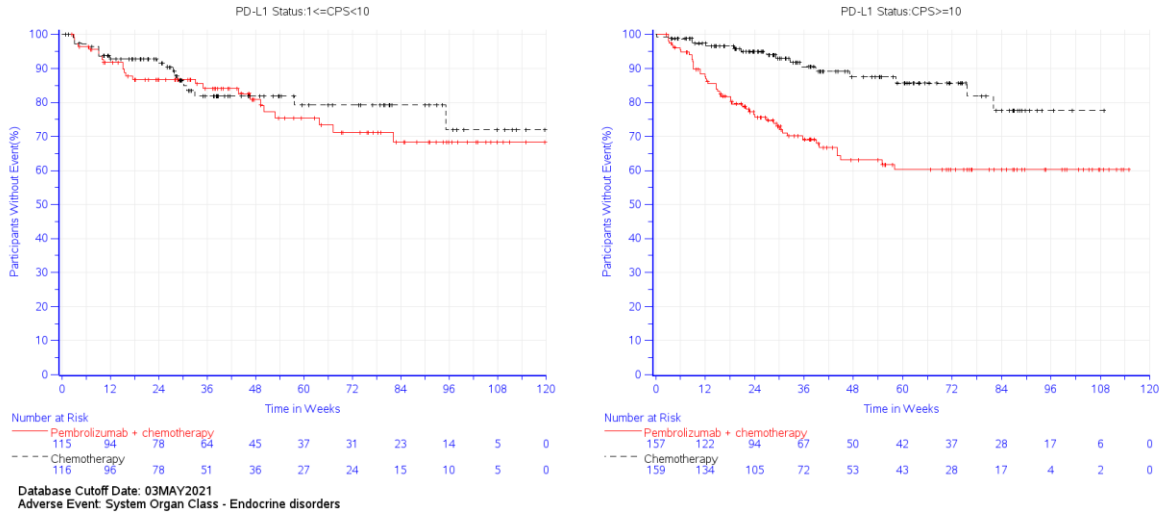

Abbildung 4G-14: Kaplan-Meier-Kurve für die Subgruppenanalyse nach PD-L1 Status ($1 \leq CPS < 10$ vs. $CPS \geq 10$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC Endokrine Erkrankungen der Studie KEYNOTE 826

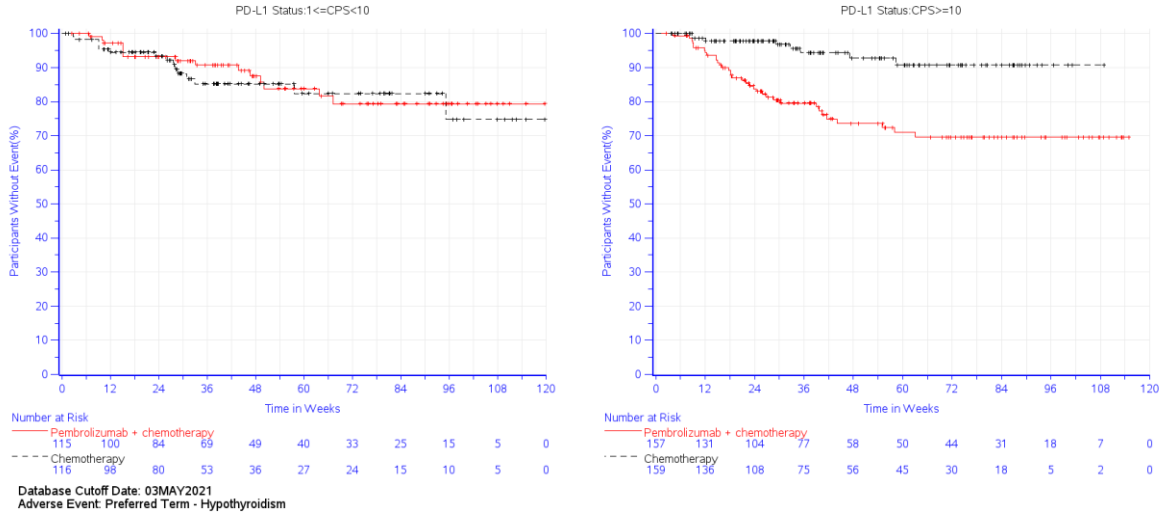

Abbildung 4G-15: Kaplan-Meier-Kurve für die Subgruppenanalyse nach PD-L1 Status (1 ≤ CPS < 10 vs. CPS ≥ 10) für den Endpunkt Unerwünschte Ereignisse (gegliedert nach SOC und PT) für den PT Hypothyreose (SOC Endokrine Erkrankungen) der Studie KEYNOTE 826

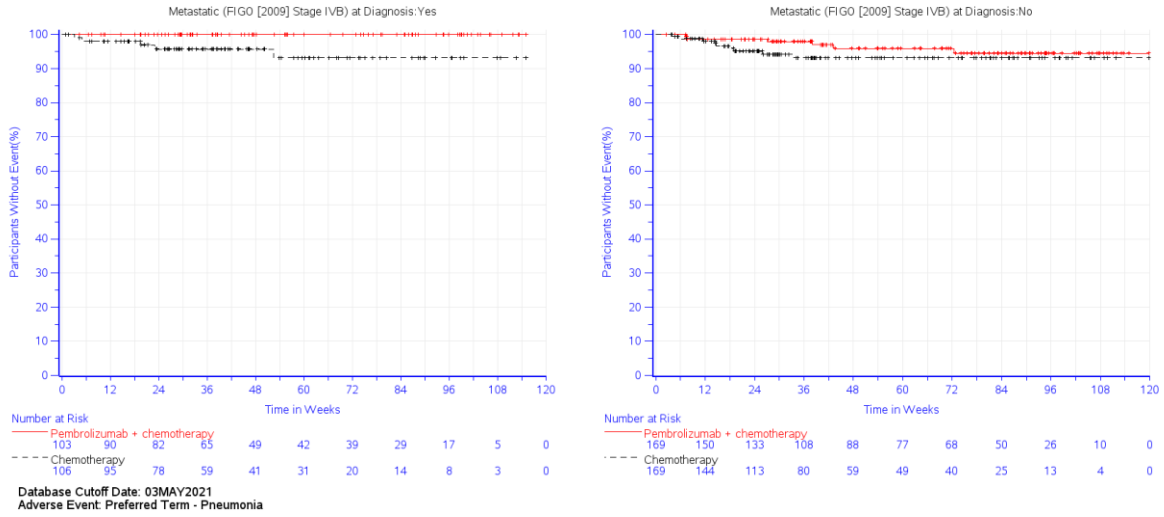

Abbildung 4G-16: Kaplan-Meier-Kurve für die Subgruppenanalyse nach FIGO (2009) Stadium IVB zum Zeitpunkt der Diagnose (Ja vs. Nein) für den Endpunkt Unerwünschte Ereignisse (gegliedert nach SOC und PT) für den PT Lungenentzündung (SOC Infektionen und Infektionskrankheiten) der Studie KEYNOTE 826

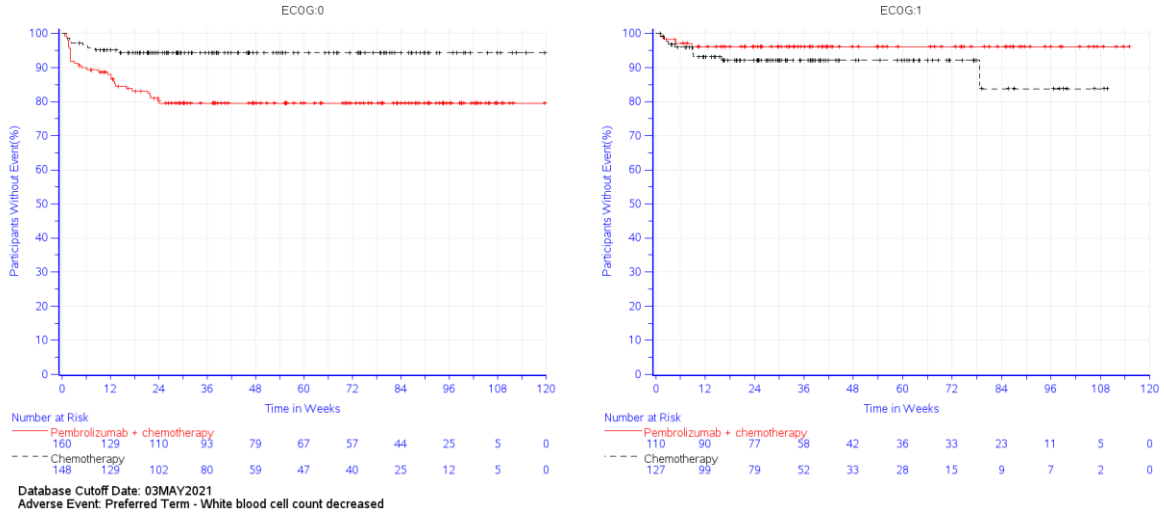

Abbildung 4G-17: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus (0 vs. 1) für den Endpunkt Unerwünschte Ereignisse (gegliedert nach SOC und PT) für den PT Leukozytenzahl erniedrigt (SOC Untersuchungen) der Studie KEYNOTE 826

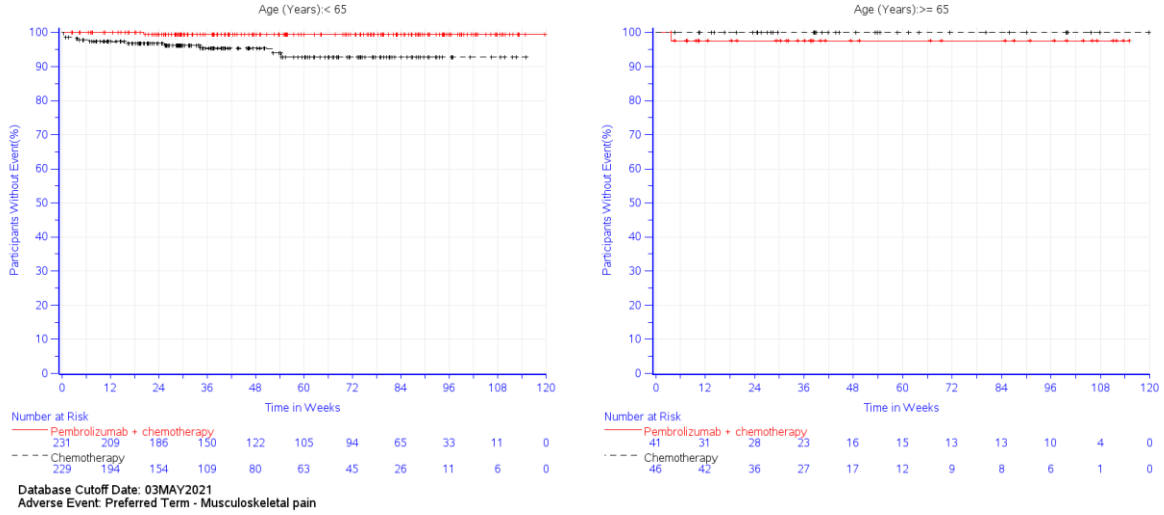

Abbildung 4G-18: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter (Jahre) (< 65 vs. ≥ 65) für den Endpunkt Unerwünschte Ereignisse (gegliedert nach SOC und PT) für den PT Schmerzen des Muskel- und Skelettsystems (SOC Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen) der Studie KEYNOTE 826

