Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD Sharp & Dohme GmbH

Modul 4 A

Anhang 4-G: Weitere Ergebnisse

Erstlinienbehandlung des lokal fortgeschrittenen nicht resezierbaren oder metastasierenden Ösophaguskarzinoms oder des HER2-negativen Adenokarzinoms des gastroösophagealen Übergangs bei Erwachsenen mit PD-L1-exprimierenden Tumoren (CPS ≥ 10)

Stand: 12.11.2021

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Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.2.2 bzw. Abschnitt 4.3.1.3.1.3.1 die Rücklaufquoten des EORTC QLQ-C30, die Rücklaufquoten des EORTC QLQ-OES18 und die Rücklaufquoten des EQ-5D VAS der Studie KEYNOTE 590 dargestellt.

Alle Ergebnisse beziehen sich auf den finalen Datenschnitt (02. Juli 2020).

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

Tabelle 4G-1: Gründe für das Fehlen von Werten im EORTC QLQ-C30 – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]		**Pembrolizumab + Chemotherapy[b]**	**Chemotherapy[b]**
Visit	**EORTC QLQ-C30**	**N[c] = 184 n (%)**	**N[c] = 192 n (%)**
BASELINE	Expected to Complete Questionnaires	184 (100.0)	192 (100.0)
	Completed	179 (97.3)	185 (96.4)
	Compliance (% in those expected to complete questionnaires)[d]	179 (97.3)	185 (96.4)
	Not completed	5 (2.7)	7 (3.6)
	Not completed due to site staff error	1 (0.5)	5 (2.6)
	Other	1 (0.5)	1 (0.5)
	With visit, no record	3 (1.6)	1 (0.5)
	Missing by Design[e]	0 (0.0)	0 (0.0)
WEEK 3	Expected to Complete Questionnaires	164 (89.1)	162 (84.4)
	Completed	158 (85.9)	147 (76.6)
	Compliance (% in those expected to complete questionnaires)[d]	158 (96.3)	147 (90.7)
	Not completed	6 (3.3)	15 (7.8)
	Subject did not complete due to disease under study	2 (1.1)	1 (0.5)
	Not completed due to site staff error	2 (1.1)	5 (2.6)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Subject did not complete due to side effects of treatment	1 (0.5)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	2 (1.0)
	Other	1 (0.5)	3 (1.6)
	With visit, no record	0 (0.0)	3 (1.6)
	Missing by Design[e]	20 (10.9)	30 (15.6)
	Subject died	3 (1.6)	3 (1.6)
	Visit not scheduled	17 (9.2)	27 (14.1)
WEEK 6	Expected to Complete Questionnaires	148 (80.4)	160 (83.3)
	Completed	143 (77.7)	154 (80.2)
	Compliance (% in those expected to complete questionnaires)[d]	143 (96.6)	154 (96.3)
	Not completed	5 (2.7)	6 (3.1)
	Not completed due to site staff error	0 (0.0)	1 (0.5)
	Subject in hospital or hospice	0 (0.0)	2 (1.0)
	Subject was physically unable to complete	1 (0.5)	0 (0.0)
	Subject refused for other reasons	2 (1.1)	1 (0.5)
	Other	1 (0.5)	1 (0.5)
	With visit, no record	1 (0.5)	1 (0.5)
	Missing by Design[e]	36 (19.6)	32 (16.7)
	Discontinued due to adverse event	5 (2.7)	5 (2.6)
	Discontinued due to clinical progression	0 (0.0)	2 (1.0)
	Discontinued due to progressive disease	1 (0.5)	1 (0.5)
	Discontinued due to withdrawal by subject	1 (0.5)	0 (0.0)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 184 n (%)	N[c] = 192 n (%)
	Visit not scheduled	29 (15.8)	24 (12.5)
WEEK 9	Expected to Complete Questionnaires	139 (75.5)	155 (80.7)
	Completed	131 (71.2)	142 (74.0)
	Compliance (% in those expected to complete questionnaires)[d]	131 (94.2)	142 (91.6)
	Not completed	8 (4.3)	13 (6.8)
	Subject did not complete due to disease under study	1 (0.5)	1 (0.5)
	Not completed due to site staff error	3 (1.6)	1 (0.5)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Subject refused for other reasons	1 (0.5)	1 (0.5)
	Other	1 (0.5)	2 (1.0)
	With visit, no record	2 (1.1)	7 (3.6)
	Missing by Design[e]	45 (24.5)	37 (19.3)
	Discontinued due to adverse event	7 (3.8)	6 (3.1)
	Discontinued due to clinical progression	2 (1.1)	3 (1.6)
	Discontinued due to progressive disease	2 (1.1)	4 (2.1)
	Discontinued due to withdrawal by subject	3 (1.6)	1 (0.5)
	Subject died	1 (0.5)	4 (2.1)
	Visit not scheduled	30 (16.3)	19 (9.9)
WEEK 12	Expected to Complete Questionnaires	139 (75.5)	144 (75.0)
	Completed	133 (72.3)	132 (68.8)
	Compliance (% in those expected to complete questionnaires)[d]	133 (95.7)	132 (91.7)
	Not completed	6 (3.3)	12 (6.3)
	Not completed due to site staff error	3 (1.6)	1 (0.5)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Subject was physically unable to complete	0 (0.0)	1 (0.5)
	Subject refused for other reasons	1 (0.5)	3 (1.6)
	Other	2 (1.1)	1 (0.5)
	With visit, no record	0 (0.0)	5 (2.6)
	Missing by Design[e]	45 (24.5)	48 (25.0)
	Discontinued due to adverse event	8 (4.3)	10 (5.2)
	Discontinued due to clinical progression	4 (2.2)	8 (4.2)
	Discontinued due to progressive disease	11 (6.0)	9 (4.7)
	Discontinued due to withdrawal by subject	5 (2.7)	1 (0.5)
	Visit not scheduled	17 (9.2)	20 (10.4)
WEEK 15	Expected to Complete Questionnaires	129 (70.1)	127 (66.1)
	Completed	117 (63.6)	122 (63.5)
	Compliance (% in those expected to complete questionnaires)[d]	117 (90.7)	122 (96.1)
	Not completed	12 (6.5)	5 (2.6)
	Subject did not complete due to disease under study	1 (0.5)	0 (0.0)
	Not completed due to site staff error	2 (1.1)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Other	2 (1.1)	1 (0.5)
	With visit, no record	7 (3.8)	3 (1.6)
	Missing by Design[e]	55 (29.9)	65 (33.9)
	Discontinued due to adverse event	8 (4.3)	12 (6.3)
	Discontinued due to clinical progression	7 (3.8)	11 (5.7)
	Discontinued due to progressive disease	13 (7.1)	14 (7.3)
	Discontinued due to withdrawal by subject	8 (4.3)	1 (0.5)
	Subject died	1 (0.5)	5 (2.6)
	Visit not scheduled	18 (9.8)	22 (11.5)
WEEK 18	Expected to Complete Questionnaires	120 (65.2)	116 (60.4)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 184 n (%)	N[c] = 192 n (%)
	Completed	109 (59.2)	105 (54.7)
	Compliance (% in those expected to complete questionnaires)[d]	109 (90.8)	105 (90.5)
	Not completed	11 (6.0)	11 (5.7)
	Subject did not complete due to disease under study	2 (1.1)	2 (1.0)
	Not completed due to site staff error	2 (1.1)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.5)
	Subject refused for other reasons	0 (0.0)	2 (1.0)
	Other	2 (1.1)	2 (1.0)
	With visit, no record	5 (2.7)	4 (2.1)
	Missing by Design[e]	64 (34.8)	76 (39.6)
	Discontinued due to adverse event	10 (5.4)	13 (6.8)
	Discontinued due to clinical progression	9 (4.9)	14 (7.3)
	Discontinued due to physician decision	0 (0.0)	2 (1.0)
	Discontinued due to progressive disease	18 (9.8)	23 (12.0)
	Discontinued due to withdrawal by subject	7 (3.8)	2 (1.0)
	Subject died	0 (0.0)	3 (1.6)
	Visit not scheduled	20 (10.9)	19 (9.9)
WEEK 21	Expected to Complete Questionnaires	111 (60.3)	102 (53.1)
	Completed	104 (56.5)	97 (50.5)
	Compliance (% in those expected to complete questionnaires)[d]	104 (93.7)	97 (95.1)
	Not completed	7 (3.8)	5 (2.6)
	Not completed due to site staff error	1 (0.5)	1 (0.5)
	Subject refused for other reasons	1 (0.5)	1 (0.5)
	Other	2 (1.1)	1 (0.5)
	With visit, no record	3 (1.6)	2 (1.0)
	Missing by Design[e]	73 (39.7)	90 (46.9)
	Discontinued due to adverse event	12 (6.5)	16 (8.3)
	Discontinued due to clinical progression	9 (4.9)	16 (8.3)
	Discontinued due to physician decision	1 (0.5)	3 (1.6)
	Discontinued due to progressive disease	30 (16.3)	37 (19.3)
	Discontinued due to withdrawal by subject	8 (4.3)	4 (2.1)
	Visit not scheduled	13 (7.1)	14 (7.3)
WEEK 24	Expected to Complete Questionnaires	113 (61.4)	104 (54.2)
	Completed	105 (57.1)	93 (48.4)
	Compliance (% in those expected to complete questionnaires)[d]	105 (92.9)	93 (89.4)
	Not completed	8 (4.3)	11 (5.7)
	Subject did not complete due to disease under study	1 (0.5)	0 (0.0)
	Not completed due to site staff error	0 (0.0)	4 (2.1)
	Subject in hospital or hospice	1 (0.5)	0 (0.0)
	Subject was physically unable to complete	2 (1.1)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.5)
	Subject refused for other reasons	1 (0.5)	1 (0.5)
	Other	1 (0.5)	4 (2.1)
	With visit, no record	2 (1.1)	1 (0.5)
	Missing by Design[e]	71 (38.6)	88 (45.8)
	Discontinued due to adverse event	13 (7.1)	17 (8.9)
	Discontinued due to clinical progression	10 (5.4)	17 (8.9)
	Discontinued due to physician decision	1 (0.5)	3 (1.6)
	Discontinued due to progressive disease	35 (19.0)	45 (23.4)
	Discontinued due to withdrawal by subject	10 (5.4)	5 (2.6)
	Subject died	0 (0.0)	1 (0.5)
	Visit not scheduled	2 (1.1)	0 (0.0)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 184 n (%)	N[c] = 192 n (%)
WEEK 33	Expected to Complete Questionnaires	97 (52.7)	70 (36.5)
	Completed	84 (45.7)	63 (32.8)
	Compliance (% in those expected to complete questionnaires)[d]	84 (86.6)	63 (90.0)
	Not completed	13 (7.1)	7 (3.6)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.5)
	Not completed due to site staff error	3 (1.6)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Subject refused for other reasons	0 (0.0)	1 (0.5)
	Other	3 (1.6)	1 (0.5)
	With visit, no record	7 (3.8)	3 (1.6)
	Missing by Design[e]	87 (47.3)	122 (63.5)
	Discontinued due to adverse event	16 (8.7)	19 (9.9)
	Discontinued due to clinical progression	11 (6.0)	19 (9.9)
	Discontinued due to physician decision	2 (1.1)	3 (1.6)
	Discontinued due to progressive disease	46 (25.0)	70 (36.5)
	Discontinued due to withdrawal by subject	11 (6.0)	8 (4.2)
	Subject died	0 (0.0)	3 (1.6)
	Visit not scheduled	1 (0.5)	0 (0.0)
WEEK 42	Expected to Complete Questionnaires	69 (37.5)	43 (22.4)
	Completed	62 (33.7)	34 (17.7)
	Compliance (% in those expected to complete questionnaires)[d]	62 (89.9)	34 (79.1)
	Not completed	7 (3.8)	9 (4.7)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.5)
	Not completed due to site staff error	1 (0.5)	2 (1.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.5)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.5)
	Other	0 (0.0)	1 (0.5)
	With visit, no record	6 (3.3)	3 (1.6)
	Missing by Design[e]	115 (62.5)	149 (77.6)
	Discontinued due to adverse event	17 (9.2)	21 (10.9)
	Discontinued due to clinical progression	14 (7.6)	20 (10.4)
	Discontinued due to physician decision	2 (1.1)	3 (1.6)
	Discontinued due to progressive disease	68 (37.0)	94 (49.0)
	Discontinued due to withdrawal by subject	13 (7.1)	10 (5.2)
	Subject died	1 (0.5)	1 (0.5)
WEEK 51	Expected to Complete Questionnaires	53 (28.8)	25 (13.0)
	Completed	47 (25.5)	18 (9.4)
	Compliance (% in those expected to complete questionnaires)[d]	47 (88.7)	18 (72.0)
	Not completed	6 (3.3)	7 (3.6)
	Subject did not complete due to disease under study	2 (1.1)	0 (0.0)
	Not completed due to site staff error	1 (0.5)	1 (0.5)
	Subject was physically unable to complete	0 (0.0)	1 (0.5)
	Subject refused for other reasons	0 (0.0)	3 (1.6)
	Other	0 (0.0)	1 (0.5)
	With visit, no record	3 (1.6)	1 (0.5)
	Missing by Design[e]	131 (71.2)	167 (87.0)
	Discontinued due to adverse event	19 (10.3)	21 (10.9)
	Discontinued due to clinical progression	17 (9.2)	23 (12.0)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	78 (42.4)	108 (56.3)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.2)
	Subject died	0 (0.0)	1 (0.5)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 184 n (%)	N[c] = 192 n (%)
	Visit not scheduled	1 (0.5)	0 (0.0)
WEEK 60	Expected to Complete Questionnaires	46 (25.0)	18 (9.4)
	Completed	21 (11.4)	7 (3.6)
	Compliance (% in those expected to complete questionnaires)[d]	21 (45.7)	7 (38.9)
	Not completed	25 (13.6)	11 (5.7)
	Not completed due to site staff error	1 (0.5)	0 (0.0)
	Other	2 (1.1)	2 (1.0)
	With visit, no record	22 (12.0)	9 (4.7)
	Missing by Design[e]	138 (75.0)	174 (90.6)
	Discontinued due to adverse event	19 (10.3)	22 (11.5)
	Discontinued due to clinical progression	18 (9.8)	24 (12.5)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	85 (46.2)	114 (59.4)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.2)
WEEK 69	Expected to Complete Questionnaires	42 (22.8)	13 (6.8)
	Completed	6 (3.3)	1 (0.5)
	Compliance (% in those expected to complete questionnaires)[d]	6 (14.3)	1 (7.7)
	Not completed	36 (19.6)	12 (6.3)
	Subject refused for other reasons	0 (0.0)	2 (1.0)
	Other	1 (0.5)	1 (0.5)
	With visit, no record	35 (19.0)	9 (4.7)
	Missing by Design[e]	142 (77.2)	179 (93.2)
	Discontinued due to adverse event	20 (10.9)	22 (11.5)
	Discontinued due to clinical progression	18 (9.8)	25 (13.0)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	88 (47.8)	118 (61.5)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.2)
WEEK 78	Expected to Complete Questionnaires	34 (18.5)	10 (5.2)
	Completed	3 (1.6)	3 (1.6)
	Compliance (% in those expected to complete questionnaires)[d]	3 (8.8)	3 (30.0)
	Not completed	31 (16.8)	7 (3.6)
	With visit, no record	31 (16.8)	7 (3.6)
	Missing by Design[e]	150 (81.5)	182 (94.8)
	Discontinued due to adverse event	20 (10.9)	23 (12.0)
	Discontinued due to clinical progression	18 (9.8)	25 (13.0)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	94 (51.1)	120 (62.5)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.2)
	Visit not reached	2 (1.1)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires	27 (14.7)	6 (3.1)
	Completed	3 (1.6)	1 (0.5)
	Compliance (% in those expected to complete questionnaires)[d]	3 (11.1)	1 (16.7)
	Not completed	24 (13.0)	5 (2.6)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	With visit, no record	24 (13.0)	4 (2.1)
	Missing by Design[e]	157 (85.3)	186 (96.9)
	Discontinued due to adverse event	20 (10.9)	23 (12.0)
	Discontinued due to clinical progression	18 (9.8)	25 (13.0)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	96 (52.2)	122 (63.5)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.2)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 184 n (%)	N[c] = 192 n (%)
	Visit not reached	7 (3.8)	2 (1.0)
WEEK 96	Expected to Complete Questionnaires	20 (10.9)	4 (2.1)
	Not completed	20 (10.9)	4 (2.1)
	With visit, no record	20 (10.9)	4 (2.1)
	Missing by Design[e]	164 (89.1)	188 (97.9)
	Discontinued due to adverse event	20 (10.9)	23 (12.0)
	Discontinued due to clinical progression	18 (9.8)	25 (13.0)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	99 (53.8)	124 (64.6)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.2)
	Visit not reached	11 (6.0)	2 (1.0)
WEEK 105	Expected to Complete Questionnaires	13 (7.1)	3 (1.6)
	Completed	5 (2.7)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	5 (38.5)	0 (0.0)
	Not completed	8 (4.3)	3 (1.6)
	With visit, no record	8 (4.3)	3 (1.6)
	Missing by Design[e]	171 (92.9)	189 (98.4)
	Discontinued due to adverse event	20 (10.9)	23 (12.0)
	Discontinued due to clinical progression	18 (9.8)	25 (13.0)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	99 (53.8)	124 (64.6)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.2)
	Visit not reached	17 (9.2)	3 (1.6)
	Visit not scheduled	1 (0.5)	0 (0.0)
WEEK 114	Expected to Complete Questionnaires	8 (4.3)	1 (0.5)
	Completed	8 (4.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	8 (100.0)	0 (0.0)
	Not completed	0 (0.0)	1 (0.5)
	With visit, no record	0 (0.0)	1 (0.5)
	Missing by Design[e]	176 (95.7)	191 (99.5)
	Discontinued due to adverse event	20 (10.9)	23 (12.0)
	Discontinued due to clinical progression	18 (9.8)	25 (13.0)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	100 (54.3)	124 (64.6)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.2)
	Completed study treatment	2 (1.1)	1 (0.5)
	Visit not reached	20 (10.9)	4 (2.1)