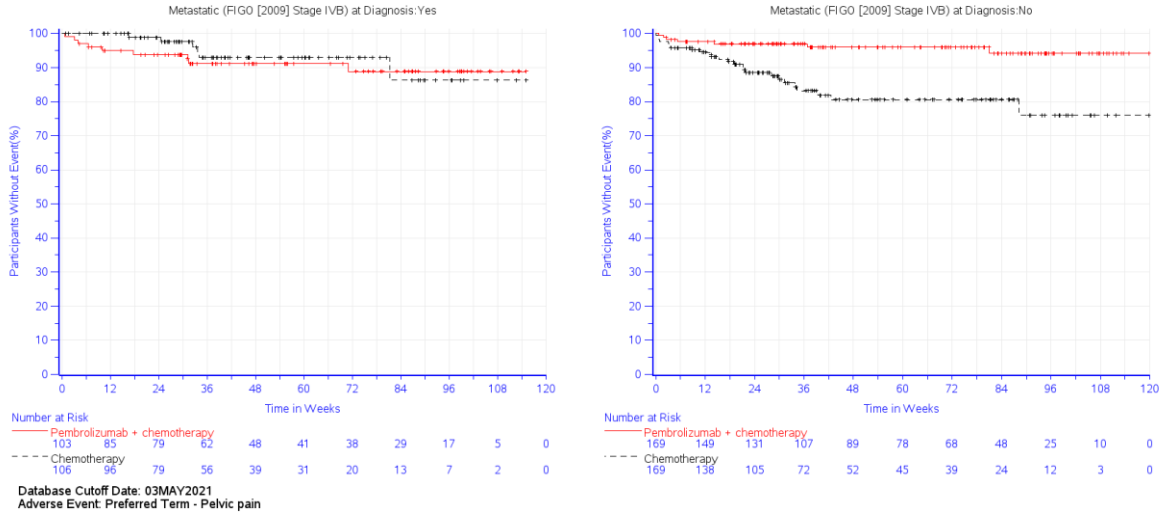

Abbildung 4G-19: Kaplan-Meier-Kurve für die Subgruppenanalyse nach FIGO (2009) Stadium IVB zum Zeitpunkt der Diagnose (Ja vs. Nein) für den Endpunkt Unerwünschte Ereignisse (gegliedert nach SOC und PT) für den PT Beckenschmerz (SOC Erkrankungen der Geschlechtsorgane und der Brustdrüse) der Studie KEYNOTE 826

Anhang 4-G3: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest (p ≥ 0,05) (KEYNOTE 826)

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.2.2 die Ergebnisse der Subgruppenanalysen, für die ein nicht signifikanter Interaktionstest (p ≥ 0,05) vorliegt, dargestellt.

Alle Ergebnisse beziehen sich auf den zulassungsbegründeten Datenschnitt (03.05.2021).

Mortalität

Gesamtüberleben

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

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
Overall Survival	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	232	100 (43.1)	Not reached [19.2; -]	229	130 (56.8)	16.4 [14.5; 19.4]	0.64 [0.49; 0.83]	< 0.001	0.670
≥ 65	41	18 (43.9)	Not reached [12.6; -]	46	24 (52.2)	15.3 [11.5; -]	0.79 [0.43; 1.45]	0.440	
ECOG									
0	160	53 (33.1)	Not reached [-; -]	148	66 (44.6)	23.5 [16.5; -]	0.65 [0.45; 0.93]	0.018	0.901
1	111	63 (56.8)	17.3 [15.0; 22.3]	127	88 (69.3)	12.6 [9.9; 15.7]	0.68 [0.49; 0.94]	0.019	
Geographic Region									
WHO Stratum A	123	42 (34.1)	Not reached [23.5; -]	115	57 (49.6)	18.9 [15.9; 26.0]	0.56 [0.37; 0.83]	0.004	0.321
Rest of World	150	76 (50.7)	18.7 [16.8; -]	160	97 (60.6)	14.5 [11.9; 18.4]	0.73 [0.54; 0.99]	0.045	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	104	46 (44.2)	24.4 [18.9; -]	106	63 (59.4)	15.7 [12.8; 18.6]	0.61 [0.41; 0.89]	0.010	0.691
No	169	72 (42.6)	Not reached [19.1; -]	169	91 (53.8)	18.3 [14.3; 25.0]	0.68 [0.50; 0.93]	0.016	
Bevacizumab Use									
Yes	175	62 (35.4)	Not reached [24.4; -]	176	87 (49.4)	24.7 [16.0; 26.0]	0.63 [0.45; 0.87]	0.005	0.780
No	98	56 (57.1)	17.3 [14.9; 22.3]	99	67 (67.7)	12.6 [10.1; 15.7]	0.67 [0.47; 0.95]	0.026	
PD-L1 Status									
1≤CPS<10	115	52 (45.2)	24.4 [18.2; -]	116	66 (56.9)	15.9 [13.4; 23.5]	0.68 [0.47; 0.98]	0.039	0.713
CPS≥10	158	66 (41.8)	Not reached [19.1; -]	159	88 (55.3)	16.4 [14.0; 25.0]	0.63 [0.46; 0.87]	0.005	
Race									
White	153	67 (43.8)	24.4 [18.7; -]	172	102 (59.3)	14.6 [12.8; 18.6]	0.60 [0.44; 0.82]	0.001	0.336
All Others	102	43	Not reached	87	44	21.0	0.76	0.211	

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
Overall Survival	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
		(42.2)	[19.1; -]		(50.6)	[15.7; -]	[0.50; 1.16]		

a: Database Cutoff Date: 03MAY2021
b: Number of participants: intention-to-treat population with CPS ≥1
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

Morbidität

Zeit bis zur ersten Folgetherapie oder Tod

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

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
Time to Subsequent Therapy or Death	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	232	125 (53.9)	17.1 [14.8; 21.7]	229	167 (72.9)	11.6 [10.1; 13.1]	0.57 [0.45; 0.72]	< 0.001	0.752
≥ 65	41	22 (53.7)	17.7 [9.3; -]	46	33 (71.7)	10.9 [9.2; 14.3]	0.67 [0.39; 1.15]	0.148	
ECOG									
0	160	72 (45.0)	Not reached [17.7; -]	148	93 (62.8)	13.3 [11.4; 15.9]	0.57 [0.42; 0.77]	< 0.001	0.733
1	111	73 (65.8)	12.8 [10.2; 15.8]	127	107 (84.3)	9.6 [8.3; 11.6]	0.62 [0.46; 0.83]	0.002	
Geographic Region									
WHO Stratum A	123	62 (50.4)	18.9 [14.8; -]	115	87 (75.7)	11.9 [10.1; 14.1]	0.50 [0.36; 0.69]	< 0.001	0.224
Rest of World	150	85 (56.7)	16.8 [12.7; 21.7]	160	113 (70.6)	10.7 [9.6; 12.7]	0.67 [0.50; 0.88]	0.005	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	104	61 (58.7)	15.8 [12.4; 18.9]	106	82 (77.4)	11.7 [10.1; 13.8]	0.62 [0.44; 0.86]	0.005	0.576
No	169	86 (50.9)	19.8 [15.4; -]	169	118 (69.8)	11.1 [9.3; 13.2]	0.57 [0.43; 0.75]	< 0.001	
Bevacizumab Use									
Yes	175	84 (48.0)	21.7 [16.4; -]	176	118 (67.0)	12.8 [11.4; 15.3]	0.59 [0.44; 0.78]	< 0.001	0.802
No	98	63 (64.3)	14.7 [11.3; 17.7]	99	82 (82.8)	9.3 [7.8; 10.5]	0.56 [0.40; 0.79]	< 0.001	
PD-L1 Status									

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
Time to Subsequent Therapy or Death	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
1≤CPS<10	115	66 (57.4)	16.0 [13.7; 21.7]	116	83 (71.6)	11.5 [9.9; 13.3]	0.64 [0.46; 0.89]	0.007	0.411
CPS≥10	158	81 (51.3)	18.7 [14.5; -]	159	117 (73.6)	11.4 [9.6; 13.8]	0.54 [0.41; 0.72]	< 0.001	

a: Database Cutoff Date: 03MAY2021
b: Number of participants: intention-to-treat population with CPS ≥1
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30: Symptomskala Erschöpfung

Tabelle 4G-6: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Erschöpfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Fatigue	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	208	132 (63.5)	3.9 [3.0; 6.3]	211	120 (56.9)	3.7 [3.2; 7.0]	1.06 [0.82; 1.35]	0.671	0.802
≥ 65	38	27 (71.1)	1.9 [0.7; 2.9]	42	31 (73.8)	2.3 [1.4; 4.4]	1.12 [0.67; 1.89]	0.658	
ECOG									
0	150	102 (68.0)	2.8 [2.1; 3.9]	140	89 (63.6)	3.2 [2.3; 4.0]	1.08 [0.81; 1.44]	0.584	0.812
1	95	57 (60.0)	5.0 [3.1; 9.3]	113	62 (54.9)	4.9 [3.5; 8.2]	0.98 [0.69; 1.41]	0.933	
Geographic Region									
WHO Stratum A	112	73 (65.2)	3.4 [2.2; 4.6]	107	65 (60.7)	3.0 [2.3; 3.7]	0.95 [0.68; 1.33]	0.768	0.427
Rest of World	134	86 (64.2)	3.7 [2.1; 6.3]	146	86 (58.9)	4.6 [3.2; 8.0]	1.12 [0.83; 1.51]	0.453	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	95	60 (63.2)	3.9 [2.9; 6.9]	100	58 (58.0)	6.2 [3.5; 8.6]	1.11 [0.78; 1.60]	0.559	0.667
No	151	99 (65.6)	3.0 [2.1; 4.6]	153	93 (60.8)	3.2 [2.3; 4.4]	1.02 [0.77; 1.35]	0.895	
Bevacizumab Use									
Yes	155	102 (65.8)	3.7 [2.1; 5.5]	164	103 (62.8)	3.6 [2.8; 4.9]	1.01 [0.77; 1.33]	0.927	0.660
No	91	57 (62.6)	3.7 [2.4; 8.1]	89	48 (53.9)	3.7 [2.4; 8.2]	1.13 [0.77; 1.66]	0.545	