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10

d: Compliance is the proportion of participants who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design

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

CPS: Combined Proportion 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

Anhang 4-G1.2: Rücklaufquoten des EORTC QLQ-OES18

Tabelle 4G-2: Gründe für das Fehlen von Werten im EORTC QLQ-OES18 – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]		**Pembrolizumab + Chemotherapy[b]**	**Chemotherapy[b]**
Visit	**EORTC QLQ-OES18**	**N[c] = 184 n (%)**	**N[c] = 188 n (%)**
BASELINE	Expected to Complete Questionnaires	184 (100.0)	188 (100.0)
	Completed	178 (96.7)	180 (95.7)
	Compliance (% in those expected to complete questionnaires)[d]	178 (96.7)	180 (95.7)
	Not completed	6 (3.3)	8 (4.3)
	Not completed due to site staff error	0 (0.0)	6 (3.2)
	Other	4 (2.2)	1 (0.5)
	With visit, no record	2 (1.1)	1 (0.5)
	Missing by Design[e]	0 (0.0)	0 (0.0)
WEEK 3	Expected to Complete Questionnaires	164 (89.1)	158 (84.0)
	Completed	156 (84.8)	143 (76.1)
	Compliance (% in those expected to complete questionnaires)[d]	156 (95.1)	143 (90.5)
	Not completed	8 (4.3)	15 (8.0)
	Subject did not complete due to disease under study	2 (1.1)	2 (1.1)
	Not completed due to site staff error	3 (1.6)	5 (2.7)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Subject did not complete due to side effects of treatment	1 (0.5)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (0.5)
	Other	2 (1.1)	3 (1.6)
	With visit, no record	0 (0.0)	3 (1.6)
	Missing by Design[e]	20 (10.9)	30 (16.0)
	Subject died	3 (1.6)	3 (1.6)
	Visit not scheduled	17 (9.2)	27 (14.4)
WEEK 6	Expected to Complete Questionnaires	148 (80.4)	155 (82.4)
	Completed	140 (76.1)	147 (78.2)
	Compliance (% in those expected to complete questionnaires)[d]	140 (94.6)	147 (94.8)
	Not completed	8 (4.3)	8 (4.3)
	Not completed due to site staff error	2 (1.1)	1 (0.5)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Subject was physically unable to complete	1 (0.5)	0 (0.0)
	Subject refused for other reasons	2 (1.1)	2 (1.1)
	Other	2 (1.1)	3 (1.6)
	With visit, no record	1 (0.5)	1 (0.5)
	Missing by Design[e]	36 (19.6)	33 (17.6)
	Discontinued due to adverse event	5 (2.7)	5 (2.7)
	Discontinued due to clinical progression	0 (0.0)	2 (1.1)
	Discontinued due to progressive disease	1 (0.5)	1 (0.5)
	Discontinued due to withdrawal by subject	1 (0.5)	0 (0.0)
	Subject died	0 (0.0)	1 (0.5)
	Visit not scheduled	29 (15.8)	24 (12.8)
WEEK 9	Expected to Complete Questionnaires	139 (75.5)	151 (80.3)
	Completed	131 (71.2)	138 (73.4)
	Compliance (% in those expected to complete questionnaires)[d]	131 (94.2)	138 (91.4)
	Not completed	8 (4.3)	13 (6.9)
	Subject did not complete due to disease under study	1 (0.5)	1 (0.5)
	Not completed due to site staff error	2 (1.1)	1 (0.5)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Subject refused for other reasons	1 (0.5)	1 (0.5)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-OES18	N[c] = 184 n (%)	N[c] = 188 n (%)
	Other	2 (1.1)	2 (1.1)
	With visit, no record	2 (1.1)	7 (3.7)
	Missing by Design[e]	45 (24.5)	37 (19.7)
	Discontinued due to adverse event	7 (3.8)	6 (3.2)
	Discontinued due to clinical progression	2 (1.1)	3 (1.6)
	Discontinued due to progressive disease	2 (1.1)	4 (2.1)
	Discontinued due to withdrawal by subject	3 (1.6)	1 (0.5)
	Subject died	1 (0.5)	4 (2.1)
	Visit not scheduled	30 (16.3)	19 (10.1)
WEEK 12	Expected to Complete Questionnaires	138 (75.0)	141 (75.0)
	Completed	134 (72.8)	128 (68.1)
	Compliance (% in those expected to complete questionnaires)[d]	134 (97.1)	128 (90.8)
	Not completed	4 (2.2)	13 (6.9)
	Not completed due to site staff error	1 (0.5)	2 (1.1)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Subject was physically unable to complete	0 (0.0)	1 (0.5)
	Subject refused for other reasons	1 (0.5)	3 (1.6)
	Other	2 (1.1)	1 (0.5)
	With visit, no record	0 (0.0)	5 (2.7)
	Missing by Design[e]	46 (25.0)	47 (25.0)
	Discontinued due to adverse event	8 (4.3)	10 (5.3)
	Discontinued due to clinical progression	4 (2.2)	8 (4.3)
	Discontinued due to progressive disease	11 (6.0)	9 (4.8)
	Discontinued due to withdrawal by subject	5 (2.7)	1 (0.5)
	Subject died	1 (0.5)	0 (0.0)
	Visit not scheduled	17 (9.2)	19 (10.1)
WEEK 15	Expected to Complete Questionnaires	129 (70.1)	125 (66.5)
	Completed	116 (63.0)	120 (63.8)
	Compliance (% in those expected to complete questionnaires)[d]	116 (89.9)	120 (96.0)
	Not completed	13 (7.1)	5 (2.7)
	Subject did not complete due to disease under study	1 (0.5)	0 (0.0)
	Not completed due to site staff error	2 (1.1)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Other	2 (1.1)	1 (0.5)
	With visit, no record	8 (4.3)	3 (1.6)
	Missing by Design[e]	55 (29.9)	63 (33.5)
	Discontinued due to adverse event	8 (4.3)	12 (6.4)
	Discontinued due to clinical progression	7 (3.8)	11 (5.9)
	Discontinued due to progressive disease	13 (7.1)	14 (7.4)
	Discontinued due to withdrawal by subject	8 (4.3)	1 (0.5)
	Subject died	1 (0.5)	5 (2.7)
	Visit not scheduled	18 (9.8)	20 (10.6)
WEEK 18	Expected to Complete Questionnaires	120 (65.2)	113 (60.1)
	Completed	109 (59.2)	103 (54.8)
	Compliance (% in those expected to complete questionnaires)[d]	109 (90.8)	103 (91.2)
	Not completed	11 (6.0)	10 (5.3)
	Subject did not complete due to disease under study	2 (1.1)	2 (1.1)
	Not completed due to site staff error	2 (1.1)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.5)
	Subject refused for other reasons	0 (0.0)	2 (1.1)
	Other	2 (1.1)	2 (1.1)
	With visit, no record	5 (2.7)	3 (1.6)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-OES18	N[c] = 184 n (%)	N[c] = 188 n (%)
	Missing by Design[e]	64 (34.8)	75 (39.9)
	Discontinued due to adverse event	10 (5.4)	13 (6.9)
	Discontinued due to clinical progression	8 (4.3)	14 (7.4)
	Discontinued due to physician decision	0 (0.0)	2 (1.1)
	Discontinued due to progressive disease	18 (9.8)	23 (12.2)
	Discontinued due to withdrawal by subject	7 (3.8)	2 (1.1)
	Subject died	1 (0.5)	2 (1.1)
	Visit not scheduled	20 (10.9)	19 (10.1)
WEEK 21	Expected to Complete Questionnaires	111 (60.3)	99 (52.7)
	Completed	104 (56.5)	95 (50.5)
	Compliance (% in those expected to complete questionnaires)[d]	104 (93.7)	95 (96.0)
	Not completed	7 (3.8)	4 (2.1)
	Not completed due to site staff error	1 (0.5)	1 (0.5)
	Subject refused for other reasons	1 (0.5)	1 (0.5)
	Other	2 (1.1)	1 (0.5)
	With visit, no record	3 (1.6)	1 (0.5)
	Missing by Design[e]	73 (39.7)	89 (47.3)
	Discontinued due to adverse event	12 (6.5)	16 (8.5)
	Discontinued due to clinical progression	9 (4.9)	15 (8.0)
	Discontinued due to physician decision	1 (0.5)	3 (1.6)
	Discontinued due to progressive disease	30 (16.3)	37 (19.7)
	Discontinued due to withdrawal by subject	8 (4.3)	4 (2.1)
	Visit not scheduled	13 (7.1)	14 (7.4)
WEEK 24	Expected to Complete Questionnaires	112 (60.9)	101 (53.7)
	Completed	104 (56.5)	91 (48.4)
	Compliance (% in those expected to complete questionnaires)[d]	104 (92.9)	91 (90.1)
	Not completed	8 (4.3)	10 (5.3)
	Subject did not complete due to disease under study	1 (0.5)	0 (0.0)
	Not completed due to site staff error	0 (0.0)	3 (1.6)
	Subject in hospital or hospice	1 (0.5)	0 (0.0)
	Subject was physically unable to complete	2 (1.1)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.5)
	Subject refused for other reasons	1 (0.5)	1 (0.5)
	Other	1 (0.5)	4 (2.1)
	With visit, no record	2 (1.1)	1 (0.5)
	Missing by Design[e]	72 (39.1)	87 (46.3)
	Discontinued due to adverse event	13 (7.1)	17 (9.0)
	Discontinued due to clinical progression	10 (5.4)	16 (8.5)
	Discontinued due to physician decision	1 (0.5)	3 (1.6)
	Discontinued due to progressive disease	35 (19.0)	45 (23.9)
	Discontinued due to withdrawal by subject	10 (5.4)	5 (2.7)
	Translation not available in subjects language	1 (0.5)	0 (0.0)
	Subject died	0 (0.0)	1 (0.5)
	Visit not scheduled	2 (1.1)	0 (0.0)
WEEK 33	Expected to Complete Questionnaires	97 (52.7)	68 (36.2)
	Completed	83 (45.1)	61 (32.4)
	Compliance (% in those expected to complete questionnaires)[d]	83 (85.6)	61 (89.7)
	Not completed	14 (7.6)	7 (3.7)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.5)
	Not completed due to site staff error	3 (1.6)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Subject refused for other reasons	0 (0.0)	1 (0.5)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-OES18	N[c] = 184 n (%)	N[c] = 188 n (%)
	Other	4 (2.2)	1 (0.5)
	With visit, no record	7 (3.8)	3 (1.6)
	Missing by Design[e]	87 (47.3)	120 (63.8)
	Discontinued due to adverse event	16 (8.7)	19 (10.1)
	Discontinued due to clinical progression	11 (6.0)	18 (9.6)
	Discontinued due to physician decision	2 (1.1)	3 (1.6)
	Discontinued due to progressive disease	46 (25.0)	70 (37.2)
	Discontinued due to withdrawal by subject	11 (6.0)	8 (4.3)
	Subject died	0 (0.0)	2 (1.1)
	Visit not scheduled	1 (0.5)	0 (0.0)
WEEK 42	Expected to Complete Questionnaires	69 (37.5)	41 (21.8)
	Completed	62 (33.7)	34 (18.1)
	Compliance (% in those expected to complete questionnaires)[d]	62 (89.9)	34 (82.9)
	Not completed	7 (3.8)	7 (3.7)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.5)
	Not completed due to site staff error	1 (0.5)	2 (1.1)
	Subject was physically unable to complete	0 (0.0)	1 (0.5)
	Other	0 (0.0)	1 (0.5)
	With visit, no record	6 (3.3)	2 (1.1)
	Missing by Design[e]	115 (62.5)	147 (78.2)
	Discontinued due to adverse event	17 (9.2)	21 (11.2)
	Discontinued due to clinical progression	14 (7.6)	19 (10.1)
	Discontinued due to physician decision	2 (1.1)	3 (1.6)
	Discontinued due to progressive disease	68 (37.0)	93 (49.5)
	Discontinued due to withdrawal by subject	13 (7.1)	10 (5.3)
	Subject died	1 (0.5)	1 (0.5)
WEEK 51	Expected to Complete Questionnaires	53 (28.8)	24 (12.8)
	Completed	47 (25.5)	18 (9.6)
	Compliance (% in those expected to complete questionnaires)[d]	47 (88.7)	18 (75.0)
	Not completed	6 (3.3)	6 (3.2)
	Subject did not complete due to disease under study	2 (1.1)	0 (0.0)
	Not completed due to site staff error	1 (0.5)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.5)
	Subject refused for other reasons	0 (0.0)	3 (1.6)
	Other	0 (0.0)	1 (0.5)
	With visit, no record	3 (1.6)	1 (0.5)
	Missing by Design[e]	131 (71.2)	164 (87.2)
	Discontinued due to adverse event	19 (10.3)	21 (11.2)
	Discontinued due to clinical progression	17 (9.2)	22 (11.7)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	78 (42.4)	106 (56.4)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
	Subject died	0 (0.0)	1 (0.5)
	Visit not scheduled	1 (0.5)	0 (0.0)
WEEK 60	Expected to Complete Questionnaires	46 (25.0)	17 (9.0)
	Completed	21 (11.4)	6 (3.2)
	Compliance (% in those expected to complete questionnaires)[d]	21 (45.7)	6 (35.3)
	Not completed	25 (13.6)	11 (5.9)
	Not completed due to site staff error	1 (0.5)	0 (0.0)
	Other	2 (1.1)	2 (1.1)
	With visit, no record	22 (12.0)	9 (4.8)
	Missing by Design[e]	138 (75.0)	171 (91.0)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-OES18	N[c] = 184 n (%)	N[c] = 188 n (%)
	Discontinued due to adverse event	19 (10.3)	22 (11.7)
	Discontinued due to clinical progression	18 (9.8)	23 (12.2)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	85 (46.2)	112 (59.6)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
WEEK 69	Expected to Complete Questionnaires	42 (22.8)	12 (6.4)
	Completed	6 (3.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	6 (14.3)	0 (0.0)
	Not completed	36 (19.6)	12 (6.4)
	Subject refused for other reasons	0 (0.0)	2 (1.1)
	Other	1 (0.5)	1 (0.5)
	With visit, no record	35 (19.0)	9 (4.8)
	Missing by Design[e]	142 (77.2)	176 (93.6)
	Discontinued due to adverse event	20 (10.9)	22 (11.7)
	Discontinued due to clinical progression	18 (9.8)	24 (12.8)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	88 (47.8)	116 (61.7)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
WEEK 78	Expected to Complete Questionnaires	34 (18.5)	9 (4.8)
	Completed	3 (1.6)	2 (1.1)
	Compliance (% in those expected to complete questionnaires)[d]	3 (8.8)	2 (22.2)
	Not completed	31 (16.8)	7 (3.7)
	With visit, no record	31 (16.8)	7 (3.7)
	Missing by Design[e]	150 (81.5)	179 (95.2)
	Discontinued due to adverse event	20 (10.9)	23 (12.2)
	Discontinued due to clinical progression	18 (9.8)	24 (12.8)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	94 (51.1)	118 (62.8)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
	Visit not reached	2 (1.1)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires	27 (14.7)	5 (2.7)
	Completed	3 (1.6)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	3 (11.1)	0 (0.0)
	Not completed	24 (13.0)	5 (2.7)
	Not completed due to site staff error	0 (0.0)	1 (0.5)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	With visit, no record	24 (13.0)	3 (1.6)
	Missing by Design[e]	157 (85.3)	183 (97.3)
	Discontinued due to adverse event	20 (10.9)	23 (12.2)
	Discontinued due to clinical progression	18 (9.8)	24 (12.8)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	96 (52.2)	120 (63.8)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
	Visit not reached	7 (3.8)	2 (1.1)
WEEK 96	Expected to Complete Questionnaires	20 (10.9)	3 (1.6)
	Not completed	20 (10.9)	3 (1.6)
	With visit, no record	20 (10.9)	3 (1.6)
	Missing by Design[e]	164 (89.1)	185 (98.4)
	Discontinued due to adverse event	20 (10.9)	23 (12.2)
	Discontinued due to clinical progression	18 (9.8)	24 (12.8)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	99 (53.8)	122 (64.9)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-OES18	N[c] = 184 n (%)	N[c] = 188 n (%)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
	Visit not reached	11 (6.0)	2 (1.1)
WEEK 105	Expected to Complete Questionnaires	13 (7.1)	2 (1.1)
	Completed	5 (2.7)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	5 (38.5)	0 (0.0)
	Not completed	8 (4.3)	2 (1.1)
	With visit, no record	8 (4.3)	2 (1.1)
	Missing by Design[e]	171 (92.9)	186 (98.9)
	Discontinued due to adverse event	20 (10.9)	23 (12.2)
	Discontinued due to clinical progression	18 (9.8)	24 (12.8)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	99 (53.8)	122 (64.9)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
	Visit not reached	17 (9.2)	3 (1.6)
	Visit not scheduled	1 (0.5)	0 (0.0)
WEEK 114	Expected to Complete Questionnaires	8 (4.3)	1 (0.5)
	Completed	7 (3.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	7 (87.5)	0 (0.0)
	Not completed	1 (0.5)	1 (0.5)
	Other	1 (0.5)	0 (0.0)
	With visit, no record	0 (0.0)	1 (0.5)
	Missing by Design[e]	176 (95.7)	187 (99.5)
	Discontinued due to adverse event	20 (10.9)	23 (12.2)
	Discontinued due to clinical progression	18 (9.8)	24 (12.8)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	100 (54.3)	122 (64.9)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
	Completed study treatment	2 (1.1)	0 (0.0)
	Visit not reached	20 (10.9)	4 (2.1)

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10

d: Compliance is the proportion of participants who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design

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

CPS: Combined Proportion Score; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

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

Tabelle 4G-3: Gründe für das Fehlen von Werten in der EQ-5D VAS – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]		**Pembrolizumab + Chemotherapy[b]**	**Chemotherapy[b]**
Visit	**EQ-5D**	**N[c] = 184 n (%)**	**N[c] = 188 n (%)**
BASELINE	Expected to Complete Questionnaires	184 (100.0)	188 (100.0)
	Completed	180 (97.8)	183 (97.3)
	Compliance (% in those expected to complete questionnaires)[d]	180 (97.8)	183 (97.3)
	Not completed	4 (2.2)	5 (2.7)
	Not completed due to site staff error	1 (0.5)	3 (1.6)
	Other	1 (0.5)	1 (0.5)
	With visit, no record	2 (1.1)	1 (0.5)
	Missing by Design[e]	0 (0.0)	0 (0.0)
WEEK 3	Expected to Complete Questionnaires	164 (89.1)	158 (84.0)
	Completed	157 (85.3)	145 (77.1)
	Compliance (% in those expected to complete questionnaires)[d]	157 (95.7)	145 (91.8)
	Not completed	7 (3.8)	13 (6.9)
	Subject did not complete due to disease under study	2 (1.1)	1 (0.5)
	Not completed due to site staff error	2 (1.1)	5 (2.7)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Subject did not complete due to side effects of treatment	1 (0.5)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (0.5)
	Other	2 (1.1)	2 (1.1)
	With visit, no record	0 (0.0)	3 (1.6)
	Missing by Design[e]	20 (10.9)	30 (16.0)
	Subject died	3 (1.6)	3 (1.6)
	Visit not scheduled	17 (9.2)	27 (14.4)
WEEK 6	Expected to Complete Questionnaires	148 (80.4)	156 (83.0)
	Completed	141 (76.6)	150 (79.8)
	Compliance (% in those expected to complete questionnaires)[d]	141 (95.3)	150 (96.2)
	Not completed	7 (3.8)	6 (3.2)
	Not completed due to site staff error	1 (0.5)	1 (0.5)
	Subject in hospital or hospice	1 (0.5)	2 (1.1)
	Subject was physically unable to complete	1 (0.5)	0 (0.0)
	Subject refused for other reasons	2 (1.1)	1 (0.5)
	Other	1 (0.5)	1 (0.5)
	With visit, no record	1 (0.5)	1 (0.5)
	Missing by Design[e]	36 (19.6)	32 (17.0)
	Discontinued due to adverse event	5 (2.7)	5 (2.7)
	Discontinued due to clinical progression	0 (0.0)	2 (1.1)
	Discontinued due to progressive disease	1 (0.5)	1 (0.5)
	Discontinued due to withdrawal by subject	1 (0.5)	0 (0.0)
	Visit not scheduled	29 (15.8)	24 (12.8)
WEEK 9	Expected to Complete Questionnaires	139 (75.5)	152 (80.9)
	Completed	131 (71.2)	138 (73.4)
	Compliance (% in those expected to complete questionnaires)[d]	131 (94.2)	138 (90.8)
	Not completed	8 (4.3)	14 (7.4)
	Subject did not complete due to disease under study	1 (0.5)	1 (0.5)
	Not completed due to site staff error	3 (1.6)	2 (1.1)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Subject refused for other reasons	1 (0.5)	1 (0.5)
	Other	1 (0.5)	2 (1.1)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 184 n (%)	N[c] = 188 n (%)
	With visit, no record	2 (1.1)	7 (3.7)
	Missing by Design[e]	45 (24.5)	36 (19.1)
	Discontinued due to adverse event	7 (3.8)	6 (3.2)
	Discontinued due to clinical progression	2 (1.1)	3 (1.6)
	Discontinued due to progressive disease	2 (1.1)	4 (2.1)
	Discontinued due to withdrawal by subject	3 (1.6)	1 (0.5)
	Subject died	1 (0.5)	4 (2.1)
	Visit not scheduled	30 (16.3)	18 (9.6)
WEEK 12	Expected to Complete Questionnaires	138 (75.0)	141 (75.0)
	Completed	133 (72.3)	129 (68.6)
	Compliance (% in those expected to complete questionnaires)[d]	133 (96.4)	129 (91.5)
	Not completed	5 (2.7)	12 (6.4)
	Not completed due to site staff error	2 (1.1)	1 (0.5)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Subject was physically unable to complete	0 (0.0)	1 (0.5)
	Subject refused for other reasons	1 (0.5)	3 (1.6)
	Other	2 (1.1)	1 (0.5)
	With visit, no record	0 (0.0)	5 (2.7)
	Missing by Design[e]	46 (25.0)	47 (25.0)
	Discontinued due to adverse event	8 (4.3)	10 (5.3)
	Discontinued due to clinical progression	4 (2.2)	8 (4.3)
	Discontinued due to progressive disease	11 (6.0)	9 (4.8)
	Discontinued due to withdrawal by subject	5 (2.7)	1 (0.5)
	Subject died	1 (0.5)	0 (0.0)
	Visit not scheduled	17 (9.2)	19 (10.1)
WEEK 15	Expected to Complete Questionnaires	129 (70.1)	125 (66.5)
	Completed	117 (63.6)	120 (63.8)
	Compliance (% in those expected to complete questionnaires)[d]	117 (90.7)	120 (96.0)
	Not completed	12 (6.5)	5 (2.7)
	Subject did not complete due to disease under study	1 (0.5)	0 (0.0)
	Not completed due to site staff error	2 (1.1)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Other	2 (1.1)	1 (0.5)
	With visit, no record	7 (3.8)	3 (1.6)
	Missing by Design[e]	55 (29.9)	63 (33.5)
	Discontinued due to adverse event	8 (4.3)	12 (6.4)
	Discontinued due to clinical progression	7 (3.8)	11 (5.9)
	Discontinued due to progressive disease	13 (7.1)	14 (7.4)
	Discontinued due to withdrawal by subject	8 (4.3)	1 (0.5)
	Subject died	1 (0.5)	5 (2.7)
	Visit not scheduled	18 (9.8)	20 (10.6)
WEEK 18	Expected to Complete Questionnaires	120 (65.2)	113 (60.1)
	Completed	110 (59.8)	103 (54.8)
	Compliance (% in those expected to complete questionnaires)[d]	110 (91.7)	103 (91.2)
	Not completed	10 (5.4)	10 (5.3)
	Subject did not complete due to disease under study	2 (1.1)	2 (1.1)
	Not completed due to site staff error	1 (0.5)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	3 (1.6)
	Other	2 (1.1)	2 (1.1)
	With visit, no record	5 (2.7)	3 (1.6)
	Missing by Design[e]	64 (34.8)	75 (39.9)
	Discontinued due to adverse event	10 (5.4)	13 (6.9)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 184 n (%)	N[c] = 188 n (%)
	Discontinued due to clinical progression	9 (4.9)	14 (7.4)
	Discontinued due to physician decision	0 (0.0)	2 (1.1)
	Discontinued due to progressive disease	18 (9.8)	23 (12.2)
	Discontinued due to withdrawal by subject	7 (3.8)	2 (1.1)
	Subject died	0 (0.0)	2 (1.1)
	Visit not scheduled	20 (10.9)	19 (10.1)
WEEK 21	Expected to Complete Questionnaires	111 (60.3)	99 (52.7)
	Completed	104 (56.5)	95 (50.5)
	Compliance (% in those expected to complete questionnaires)[d]	104 (93.7)	95 (96.0)
	Not completed	7 (3.8)	4 (2.1)
	Not completed due to site staff error	1 (0.5)	1 (0.5)
	Subject refused for other reasons	1 (0.5)	1 (0.5)
	Other	2 (1.1)	1 (0.5)
	With visit, no record	3 (1.6)	1 (0.5)
	Missing by Design[e]	73 (39.7)	89 (47.3)
	Discontinued due to adverse event	12 (6.5)	16 (8.5)
	Discontinued due to clinical progression	9 (4.9)	15 (8.0)
	Discontinued due to physician decision	1 (0.5)	3 (1.6)
	Discontinued due to progressive disease	30 (16.3)	37 (19.7)
	Discontinued due to withdrawal by subject	8 (4.3)	4 (2.1)
	Visit not scheduled	13 (7.1)	14 (7.4)
WEEK 24	Expected to Complete Questionnaires	113 (61.4)	101 (53.7)
	Completed	105 (57.1)	91 (48.4)
	Compliance (% in those expected to complete questionnaires)[d]	105 (92.9)	91 (90.1)
	Not completed	8 (4.3)	10 (5.3)
	Subject did not complete due to disease under study	1 (0.5)	0 (0.0)
	Not completed due to site staff error	0 (0.0)	3 (1.6)
	Subject in hospital or hospice	1 (0.5)	0 (0.0)
	Subject was physically unable to complete	2 (1.1)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.5)
	Subject refused for other reasons	1 (0.5)	1 (0.5)
	Other	1 (0.5)	4 (2.1)
	With visit, no record	2 (1.1)	1 (0.5)
	Missing by Design[e]	71 (38.6)	87 (46.3)
	Discontinued due to adverse event	13 (7.1)	17 (9.0)
	Discontinued due to clinical progression	10 (5.4)	16 (8.5)
	Discontinued due to physician decision	1 (0.5)	3 (1.6)
	Discontinued due to progressive disease	35 (19.0)	45 (23.9)
	Discontinued due to withdrawal by subject	10 (5.4)	5 (2.7)
	Subject died	0 (0.0)	1 (0.5)
	Visit not scheduled	2 (1.1)	0 (0.0)
WEEK 33	Expected to Complete Questionnaires	97 (52.7)	68 (36.2)
	Completed	84 (45.7)	61 (32.4)
	Compliance (% in those expected to complete questionnaires)[d]	84 (86.6)	61 (89.7)
	Not completed	13 (7.1)	7 (3.7)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.5)
	Not completed due to site staff error	3 (1.6)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	Subject refused for other reasons	0 (0.0)	1 (0.5)
	Other	3 (1.6)	1 (0.5)
	With visit, no record	7 (3.8)	3 (1.6)
	Missing by Design[e]	87 (47.3)	120 (63.8)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 184 n (%)	N[c] = 188 n (%)
	Discontinued due to adverse event	16 (8.7)	19 (10.1)
	Discontinued due to clinical progression	11 (6.0)	18 (9.6)
	Discontinued due to physician decision	2 (1.1)	3 (1.6)
	Discontinued due to progressive disease	46 (25.0)	70 (37.2)
	Discontinued due to withdrawal by subject	11 (6.0)	8 (4.3)
	Subject died	0 (0.0)	2 (1.1)
	Visit not scheduled	1 (0.5)	0 (0.0)
WEEK 42	Expected to Complete Questionnaires	69 (37.5)	41 (21.8)
	Completed	62 (33.7)	34 (18.1)
	Compliance (% in those expected to complete questionnaires)[d]	62 (89.9)	34 (82.9)
	Not completed	7 (3.8)	7 (3.7)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.5)
	Not completed due to site staff error	1 (0.5)	2 (1.1)
	Subject was physically unable to complete	0 (0.0)	1 (0.5)
	Other	0 (0.0)	1 (0.5)
	With visit, no record	6 (3.3)	2 (1.1)
	Missing by Design[e]	115 (62.5)	147 (78.2)
	Discontinued due to adverse event	17 (9.2)	21 (11.2)
	Discontinued due to clinical progression	14 (7.6)	19 (10.1)
	Discontinued due to physician decision	2 (1.1)	3 (1.6)
	Discontinued due to progressive disease	68 (37.0)	93 (49.5)
	Discontinued due to withdrawal by subject	13 (7.1)	10 (5.3)
	Subject died	1 (0.5)	1 (0.5)
WEEK 51	Expected to Complete Questionnaires	53 (28.8)	24 (12.8)
	Completed	47 (25.5)	18 (9.6)
	Compliance (% in those expected to complete questionnaires)[d]	47 (88.7)	18 (75.0)
	Not completed	6 (3.3)	6 (3.2)
	Subject did not complete due to disease under study	2 (1.1)	0 (0.0)
	Not completed due to site staff error	1 (0.5)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.5)
	Subject refused for other reasons	0 (0.0)	3 (1.6)
	Other	0 (0.0)	1 (0.5)
	With visit, no record	3 (1.6)	1 (0.5)
	Missing by Design[e]	131 (71.2)	164 (87.2)
	Discontinued due to adverse event	19 (10.3)	21 (11.2)
	Discontinued due to clinical progression	17 (9.2)	22 (11.7)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	78 (42.4)	106 (56.4)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
	Subject died	0 (0.0)	1 (0.5)
	Visit not scheduled	1 (0.5)	0 (0.0)
WEEK 60	Expected to Complete Questionnaires	46 (25.0)	17 (9.0)
	Completed	21 (11.4)	6 (3.2)
	Compliance (% in those expected to complete questionnaires)[d]	21 (45.7)	6 (35.3)
	Not completed	25 (13.6)	11 (5.9)
	Not completed due to site staff error	1 (0.5)	0 (0.0)
	Other	2 (1.1)	2 (1.1)
	With visit, no record	22 (12.0)	9 (4.8)
	Missing by Design[e]	138 (75.0)	171 (91.0)
	Discontinued due to adverse event	19 (10.3)	22 (11.7)
	Discontinued due to clinical progression	18 (9.8)	23 (12.2)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 184 n (%)	N[c] = 188 n (%)
	Discontinued due to progressive disease	85 (46.2)	112 (59.6)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
WEEK 69	Expected to Complete Questionnaires	42 (22.8)	12 (6.4)
	Completed	6 (3.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	6 (14.3)	0 (0.0)
	Not completed	36 (19.6)	12 (6.4)
	Subject refused for other reasons	0 (0.0)	2 (1.1)
	Other	1 (0.5)	1 (0.5)
	With visit, no record	35 (19.0)	9 (4.8)
	Missing by Design[e]	142 (77.2)	176 (93.6)
	Discontinued due to adverse event	20 (10.9)	22 (11.7)
	Discontinued due to clinical progression	18 (9.8)	24 (12.8)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	88 (47.8)	116 (61.7)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
WEEK 78	Expected to Complete Questionnaires	34 (18.5)	9 (4.8)
	Completed	3 (1.6)	2 (1.1)
	Compliance (% in those expected to complete questionnaires)[d]	3 (8.8)	2 (22.2)
	Not completed	31 (16.8)	7 (3.7)
	With visit, no record	31 (16.8)	7 (3.7)
	Missing by Design[e]	150 (81.5)	179 (95.2)
	Discontinued due to adverse event	20 (10.9)	23 (12.2)
	Discontinued due to clinical progression	18 (9.8)	24 (12.8)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	94 (51.1)	118 (62.8)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
	Visit not reached	2 (1.1)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires	27 (14.7)	5 (2.7)
	Completed	3 (1.6)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	3 (11.1)	0 (0.0)
	Not completed	24 (13.0)	5 (2.7)
	Not completed due to site staff error	0 (0.0)	1 (0.5)
	Subject in hospital or hospice	0 (0.0)	1 (0.5)
	With visit, no record	24 (13.0)	3 (1.6)
	Missing by Design[e]	157 (85.3)	183 (97.3)
	Discontinued due to adverse event	20 (10.9)	23 (12.2)
	Discontinued due to clinical progression	18 (9.8)	24 (12.8)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	96 (52.2)	120 (63.8)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
	Visit not reached	7 (3.8)	2 (1.1)
WEEK 96	Expected to Complete Questionnaires	20 (10.9)	3 (1.6)
	Not completed	20 (10.9)	3 (1.6)
	With visit, no record	20 (10.9)	3 (1.6)
	Missing by Design[e]	164 (89.1)	185 (98.4)
	Discontinued due to adverse event	20 (10.9)	23 (12.2)
	Discontinued due to clinical progression	18 (9.8)	24 (12.8)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	99 (53.8)	122 (64.9)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
	Visit not reached	11 (6.0)	2 (1.1)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
		N[c] = 184	N[c] = 188
Visit	EQ-5D	n (%)	n (%)
WEEK 105	Expected to Complete Questionnaires	13 (7.1)	2 (1.1)
	Completed	5 (2.7)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	5 (38.5)	0 (0.0)
	Not completed	8 (4.3)	2 (1.1)
	With visit, no record	8 (4.3)	2 (1.1)
	Missing by Design[e]	171 (92.9)	186 (98.9)
	Discontinued due to adverse event	20 (10.9)	23 (12.2)
	Discontinued due to clinical progression	18 (9.8)	24 (12.8)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	99 (53.8)	122 (64.9)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
	Visit not reached	17 (9.2)	3 (1.6)
	Visit not scheduled	1 (0.5)	0 (0.0)
WEEK 114	Expected to Complete Questionnaires	8 (4.3)	1 (0.5)
	Completed	8 (4.3)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	8 (100.0)	0 (0.0)
	Not completed	0 (0.0)	1 (0.5)
	With visit, no record	0 (0.0)	1 (0.5)
	Missing by Design[e]	176 (95.7)	187 (99.5)
	Discontinued due to adverse event	20 (10.9)	23 (12.2)
	Discontinued due to clinical progression	18 (9.8)	24 (12.8)
	Discontinued due to physician decision	2 (1.1)	4 (2.1)
	Discontinued due to progressive disease	100 (54.3)	122 (64.9)
	Discontinued due to withdrawal by subject	14 (7.6)	10 (5.3)
	Completed study treatment	2 (1.1)	0 (0.0)
	Visit not reached	20 (10.9)	4 (2.1)