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Fatigue	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
PD-L1 Status									
1≤CPS<10	108	72 (66.7)	2.9 [2.1; 5.5]	104	62 (59.6)	3.7 [2.7; 8.0]	1.08 [0.77; 1.51]	0.665	0.752
CPS≥10	138	87 (63.0)	4.2 [2.8; 6.3]	149	89 (59.7)	3.5 [2.8; 7.0]	1.02 [0.76; 1.37]	0.891	

a: Database Cutoff Date: 03MAY2021
b: Number of participants: all-comer full analysis set with CPS ≥1
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-7: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Übelkeit und Erbrechen des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Nausea and Vomiting	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	208	145 (69.7)	3.0 [2.4; 3.7]	211	144 (68.2)	2.8 [2.1; 4.1]	0.97 [0.77; 1.22]	0.768	0.991
≥ 65	38	25 (65.8)	2.8 [1.5; 5.5]	42	27 (64.3)	2.1 [1.2; 3.4]	1.00 [0.58; 1.73]	0.991	
ECOG									
0	150	103 (68.7)	2.8 [2.1; 3.9]	140	104 (74.3)	2.3 [2.0; 3.4]	0.87 [0.66; 1.14]	0.310	0.226
1	95	67 (70.5)	3.0 [2.1; 4.1]	113	67 (59.3)	3.6 [2.1; 5.7]	1.14 [0.81; 1.60]	0.439	
Geographic Region									
WHO Stratum A	112	81 (72.3)	3.0 [2.2; 4.2]	107	74 (69.2)	3.4 [2.1; 5.6]	1.00 [0.73; 1.36]	0.976	0.767
Rest of World	134	89 (66.4)	2.9 [2.1; 4.0]	146	97 (66.4)	2.3 [1.7; 3.9]	0.94 [0.71; 1.26]	0.700	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	95	65 (68.4)	3.8 [2.8; 4.8]	100	67 (67.0)	3.4 [2.1; 5.6]	0.97 [0.69; 1.37]	0.866	0.979
No	151	105 (69.5)	2.7 [2.1; 3.4]	153	104 (68.0)	2.3 [1.9; 3.5]	0.97 [0.74; 1.27]	0.830	
Bevacizumab Use									
Yes	155	109 (70.3)	3.0 [2.3; 3.9]	164	118 (72.0)	2.8 [2.1; 3.9]	0.92 [0.71; 1.20]	0.555	0.495

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Nausea and Vomiting	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
No	91	61 (67.0)	2.9 [2.1; 4.5]	89	53 (59.6)	2.6 [2.0; 6.9]	1.07 [0.74; 1.54]	0.723	
PD-L1 Status									
1≤CPS<10	108	72 (66.7)	3.7 [2.8; 4.9]	104	72 (69.2)	2.2 [1.4; 4.0]	0.80 [0.57; 1.10]	0.172	0.134
CPS≥10	138	98 (71.0)	2.7 [2.1; 3.5]	149	99 (66.4)	2.8 [2.1; 4.2]	1.12 [0.85; 1.48]	0.425	

a: Database Cutoff Date: 03MAY2021
b: Number of participants: all-comer full analysis set with CPS ≥1
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Schmerz

Tabelle 4G-8: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schmerz des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Pain	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	208	132 (63.5)	4.6 [3.5; 6.3]	211	131 (62.1)	3.8 [2.7; 5.2]	0.95 [0.75; 1.21]	0.702	0.408
≥ 65	38	23 (60.5)	2.1 [1.0; 18.0]	42	33 (78.6)	2.1 [0.9; 3.5]	0.73 [0.43; 1.26]	0.262	
ECOG									
0	150	95 (63.3)	3.5 [2.1; 5.3]	140	102 (72.9)	2.8 [1.4; 3.7]	0.82 [0.62; 1.08]	0.163	0.253
1	95	59 (62.1)	5.8 [4.2; 7.6]	113	62 (54.9)	5.2 [2.8; 9.3]	1.04 [0.73; 1.49]	0.815	
Geographic Region									
WHO Stratum A	112	69 (61.6)	3.7 [2.1; 7.6]	107	73 (68.2)	2.7 [1.4; 4.7]	0.81 [0.59; 1.13]	0.222	0.316
Rest of World	134	86 (64.2)	5.0 [3.4; 6.3]	146	91 (62.3)	4.3 [2.8; 6.0]	1.00 [0.74; 1.34]	0.994	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	95	61 (64.2)	3.9 [2.1; 6.3]	100	61 (61.0)	4.7 [2.8; 7.0]	1.08 [0.76; 1.54]	0.670	0.226
No	151	94 (62.3)	4.6 [3.4; 6.9]	153	103 (67.3)	2.8 [2.1; 3.8]	0.82 [0.62; 1.09]	0.165	

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Pain	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Bevacizumab Use									
Yes	155	106 (68.4)	3.7 [2.1; 5.0]	164	108 (65.9)	2.8 [2.1; 4.3]	0.97 [0.74; 1.27]	0.825	0.473
No	91	49 (53.8)	5.8 [3.4; 16.6]	89	56 (62.9)	4.3 [2.3; 5.7]	0.81 [0.55; 1.19]	0.292	
PD-L1 Status									
1≤CPS<10	108	68 (63.0)	4.2 [2.1; 5.6]	104	67 (64.4)	2.8 [1.5; 4.7]	0.89 [0.63; 1.24]	0.481	0.776
CPS≥10	138	87 (63.0)	4.6 [3.0; 6.9]	149	97 (65.1)	3.8 [2.3; 5.6]	0.93 [0.70; 1.25]	0.635	

a: Database Cutoff Date: 03MAY2021
b: Number of participants: all-comer full analysis set with CPS ≥1
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Dyspnoe

Tabelle 4G-9: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Dyspnoe des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Dyspnoea	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	208	136 (65.4)	4.2 [2.8; 4.9]	211	111 (52.6)	6.2 [4.2; 8.6]	1.28 [1.00; 1.65]	0.051	0.745
≥ 65	38	28 (73.7)	2.1 [1.4; 3.9]	42	29 (69.0)	3.2 [1.4; 9.2]	1.39 [0.82; 2.34]	0.221	
ECOG									
0	150	105 (70.0)	2.8 [2.1; 4.1]	140	79 (56.4)	6.7 [3.3; 9.8]	1.40 [1.05; 1.88]	0.023	0.330
1	95	59 (62.1)	4.9 [2.9; 6.7]	113	61 (54.0)	6.2 [3.5; 8.5]	1.11 [0.77; 1.59]	0.574	
Geographic Region									
WHO Stratum A	112	80 (71.4)	2.9 [2.1; 4.4]	107	66 (61.7)	3.5 [2.8; 6.7]	1.16 [0.84; 1.61]	0.371	0.485
Rest of World	134	84 (62.7)	4.5 [2.8; 5.6]	146	74 (50.7)	7.7 [5.6; 16.8]	1.37 [1.00; 1.87]	0.050[g]	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	95	58 (61.1)	3.9 [2.2; 6.3]	100	61 (61.0)	5.6 [3.3; 8.3]	1.09 [0.76; 1.57]	0.629	0.257

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Dyspnoea	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
No	151	106 (70.2)	3.3 [2.6; 4.9]	153	79 (51.6)	6.2 [3.5; 16.8]	1.42 [1.06; 1.91]	0.018	
Bevacizumab Use									
Yes	155	105 (67.7)	3.9 [2.6; 4.8]	164	90 (54.9)	6.7 [3.5; 9.3]	1.31 [0.99; 1.74]	0.060	0.719
No	91	59 (64.8)	2.9 [2.2; 4.9]	89	50 (56.2)	5.4 [2.8; 8.5]	1.20 [0.82; 1.75]	0.352	
PD-L1 Status									
1≤CPS<10	108	70 (64.8)	4.6 [2.8; 5.6]	104	62 (59.6)	5.4 [2.8; 8.6]	1.06 [0.75; 1.49]	0.755	0.139
CPS≥10	138	94 (68.1)	3.0 [2.1; 4.4]	149	78 (52.3)	6.7 [3.5; 9.3]	1.48 [1.10; 2.01]	0.010	

a: Database Cutoff Date: 03MAY2021
b: Number of participants: all-comer full analysis set with CPS ≥1
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: Unrounded p-value < 0.050
CI: Confidence Interval; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

Tabelle 4G-10: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schlaflosigkeit des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Insomnia	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	208	117 (56.3)	5.6 [3.5; 10.6]	211	108 (51.2)	7.2 [4.9; 13.3]	1.13 [0.87; 1.47]	0.360	0.279
≥ 65	38	24 (63.2)	5.5 [1.5; 7.6]	42	29 (69.0)	3.5 [2.1; 6.3]	0.78 [0.45; 1.35]	0.382	
ECOG									
0	150	89 (59.3)	5.0 [3.5; 7.5]	140	83 (59.3)	5.9 [4.4; 8.7]	1.03 [0.76; 1.39]	0.847	0.854
1	95	51 (53.7)	6.3 [2.8; 19.4]	113	54 (47.8)	7.6 [4.9; 17.5]	1.08 [0.74; 1.59]	0.684	
Geographic Region									
WHO Stratum A	112	65 (58.0)	5.7 [3.5; 12.2]	107	53 (49.5)	8.3 [4.9; 15.6]	1.12 [0.78; 1.61]	0.543	0.705
Rest of World	134	76 (56.7)	5.1 [3.0; 7.2]	146	84 (57.5)	5.9 [4.3; 8.3]	1.03 [0.76; 1.41]	0.847	

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Insomnia	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	95	56 (58.9)	5.1 [2.9; 9.0]	100	55 (55.0)	6.2 [3.5; 11.6]	1.09 [0.75; 1.58]	0.664	0.905
No	151	85 (56.3)	5.6 [3.5; 11.9]	153	82 (53.6)	6.5 [4.8; 10.5]	1.04 [0.77; 1.41]	0.794	
Bevacizumab Use									
Yes	155	93 (60.0)	5.5 [3.4; 10.6]	164	89 (54.3)	7.1 [4.8; 13.3]	1.10 [0.82; 1.47]	0.532	0.649
No	91	48 (52.7)	5.6 [3.4; 19.5]	89	48 (53.9)	5.7 [4.3; 9.2]	0.98 [0.66; 1.46]	0.921	
PD-L1 Status									
1≤CPS<10	108	58 (53.7)	6.3 [3.5; 19.5]	104	59 (56.7)	5.0 [3.6; 7.2]	0.90 [0.63; 1.29]	0.569	0.234
CPS≥10	138	83 (60.1)	5.0 [3.1; 7.5]	149	78 (52.3)	8.3 [4.7; 14.8]	1.20 [0.88; 1.63]	0.255	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Appetitverlust

Tabelle 4G-11: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Appetitverlust des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Appetite Loss	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	208	117 (56.3)	6.9 [4.6; 10.3]	211	114 (54.0)	6.2 [4.7; 9.2]	0.93 [0.71; 1.20]	0.558	0.131
≥ 65	38	27 (71.1)	2.4 [1.4; 4.3]	42	25 (59.5)	3.6 [2.4; -]	1.51 [0.87; 2.61]	0.144	
ECOG									
0	150	92 (61.3)	5.2 [3.5; 8.3]	140	83 (59.3)	5.3 [3.7; 7.6]	0.98 [0.73; 1.32]	0.912	0.949
1	95	52 (54.7)	6.0 [3.9; 14.7]	113	56 (49.6)	6.6 [4.2; 17.5]	1.01 [0.69; 1.48]	0.955	
Geographic Region									
WHO Stratum A	112	65 (58.0)	5.6 [3.5; 14.7]	107	64 (59.8)	6.2 [4.2; 9.2]	0.87 [0.62; 1.24]	0.440	0.431