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10

d: Compliance is the proportion of participants who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design

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

CPS: Combined Proportion Score; EQ-5D: European Quality of Life 5 Dimensions; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G2: Rücklaufquoten des EORTC QLQ-C30, des EORTC QLQ-OES18 und EQ-5D VAS – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G2.1: Rücklaufquoten des EORTC QLQ-C30

Tabelle 4G-4: Gründe für das Fehlen von Werten im EORTC QLQ-C30 – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 142 n (%)	N[c] = 139 n (%)
BASELINE	Expected to Complete Questionnaires	142 (100.0)	139 (100.0)
	Completed	138 (97.2)	136 (97.8)
	Compliance (% in those expected to complete questionnaires)[d]	138 (97.2)	136 (97.8)
	Not completed	4 (2.8)	3 (2.2)
	Not completed due to site staff error	1 (0.7)	2 (1.4)
	Other	1 (0.7)	0 (0.0)
	With visit, no record	2 (1.4)	1 (0.7)
	Missing by Design[e]	0 (0.0)	0 (0.0)
WEEK 3	Expected to Complete Questionnaires	125 (88.0)	115 (82.7)
	Completed	122 (85.9)	108 (77.7)
	Compliance (% in those expected to complete questionnaires)[d]	122 (97.6)	108 (93.9)
	Not completed	3 (2.1)	7 (5.0)
	Subject did not complete due to disease under study	2 (1.4)	1 (0.7)
	Not completed due to site staff error	1 (0.7)	1 (0.7)
	Other	0 (0.0)	2 (1.4)
	With visit, no record	0 (0.0)	3 (2.2)
	Missing by Design[e]	17 (12.0)	24 (17.3)
	Subject died	3 (2.1)	2 (1.4)
	Visit not scheduled	14 (9.9)	22 (15.8)
WEEK 6	Expected to Complete Questionnaires	109 (76.8)	112 (80.6)
	Completed	105 (73.9)	109 (78.4)
	Compliance (% in those expected to complete questionnaires)[d]	105 (96.3)	109 (97.3)
	Not completed	4 (2.8)	3 (2.2)
	Subject in hospital or hospice	0 (0.0)	1 (0.7)
	Subject refused for other reasons	2 (1.4)	0 (0.0)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	1 (0.7)	1 (0.7)
	Missing by Design[e]	33 (23.2)	27 (19.4)
	Discontinued due to adverse event	3 (2.1)	3 (2.2)
	Discontinued due to clinical progression	0 (0.0)	2 (1.4)
	Discontinued due to progressive disease	1 (0.7)	1 (0.7)
	Discontinued due to withdrawal by subject	1 (0.7)	0 (0.0)
	Visit not scheduled	28 (19.7)	21 (15.1)
WEEK 9	Expected to Complete Questionnaires	107 (75.4)	108 (77.7)
	Completed	103 (72.5)	101 (72.7)
	Compliance (% in those expected to complete questionnaires)[d]	103 (96.3)	101 (93.5)
	Not completed	4 (2.8)	7 (5.0)
	Subject did not complete due to disease under study	1 (0.7)	1 (0.7)
	Not completed due to site staff error	2 (1.4)	0 (0.0)
	Subject refused for other reasons	1 (0.7)	1 (0.7)
	Other	0 (0.0)	1 (0.7)
	With visit, no record	0 (0.0)	4 (2.9)
	Missing by Design[e]	35 (24.6)	31 (22.3)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 142 n (%)	N[c] = 139 n (%)
	Discontinued due to adverse event	4 (2.8)	5 (3.6)
	Discontinued due to clinical progression	2 (1.4)	2 (1.4)
	Discontinued due to progressive disease	2 (1.4)	3 (2.2)
	Discontinued due to withdrawal by subject	3 (2.1)	1 (0.7)
	Subject died	1 (0.7)	4 (2.9)
	Visit not scheduled	23 (16.2)	16 (11.5)
WEEK 12	Expected to Complete Questionnaires	109 (76.8)	100 (71.9)
	Completed	106 (74.6)	95 (68.3)
	Compliance (% in those expected to complete questionnaires)[d]	106 (97.2)	95 (95.0)
	Not completed	3 (2.1)	5 (3.6)
	Not completed due to site staff error	2 (1.4)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.7)
	Subject refused for other reasons	1 (0.7)	2 (1.4)
	Other	0 (0.0)	1 (0.7)
	With visit, no record	0 (0.0)	1 (0.7)
	Missing by Design[e]	33 (23.2)	39 (28.1)
	Discontinued due to adverse event	5 (3.5)	8 (5.8)
	Discontinued due to clinical progression	4 (2.8)	5 (3.6)
	Discontinued due to progressive disease	10 (7.0)	8 (5.8)
	Discontinued due to withdrawal by subject	5 (3.5)	1 (0.7)
	Visit not scheduled	9 (6.3)	17 (12.2)
WEEK 15	Expected to Complete Questionnaires	99 (69.7)	88 (63.3)
	Completed	88 (62.0)	84 (60.4)
	Compliance (% in those expected to complete questionnaires)[d]	88 (88.9)	84 (95.5)
	Not completed	11 (7.7)	4 (2.9)
	Subject did not complete due to disease under study	1 (0.7)	0 (0.0)
	Not completed due to site staff error	2 (1.4)	0 (0.0)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	7 (4.9)	3 (2.2)
	Missing by Design[e]	43 (30.3)	51 (36.7)
	Discontinued due to adverse event	5 (3.5)	10 (7.2)
	Discontinued due to clinical progression	6 (4.2)	7 (5.0)
	Discontinued due to progressive disease	11 (7.7)	13 (9.4)
	Discontinued due to withdrawal by subject	8 (5.6)	1 (0.7)
	Subject died	1 (0.7)	2 (1.4)
	Visit not scheduled	12 (8.5)	18 (12.9)
WEEK 18	Expected to Complete Questionnaires	91 (64.1)	80 (57.6)
	Completed	82 (57.7)	71 (51.1)
	Compliance (% in those expected to complete questionnaires)[d]	82 (90.1)	71 (88.8)
	Not completed	9 (6.3)	9 (6.5)
	Subject did not complete due to disease under study	2 (1.4)	1 (0.7)
	Not completed due to site staff error	2 (1.4)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.7)
	Subject refused for other reasons	0 (0.0)	2 (1.4)
	Other	0 (0.0)	2 (1.4)
	With visit, no record	5 (3.5)	3 (2.2)
	Missing by Design[e]	51 (35.9)	59 (42.4)
	Discontinued due to adverse event	7 (4.9)	10 (7.2)
	Discontinued due to clinical progression	7 (4.9)	9 (6.5)
	Discontinued due to progressive disease	14 (9.9)	19 (13.7)
	Discontinued due to withdrawal by subject	7 (4.9)	2 (1.4)
	Subject died	0 (0.0)	2 (1.4)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 142 n (%)	N[c] = 139 n (%)
	Visit not scheduled	16 (11.3)	17 (12.2)
WEEK 21	Expected to Complete Questionnaires	83 (58.5)	73 (52.5)
	Completed	80 (56.3)	69 (49.6)
	Compliance (% in those expected to complete questionnaires)[d]	80 (96.4)	69 (94.5)
	Not completed	3 (2.1)	4 (2.9)
	Not completed due to site staff error	1 (0.7)	0 (0.0)
	Subject refused for other reasons	1 (0.7)	1 (0.7)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	0 (0.0)	2 (1.4)
	Missing by Design[e]	59 (41.5)	66 (47.5)
	Discontinued due to adverse event	9 (6.3)	13 (9.4)
	Discontinued due to clinical progression	7 (4.9)	9 (6.5)
	Discontinued due to physician decision	1 (0.7)	1 (0.7)
	Discontinued due to progressive disease	24 (16.9)	31 (22.3)
	Discontinued due to withdrawal by subject	8 (5.6)	4 (2.9)
	Visit not scheduled	10 (7.0)	8 (5.8)
WEEK 24	Expected to Complete Questionnaires	87 (61.3)	70 (50.4)
	Completed	80 (56.3)	65 (46.8)
	Compliance (% in those expected to complete questionnaires)[d]	80 (92.0)	65 (92.9)
	Not completed	7 (4.9)	5 (3.6)
	Subject did not complete due to disease under study	1 (0.7)	0 (0.0)
	Not completed due to site staff error	0 (0.0)	1 (0.7)
	Subject in hospital or hospice	1 (0.7)	0 (0.0)
	Subject was physically unable to complete	1 (0.7)	0 (0.0)
	Subject refused for other reasons	1 (0.7)	1 (0.7)
	Other	1 (0.7)	2 (1.4)
	With visit, no record	2 (1.4)	1 (0.7)
	Missing by Design[e]	55 (38.7)	69 (49.6)
	Discontinued due to adverse event	9 (6.3)	14 (10.1)
	Discontinued due to clinical progression	7 (4.9)	9 (6.5)
	Discontinued due to physician decision	1 (0.7)	1 (0.7)
	Discontinued due to progressive disease	27 (19.0)	39 (28.1)
	Discontinued due to withdrawal by subject	10 (7.0)	5 (3.6)
	Subject died	0 (0.0)	1 (0.7)
	Visit not scheduled	1 (0.7)	0 (0.0)
WEEK 33	Expected to Complete Questionnaires	74 (52.1)	46 (33.1)
	Completed	65 (45.8)	41 (29.5)
	Compliance (% in those expected to complete questionnaires)[d]	65 (87.8)	41 (89.1)
	Not completed	9 (6.3)	5 (3.6)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.7)
	Not completed due to site staff error	2 (1.4)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.7)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	6 (4.2)	2 (1.4)
	Missing by Design[e]	68 (47.9)	93 (66.9)
	Discontinued due to adverse event	11 (7.7)	16 (11.5)
	Discontinued due to clinical progression	8 (5.6)	11 (7.9)
	Discontinued due to physician decision	2 (1.4)	1 (0.7)
	Discontinued due to progressive disease	35 (24.6)	57 (41.0)
	Discontinued due to withdrawal by subject	11 (7.7)	6 (4.3)
	Subject died	0 (0.0)	2 (1.4)
	Visit not scheduled	1 (0.7)	0 (0.0)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 142 n (%)	N[c] = 139 n (%)
WEEK 42	Expected to Complete Questionnaires	54 (38.0)	29 (20.9)
	Completed	49 (34.5)	23 (16.5)
	Compliance (% in those expected to complete questionnaires)[d]	49 (90.7)	23 (79.3)
	Not completed	5 (3.5)	6 (4.3)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.7)
	Not completed due to site staff error	1 (0.7)	1 (0.7)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.7)
	Other	0 (0.0)	1 (0.7)
	With visit, no record	4 (2.8)	2 (1.4)
	Missing by Design[e]	88 (62.0)	110 (79.1)
	Discontinued due to adverse event	12 (8.5)	18 (12.9)
	Discontinued due to clinical progression	9 (6.3)	12 (8.6)
	Discontinued due to physician decision	2 (1.4)	1 (0.7)
	Discontinued due to progressive disease	52 (36.6)	71 (51.1)
	Discontinued due to withdrawal by subject	12 (8.5)	8 (5.8)
	Subject died	1 (0.7)	0 (0.0)
WEEK 51	Expected to Complete Questionnaires	41 (28.9)	16 (11.5)
	Completed	35 (24.6)	12 (8.6)
	Compliance (% in those expected to complete questionnaires)[d]	35 (85.4)	12 (75.0)
	Not completed	6 (4.2)	4 (2.9)
	Subject did not complete due to disease under study	2 (1.4)	0 (0.0)
	Not completed due to site staff error	1 (0.7)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.7)
	Subject refused for other reasons	0 (0.0)	2 (1.4)
	Other	0 (0.0)	1 (0.7)
	With visit, no record	3 (2.1)	0 (0.0)
	Missing by Design[e]	101 (71.1)	123 (88.5)
	Discontinued due to adverse event	14 (9.9)	18 (12.9)
	Discontinued due to clinical progression	11 (7.7)	13 (9.4)
	Discontinued due to physician decision	2 (1.4)	2 (1.4)
	Discontinued due to progressive disease	60 (42.3)	81 (58.3)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.8)
	Subject died	0 (0.0)	1 (0.7)
	Visit not scheduled	1 (0.7)	0 (0.0)
WEEK 60	Expected to Complete Questionnaires	34 (23.9)	11 (7.9)
	Completed	15 (10.6)	4 (2.9)
	Compliance (% in those expected to complete questionnaires)[d]	15 (44.1)	4 (36.4)
	Not completed	19 (13.4)	7 (5.0)
	Not completed due to site staff error	1 (0.7)	0 (0.0)
	Other	2 (1.4)	2 (1.4)
	With visit, no record	16 (11.3)	5 (3.6)
	Missing by Design[e]	108 (76.1)	128 (92.1)
	Discontinued due to adverse event	14 (9.9)	19 (13.7)
	Discontinued due to clinical progression	12 (8.5)	14 (10.1)
	Discontinued due to physician decision	2 (1.4)	2 (1.4)
	Discontinued due to progressive disease	67 (47.2)	85 (61.2)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.8)
WEEK 69	Expected to Complete Questionnaires	31 (21.8)	9 (6.5)
	Completed	3 (2.1)	1 (0.7)
	Compliance (% in those expected to complete questionnaires)[d]	3 (9.7)	1 (11.1)
	Not completed	28 (19.7)	8 (5.8)
	Subject refused for other reasons	0 (0.0)	1 (0.7)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 142 n (%)	N[c] = 139 n (%)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	27 (19.0)	6 (4.3)
	Missing by Design[e]	111 (78.2)	130 (93.5)
	Discontinued due to adverse event	15 (10.6)	19 (13.7)
	Discontinued due to clinical progression	12 (8.5)	14 (10.1)
	Discontinued due to physician decision	2 (1.4)	2 (1.4)
	Discontinued due to progressive disease	69 (48.6)	87 (62.6)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.8)
WEEK 78	Expected to Complete Questionnaires	27 (19.0)	7 (5.0)
	Completed	3 (2.1)	2 (1.4)
	Compliance (% in those expected to complete questionnaires)[d]	3 (11.1)	2 (28.6)
	Not completed	24 (16.9)	5 (3.6)
	With visit, no record	24 (16.9)	5 (3.6)
	Missing by Design[e]	115 (81.0)	132 (95.0)
	Discontinued due to adverse event	15 (10.6)	20 (14.4)
	Discontinued due to clinical progression	12 (8.5)	14 (10.1)
	Discontinued due to physician decision	2 (1.4)	2 (1.4)
	Discontinued due to progressive disease	72 (50.7)	88 (63.3)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.8)
	Visit not reached	1 (0.7)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires	20 (14.1)	4 (2.9)
	Completed	3 (2.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	3 (15.0)	0 (0.0)
	Not completed	17 (12.0)	4 (2.9)
	With visit, no record	17 (12.0)	4 (2.9)
	Missing by Design[e]	122 (85.9)	135 (97.1)
	Discontinued due to adverse event	15 (10.6)	20 (14.4)
	Discontinued due to clinical progression	12 (8.5)	14 (10.1)
	Discontinued due to physician decision	2 (1.4)	2 (1.4)
	Discontinued due to progressive disease	74 (52.1)	89 (64.0)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.8)
	Visit not reached	6 (4.2)	2 (1.4)
WEEK 96	Expected to Complete Questionnaires	13 (9.2)	4 (2.9)
	Not completed	13 (9.2)	4 (2.9)
	With visit, no record	13 (9.2)	4 (2.9)
	Missing by Design[e]	129 (90.8)	135 (97.1)
	Discontinued due to adverse event	15 (10.6)	20 (14.4)
	Discontinued due to clinical progression	12 (8.5)	14 (10.1)
	Discontinued due to physician decision	2 (1.4)	2 (1.4)
	Discontinued due to progressive disease	77 (54.2)	89 (64.0)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.8)
	Visit not reached	10 (7.0)	2 (1.4)
WEEK 105	Expected to Complete Questionnaires	8 (5.6)	3 (2.2)
	Completed	3 (2.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	3 (37.5)	0 (0.0)
	Not completed	5 (3.5)	3 (2.2)
	With visit, no record	5 (3.5)	3 (2.2)
	Missing by Design[e]	134 (94.4)	136 (97.8)
	Discontinued due to adverse event	15 (10.6)	20 (14.4)
	Discontinued due to clinical progression	12 (8.5)	14 (10.1)
	Discontinued due to physician decision	2 (1.4)	2 (1.4)
	Discontinued due to progressive disease	77 (54.2)	89 (64.0)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 142 n (%)	N[c] = 139 n (%)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.8)
	Visit not reached	14 (9.9)	3 (2.2)
	Visit not scheduled	1 (0.7)	0 (0.0)
WEEK 114	Expected to Complete Questionnaires	6 (4.2)	1 (0.7)
	Completed	6 (4.2)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	6 (100.0)	0 (0.0)
	Not completed	0 (0.0)	1 (0.7)
	With visit, no record	0 (0.0)	1 (0.7)
	Missing by Design[e]	136 (95.8)	138 (99.3)
	Discontinued due to adverse event	15 (10.6)	20 (14.4)
	Discontinued due to clinical progression	12 (8.5)	14 (10.1)
	Discontinued due to physician decision	2 (1.4)	2 (1.4)
	Discontinued due to progressive disease	77 (54.2)	89 (64.0)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.8)
	Completed study treatment	1 (0.7)	1 (0.7)
	Visit not reached	16 (11.3)	4 (2.9)

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10

d: Compliance is the proportion of participants who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design

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

CPS: Combined Proportion 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

Anhang 4-G2.2: Rücklaufquoten des EORTC QLQ-OES18

Tabelle 4G-5: Gründe für das Fehlen von Werten im EORTC QLQ-OES18 – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-OES18	N[c] = 142 n (%)	N[c] = 136 n (%)
BASELINE	Expected to Complete Questionnaires	142 (100.0)	136 (100.0)
	Completed	137 (96.5)	133 (97.8)
	Compliance (% in those expected to complete questionnaires)[d]	137 (96.5)	133 (97.8)
	Not completed	5 (3.5)	3 (2.2)
	Not completed due to site staff error	0 (0.0)	2 (1.5)
	Other	4 (2.8)	0 (0.0)
	With visit, no record	1 (0.7)	1 (0.7)
	Missing by Design[e]	0 (0.0)	0 (0.0)
WEEK 3	Expected to Complete Questionnaires	125 (88.0)	112 (82.4)
	Completed	120 (84.5)	105 (77.2)
	Compliance (% in those expected to complete questionnaires)[d]	120 (96.0)	105 (93.8)
	Not completed	5 (3.5)	7 (5.1)
	Subject did not complete due to disease under study	2 (1.4)	1 (0.7)
	Not completed due to site staff error	2 (1.4)	1 (0.7)
	Other	1 (0.7)	2 (1.5)
	With visit, no record	0 (0.0)	3 (2.2)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-OES18	N[c] = 142 n (%)	N[c] = 136 n (%)
	Missing by Design[e]	17 (12.0)	24 (17.6)
	Subject died	3 (2.1)	2 (1.5)
	Visit not scheduled	14 (9.9)	22 (16.2)
WEEK 6	Expected to Complete Questionnaires	109 (76.8)	109 (80.1)
	Completed	103 (72.5)	104 (76.5)
	Compliance (% in those expected to complete questionnaires)[d]	103 (94.5)	104 (95.4)
	Not completed	6 (4.2)	5 (3.7)
	Not completed due to site staff error	1 (0.7)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.7)
	Subject refused for other reasons	2 (1.4)	0 (0.0)
	Other	2 (1.4)	3 (2.2)
	With visit, no record	1 (0.7)	1 (0.7)
	Missing by Design[e]	33 (23.2)	27 (19.9)
	Discontinued due to adverse event	3 (2.1)	3 (2.2)
	Discontinued due to clinical progression	0 (0.0)	2 (1.5)
	Discontinued due to progressive disease	1 (0.7)	1 (0.7)
	Discontinued due to withdrawal by subject	1 (0.7)	0 (0.0)
	Visit not scheduled	28 (19.7)	21 (15.4)
WEEK 9	Expected to Complete Questionnaires	107 (75.4)	105 (77.2)
	Completed	103 (72.5)	98 (72.1)
	Compliance (% in those expected to complete questionnaires)[d]	103 (96.3)	98 (93.3)
	Not completed	4 (2.8)	7 (5.1)
	Subject did not complete due to disease under study	1 (0.7)	1 (0.7)
	Not completed due to site staff error	1 (0.7)	0 (0.0)
	Subject refused for other reasons	1 (0.7)	1 (0.7)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	0 (0.0)	4 (2.9)
	Missing by Design[e]	35 (24.6)	31 (22.8)
	Discontinued due to adverse event	4 (2.8)	5 (3.7)
	Discontinued due to clinical progression	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	2 (1.4)	3 (2.2)
	Discontinued due to withdrawal by subject	3 (2.1)	1 (0.7)
	Subject died	1 (0.7)	4 (2.9)
	Visit not scheduled	23 (16.2)	16 (11.8)
WEEK 12	Expected to Complete Questionnaires	109 (76.8)	97 (71.3)
	Completed	107 (75.4)	92 (67.6)
	Compliance (% in those expected to complete questionnaires)[d]	107 (98.2)	92 (94.8)
	Not completed	2 (1.4)	5 (3.7)
	Not completed due to site staff error	1 (0.7)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.7)
	Subject refused for other reasons	1 (0.7)	2 (1.5)
	Other	0 (0.0)	1 (0.7)
	With visit, no record	0 (0.0)	1 (0.7)
	Missing by Design[e]	33 (23.2)	39 (28.7)
	Discontinued due to adverse event	5 (3.5)	8 (5.9)
	Discontinued due to clinical progression	4 (2.8)	5 (3.7)
	Discontinued due to progressive disease	10 (7.0)	8 (5.9)
	Discontinued due to withdrawal by subject	5 (3.5)	1 (0.7)
	Visit not scheduled	9 (6.3)	17 (12.5)
WEEK 15	Expected to Complete Questionnaires	99 (69.7)	86 (63.2)
	Completed	87 (61.3)	82 (60.3)
	Compliance (% in those expected to complete questionnaires)[d]	87 (87.9)	82 (95.3)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-OES18	N[c] = 142 n (%)	N[c] = 136 n (%)
	Not completed	12 (8.5)	4 (2.9)
	Subject did not complete due to disease under study	1 (0.7)	0 (0.0)
	Not completed due to site staff error	2 (1.4)	0 (0.0)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	8 (5.6)	3 (2.2)
	Missing by Design[e]	43 (30.3)	50 (36.8)
	Discontinued due to adverse event	5 (3.5)	10 (7.4)
	Discontinued due to clinical progression	6 (4.2)	7 (5.1)
	Discontinued due to progressive disease	11 (7.7)	13 (9.6)
	Discontinued due to withdrawal by subject	8 (5.6)	1 (0.7)
	Subject died	1 (0.7)	2 (1.5)
	Visit not scheduled	12 (8.5)	17 (12.5)
WEEK 18	Expected to Complete Questionnaires	91 (64.1)	77 (56.6)
	Completed	82 (57.7)	69 (50.7)
	Compliance (% in those expected to complete questionnaires)[d]	82 (90.1)	69 (89.6)
	Not completed	9 (6.3)	8 (5.9)
	Subject did not complete due to disease under study	2 (1.4)	1 (0.7)
	Not completed due to site staff error	2 (1.4)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.7)
	Subject refused for other reasons	0 (0.0)	2 (1.5)
	Other	0 (0.0)	2 (1.5)
	With visit, no record	5 (3.5)	2 (1.5)
	Missing by Design[e]	51 (35.9)	59 (43.4)
	Discontinued due to adverse event	7 (4.9)	10 (7.4)
	Discontinued due to clinical progression	6 (4.2)	9 (6.6)
	Discontinued due to progressive disease	14 (9.9)	19 (14.0)
	Discontinued due to withdrawal by subject	7 (4.9)	2 (1.5)
	Subject died	1 (0.7)	2 (1.5)
	Visit not scheduled	16 (11.3)	17 (12.5)
WEEK 21	Expected to Complete Questionnaires	83 (58.5)	70 (51.5)
	Completed	80 (56.3)	67 (49.3)
	Compliance (% in those expected to complete questionnaires)[d]	80 (96.4)	67 (95.7)
	Not completed	3 (2.1)	3 (2.2)
	Not completed due to site staff error	1 (0.7)	0 (0.0)
	Subject refused for other reasons	1 (0.7)	1 (0.7)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	0 (0.0)	1 (0.7)
	Missing by Design[e]	59 (41.5)	66 (48.5)
	Discontinued due to adverse event	9 (6.3)	13 (9.6)
	Discontinued due to clinical progression	7 (4.9)	9 (6.6)
	Discontinued due to physician decision	1 (0.7)	1 (0.7)
	Discontinued due to progressive disease	24 (16.9)	31 (22.8)
	Discontinued due to withdrawal by subject	8 (5.6)	4 (2.9)
	Visit not scheduled	10 (7.0)	8 (5.9)
WEEK 24	Expected to Complete Questionnaires	86 (60.6)	67 (49.3)
	Completed	79 (55.6)	63 (46.3)
	Compliance (% in those expected to complete questionnaires)[d]	79 (91.9)	63 (94.0)
	Not completed	7 (4.9)	4 (2.9)
	Subject did not complete due to disease under study	1 (0.7)	0 (0.0)
	Subject in hospital or hospice	1 (0.7)	0 (0.0)
	Subject was physically unable to complete	1 (0.7)	0 (0.0)
	Subject refused for other reasons	1 (0.7)	1 (0.7)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-OES18	N[c] = 142 n (%)	N[c] = 136 n (%)
	Other	1 (0.7)	2 (1.5)
	With visit, no record	2 (1.4)	1 (0.7)
	Missing by Design[e]	56 (39.4)	69 (50.7)
	Discontinued due to adverse event	9 (6.3)	14 (10.3)
	Discontinued due to clinical progression	7 (4.9)	9 (6.6)
	Discontinued due to physician decision	1 (0.7)	1 (0.7)
	Discontinued due to progressive disease	27 (19.0)	39 (28.7)
	Discontinued due to withdrawal by subject	10 (7.0)	5 (3.7)
	Translation not available in subjects language	1 (0.7)	0 (0.0)
	Subject died	0 (0.0)	1 (0.7)
	Visit not scheduled	1 (0.7)	0 (0.0)
WEEK 33	Expected to Complete Questionnaires	74 (52.1)	44 (32.4)
	Completed	65 (45.8)	39 (28.7)
	Compliance (% in those expected to complete questionnaires)[d]	65 (87.8)	39 (88.6)
	Not completed	9 (6.3)	5 (3.7)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.7)
	Not completed due to site staff error	2 (1.4)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.7)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	6 (4.2)	2 (1.5)
	Missing by Design[e]	68 (47.9)	92 (67.6)
	Discontinued due to adverse event	11 (7.7)	16 (11.8)
	Discontinued due to clinical progression	8 (5.6)	11 (8.1)
	Discontinued due to physician decision	2 (1.4)	1 (0.7)
	Discontinued due to progressive disease	35 (24.6)	57 (41.9)
	Discontinued due to withdrawal by subject	11 (7.7)	6 (4.4)
	Subject died	0 (0.0)	1 (0.7)
	Visit not scheduled	1 (0.7)	0 (0.0)
WEEK 42	Expected to Complete Questionnaires	54 (38.0)	27 (19.9)
	Completed	49 (34.5)	23 (16.9)
	Compliance (% in those expected to complete questionnaires)[d]	49 (90.7)	23 (85.2)
	Not completed	5 (3.5)	4 (2.9)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.7)
	Not completed due to site staff error	1 (0.7)	1 (0.7)
	Other	0 (0.0)	1 (0.7)
	With visit, no record	4 (2.8)	1 (0.7)
	Missing by Design[e]	88 (62.0)	109 (80.1)
	Discontinued due to adverse event	12 (8.5)	18 (13.2)
	Discontinued due to clinical progression	9 (6.3)	12 (8.8)
	Discontinued due to physician decision	2 (1.4)	1 (0.7)
	Discontinued due to progressive disease	52 (36.6)	70 (51.5)
	Discontinued due to withdrawal by subject	12 (8.5)	8 (5.9)
	Subject died	1 (0.7)	0 (0.0)
WEEK 51	Expected to Complete Questionnaires	41 (28.9)	15 (11.0)
	Completed	35 (24.6)	11 (8.1)
	Compliance (% in those expected to complete questionnaires)[d]	35 (85.4)	11 (73.3)
	Not completed	6 (4.2)	4 (2.9)
	Subject did not complete due to disease under study	2 (1.4)	0 (0.0)
	Not completed due to site staff error	1 (0.7)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.7)
	Subject refused for other reasons	0 (0.0)	2 (1.5)
	Other	0 (0.0)	1 (0.7)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-OES18	N[c] = 142 n (%)	N[c] = 136 n (%)
	With visit, no record	3 (2.1)	0 (0.0)
	Missing by Design[e]	101 (71.1)	121 (89.0)
	Discontinued due to adverse event	14 (9.9)	18 (13.2)
	Discontinued due to clinical progression	11 (7.7)	13 (9.6)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	60 (42.3)	79 (58.1)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
	Subject died	0 (0.0)	1 (0.7)
	Visit not scheduled	1 (0.7)	0 (0.0)
WEEK 60	Expected to Complete Questionnaires	34 (23.9)	10 (7.4)
	Completed	15 (10.6)	3 (2.2)
	Compliance (% in those expected to complete questionnaires)[d]	15 (44.1)	3 (30.0)
	Not completed	19 (13.4)	7 (5.1)
	Not completed due to site staff error	1 (0.7)	0 (0.0)
	Other	2 (1.4)	2 (1.5)
	With visit, no record	16 (11.3)	5 (3.7)
	Missing by Design[e]	108 (76.1)	126 (92.6)
	Discontinued due to adverse event	14 (9.9)	19 (14.0)
	Discontinued due to clinical progression	12 (8.5)	14 (10.3)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	67 (47.2)	83 (61.0)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
WEEK 69	Expected to Complete Questionnaires	31 (21.8)	8 (5.9)
	Completed	3 (2.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	3 (9.7)	0 (0.0)
	Not completed	28 (19.7)	8 (5.9)
	Subject refused for other reasons	0 (0.0)	1 (0.7)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	27 (19.0)	6 (4.4)
	Missing by Design[e]	111 (78.2)	128 (94.1)
	Discontinued due to adverse event	15 (10.6)	19 (14.0)
	Discontinued due to clinical progression	12 (8.5)	14 (10.3)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	69 (48.6)	85 (62.5)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
WEEK 78	Expected to Complete Questionnaires	27 (19.0)	6 (4.4)
	Completed	3 (2.1)	1 (0.7)
	Compliance (% in those expected to complete questionnaires)[d]	3 (11.1)	1 (16.7)
	Not completed	24 (16.9)	5 (3.7)
	With visit, no record	24 (16.9)	5 (3.7)
	Missing by Design[e]	115 (81.0)	130 (95.6)
	Discontinued due to adverse event	15 (10.6)	20 (14.7)
	Discontinued due to clinical progression	12 (8.5)	14 (10.3)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	72 (50.7)	86 (63.2)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
	Visit not reached	1 (0.7)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires	20 (14.1)	3 (2.2)
	Completed	3 (2.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	3 (15.0)	0 (0.0)
	Not completed	17 (12.0)	3 (2.2)
	With visit, no record	17 (12.0)	3 (2.2)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-OES18	N[c] = 142 n (%)	N[c] = 136 n (%)
	Missing by Design[e]	122 (85.9)	133 (97.8)
	Discontinued due to adverse event	15 (10.6)	20 (14.7)
	Discontinued due to clinical progression	12 (8.5)	14 (10.3)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	74 (52.1)	87 (64.0)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
	Visit not reached	6 (4.2)	2 (1.5)
WEEK 96	Expected to Complete Questionnaires	13 (9.2)	3 (2.2)
	Not completed	13 (9.2)	3 (2.2)
	With visit, no record	13 (9.2)	3 (2.2)
	Missing by Design[e]	129 (90.8)	133 (97.8)
	Discontinued due to adverse event	15 (10.6)	20 (14.7)
	Discontinued due to clinical progression	12 (8.5)	14 (10.3)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	77 (54.2)	87 (64.0)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
	Visit not reached	10 (7.0)	2 (1.5)
WEEK 105	Expected to Complete Questionnaires	8 (5.6)	2 (1.5)
	Completed	3 (2.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	3 (37.5)	0 (0.0)
	Not completed	5 (3.5)	2 (1.5)
	With visit, no record	5 (3.5)	2 (1.5)
	Missing by Design[e]	134 (94.4)	134 (98.5)
	Discontinued due to adverse event	15 (10.6)	20 (14.7)
	Discontinued due to clinical progression	12 (8.5)	14 (10.3)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	77 (54.2)	87 (64.0)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
	Visit not reached	14 (9.9)	3 (2.2)
	Visit not scheduled	1 (0.7)	0 (0.0)
WEEK 114	Expected to Complete Questionnaires	6 (4.2)	1 (0.7)
	Completed	5 (3.5)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	5 (83.3)	0 (0.0)
	Not completed	1 (0.7)	1 (0.7)
	Other	1 (0.7)	0 (0.0)
	With visit, no record	0 (0.0)	1 (0.7)
	Missing by Design[e]	136 (95.8)	135 (99.3)
	Discontinued due to adverse event	15 (10.6)	20 (14.7)
	Discontinued due to clinical progression	12 (8.5)	14 (10.3)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	77 (54.2)	87 (64.0)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
	Completed study treatment	1 (0.7)	0 (0.0)
	Visit not reached	16 (11.3)	4 (2.9)

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10

d: Compliance is the proportion of participants who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design

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

CPS: Combined Proportion Score; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G2.3: Rücklaufquoten des EQ-5D VAS