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Appetite Loss	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Rest of World	134	79 (59.0)	5.5 [3.9; 8.6]	146	75 (51.4)	5.9 [3.5; -]	1.09 [0.80; 1.50]	0.577	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	95	59 (62.1)	5.3 [2.9; 8.4]	100	52 (52.0)	6.9 [4.9; 12.0]	1.27 [0.87; 1.84]	0.212	0.098
No	151	85 (56.3)	6.0 [4.2; 13.4]	153	87 (56.9)	4.4 [2.8; 7.0]	0.84 [0.63; 1.14]	0.270	
Bevacizumab Use									
Yes	155	98 (63.2)	5.0 [3.6; 8.0]	164	96 (58.5)	5.6 [3.5; 7.0]	0.99 [0.75; 1.32]	0.953	> 0.999
No	91	46 (50.5)	7.7 [3.8; 16.6]	89	43 (48.3)	6.6 [4.4; 17.5]	0.99 [0.65; 1.51]	0.974	
PD-L1 Status									
1≤CPS<10	108	65 (60.2)	5.5 [3.7; 10.3]	104	62 (59.6)	4.9 [3.6; 7.0]	0.85 [0.60; 1.21]	0.372	0.439
CPS≥10	138	79 (57.2)	5.6 [3.7; 9.1]	149	77 (51.7)	6.2 [4.2; 17.5]	1.07 [0.78; 1.47]	0.658	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Verstopfung

Tabelle 4G-12: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Verstopfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Constipation	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
ECOG									
0	150	92 (61.3)	2.9 [2.1; 6.3]	140	92 (65.7)	3.3 [2.1; 5.5]	0.93 [0.69; 1.24]	0.610	0.438
1	95	50 (52.6)	5.1 [2.1; -]	113	56 (49.6)	7.2 [4.1; -]	1.12 [0.76; 1.64]	0.565	
Geographic Region									
WHO Stratum A	112	70 (62.5)	2.8 [2.1; 6.3]	107	66 (61.7)	2.9 [2.1; 6.2]	0.98 [0.70; 1.38]	0.922	0.886
Rest of World	134	72 (53.7)	6.2 [2.2; 14.5]	146	82 (56.2)	5.8 [3.6; 11.1]	1.01 [0.73; 1.38]	0.970	

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Constipation	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	95	54 (56.8)	6.3 [2.1; 9.3]	100	59 (59.0)	6.6 [2.3; 8.5]	0.96 [0.67; 1.39]	0.837	0.759
No	151	88 (58.3)	3.5 [2.1; 6.3]	153	89 (58.2)	4.1 [2.8; 6.2]	1.04 [0.78; 1.40]	0.780	
Bevacizumab Use									
Yes	155	92 (59.4)	4.1 [2.1; 7.5]	164	102 (62.2)	4.3 [2.2; 7.0]	0.94 [0.71; 1.24]	0.656	0.410
No	91	50 (54.9)	5.1 [2.1; 9.3]	89	46 (51.7)	4.9 [3.3; -]	1.15 [0.77; 1.72]	0.485	
PD-L1 Status									
1≤CPS<10	108	66 (61.1)	3.5 [2.1; 7.4]	104	61 (58.7)	4.9 [2.8; 10.7]	1.11 [0.78; 1.57]	0.570	0.461
CPS≥10	138	76 (55.1)	5.6 [2.1; 14.4]	149	87 (58.4)	4.2 [2.8; 7.0]	0.94 [0.69; 1.27]	0.669	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Diarrhö

Tabelle 4G-13: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Diarrhö des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Diarrhea	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	208	126 (60.6)	4.7 [3.0; 7.5]	211	110 (52.1)	6.4 [4.8; 10.6]	1.17 [0.91; 1.51]	0.225	0.520
≥ 65	38	20 (52.6)	2.1 [1.4; -]	42	21 (50.0)	6.9 [3.0; -]	1.46 [0.78; 2.70]	0.235	
ECOG									
0	150	93 (62.0)	3.8 [2.3; 7.0]	140	74 (52.9)	6.9 [4.8; 10.6]	1.28 [0.94; 1.73]	0.119	0.619
1	95	53 (55.8)	5.1 [3.0; 9.2]	113	57 (50.4)	6.2 [3.6; 13.4]	1.13 [0.78; 1.65]	0.509	
Geographic Region									
WHO Stratum A	112	67 (59.8)	4.9 [2.9; 7.5]	107	52 (48.6)	8.3 [3.2; -]	1.19 [0.83; 1.71]	0.353	0.834

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Diarrhea	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Rest of World	134	79 (59.0)	3.8 [2.4; 9.0]	146	79 (54.1)	6.4 [4.8; 8.0]	1.24 [0.91; 1.70]	0.174	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	95	54 (56.8)	4.1 [2.1; 7.7]	100	47 (47.0)	8.3 [5.6; -]	1.55 [1.05; 2.30]	0.028	0.111
No	151	92 (60.9)	4.8 [2.9; 9.0]	153	84 (54.9)	5.0 [3.1; 8.0]	1.04 [0.77; 1.39]	0.814	
Bevacizumab Use									
Yes	155	99 (63.9)	4.1 [2.8; 6.2]	164	91 (55.5)	6.2 [4.2; 9.9]	1.24 [0.93; 1.65]	0.136	0.859
No	91	47 (51.6)	6.5 [2.8; 21.8]	89	40 (44.9)	7.5 [4.8; -]	1.19 [0.78; 1.82]	0.409	
PD-L1 Status									
1≤CPS<10	108	60 (55.6)	5.6 [3.7; 11.8]	104	53 (51.0)	6.9 [4.9; -]	1.14 [0.78; 1.64]	0.499	0.623
CPS≥10	138	86 (62.3)	3.5 [2.3; 7.0]	149	78 (52.3)	6.0 [4.2; 10.6]	1.28 [0.94; 1.74]	0.119	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-CX24: Symptomskala Symptomerleben

Tabelle 4G-14: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Symptomerleben des EORTC QLQ-CX24 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-CX24 Symptom Experience	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	207	57 (27.5)	Not reached [-; -]	210	54 (25.7)	Not reached [-; -]	0.99 [0.68; 1.43]	0.942	0.233
≥ 65	37	13 (35.1)	Not reached [8.3; -]	41	9 (22.0)	Not reached [-; -]	1.69 [0.72; 3.95]	0.230	
ECOG									
0	148	36 (24.3)	Not reached [-; -]	139	37 (26.6)	Not reached [-; -]	0.89 [0.56; 1.40]	0.608	0.165
1	95	34 (35.8)	Not reached [12.0; -]	112	26 (23.2)	Not reached [-; -]	1.40 [0.84; 2.34]	0.197	

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-CX24 Symptom Experience	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Geographic Region									
WHO Stratum A	111	31 (27.9)	Not reached [-; -]	106	22 (20.8)	Not reached [-; -]	1.29 [0.74; 2.22]	0.368	0.413
Rest of World	133	39 (29.3)	Not reached [19.7; -]	145	41 (28.3)	Not reached [-; -]	0.96 [0.62; 1.48]	0.840	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	94	26 (27.7)	Not reached [19.7; -]	100	21 (21.0)	Not reached [-; -]	1.24 [0.70; 2.21]	0.458	0.465
No	150	44 (29.3)	Not reached [-; -]	151	42 (27.8)	Not reached [-; -]	0.98 [0.64; 1.49]	0.917	
Bevacizumab Use									
Yes	154	44 (28.6)	Not reached [-; -]	164	40 (24.4)	Not reached [-; -]	1.09 [0.71; 1.67]	0.705	0.930
No	90	26 (28.9)	Not reached [12.0; -]	87	23 (26.4)	Not reached [11.5; -]	1.04 [0.59; 1.82]	0.902	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

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

f: 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CX24; FIGO: International Federation of Gynecology and Obstetrics; WHO: World Health Organization

EORTC QLQ-CX24: Symptomskala Lymphödem

Tabelle 4G-15: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Lymphödem des EORTC QLQ-CX24 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-CX24 Lymphoedema	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	207	101 (48.8)	10.3 [6.7; -]	210	88 (41.9)	11.6 [7.1; -]	1.07 [0.80; 1.43]	0.640	0.991
≥ 65	37	22 (59.5)	5.0 [2.9; 10.6]	41	24 (58.5)	4.4 [2.8; -]	1.04 [0.58; 1.85]	0.899	
ECOG									
0	148	73 (49.3)	10.5 [6.5; -]	139	65 (46.8)	11.1 [4.9; -]	0.98 [0.70; 1.37]	0.894	0.477
1	95	49 (51.6)	6.2 [4.2; 22.5]	112	47 (42.0)	11.2 [5.7; -]	1.16 [0.78; 1.74]	0.461	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	94	44 (46.8)	12.7 [5.2; -]	100	44 (44.0)	12.0 [5.1; -]	0.99 [0.65; 1.51]	0.977	0.804

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-CX24 Lymphoedema	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
No	150	79 (52.7)	7.7 [5.4; 17.4]	151	68 (45.0)	8.3 [5.5; -]	1.08 [0.78; 1.49]	0.643	
Bevacizumab Use									
Yes	154	84 (54.5)	8.4 [5.7; 14.8]	164	76 (46.3)	11.2 [5.7; -]	1.11 [0.82; 1.52]	0.495	0.530
No	90	39 (43.3)	12.7 [4.5; -]	87	36 (41.4)	8.3 [4.4; -]	0.97 [0.62; 1.53]	0.902	
PD-L1 Status									
1≤CPS<10	106	56 (52.8)	7.2 [5.4; 17.5]	104	52 (50.0)	7.8 [4.4; 12.0]	0.92 [0.63; 1.35]	0.668	0.456
CPS≥10	138	67 (48.6)	9.9 [5.1; -]	147	60 (40.8)	Not reached [6.3; -]	1.17 [0.83; 1.66]	0.376	

a: Database Cutoff Date: 03MAY2021
b: Number of participants: all-comer full analysis set with CPS ≥1
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CX24; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1

EORTC QLQ-CX24: Symptomskala Periphere Neuropathie

Tabelle 4G-16: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Periphere Neuropathie des EORTC QLQ-CX24 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-CX24 Peripheral Neuropathy	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	207	178 (86.0)	1.4 [1.1; 1.6]	210	162 (77.1)	1.7 [1.4; 2.1]	1.22 [0.98; 1.51]	0.070	0.786
≥ 65	37	29 (78.4)	1.4 [0.7; 2.1]	41	35 (85.4)	2.0 [1.2; 2.2]	1.15 [0.70; 1.89]	0.580	
ECOG									
0	148	127 (85.8)	1.4 [0.9; 1.6]	139	113 (81.3)	1.4 [0.8; 1.7]	1.07 [0.83; 1.39]	0.580	0.368
1	95	79 (83.2)	1.4 [0.8; 2.1]	112	84 (75.0)	2.1 [1.8; 2.5]	1.33 [0.98; 1.82]	0.066	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	94	80 (85.1)	1.4 [0.8; 1.6]	100	82 (82.0)	1.6 [1.4; 2.1]	1.24 [0.91; 1.69]	0.169	0.908
No	150	127 (84.7)	1.4 [0.9; 2.0]	151	115 (76.2)	2.1 [1.4; 2.2]	1.19 [0.92; 1.53]	0.186	