Tabelle 4G-6: Gründe für das Fehlen von Werten in der EQ-5D VAS – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]		**Pembrolizumab + Chemotherapy[b]**	**Chemotherapy[b]**
Visit	**EQ-5D**	**N[c] = 142 n (%)**	**N[c] = 136 n (%)**
BASELINE	Expected to Complete Questionnaires	142 (100.0)	136 (100.0)
	Completed	139 (97.9)	134 (98.5)
	Compliance (% in those expected to complete questionnaires)[d]	139 (97.9)	134 (98.5)
	Not completed	3 (2.1)	2 (1.5)
	Not completed due to site staff error	1 (0.7)	1 (0.7)
	Other	1 (0.7)	0 (0.0)
	With visit, no record	1 (0.7)	1 (0.7)
	Missing by Design[e]	0 (0.0)	0 (0.0)
WEEK 3	Expected to Complete Questionnaires	125 (88.0)	112 (82.4)
	Completed	121 (85.2)	105 (77.2)
	Compliance (% in those expected to complete questionnaires)[d]	121 (96.8)	105 (93.8)
	Not completed	4 (2.8)	7 (5.1)
	Subject did not complete due to disease under study	2 (1.4)	1 (0.7)
	Not completed due to site staff error	1 (0.7)	1 (0.7)
	Other	1 (0.7)	2 (1.5)
	With visit, no record	0 (0.0)	3 (2.2)
	Missing by Design[e]	17 (12.0)	24 (17.6)
	Subject died	3 (2.1)	2 (1.5)
	Visit not scheduled	14 (9.9)	22 (16.2)
WEEK 6	Expected to Complete Questionnaires	109 (76.8)	109 (80.1)
	Completed	104 (73.2)	106 (77.9)
	Compliance (% in those expected to complete questionnaires)[d]	104 (95.4)	106 (97.2)
	Not completed	5 (3.5)	3 (2.2)
	Not completed due to site staff error	1 (0.7)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.7)
	Subject refused for other reasons	2 (1.4)	0 (0.0)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	1 (0.7)	1 (0.7)
	Missing by Design[e]	33 (23.2)	27 (19.9)
	Discontinued due to adverse event	3 (2.1)	3 (2.2)
	Discontinued due to clinical progression	0 (0.0)	2 (1.5)
	Discontinued due to progressive disease	1 (0.7)	1 (0.7)
	Discontinued due to withdrawal by subject	1 (0.7)	0 (0.0)
	Visit not scheduled	28 (19.7)	21 (15.4)
WEEK 9	Expected to Complete Questionnaires	107 (75.4)	105 (77.2)
	Completed	103 (72.5)	98 (72.1)
	Compliance (% in those expected to complete questionnaires)[d]	103 (96.3)	98 (93.3)
	Not completed	4 (2.8)	7 (5.1)
	Subject did not complete due to disease under study	1 (0.7)	1 (0.7)
	Not completed due to site staff error	2 (1.4)	0 (0.0)
	Subject refused for other reasons	1 (0.7)	1 (0.7)
	Other	0 (0.0)	1 (0.7)
	With visit, no record	0 (0.0)	4 (2.9)
	Missing by Design[e]	35 (24.6)	31 (22.8)
	Discontinued due to adverse event	4 (2.8)	5 (3.7)
	Discontinued due to clinical progression	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	2 (1.4)	3 (2.2)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 142 n (%)	N[c] = 136 n (%)
	Discontinued due to withdrawal by subject	3 (2.1)	1 (0.7)
	Subject died	1 (0.7)	4 (2.9)
	Visit not scheduled	23 (16.2)	16 (11.8)
WEEK 12	Expected to Complete Questionnaires	109 (76.8)	97 (71.3)
	Completed	106 (74.6)	92 (67.6)
	Compliance (% in those expected to complete questionnaires)[d]	106 (97.2)	92 (94.8)
	Not completed	3 (2.1)	5 (3.7)
	Not completed due to site staff error	2 (1.4)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.7)
	Subject refused for other reasons	1 (0.7)	2 (1.5)
	Other	0 (0.0)	1 (0.7)
	With visit, no record	0 (0.0)	1 (0.7)
	Missing by Design[e]	33 (23.2)	39 (28.7)
	Discontinued due to adverse event	5 (3.5)	8 (5.9)
	Discontinued due to clinical progression	4 (2.8)	5 (3.7)
	Discontinued due to progressive disease	10 (7.0)	8 (5.9)
	Discontinued due to withdrawal by subject	5 (3.5)	1 (0.7)
	Visit not scheduled	9 (6.3)	17 (12.5)
WEEK 15	Expected to Complete Questionnaires	99 (69.7)	86 (63.2)
	Completed	88 (62.0)	82 (60.3)
	Compliance (% in those expected to complete questionnaires)[d]	88 (88.9)	82 (95.3)
	Not completed	11 (7.7)	4 (2.9)
	Subject did not complete due to disease under study	1 (0.7)	0 (0.0)
	Not completed due to site staff error	2 (1.4)	0 (0.0)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	7 (4.9)	3 (2.2)
	Missing by Design[e]	43 (30.3)	50 (36.8)
	Discontinued due to adverse event	5 (3.5)	10 (7.4)
	Discontinued due to clinical progression	6 (4.2)	7 (5.1)
	Discontinued due to progressive disease	11 (7.7)	13 (9.6)
	Discontinued due to withdrawal by subject	8 (5.6)	1 (0.7)
	Subject died	1 (0.7)	2 (1.5)
	Visit not scheduled	12 (8.5)	17 (12.5)
WEEK 18	Expected to Complete Questionnaires	91 (64.1)	77 (56.6)
	Completed	83 (58.5)	69 (50.7)
	Compliance (% in those expected to complete questionnaires)[d]	83 (91.2)	69 (89.6)
	Not completed	8 (5.6)	8 (5.9)
	Subject did not complete due to disease under study	2 (1.4)	1 (0.7)
	Not completed due to site staff error	1 (0.7)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	3 (2.2)
	Other	0 (0.0)	2 (1.5)
	With visit, no record	5 (3.5)	2 (1.5)
	Missing by Design[e]	51 (35.9)	59 (43.4)
	Discontinued due to adverse event	7 (4.9)	10 (7.4)
	Discontinued due to clinical progression	7 (4.9)	9 (6.6)
	Discontinued due to progressive disease	14 (9.9)	19 (14.0)
	Discontinued due to withdrawal by subject	7 (4.9)	2 (1.5)
	Subject died	0 (0.0)	2 (1.5)
	Visit not scheduled	16 (11.3)	17 (12.5)
WEEK 21	Expected to Complete Questionnaires	83 (58.5)	70 (51.5)
	Completed	80 (56.3)	67 (49.3)
	Compliance (% in those expected to complete questionnaires)[d]	80 (96.4)	67 (95.7)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 142 n (%)	N[c] = 136 n (%)
	Not completed	3 (2.1)	3 (2.2)
	Not completed due to site staff error	1 (0.7)	0 (0.0)
	Subject refused for other reasons	1 (0.7)	1 (0.7)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	0 (0.0)	1 (0.7)
	Missing by Design[e]	59 (41.5)	66 (48.5)
	Discontinued due to adverse event	9 (6.3)	13 (9.6)
	Discontinued due to clinical progression	7 (4.9)	9 (6.6)
	Discontinued due to physician decision	1 (0.7)	1 (0.7)
	Discontinued due to progressive disease	24 (16.9)	31 (22.8)
	Discontinued due to withdrawal by subject	8 (5.6)	4 (2.9)
	Visit not scheduled	10 (7.0)	8 (5.9)
WEEK 24	Expected to Complete Questionnaires	87 (61.3)	67 (49.3)
	Completed	80 (56.3)	63 (46.3)
	Compliance (% in those expected to complete questionnaires)[d]	80 (92.0)	63 (94.0)
	Not completed	7 (4.9)	4 (2.9)
	Subject did not complete due to disease under study	1 (0.7)	0 (0.0)
	Subject in hospital or hospice	1 (0.7)	0 (0.0)
	Subject was physically unable to complete	1 (0.7)	0 (0.0)
	Subject refused for other reasons	1 (0.7)	1 (0.7)
	Other	1 (0.7)	2 (1.5)
	With visit, no record	2 (1.4)	1 (0.7)
	Missing by Design[e]	55 (38.7)	69 (50.7)
	Discontinued due to adverse event	9 (6.3)	14 (10.3)
	Discontinued due to clinical progression	7 (4.9)	9 (6.6)
	Discontinued due to physician decision	1 (0.7)	1 (0.7)
	Discontinued due to progressive disease	27 (19.0)	39 (28.7)
	Discontinued due to withdrawal by subject	10 (7.0)	5 (3.7)
	Subject died	0 (0.0)	1 (0.7)
	Visit not scheduled	1 (0.7)	0 (0.0)
WEEK 33	Expected to Complete Questionnaires	74 (52.1)	44 (32.4)
	Completed	65 (45.8)	39 (28.7)
	Compliance (% in those expected to complete questionnaires)[d]	65 (87.8)	39 (88.6)
	Not completed	9 (6.3)	5 (3.7)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.7)
	Not completed due to site staff error	2 (1.4)	0 (0.0)
	Subject in hospital or hospice	0 (0.0)	1 (0.7)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	6 (4.2)	2 (1.5)
	Missing by Design[e]	68 (47.9)	92 (67.6)
	Discontinued due to adverse event	11 (7.7)	16 (11.8)
	Discontinued due to clinical progression	8 (5.6)	11 (8.1)
	Discontinued due to physician decision	2 (1.4)	1 (0.7)
	Discontinued due to progressive disease	35 (24.6)	57 (41.9)
	Discontinued due to withdrawal by subject	11 (7.7)	6 (4.4)
	Subject died	0 (0.0)	1 (0.7)
	Visit not scheduled	1 (0.7)	0 (0.0)
WEEK 42	Expected to Complete Questionnaires	54 (38.0)	27 (19.9)
	Completed	49 (34.5)	23 (16.9)
	Compliance (% in those expected to complete questionnaires)[d]	49 (90.7)	23 (85.2)
	Not completed	5 (3.5)	4 (2.9)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.7)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 142 n (%)	N[c] = 136 n (%)
	Not completed due to site staff error	1 (0.7)	1 (0.7)
	Other	0 (0.0)	1 (0.7)
	With visit, no record	4 (2.8)	1 (0.7)
	Missing by Design[e]	88 (62.0)	109 (80.1)
	Discontinued due to adverse event	12 (8.5)	18 (13.2)
	Discontinued due to clinical progression	9 (6.3)	12 (8.8)
	Discontinued due to physician decision	2 (1.4)	1 (0.7)
	Discontinued due to progressive disease	52 (36.6)	70 (51.5)
	Discontinued due to withdrawal by subject	12 (8.5)	8 (5.9)
	Subject died	1 (0.7)	0 (0.0)
WEEK 51	Expected to Complete Questionnaires	41 (28.9)	15 (11.0)
	Completed	35 (24.6)	11 (8.1)
	Compliance (% in those expected to complete questionnaires)[d]	35 (85.4)	11 (73.3)
	Not completed	6 (4.2)	4 (2.9)
	Subject did not complete due to disease under study	2 (1.4)	0 (0.0)
	Not completed due to site staff error	1 (0.7)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.7)
	Subject refused for other reasons	0 (0.0)	2 (1.5)
	Other	0 (0.0)	1 (0.7)
	With visit, no record	3 (2.1)	0 (0.0)
	Missing by Design[e]	101 (71.1)	121 (89.0)
	Discontinued due to adverse event	14 (9.9)	18 (13.2)
	Discontinued due to clinical progression	11 (7.7)	13 (9.6)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	60 (42.3)	79 (58.1)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
	Subject died	0 (0.0)	1 (0.7)
	Visit not scheduled	1 (0.7)	0 (0.0)
WEEK 60	Expected to Complete Questionnaires	34 (23.9)	10 (7.4)
	Completed	15 (10.6)	3 (2.2)
	Compliance (% in those expected to complete questionnaires)[d]	15 (44.1)	3 (30.0)
	Not completed	19 (13.4)	7 (5.1)
	Not completed due to site staff error	1 (0.7)	0 (0.0)
	Other	2 (1.4)	2 (1.5)
	With visit, no record	16 (11.3)	5 (3.7)
	Missing by Design[e]	108 (76.1)	126 (92.6)
	Discontinued due to adverse event	14 (9.9)	19 (14.0)
	Discontinued due to clinical progression	12 (8.5)	14 (10.3)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	67 (47.2)	83 (61.0)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
WEEK 69	Expected to Complete Questionnaires	31 (21.8)	8 (5.9)
	Completed	3 (2.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	3 (9.7)	0 (0.0)
	Not completed	28 (19.7)	8 (5.9)
	Subject refused for other reasons	0 (0.0)	1 (0.7)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	27 (19.0)	6 (4.4)
	Missing by Design[e]	111 (78.2)	128 (94.1)
	Discontinued due to adverse event	15 (10.6)	19 (14.0)
	Discontinued due to clinical progression	12 (8.5)	14 (10.3)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 142 n (%)	N[c] = 136 n (%)
	Discontinued due to progressive disease	69 (48.6)	85 (62.5)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
WEEK 78	Expected to Complete Questionnaires	27 (19.0)	6 (4.4)
	Completed	3 (2.1)	1 (0.7)
	Compliance (% in those expected to complete questionnaires)[d]	3 (11.1)	1 (16.7)
	Not completed	24 (16.9)	5 (3.7)
	With visit, no record	24 (16.9)	5 (3.7)
	Missing by Design[e]	115 (81.0)	130 (95.6)
	Discontinued due to adverse event	15 (10.6)	20 (14.7)
	Discontinued due to clinical progression	12 (8.5)	14 (10.3)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	72 (50.7)	86 (63.2)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
	Visit not reached	1 (0.7)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires	20 (14.1)	3 (2.2)
	Completed	3 (2.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	3 (15.0)	0 (0.0)
	Not completed	17 (12.0)	3 (2.2)
	With visit, no record	17 (12.0)	3 (2.2)
	Missing by Design[e]	122 (85.9)	133 (97.8)
	Discontinued due to adverse event	15 (10.6)	20 (14.7)
	Discontinued due to clinical progression	12 (8.5)	14 (10.3)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	74 (52.1)	87 (64.0)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
	Visit not reached	6 (4.2)	2 (1.5)
WEEK 96	Expected to Complete Questionnaires	13 (9.2)	3 (2.2)
	Not completed	13 (9.2)	3 (2.2)
	With visit, no record	13 (9.2)	3 (2.2)
	Missing by Design[e]	129 (90.8)	133 (97.8)
	Discontinued due to adverse event	15 (10.6)	20 (14.7)
	Discontinued due to clinical progression	12 (8.5)	14 (10.3)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	77 (54.2)	87 (64.0)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
	Visit not reached	10 (7.0)	2 (1.5)
WEEK 105	Expected to Complete Questionnaires	8 (5.6)	2 (1.5)
	Completed	3 (2.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	3 (37.5)	0 (0.0)
	Not completed	5 (3.5)	2 (1.5)
	With visit, no record	5 (3.5)	2 (1.5)
	Missing by Design[e]	134 (94.4)	134 (98.5)
	Discontinued due to adverse event	15 (10.6)	20 (14.7)
	Discontinued due to clinical progression	12 (8.5)	14 (10.3)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	77 (54.2)	87 (64.0)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
	Visit not reached	14 (9.9)	3 (2.2)
	Visit not scheduled	1 (0.7)	0 (0.0)
WEEK 114	Expected to Complete Questionnaires	6 (4.2)	1 (0.7)
	Completed	6 (4.2)	0 (0.0)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 142 n (%)	N[c] = 136 n (%)
	Compliance (% in those expected to complete questionnaires)[d]	6 (100.0)	0 (0.0)
	Not completed	0 (0.0)	1 (0.7)
	With visit, no record	0 (0.0)	1 (0.7)
	Missing by Design[e]	136 (95.8)	135 (99.3)
	Discontinued due to adverse event	15 (10.6)	20 (14.7)
	Discontinued due to clinical progression	12 (8.5)	14 (10.3)
	Discontinued due to physician decision	2 (1.4)	2 (1.5)
	Discontinued due to progressive disease	77 (54.2)	87 (64.0)
	Discontinued due to withdrawal by subject	13 (9.2)	8 (5.9)
	Completed study treatment	1 (0.7)	0 (0.0)
	Visit not reached	16 (11.3)	4 (2.9)

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10

d: Compliance is the proportion of participants who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design

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

CPS: Combined Proportion Score; EQ-5D: European Quality of Life 5 Dimensions; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G3: Rücklaufquoten des EORTC QLQ-C30, des EORTC QLQ-OES18 und EQ-5D VAS – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G3.1: Rücklaufquoten des EORTC QLQ-C30