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-CX24 Peripheral Neuropathy	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Bevacizumab Use									
Yes	154	136 (88.3)	1.4 [0.8; 1.6]	164	127 (77.4)	1.9 [1.4; 2.2]	1.33 [1.04; 1.70]	0.021	0.152
No	90	71 (78.9)	1.4 [1.1; 2.2]	87	70 (80.5)	1.7 [1.4; 2.1]	0.98 [0.70; 1.36]	0.904	
PD-L1 Status									
1≤CPS<10	106	88 (83.0)	1.5 [1.0; 2.1]	104	81 (77.9)	1.6 [1.4; 2.1]	1.11 [0.82; 1.51]	0.484	0.521
CPS≥10	138	119 (86.2)	1.4 [0.8; 1.5]	147	116 (78.9)	1.9 [1.4; 2.2]	1.27 [0.98; 1.64]	0.067	

a: Database Cutoff Date: 03MAY2021
b: Number of participants: all-comer full analysis set with CPS ≥1
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CX24; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1

EORTC QLQ-CX24: Symptomskala Menopausale Symptome

Tabelle 4G-17: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Menopausale Symptome des EORTC QLQ-CX24 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-CX24 Menopausal Symptoms	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	207	115 (55.6)	5.5 [3.0; 9.1]	210	108 (51.4)	6.6 [4.6; 10.4]	1.05 [0.81; 1.37]	0.697	0.418
≥ 65	37	19 (51.4)	6.8 [1.4; -]	41	18 (43.9)	12.1 [3.0; -]	1.38 [0.72; 2.64]	0.327	
Geographic Region									
WHO Stratum A	111	64 (57.7)	3.4 [2.8; 10.3]	106	49 (46.2)	10.4 [5.0; -]	1.28 [0.88; 1.86]	0.190	0.324
Rest of World	133	70 (52.6)	6.2 [2.9; 15.8]	145	77 (53.1)	6.2 [4.1; 8.8]	0.99 [0.71; 1.37]	0.946	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	94	57 (60.6)	3.4 [2.1; 6.9]	100	49 (49.0)	7.1 [5.3; -]	1.44 [0.98; 2.11]	0.062	0.107
No	150	77 (51.3)	9.0 [2.9; -]	151	77 (51.0)	6.9 [3.5; 16.1]	0.94 [0.69; 1.29]	0.718	
Bevacizumab Use									
Yes	154	84 (54.5)	6.8 [3.0; 16.4]	164	83 (50.6)	7.1 [5.7; 16.1]	1.05 [0.78; 1.42]	0.746	0.634

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-CX24 Menopausal Symptoms	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
No	90	50 (55.6)	3.3 [2.4; 9.0]	87	43 (49.4)	5.7 [3.0; -]	1.21 [0.81; 1.82]	0.358	
PD-L1 Status									
1≤CPS<10	106	49 (46.2)	11.8 [4.5; -]	104	51 (49.0)	6.5 [4.1; -]	0.87 [0.59; 1.30]	0.504	0.094
CPS≥10	138	85 (61.6)	2.9 [2.1; 6.9]	147	75 (51.0)	7.1 [4.3; 12.1]	1.31 [0.96; 1.79]	0.085	

a: Database Cutoff Date: 03MAY2021
b: Number of participants: all-comer full analysis set with CPS ≥1
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: 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; CPS: Combined Positive Score; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CX24; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-CX24: Symptomskala Sorge vor schmerzhaften Geschlechtsverkehr, sexueller Aktivität und sexuellem Erleben

Tabelle 4G-18: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Sorge vor schmerzhaftem Geschlechtsverkehr, sexueller Aktivität und sexuellem Erleben des EORTC QLQ-CX24 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-CX24 Sexual Worry	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	197	67 (34.0)	Not reached [-; -]	206	57 (27.7)	Not reached [16.3; -]	1.11 [0.78; 1.58]	0.571	0.430
≥ 65	37	6 (16.2)	Not reached [-; -]	38	8 (21.1)	Not reached [12.2; -]	0.69 [0.24; 2.01]	0.496	
ECOG									
0	143	44 (30.8)	Not reached [-; -]	136	39 (28.7)	Not reached [14.5; -]	0.96 [0.62; 1.48]	0.850	0.484
1	90	29 (32.2)	Not reached [-; -]	108	26 (24.1)	Not reached [15.2; -]	1.23 [0.72; 2.09]	0.446	
Geographic Region									
WHO Stratum A	106	33 (31.1)	Not reached [-; -]	105	31 (29.5)	Not reached [16.3; -]	0.91 [0.55; 1.48]	0.693	0.336
Rest of World	128	40 (31.3)	Not reached [-; -]	139	34 (24.5)	Not reached [15.2; -]	1.21 [0.77; 1.92]	0.412	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	89	25 (28.1)	Not reached [-; -]	99	19 (19.2)	Not reached [-; -]	1.45 [0.80; 2.64]	0.221	0.243
No	145	48	Not reached	145	46	16.3	0.88	0.546	

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-CX24 Sexual Worry	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
		(33.1)	[-; -]		(31.7)	[12.5; -]	[0.59; 1.33]		
Bevacizumab Use									
Yes	149	48 (32.2)	Not reached [-; -]	158	51 (32.3)	Not reached [15.2; -]	0.90 [0.60; 1.33]	0.595	0.110
No	85	25 (29.4)	Not reached [15.3; -]	86	14 (16.3)	Not reached [16.1; -]	1.62 [0.84; 3.13]	0.148	
PD-L1 Status									
1≤CPS<10	101	36 (35.6)	Not reached [15.3; -]	100	25 (25.0)	Not reached [14.5; -]	1.39 [0.83; 2.32]	0.206	0.141
CPS≥10	133	37 (27.8)	Not reached [-; -]	144	40 (27.8)	Not reached [16.1; -]	0.86 [0.55; 1.34]	0.503	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CX24; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

Gesundheitszustand: EQ-5D VAS

Tabelle 4G-19: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesundheitszustand: EQ-5D VAS aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EQ-5D VAS (15 points)	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Geographic Region									
WHO Stratum A	114	53 (46.5)	14.7 [9.6; -]	108	59 (54.6)	6.9 [3.5; 13.6]	0.70 [0.48; 1.01]	0.060	0.538
Rest of World	134	63 (47.0)	10.6 [5.6; -]	146	74 (50.7)	7.7 [4.6; -]	0.85 [0.61; 1.19]	0.356	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	95	44 (46.3)	14.5 [6.9; -]	100	50 (50.0)	8.7 [6.9; -]	0.85 [0.56; 1.27]	0.427	0.546
No	153	72 (47.1)	17.2 [6.0; -]	154	83 (53.9)	5.9 [3.5; 13.1]	0.74 [0.54; 1.01]	0.061	
Bevacizumab Use									
Yes	156	73 (46.8)	19.3 [7.5; -]	164	89 (54.3)	7.7 [4.4; 13.6]	0.73 [0.53; 0.99]	0.046	0.447
No	92	43 (46.7)	9.6 [5.1; -]	90	44 (48.9)	7.2 [4.3; -]	0.89 [0.58; 1.36]	0.591	
PD-L1 Status									

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EQ-5D VAS (15 points)	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
1≤CPS<10	108	51 (47.2)	14.5 [6.0; -]	105	62 (59.0)	5.0 [2.8; 7.9]	0.66 [0.46; 0.96]	0.031	0.309
CPS≥10	140	65 (46.4)	17.2 [6.7; -]	149	71 (47.7)	9.7 [6.2; -]	0.88 [0.62; 1.23]	0.444	

a: Database Cutoff Date: 03MAY2021
b: Number of participants: all-comer full analysis set with CPS ≥1
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: 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; CPS: Combined Positive Score; EQ-5D: European Quality of Life 5 Dimensions; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; VAS: Visual Analog Scale; WHO: World Health Organization

Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-20: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den globalen Gesundheitsstatus des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Global Health Status/QoL	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
ECOG									
0	150	97 (64.7)	3.7 [2.8; 7.0]	140	108 (77.1)	2.8 [2.1; 3.4]	0.72 [0.55; 0.95]	0.022	0.071
1	95	59 (62.1)	4.1 [3.1; 8.3]	113	64 (56.6)	5.0 [3.6; 7.5]	1.08 [0.76; 1.54]	0.679	
Geographic Region									
WHO Stratum A	112	79 (70.5)	3.5 [2.3; 4.9]	107	79 (73.8)	2.9 [2.1; 4.6]	0.86 [0.63; 1.18]	0.348	0.862
Rest of World	134	77 (57.5)	6.3 [3.5; 9.0]	146	93 (63.7)	4.2 [2.8; 6.0]	0.82 [0.61; 1.12]	0.211	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	95	60 (63.2)	3.8 [2.3; 8.3]	100	66 (66.0)	3.5 [2.1; 6.0]	0.89 [0.63; 1.27]	0.527	0.752
No	151	96 (63.6)	4.4 [3.1; 7.0]	153	106 (69.3)	3.5 [2.8; 4.6]	0.82 [0.62; 1.08]	0.158	
Bevacizumab Use									
Yes	155	96 (61.9)	4.8 [3.3; 7.8]	164	116 (70.7)	3.3 [2.3; 4.6]	0.73 [0.56; 0.96]	0.025	0.062
No	91	60 (65.9)	3.5 [2.1; 7.9]	89	56 (62.9)	4.2 [2.3; 6.3]	1.12 [0.78; 1.62]	0.533	
PD-L1 Status									
1≤CPS<10	108	77 (71.3)	3.8 [2.1; 6.3]	104	70 (67.3)	3.5 [2.8; 5.0]	1.02 [0.74; 1.42]	0.891	0.107

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Global Health Status/QoL	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
CPS≥10	138	79 (57.2)	4.6 [3.3; 14.5]	149	102 (68.5)	3.5 [2.1; 5.6]	0.73 [0.54; 0.98]	0.037	

a: Database Cutoff Date: 03MAY2021
b: Number of participants: all-comer full analysis set with CPS ≥1
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-21: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Physical Functioning	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
ECOG									
0	150	85 (56.7)	5.7 [4.6; 9.0]	140	79 (56.4)	6.9 [4.9; 10.6]	0.98 [0.72; 1.33]	0.886	0.879
1	95	49 (51.6)	8.3 [4.9; -]	113	57 (50.4)	7.9 [4.4; 15.9]	0.94 [0.64; 1.38]	0.760	
Geographic Region									
WHO Stratum A	112	66 (58.9)	5.1 [3.5; 9.0]	107	61 (57.0)	6.5 [4.4; 10.6]	1.00 [0.70; 1.41]	0.985	0.802
Rest of World	134	69 (51.5)	7.3 [5.5; -]	146	75 (51.4)	7.7 [4.9; 18.6]	0.94 [0.67; 1.30]	0.693	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	95	51 (53.7)	7.3 [3.8; -]	100	53 (53.0)	9.8 [6.3; 15.9]	1.07 [0.73; 1.58]	0.729	0.441
No	151	84 (55.6)	6.3 [4.8; 10.6]	153	83 (54.2)	5.1 [3.9; 10.5]	0.91 [0.67; 1.23]	0.529	
Bevacizumab Use									
Yes	155	86 (55.5)	7.3 [4.8; 13.3]	164	91 (55.5)	7.7 [5.0; 12.5]	0.94 [0.70; 1.26]	0.668	0.783
No	91	49 (53.8)	5.5 [3.7; 9.3]	89	45 (50.6)	6.9 [3.5; 17.8]	1.03 [0.69; 1.54]	0.892	
PD-L1 Status									
1≤CPS<10	108	64 (59.3)	5.5 [3.8; 9.3]	104	57 (54.8)	7.0 [4.8; 10.5]	1.06 [0.74; 1.52]	0.730	0.464
CPS≥10	138	71 (51.4)	6.9 [5.0; -]	149	79 (53.0)	7.0 [4.9; 15.9]	0.91 [0.66; 1.25]	0.556	

a: Database Cutoff Date: 03MAY2021
b: Number of participants: all-comer full analysis set with CPS ≥1

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Physical Functioning	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
c: From product-limit (Kaplan-Meier) method for censored data									
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval									
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)									
f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization									

EORTC QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-22: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Rollenfunktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Role Functioning	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	208	158 (76.0)	2.2 [1.6; 3.0]	211	154 (73.0)	2.5 [2.1; 3.3]	0.98 [0.79; 1.23]	0.865	0.394
≥ 65	38	31 (81.6)	1.4 [1.0; 2.9]	42	34 (81.0)	2.8 [1.4; 3.6]	1.25 [0.76; 2.03]	0.378	
ECOG									
0	150	118 (78.7)	2.0 [1.4; 2.8]	140	114 (81.4)	2.4 [1.8; 3.0]	0.97 [0.75; 1.25]	0.800	0.589
1	95	71 (74.7)	2.2 [1.4; 4.2]	113	74 (65.5)	2.8 [2.1; 5.1]	1.08 [0.78; 1.50]	0.651	
Geographic Region									
WHO Stratum A	112	94 (83.9)	1.4 [1.4; 2.3]	107	84 (78.5)	2.2 [1.4; 2.8]	1.11 [0.82; 1.48]	0.503	0.412
Rest of World	134	95 (70.9)	2.7 [2.0; 4.5]	146	104 (71.2)	2.9 [2.2; 4.1]	0.93 [0.70; 1.23]	0.592	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	95	72 (75.8)	2.1 [1.4; 3.5]	100	71 (71.0)	2.8 [1.5; 5.6]	1.12 [0.81; 1.56]	0.488	0.343
No	151	117 (77.5)	2.0 [1.4; 2.9]	153	117 (76.5)	2.8 [2.1; 3.0]	0.93 [0.72; 1.21]	0.594	
Bevacizumab Use									
Yes	155	122 (78.7)	2.1 [1.4; 3.0]	164	125 (76.2)	2.8 [2.1; 3.4]	1.02 [0.80; 1.31]	0.870	0.854
No	91	67 (73.6)	1.9 [1.4; 3.5]	89	63 (70.8)	2.8 [1.4; 3.6]	0.99 [0.70; 1.40]	0.975	
PD-L1 Status									
1≤CPS<10	108	84 (77.8)	2.1 [1.5; 2.9]	104	83 (79.8)	2.3 [1.4; 3.4]	0.86 [0.63; 1.17]	0.342	0.261
CPS≥10	138	105 (76.1)	2.1 [1.4; 3.0]	149	105 (70.5)	2.8 [2.2; 3.5]	1.11 [0.85; 1.46]	0.441	
a: Database Cutoff Date: 03MAY2021									

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Role Functioning	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-23: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	Pembrolizumab + chemotherapy			Chemotherapy			Pembrolizumab + chemotherapy vs. Chemotherapy		
EORTC QLQ-C30 Emotional Functioning	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age (Years)									
< 65	208	108 (51.9)	8.3 [5.4; 18.1]	211	103 (48.8)	7.6 [6.2; 15.9]	1.03 [0.78; 1.34]	0.852	0.753
≥ 65	38	22 (57.9)	5.6 [2.1; 10.3]	42	25 (59.5)	3.5 [1.6; 15.9]	0.93 [0.52; 1.65]	0.797	
Geographic Region									
WHO Stratum A	112	55 (49.1)	12.9 [4.7; -]	107	50 (46.7)	8.6 [5.1; -]	0.95 [0.65; 1.40]	0.813	0.636
Rest of World	134	75 (56.0)	5.7 [4.2; 8.3]	146	78 (53.4)	6.6 [4.9; 13.9]	1.08 [0.78; 1.48]	0.648	
Bevacizumab Use									
Yes	155	85 (54.8)	7.5 [4.4; 18.1]	164	83 (50.6)	8.6 [5.7; 18.2]	1.05 [0.78; 1.42]	0.742	0.638
No	91	45 (49.5)	6.9 [4.3; -]	89	45 (50.6)	5.9 [4.3; 12.4]	0.92 [0.61; 1.39]	0.692	
PD-L1 Status									
1≤CPS<10	108	54 (50.0)	10.2 [5.4; -]	104	58 (55.8)	5.7 [4.0; 14.0]	0.76 [0.53; 1.11]	0.157	0.064
CPS≥10	138	76 (55.1)	6.5 [4.0; 12.0]	149	70 (47.0)	10.4 [6.2; -]	1.24 [0.89; 1.71]	0.202	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-24: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Kognitive Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	**Pembrolizumab + chemotherapy**			**Chemotherapy**			**Pembrolizumab + chemotherapy vs. Chemotherapy**		
EORTC QLQ-C30 Cognitive Functioning	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Age (Years)									
< 65	208	152 (73.1)	2.9 [2.1; 4.1]	211	134 (63.5)	3.5 [2.8; 4.7]	1.10 [0.87; 1.39]	0.423	0.853
≥ 65	38	28 (73.7)	2.4 [1.5; 5.3]	42	32 (76.2)	3.2 [1.4; 4.7]	1.04 [0.62; 1.73]	0.886	
ECOG									
0	150	113 (75.3)	3.3 [2.1; 4.5]	140	100 (71.4)	3.3 [2.1; 4.3]	0.96 [0.73; 1.26]	0.779	0.221
1	95	66 (69.5)	2.1 [1.5; 3.5]	113	66 (58.4)	3.7 [2.8; 6.7]	1.28 [0.91; 1.80]	0.156	
Geographic Region									
WHO Stratum A	112	83 (74.1)	2.4 [2.0; 3.9]	107	73 (68.2)	3.0 [2.1; 4.4]	1.03 [0.75; 1.42]	0.832	0.667
Rest of World	134	97 (72.4)	2.9 [2.1; 4.6]	146	93 (63.7)	3.6 [2.9; 5.0]	1.12 [0.84; 1.49]	0.441	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	95	68 (71.6)	2.9 [2.1; 4.9]	100	63 (63.0)	3.9 [3.2; 5.8]	1.19 [0.85; 1.68]	0.315	0.489
No	151	112 (74.2)	2.8 [1.7; 4.1]	153	103 (67.3)	3.0 [2.1; 4.4]	1.02 [0.78; 1.34]	0.882	
Bevacizumab Use									
Yes	155	114 (73.5)	2.8 [2.1; 4.3]	164	115 (70.1)	3.2 [2.1; 3.9]	0.97 [0.75; 1.25]	0.799	0.126
No	91	66 (72.5)	2.8 [2.0; 4.5]	89	51 (57.3)	4.9 [3.0; 6.2]	1.38 [0.95; 1.99]	0.087	
PD-L1 Status									
1≤CPS<10	108	76 (70.4)	2.8 [2.1; 4.9]	104	69 (66.3)	3.6 [2.8; 4.7]	0.93 [0.67; 1.29]	0.644	0.224
CPS≥10	138	104 (75.4)	2.8 [1.9; 4.1]	149	97 (65.1)	3.4 [2.3; 4.9]	1.21 [0.92; 1.60]	0.175	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-25: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Soziale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	**Pembrolizumab + chemotherapy**			**Chemotherapy**			**Pembrolizumab + chemotherapy vs. Chemotherapy**		
EORTC QLQ-C30 Social Functioning	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Age (Years)									
< 65	208	145 (69.7)	3.0 [2.1; 4.2]	211	134 (63.5)	3.4 [2.3; 4.8]	1.05 [0.83; 1.33]	0.660	0.347
≥ 65	38	28 (73.7)	1.8 [1.4; 3.9]	42	29 (69.0)	3.5 [2.1; 5.1]	1.43 [0.85; 2.41]	0.179	
ECOG									
0	150	110 (73.3)	2.4 [2.1; 4.1]	140	99 (70.7)	3.0 [2.3; 3.7]	1.03 [0.78; 1.35]	0.832	0.599
1	95	62 (65.3)	3.7 [1.4; 4.9]	113	64 (56.6)	4.2 [2.2; 6.8]	1.16 [0.82; 1.65]	0.397	
Geographic Region									
WHO Stratum A	112	80 (71.4)	2.3 [1.6; 3.9]	107	75 (70.1)	3.0 [2.1; 4.1]	0.98 [0.72; 1.34]	0.903	0.383
Rest of World	134	93 (69.4)	3.5 [2.1; 4.6]	146	88 (60.3)	3.9 [2.6; 5.4]	1.19 [0.89; 1.59]	0.253	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	95	70 (73.7)	2.1 [1.5; 4.1]	100	64 (64.0)	3.5 [2.1; 5.7]	1.30 [0.92; 1.82]	0.133	0.205
No	151	103 (68.2)	3.5 [2.1; 4.8]	153	99 (64.7)	3.2 [2.3; 4.6]	0.98 [0.74; 1.29]	0.873	
Bevacizumab Use									
Yes	155	111 (71.6)	2.3 [2.1; 4.2]	164	109 (66.5)	3.3 [2.1; 4.2]	1.05 [0.81; 1.37]	0.698	0.588
No	91	62 (68.1)	3.6 [1.8; 5.3]	89	54 (60.7)	3.5 [2.6; 5.7]	1.17 [0.81; 1.69]	0.391	
PD-L1 Status									
1≤CPS<10	108	77 (71.3)	3.3 [2.1; 4.8]	104	69 (66.3)	3.6 [2.1; 5.1]	1.02 [0.74; 1.42]	0.886	0.725
CPS≥10	138	96 (69.6)	2.3 [1.8; 3.8]	149	94 (63.1)	3.1 [2.3; 4.8]	1.14 [0.85; 1.51]	0.381	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-CX24: Funktionsskala Sexuelle Aktivität