Tabelle 4G-7: Gründe für das Fehlen von Werten im EORTC QLQ-C30 – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 42 n (%)	N[c] = 53 n (%)
BASELINE	Expected to Complete Questionnaires	42 (100.0)	53 (100.0)
	Completed	41 (97.6)	49 (92.5)
	Compliance (% in those expected to complete questionnaires)[d]	41 (97.6)	49 (92.5)
	Not completed	1 (2.4)	4 (7.5)
	Not completed due to site staff error	0 (0.0)	3 (5.7)
	Other	0 (0.0)	1 (1.9)
	With visit, no record	1 (2.4)	0 (0.0)
	Missing by Design[e]	0 (0.0)	0 (0.0)
WEEK 3	Expected to Complete Questionnaires	39 (92.9)	47 (88.7)
	Completed	36 (85.7)	39 (73.6)
	Compliance (% in those expected to complete questionnaires)[d]	36 (92.3)	39 (83.0)
	Not completed	3 (7.1)	8 (15.1)
	Not completed due to site staff error	1 (2.4)	4 (7.5)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	Subject did not complete due to side effects of treatment	1 (2.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	2 (3.8)
	Other	1 (2.4)	1 (1.9)
	Missing by Design[e]	3 (7.1)	6 (11.3)
	Subject died	0 (0.0)	1 (1.9)
	Visit not scheduled	3 (7.1)	5 (9.4)
WEEK 6	Expected to Complete Questionnaires	39 (92.9)	48 (90.6)
	Completed	38 (90.5)	45 (84.9)
	Compliance (% in those expected to complete questionnaires)[d]	38 (97.4)	45 (93.8)
	Not completed	1 (2.4)	3 (5.7)
	Not completed due to site staff error	0 (0.0)	1 (1.9)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	Subject was physically unable to complete	1 (2.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	Missing by Design[e]	3 (7.1)	5 (9.4)
	Discontinued due to adverse event	2 (4.8)	2 (3.8)
	Visit not scheduled	1 (2.4)	3 (5.7)
WEEK 9	Expected to Complete Questionnaires	32 (76.2)	47 (88.7)
	Completed	28 (66.7)	41 (77.4)
	Compliance (% in those expected to complete questionnaires)[d]	28 (87.5)	41 (87.2)
	Not completed	4 (9.5)	6 (11.3)
	Not completed due to site staff error	1 (2.4)	1 (1.9)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	Other	1 (2.4)	1 (1.9)
	With visit, no record	2 (4.8)	3 (5.7)
	Missing by Design[e]	10 (23.8)	6 (11.3)
	Discontinued due to adverse event	3 (7.1)	1 (1.9)
	Discontinued due to clinical progression	0 (0.0)	1 (1.9)
	Discontinued due to progressive disease	0 (0.0)	1 (1.9)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 42 n (%)	N[c] = 53 n (%)
	Visit not scheduled	7 (16.7)	3 (5.7)
WEEK 12	Expected to Complete Questionnaires	30 (71.4)	44 (83.0)
	Completed	27 (64.3)	37 (69.8)
	Compliance (% in those expected to complete questionnaires)[d]	27 (90.0)	37 (84.1)
	Not completed	3 (7.1)	7 (13.2)
	Not completed due to site staff error	1 (2.4)	1 (1.9)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	Other	2 (4.8)	0 (0.0)
	With visit, no record	0 (0.0)	4 (7.5)
	Missing by Design[e]	12 (28.6)	9 (17.0)
	Discontinued due to adverse event	3 (7.1)	2 (3.8)
	Discontinued due to clinical progression	0 (0.0)	3 (5.7)
	Discontinued due to progressive disease	1 (2.4)	1 (1.9)
	Visit not scheduled	8 (19.0)	3 (5.7)
WEEK 15	Expected to Complete Questionnaires	30 (71.4)	39 (73.6)
	Completed	29 (69.0)	38 (71.7)
	Compliance (% in those expected to complete questionnaires)[d]	29 (96.7)	38 (97.4)
	Not completed	1 (2.4)	1 (1.9)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	Other	1 (2.4)	0 (0.0)
	Missing by Design[e]	12 (28.6)	14 (26.4)
	Discontinued due to adverse event	3 (7.1)	2 (3.8)
	Discontinued due to clinical progression	1 (2.4)	4 (7.5)
	Discontinued due to progressive disease	2 (4.8)	1 (1.9)
	Subject died	0 (0.0)	3 (5.7)
	Visit not scheduled	6 (14.3)	4 (7.5)
WEEK 18	Expected to Complete Questionnaires	29 (69.0)	36 (67.9)
	Completed	27 (64.3)	34 (64.2)
	Compliance (% in those expected to complete questionnaires)[d]	27 (93.1)	34 (94.4)
	Not completed	2 (4.8)	2 (3.8)
	Subject did not complete due to disease under study	0 (0.0)	1 (1.9)
	Other	2 (4.8)	0 (0.0)
	With visit, no record	0 (0.0)	1 (1.9)
	Missing by Design[e]	13 (31.0)	17 (32.1)
	Discontinued due to adverse event	3 (7.1)	3 (5.7)
	Discontinued due to clinical progression	2 (4.8)	5 (9.4)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	4 (9.5)	4 (7.5)
	Subject died	0 (0.0)	1 (1.9)
	Visit not scheduled	4 (9.5)	2 (3.8)
WEEK 21	Expected to Complete Questionnaires	28 (66.7)	29 (54.7)
	Completed	24 (57.1)	28 (52.8)
	Compliance (% in those expected to complete questionnaires)[d]	24 (85.7)	28 (96.6)
	Not completed	4 (9.5)	1 (1.9)
	Not completed due to site staff error	0 (0.0)	1 (1.9)
	Other	1 (2.4)	0 (0.0)
	With visit, no record	3 (7.1)	0 (0.0)
	Missing by Design[e]	14 (33.3)	24 (45.3)
	Discontinued due to adverse event	3 (7.1)	3 (5.7)
	Discontinued due to clinical progression	2 (4.8)	7 (13.2)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 42 n (%)	N[c] = 53 n (%)
	Discontinued due to progressive disease	6 (14.3)	6 (11.3)
	Visit not scheduled	3 (7.1)	6 (11.3)
WEEK 24	Expected to Complete Questionnaires	26 (61.9)	34 (64.2)
	Completed	25 (59.5)	28 (52.8)
	Compliance (% in those expected to complete questionnaires)[d]	25 (96.2)	28 (82.4)
	Not completed	1 (2.4)	6 (11.3)
	Not completed due to site staff error	0 (0.0)	3 (5.7)
	Subject was physically unable to complete	1 (2.4)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (1.9)
	Other	0 (0.0)	2 (3.8)
	Missing by Design[e]	16 (38.1)	19 (35.8)
	Discontinued due to adverse event	4 (9.5)	3 (5.7)
	Discontinued due to clinical progression	3 (7.1)	8 (15.1)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	8 (19.0)	6 (11.3)
	Visit not scheduled	1 (2.4)	0 (0.0)
WEEK 33	Expected to Complete Questionnaires	23 (54.8)	24 (45.3)
	Completed	19 (45.2)	22 (41.5)
	Compliance (% in those expected to complete questionnaires)[d]	19 (82.6)	22 (91.7)
	Not completed	4 (9.5)	2 (3.8)
	Not completed due to site staff error	1 (2.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	Other	2 (4.8)	0 (0.0)
	With visit, no record	1 (2.4)	1 (1.9)
	Missing by Design[e]	19 (45.2)	29 (54.7)
	Discontinued due to adverse event	5 (11.9)	3 (5.7)
	Discontinued due to clinical progression	3 (7.1)	8 (15.1)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	11 (26.2)	13 (24.5)
	Discontinued due to withdrawal by subject	0 (0.0)	2 (3.8)
	Subject died	0 (0.0)	1 (1.9)
WEEK 42	Expected to Complete Questionnaires	15 (35.7)	14 (26.4)
	Completed	13 (31.0)	11 (20.8)
	Compliance (% in those expected to complete questionnaires)[d]	13 (86.7)	11 (78.6)
	Not completed	2 (4.8)	3 (5.7)
	Not completed due to site staff error	0 (0.0)	1 (1.9)
	Subject was physically unable to complete	0 (0.0)	1 (1.9)
	With visit, no record	2 (4.8)	1 (1.9)
	Missing by Design[e]	27 (64.3)	39 (73.6)
	Discontinued due to adverse event	5 (11.9)	3 (5.7)
	Discontinued due to clinical progression	5 (11.9)	8 (15.1)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	16 (38.1)	23 (43.4)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Subject died	0 (0.0)	1 (1.9)
WEEK 51	Expected to Complete Questionnaires	12 (28.6)	9 (17.0)
	Completed	12 (28.6)	6 (11.3)
	Compliance (% in those expected to complete questionnaires)[d]	12 (100.0)	6 (66.7)
	Not completed	0 (0.0)	3 (5.7)
	Not completed due to site staff error	0 (0.0)	1 (1.9)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	With visit, no record	0 (0.0)	1 (1.9)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 42 n (%)	N[c] = 53 n (%)
	Missing by Design[e]	30 (71.4)	44 (83.0)
	Discontinued due to adverse event	5 (11.9)	3 (5.7)
	Discontinued due to clinical progression	6 (14.3)	10 (18.9)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	18 (42.9)	27 (50.9)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
WEEK 60	Expected to Complete Questionnaires	12 (28.6)	7 (13.2)
	Completed	6 (14.3)	3 (5.7)
	Compliance (% in those expected to complete questionnaires)[d]	6 (50.0)	3 (42.9)
	Not completed	6 (14.3)	4 (7.5)
	With visit, no record	6 (14.3)	4 (7.5)
	Missing by Design[e]	30 (71.4)	46 (86.8)
	Discontinued due to adverse event	5 (11.9)	3 (5.7)
	Discontinued due to clinical progression	6 (14.3)	10 (18.9)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	18 (42.9)	29 (54.7)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
WEEK 69	Expected to Complete Questionnaires	11 (26.2)	4 (7.5)
	Completed	3 (7.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	3 (27.3)	0 (0.0)
	Not completed	8 (19.0)	4 (7.5)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	With visit, no record	8 (19.0)	3 (5.7)
	Missing by Design[e]	31 (73.8)	49 (92.5)
	Discontinued due to adverse event	5 (11.9)	3 (5.7)
	Discontinued due to clinical progression	6 (14.3)	11 (20.8)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	19 (45.2)	31 (58.5)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
WEEK 78	Expected to Complete Questionnaires	7 (16.7)	3 (5.7)
	Completed	0 (0.0)	1 (1.9)
	Compliance (% in those expected to complete questionnaires)[d]	0 (0.0)	1 (33.3)
	Not completed	7 (16.7)	2 (3.8)
	With visit, no record	7 (16.7)	2 (3.8)
	Missing by Design[e]	35 (83.3)	50 (94.3)
	Discontinued due to adverse event	5 (11.9)	3 (5.7)
	Discontinued due to clinical progression	6 (14.3)	11 (20.8)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	22 (52.4)	32 (60.4)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Visit not reached	1 (2.4)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires	7 (16.7)	2 (3.8)
	Completed	0 (0.0)	1 (1.9)
	Compliance (% in those expected to complete questionnaires)[d]	0 (0.0)	1 (50.0)