Tabelle 4G-26: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Sexuelle Aktivität des EORTC QLQ-CX24 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	**Pembrolizumab + chemotherapy**			**Chemotherapy**			**Pembrolizumab + chemotherapy vs. Chemotherapy**		
EORTC QLQ-CX24 Sexual Activity	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Age (Years)									
< 65	200	37 (18.5)	Not reached [-; -]	207	28 (13.5)	Not reached [-; -]	1.18 [0.72; 1.94]	0.508	0.644
≥ 65	36	4 (11.1)	Not reached [-; -]	41	5 (12.2)	Not reached [-; -]	0.89 [0.24; 3.31]	0.861	
ECOG									
0	145	29 (20.0)	Not reached [-; -]	137	17 (12.4)	Not reached [-; -]	1.48 [0.81; 2.70]	0.199	0.195
1	90	12 (13.3)	Not reached [-; -]	111	16 (14.4)	Not reached [-; -]	0.74 [0.35; 1.58]	0.440	
Geographic Region									
WHO Stratum A	109	22 (20.2)	Not reached [-; -]	104	14 (13.5)	Not reached [-; -]	1.34 [0.68; 2.62]	0.393	0.548
Rest of World	127	19 (15.0)	Not reached [-; -]	144	19 (13.2)	Not reached [-; -]	0.98 [0.51; 1.85]	0.939	
Bevacizumab Use									
Yes	151	32 (21.2)	Not reached [-; -]	162	28 (17.3)	Not reached [-; -]	1.06 [0.64; 1.77]	0.817	0.471
No	85	9 (10.6)	Not reached [-; -]	86	5 (5.8)	Not reached [-; -]	1.63 [0.54; 4.89]	0.383	
PD-L1 Status									
1≤CPS<10	104	17 (16.3)	Not reached [-; -]	103	15 (14.6)	Not reached [-; -]	1.01 [0.51; 2.04]	0.967	0.566
CPS≥10	132	24 (18.2)	Not reached [-; -]	145	18 (12.4)	Not reached [-; -]	1.26 [0.68; 2.33]	0.466	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CX24; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-CX24: Funktionsskala Sexueller Genuss

Tabelle 4G-27: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Sexueller Genuss des EORTC QLQ-CX24 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	**Pembrolizumab + chemotherapy**			**Chemotherapy**			**Pembrolizumab + chemotherapy vs. Chemotherapy**		
EORTC QLQ-CX24 Sexual Enjoyment	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Age (Years)									
< 65	92	21 (22.8)	Not reached [17.0; -]	100	16 (16.0)	Not reached [-; -]	1.30 [0.68; 2.50]	0.426	0.756
≥ 65	17	2 (11.8)	Not reached [16.8; -]	15	1 (6.7)	Not reached [-; -]	1.95 [0.18; 21.49]	0.586	
ECOG									
0	64	15 (23.4)	Not reached [13.2; -]	64	10 (15.6)	Not reached [-; -]	1.44 [0.65; 3.20]	0.374	0.740
1	45	8 (17.8)	Not reached [17.0; -]	51	7 (13.7)	Not reached [13.8; -]	1.20 [0.43; 3.34]	0.727	
Geographic Region									
WHO Stratum A	48	9 (18.8)	Not reached [13.2; -]	52	8 (15.4)	Not reached [-; -]	1.22 [0.47; 3.17]	0.682	0.805
Rest of World	61	14 (23.0)	Not reached [14.8; -]	63	9 (14.3)	Not reached [14.8; -]	1.39 [0.60; 3.24]	0.439	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	34	9 (26.5)	Not reached [14.8; -]	47	7 (14.9)	Not reached [-; -]	1.35 [0.49; 3.69]	0.559	0.948
No	75	14 (18.7)	Not reached [-; -]	68	10 (14.7)	Not reached [-; -]	1.34 [0.59; 3.01]	0.483	
Bevacizumab Use									
Yes	77	16 (20.8)	Not reached [17.0; -]	82	12 (14.6)	Not reached [-; -]	1.43 [0.67; 3.02]	0.353	0.701
No	32	7 (21.9)	Not reached [14.8; -]	33	5 (15.2)	Not reached [-; -]	1.08 [0.33; 3.52]	0.899	
PD-L1 Status									
1≤CPS<10	48	10 (20.8)	Not reached [12.2; -]	51	7 (13.7)	Not reached [-; -]	1.56 [0.59; 4.11]	0.366	0.633
CPS≥10	61	13 (21.3)	Not reached [16.8; -]	64	10 (15.6)	Not reached [14.8; -]	1.18 [0.51; 2.71]	0.696	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CX24; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-CX24: Funktionsskala Sexuelle / Vaginale Funktionsfähigkeit

Tabelle 4G-28: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Sexuelle / Vaginale Funktionsfähigkeit des EORTC QLQ-CX24 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	**Pembrolizumab + chemotherapy**			**Chemotherapy**			**Pembrolizumab + chemotherapy vs. Chemotherapy**		
EORTC QLQ-CX24 Sexual / vaginal Functioning	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
ECOG									
0	67	14 (20.9)	Not reached [19.8; -]	67	21 (31.3)	Not reached [8.0; -]	0.69 [0.35; 1.35]	0.273	0.461
1	45	9 (20.0)	Not reached [-; -]	51	10 (19.6)	Not reached [13.8; -]	1.09 [0.44; 2.69]	0.851	
Geographic Region									
WHO Stratum A	51	10 (19.6)	Not reached [19.8; -]	53	17 (32.1)	Not reached [5.6; -]	0.66 [0.30; 1.43]	0.291	0.448
Rest of World	61	13 (21.3)	Not reached [-; -]	65	14 (21.5)	Not reached [11.6; -]	0.98 [0.46; 2.08]	0.949	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	36	7 (19.4)	Not reached [-; -]	48	13 (27.1)	Not reached [8.0; -]	0.65 [0.26; 1.64]	0.363	0.583
No	76	16 (21.1)	Not reached [19.8; -]	70	18 (25.7)	Not reached [8.6; -]	0.90 [0.46; 1.77]	0.763	
Bevacizumab Use									
Yes	78	18 (23.1)	Not reached [-; -]	84	25 (29.8)	Not reached [8.6; -]	0.84 [0.46; 1.55]	0.579	0.809
No	34	5 (14.7)	Not reached [19.8; -]	34	6 (17.6)	Not reached [5.6; -]	0.70 [0.21; 2.31]	0.555	
PD-L1 Status									
1≤CPS<10	49	12 (24.5)	Not reached [6.3; -]	53	14 (26.4)	Not reached [9.8; -]	1.20 [0.56; 2.61]	0.639	0.171
CPS≥10	63	11 (17.5)	Not reached [19.8; -]	65	17 (26.2)	Not reached [8.6; -]	0.58 [0.27; 1.24]	0.159	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CX24; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

EORTC QLQ-CX24: Funktionsskala Körperbild

Tabelle 4G-29: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Körperbild des EORTC QLQ-CX24 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	**Pembrolizumab + chemotherapy**			**Chemotherapy**			**Pembrolizumab + chemotherapy vs. Chemotherapy**		
EORTC QLQ-CX24 Body Image	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Age (Years)									
< 65	207	109 (52.7)	6.9 [4.3; 14.3]	210	115 (54.8)	5.1 [3.0; 7.2]	0.86 [0.66; 1.12]	0.255	0.146
≥ 65	37	22 (59.5)	3.3 [1.4; 10.3]	41	22 (53.7)	7.3 [2.0; -]	1.38 [0.76; 2.50]	0.287	
ECOG									
0	148	82 (55.4)	5.2 [3.9; 11.8]	139	79 (56.8)	4.9 [2.8; 9.2]	0.92 [0.67; 1.25]	0.573	0.917
1	95	49 (51.6)	6.9 [3.3; -]	112	58 (51.8)	5.6 [3.0; -]	0.94 [0.64; 1.38]	0.757	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	94	48 (51.1)	5.2 [2.1; -]	100	53 (53.0)	7.1 [3.3; -]	1.02 [0.69; 1.50]	0.936	0.528
No	150	83 (55.3)	5.4 [4.2; 11.8]	151	84 (55.6)	4.6 [2.8; 7.3]	0.86 [0.64; 1.17]	0.336	
Bevacizumab Use									
Yes	154	90 (58.4)	4.8 [3.5; 10.5]	164	91 (55.5)	5.6 [3.3; 8.6]	1.00 [0.74; 1.33]	0.978	0.403
No	90	41 (45.6)	8.5 [3.7; -]	87	46 (52.9)	5.9 [2.6; -]	0.81 [0.53; 1.24]	0.334	
PD-L1 Status									
1≤CPS<10	106	58 (54.7)	5.3 [3.7; 11.8]	104	58 (55.8)	6.2 [2.6; 9.2]	0.92 [0.64; 1.32]	0.638	0.998
CPS≥10	138	73 (52.9)	6.9 [3.4; -]	147	79 (53.7)	5.3 [2.9; 17.7]	0.93 [0.67; 1.27]	0.640	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-comer full analysis set with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CX24; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1

Nebenwirkungen

Unerwünschte Ereignisse

Unerwünschte Ereignisse gesamt

Tabelle 4G-30: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	**Pembrolizumab + chemotherapy**			**Chemotherapy**			**Pembrolizumab + chemotherapy vs. Chemotherapy**		
Adverse Events	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Age (Years)									
< 65	231	229 (99.1)	0.6 [0.4; 0.6]	229	228 (99.6)	0.4 [0.4; 0.6]	0.91 [0.76; 1.10]	0.338	0.709
≥ 65	41	41 (100.0)	0.4 [0.4; 0.6]	46	45 (97.8)	0.4 [0.3; 0.6]	0.97 [0.63; 1.49]	0.893	
ECOG									
0	160	159 (99.4)	0.4 [0.4; 0.6]	148	146 (98.6)	0.4 [0.3; 0.6]	0.93 [0.75; 1.17]	0.560	0.970
1	110	109 (99.1)	0.6 [0.4; 1.0]	127	127 (100.0)	0.4 [0.3; 0.9]	0.95 [0.73; 1.22]	0.667	
Geographic Region									
WHO Stratum A	123	121 (98.4)	0.3 [0.3; 0.4]	115	114 (99.1)	0.3 [-; -]	0.88 [0.68; 1.13]	0.315	0.939
Rest of World	149	149 (100.0)	0.9 [0.6; 1.3]	160	159 (99.4)	0.7 [0.6; 1.0]	0.89 [0.71; 1.11]	0.301	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	103	102 (99.0)	0.6 [0.4; 0.7]	106	106 (100.0)	0.4 [0.3; 0.6]	0.82 [0.62; 1.07]	0.148	0.251
No	169	168 (99.4)	0.6 [0.4; 0.6]	169	167 (98.8)	0.4 [0.4; 0.7]	0.99 [0.80; 1.23]	0.937	
PD-L1 Status									
1≤CPS<10	115	115 (100.0)	0.6 [0.4; 0.7]	116	115 (99.1)	0.5 [0.4; 0.7]	0.96 [0.74; 1.25]	0.766	0.555
CPS≥10	157	155 (98.7)	0.4 [0.3; 0.6]	159	158 (99.4)	0.4 [0.3; 0.6]	0.88 [0.71; 1.10]	0.262	
Bevacizumab Use									
Yes	174	174 (100.0)	0.4 [0.4; 0.6]	176	176 (100.0)	0.4 [0.3; 0.6]	0.95 [0.77; 1.17]	0.613	0.675
No	98	96 (98.0)	0.6 [0.4; 0.9]	99	97 (98.0)	0.6 [0.4; 0.6]	0.89 [0.67; 1.18]	0.430	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-participants-as-treated population with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-31: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	**Pembrolizumab + chemotherapy**			**Chemotherapy**			**Pembrolizumab + chemotherapy vs. Chemotherapy**		
Serious Adverse Events	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Age (Years)									
< 65	231	115 (49.8)	71.0 [35.0; -]	229	100 (43.7)	85.3 [52.4; -]	1.13 [0.86; 1.48]	0.367	0.334
≥ 65	41	22 (53.7)	26.3 [8.7; -]	46	17 (37.0)	Not reached [25.7; -]	1.64 [0.87; 3.10]	0.125	
ECOG									
0	160	81 (50.6)	83.9 [29.0; -]	148	54 (36.5)	Not reached [71.1; -]	1.44 [1.02; 2.03]	0.039	0.115
1	110	54 (49.1)	68.6 [17.3; -]	127	63 (49.6)	45.4 [19.7; -]	0.98 [0.68; 1.41]	0.919	
Geographic Region									
WHO Stratum A	123	68 (55.3)	39.4 [13.1; 96.9]	115	50 (43.5)	85.3 [33.3; -]	1.33 [0.92; 1.91]	0.129	0.413
Rest of World	149	69 (46.3)	92.4 [35.4; -]	160	67 (41.9)	Not reached [45.4; -]	1.09 [0.78; 1.53]	0.621	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	103	57 (55.3)	35.0 [17.0; 92.4]	106	40 (37.7)	Not reached [61.4; -]	1.57 [1.05; 2.36]	0.029	0.093
No	169	80 (47.3)	88.4 [35.4; -]	169	77 (45.6)	73.3 [28.6; -]	1.02 [0.74; 1.40]	0.904	
PD-L1 Status									
1≤CPS<10	115	61 (53.0)	41.7 [20.9; -]	116	49 (42.2)	85.3 [56.1; -]	1.27 [0.87; 1.85]	0.214	0.631
CPS≥10	157	76 (48.4)	71.0 [26.3; -]	159	68 (42.8)	Not reached [33.4; -]	1.14 [0.82; 1.59]	0.424	
Bevacizumab Use									
Yes	174	88 (50.6)	68.6 [26.3; -]	176	79 (44.9)	85.3 [45.4; -]	1.15 [0.85; 1.56]	0.366	0.646
No	98	49 (50.0)	70.6 [17.0; -]	99	38 (38.4)	Not reached [-; -]	1.31 [0.85; 2.00]	0.218	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-participants-as-treated population with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

Tabelle 4G-32: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	**Pembrolizumab + chemotherapy**			**Chemotherapy**			**Pembrolizumab + chemotherapy vs. Chemotherapy**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Age (Years)									
< 65	231	187 (81.0)	9.6 [8.6; 12.4]	229	168 (73.4)	12.0 [9.0; 14.9]	1.17 [0.95; 1.44]	0.139	0.409
≥ 65	41	35 (85.4)	5.3 [3.1; 7.4]	46	38 (82.6)	9.3 [5.7; 13.0]	1.53 [0.96; 2.44]	0.074	
ECOG									
0	160	135 (84.4)	8.7 [6.0; 11.0]	148	107 (72.3)	12.7 [9.4; 17.3]	1.35 [1.05; 1.74]	0.021	0.164
1	110	85 (77.3)	9.3 [7.1; 13.9]	127	99 (78.0)	9.3 [6.1; 13.1]	1.02 [0.76; 1.36]	0.903	
Geographic Region									
WHO Stratum A	123	109 (88.6)	5.9 [4.0; 7.4]	115	92 (80.0)	9.3 [6.1; 12.0]	1.35 [1.02; 1.78]	0.034	0.240
Rest of World	149	113 (75.8)	12.3 [9.4; 15.9]	160	114 (71.3)	13.4 [9.3; 19.0]	1.08 [0.83; 1.40]	0.553	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	103	83 (80.6)	9.0 [6.1; 12.6]	106	78 (73.6)	12.1 [8.1; 19.0]	1.27 [0.93; 1.73]	0.130	0.598
No	169	139 (82.2)	9.1 [6.4; 12.0]	169	128 (75.7)	10.3 [8.7; 13.0]	1.14 [0.90; 1.46]	0.270	
PD-L1 Status									
1≤CPS<10	115	93 (80.9)	9.6 [7.4; 13.3]	116	88 (75.9)	10.3 [8.7; 14.1]	1.07 [0.80; 1.44]	0.635	0.301
CPS≥10	157	129 (82.2)	8.6 [5.9; 10.7]	159	118 (74.2)	12.0 [9.0; 17.3]	1.30 [1.01; 1.67]	0.039	
Bevacizumab Use									
Yes	174	146 (83.9)	9.3 [7.3; 12.1]	176	132 (75.0)	12.1 [9.3; 17.7]	1.26 [1.00; 1.60]	0.051	0.404
No	98	76 (77.6)	8.9 [5.7; 12.1]	99	74 (74.7)	9.3 [5.9; 14.1]	1.07 [0.78; 1.48]	0.669	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-participants-as-treated population with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-33: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-826[a]	**Pembrolizumab + chemotherapy**			**Chemotherapy**			**Pembrolizumab + chemotherapy vs. Chemotherapy**		
Adverse Events Leading to Treatment Discontinuation	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Age (Years)									
< 65	231	88 (38.1)	Not reached [66.1; -]	229	59 (25.8)	Not reached [-; -]	1.42 [1.02; 1.97]	0.039	0.213
≥ 65	41	18 (43.9)	80.7 [12.4; -]	46	10 (21.7)	Not reached [-; -]	2.39 [1.10; 5.19]	0.027	
ECOG									
0	160	65 (40.6)	Not reached [52.7; -]	148	32 (21.6)	Not reached [-; -]	1.90 [1.24; 2.90]	0.003	0.158
1	110	41 (37.3)	Not reached [32.3; -]	127	37 (29.1)	Not reached [-; -]	1.24 [0.80; 1.94]	0.336	
Geographic Region									
WHO Stratum A	123	54 (43.9)	80.7 [35.0; -]	115	28 (24.3)	Not reached [-; -]	1.79 [1.13; 2.82]	0.013	0.324
Rest of World	149	52 (34.9)	Not reached [98.9; -]	160	41 (25.6)	Not reached [-; -]	1.35 [0.89; 2.03]	0.155	
Metastatic (FIGO [2009] Stage IVB) at Diagnosis									
Yes	103	37 (35.9)	Not reached [52.7; -]	106	25 (23.6)	Not reached [-; -]	1.47 [0.89; 2.45]	0.135	0.822
No	169	69 (40.8)	Not reached [44.3; -]	169	44 (26.0)	Not reached [-; -]	1.59 [1.09; 2.32]	0.017	
PD-L1 Status									
1≤CPS<10	115	43 (37.4)	98.9 [58.1; -]	116	27 (23.3)	Not reached [-; -]	1.58 [0.97; 2.55]	0.064	0.916
CPS≥10	157	63 (40.1)	Not reached [44.0; -]	159	42 (26.4)	Not reached [-; -]	1.53 [1.03; 2.26]	0.033	
Bevacizumab Use									
Yes	174	81 (46.6)	80.7 [35.4; -]	176	54 (30.7)	Not reached [-; -]	1.51 [1.07; 2.13]	0.019	0.791
No	98	25 (25.5)	Not reached [-; -]	99	15 (15.2)	Not reached [-; -]	1.70 [0.90; 3.23]	0.104	

a: Database Cutoff Date: 03MAY2021

b: Number of participants: all-participants-as-treated population with CPS ≥1

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

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

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

f: 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; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; PD-L1: Programmed Cell Death-Ligand 1; WHO: World Health Organization

Anhang 4-G4: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT (KEYNOTE 826)

Tabelle 4G-34: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT in der Studie KEYNOTE 826

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Pneumonitis	Acute interstitial pneumonitis, Autoimmune lung disease, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organising pneumonia, Immune-mediated lung disease	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, Immune-mediated adrenal insufficiency, Immune-mediated adrenal insuficiency	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis, Immune-mediated hypophysitis	Yes
Hyperthyroidism	Hyperthyroidism, Basedow's disease, Thyrotoxic crisis, Immune-mediated hyperthyroidism	Yes
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism, Autoimmune hypothyroidism, Immune-mediated hypothyroidism	Yes
Thyroiditis	Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute, Silent thyroiditis, Autoimmune thyroid disorder, Immune-mediated thyroiditis	Yes
Type 1 Diabetes Mellitus	Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus, Euglycaemic diabetic ketoacidosis, Diabetic ketosis, Ketosis-prone diabetes mellitus	Yes
Severe Skin Reactions Including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): or	Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Pemphigoid, Pemphigus, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, SJS-TEN overlap	Yes
Severe Skin (continued): If Grade 3 or higher:	Rash, Rash erythematous, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus genital, Lichen planus, Oral lichen planus, Cutaneous vasculitis, Vasculitic rash	Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis, Vogt-Koyanagi-Harada disease, Chorioretinitis, Choroiditis, Immune-mediated uveitis, Choroidal effusion, Choroidal detachment, Serous retinal detachment	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

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis	Yes
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis, Immune-mediated encephalitis	Yes
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis	Yes
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction, Infusion related hypersensitivity reaction	No
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia	Yes
Myelitis	Myelitis, Myelitis transverse	Yes
Vasculitis	Anti-neutrophil cytoplasmic antibody positive vasculitis, Aortitis, Arteritis, Arteritis coronary, Behcet's syndrome, Central nervous system vasculitis, Cerebral arteritis, Diffuse vasculitis, Eosinophilic granulomatosis with polyangiitis, Granulomatosis with polyangiitis, Haemorrhagic vasculitis, Hypersensitivity vasculitis, Microscopic polyangiitis, Ocular vasculitis, Polyarteritis nodosa, Pulmonary vasculitis, Renal arteritis, Renal vasculitis, Retinal vasculitis, Takayasu's arteritis, Giant cell arteritis, Vasculitis, Vasculitis gastrointestinal, Vasculitis necrotising	Yes
Cholangitis Sclerosing	Cholangitis sclerosing, Autoimmune cholangitis, Immune-mediated cholangitis	Yes