	Not completed	7 (16.7)	1 (1.9)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	With visit, no record	7 (16.7)	0 (0.0)
	Missing by Design[e]	35 (83.3)	51 (96.2)
	Discontinued due to adverse event	5 (11.9)	3 (5.7)
	Discontinued due to clinical progression	6 (14.3)	11 (20.8)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	22 (52.4)	33 (62.3)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 42 n (%)	N[c] = 53 n (%)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Visit not reached	1 (2.4)	0 (0.0)
WEEK 96	Expected to Complete Questionnaires	7 (16.7)	0 (0.0)
	Not completed	7 (16.7)	0 (0.0)
	With visit, no record	7 (16.7)	0 (0.0)
	Missing by Design[e]	35 (83.3)	53 (100.0)
	Discontinued due to adverse event	5 (11.9)	3 (5.7)
	Discontinued due to clinical progression	6 (14.3)	11 (20.8)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	22 (52.4)	35 (66.0)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Visit not reached	1 (2.4)	0 (0.0)
WEEK 105	Expected to Complete Questionnaires	5 (11.9)	0 (0.0)
	Completed	2 (4.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	2 (40.0)	0 (0.0)
	Not completed	3 (7.1)	0 (0.0)
	With visit, no record	3 (7.1)	0 (0.0)
	Missing by Design[e]	37 (88.1)	53 (100.0)
	Discontinued due to adverse event	5 (11.9)	3 (5.7)
	Discontinued due to clinical progression	6 (14.3)	11 (20.8)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	22 (52.4)	35 (66.0)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Visit not reached	3 (7.1)	0 (0.0)
WEEK 114	Expected to Complete Questionnaires	2 (4.8)	0 (0.0)
	Completed	2 (4.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	2 (100.0)	0 (0.0)
	Missing by Design[e]	40 (95.2)	53 (100.0)
	Discontinued due to adverse event	5 (11.9)	3 (5.7)
	Discontinued due to clinical progression	6 (14.3)	11 (20.8)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	23 (54.8)	35 (66.0)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Completed study treatment	1 (2.4)	0 (0.0)
	Visit not reached	4 (9.5)	0 (0.0)

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10

d: Compliance is the proportion of participants who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design

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

CPS: Combined Proportion 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

Anhang 4-G3.2: Rücklaufquoten des EORTC QLQ-OES18

Tabelle 4G-8: Gründe für das Fehlen von Werten im EORTC QLQ-OES18 – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]		**Pembrolizumab + Chemotherapy[b]**	**Chemotherapy[b]**
Visit	**EORTC QLQ-OES18**	**N[c] = 42 n (%)**	**N[c] = 52 n (%)**
BASELINE	Expected to Complete Questionnaires	42 (100.0)	52 (100.0)
	Completed	41 (97.6)	47 (90.4)
	Compliance (% in those expected to complete questionnaires)[d]	41 (97.6)	47 (90.4)
	Not completed	1 (2.4)	5 (9.6)
	Not completed due to site staff error	0 (0.0)	4 (7.7)
	Other	0 (0.0)	1 (1.9)
	With visit, no record	1 (2.4)	0 (0.0)
	Missing by Design[e]	0 (0.0)	0 (0.0)
WEEK 3	Expected to Complete Questionnaires	39 (92.9)	46 (88.5)
	Completed	36 (85.7)	38 (73.1)
	Compliance (% in those expected to complete questionnaires)[d]	36 (92.3)	38 (82.6)
	Not completed	3 (7.1)	8 (15.4)
	Subject did not complete due to disease under study	0 (0.0)	1 (1.9)
	Not completed due to site staff error	1 (2.4)	4 (7.7)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	Subject did not complete due to side effects of treatment	1 (2.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	Other	1 (2.4)	1 (1.9)
	Missing by Design[e]	3 (7.1)	6 (11.5)
	Subject died	0 (0.0)	1 (1.9)
	Visit not scheduled	3 (7.1)	5 (9.6)
WEEK 6	Expected to Complete Questionnaires	39 (92.9)	46 (88.5)
	Completed	37 (88.1)	43 (82.7)
	Compliance (% in those expected to complete questionnaires)[d]	37 (94.9)	43 (93.5)
	Not completed	2 (4.8)	3 (5.8)
	Not completed due to site staff error	1 (2.4)	1 (1.9)
	Subject was physically unable to complete	1 (2.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	2 (3.8)
	Missing by Design[e]	3 (7.1)	6 (11.5)
	Discontinued due to adverse event	2 (4.8)	2 (3.8)
	Subject died	0 (0.0)	1 (1.9)
	Visit not scheduled	1 (2.4)	3 (5.8)
WEEK 9	Expected to Complete Questionnaires	32 (76.2)	46 (88.5)
	Completed	28 (66.7)	40 (76.9)
	Compliance (% in those expected to complete questionnaires)[d]	28 (87.5)	40 (87.0)
	Not completed	4 (9.5)	6 (11.5)
	Not completed due to site staff error	1 (2.4)	1 (1.9)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	Other	1 (2.4)	1 (1.9)
	With visit, no record	2 (4.8)	3 (5.8)
	Missing by Design[e]	10 (23.8)	6 (11.5)
	Discontinued due to adverse event	3 (7.1)	1 (1.9)
	Discontinued due to clinical progression	0 (0.0)	1 (1.9)
	Discontinued due to progressive disease	0 (0.0)	1 (1.9)
	Visit not scheduled	7 (16.7)	3 (5.8)
WEEK 12	Expected to Complete Questionnaires	29 (69.0)	44 (84.6)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-OES18	N[c] = 42 n (%)	N[c] = 52 n (%)
	Completed	27 (64.3)	36 (69.2)
	Compliance (% in those expected to complete questionnaires)[d]	27 (93.1)	36 (81.8)
	Not completed	2 (4.8)	8 (15.4)
	Not completed due to site staff error	0 (0.0)	2 (3.8)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	Other	2 (4.8)	0 (0.0)
	With visit, no record	0 (0.0)	4 (7.7)
	Missing by Design[e]	13 (31.0)	8 (15.4)
	Discontinued due to adverse event	3 (7.1)	2 (3.8)
	Discontinued due to clinical progression	0 (0.0)	3 (5.8)
	Discontinued due to progressive disease	1 (2.4)	1 (1.9)
	Subject died	1 (2.4)	0 (0.0)
	Visit not scheduled	8 (19.0)	2 (3.8)
WEEK 15	Expected to Complete Questionnaires	30 (71.4)	39 (75.0)
	Completed	29 (69.0)	38 (73.1)
	Compliance (% in those expected to complete questionnaires)[d]	29 (96.7)	38 (97.4)
	Not completed	1 (2.4)	1 (1.9)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	Other	1 (2.4)	0 (0.0)
	Missing by Design[e]	12 (28.6)	13 (25.0)
	Discontinued due to adverse event	3 (7.1)	2 (3.8)
	Discontinued due to clinical progression	1 (2.4)	4 (7.7)
	Discontinued due to progressive disease	2 (4.8)	1 (1.9)
	Subject died	0 (0.0)	3 (5.8)
	Visit not scheduled	6 (14.3)	3 (5.8)
WEEK 18	Expected to Complete Questionnaires	29 (69.0)	36 (69.2)
	Completed	27 (64.3)	34 (65.4)
	Compliance (% in those expected to complete questionnaires)[d]	27 (93.1)	34 (94.4)
	Not completed	2 (4.8)	2 (3.8)
	Subject did not complete due to disease under study	0 (0.0)	1 (1.9)
	Other	2 (4.8)	0 (0.0)
	With visit, no record	0 (0.0)	1 (1.9)
	Missing by Design[e]	13 (31.0)	16 (30.8)
	Discontinued due to adverse event	3 (7.1)	3 (5.8)
	Discontinued due to clinical progression	2 (4.8)	5 (9.6)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	4 (9.5)	4 (7.7)
	Visit not scheduled	4 (9.5)	2 (3.8)
WEEK 21	Expected to Complete Questionnaires	28 (66.7)	29 (55.8)
	Completed	24 (57.1)	28 (53.8)
	Compliance (% in those expected to complete questionnaires)[d]	24 (85.7)	28 (96.6)
	Not completed	4 (9.5)	1 (1.9)
	Not completed due to site staff error	0 (0.0)	1 (1.9)
	Other	1 (2.4)	0 (0.0)
	With visit, no record	3 (7.1)	0 (0.0)
	Missing by Design[e]	14 (33.3)	23 (44.2)
	Discontinued due to adverse event	3 (7.1)	3 (5.8)
	Discontinued due to clinical progression	2 (4.8)	6 (11.5)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	6 (14.3)	6 (11.5)
	Visit not scheduled	3 (7.1)	6 (11.5)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
		N[c] = 42	N[c] = 52
Visit	EORTC QLQ-OES18	n (%)	n (%)
WEEK 24	Expected to Complete Questionnaires	26 (61.9)	34 (65.4)
	Completed	25 (59.5)	28 (53.8)
	Compliance (% in those expected to complete questionnaires)[d]	25 (96.2)	28 (82.4)
	Not completed	1 (2.4)	6 (11.5)
	Not completed due to site staff error	0 (0.0)	3 (5.8)
	Subject was physically unable to complete	1 (2.4)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (1.9)
	Other	0 (0.0)	2 (3.8)
	Missing by Design[e]	16 (38.1)	18 (34.6)
	Discontinued due to adverse event	4 (9.5)	3 (5.8)
	Discontinued due to clinical progression	3 (7.1)	7 (13.5)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	8 (19.0)	6 (11.5)
	Visit not scheduled	1 (2.4)	0 (0.0)
WEEK 33	Expected to Complete Questionnaires	23 (54.8)	24 (46.2)
	Completed	18 (42.9)	22 (42.3)
	Compliance (% in those expected to complete questionnaires)[d]	18 (78.3)	22 (91.7)
	Not completed	5 (11.9)	2 (3.8)
	Not completed due to site staff error	1 (2.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	Other	3 (7.1)	0 (0.0)
	With visit, no record	1 (2.4)	1 (1.9)
	Missing by Design[e]	19 (45.2)	28 (53.8)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	3 (7.1)	7 (13.5)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	11 (26.2)	13 (25.0)
	Discontinued due to withdrawal by subject	0 (0.0)	2 (3.8)
	Subject died	0 (0.0)	1 (1.9)
WEEK 42	Expected to Complete Questionnaires	15 (35.7)	14 (26.9)
	Completed	13 (31.0)	11 (21.2)
	Compliance (% in those expected to complete questionnaires)[d]	13 (86.7)	11 (78.6)
	Not completed	2 (4.8)	3 (5.8)
	Not completed due to site staff error	0 (0.0)	1 (1.9)
	Subject was physically unable to complete	0 (0.0)	1 (1.9)
	With visit, no record	2 (4.8)	1 (1.9)
	Missing by Design[e]	27 (64.3)	38 (73.1)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	5 (11.9)	7 (13.5)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	16 (38.1)	23 (44.2)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Subject died	0 (0.0)	1 (1.9)
WEEK 51	Expected to Complete Questionnaires	12 (28.6)	9 (17.3)
	Completed	12 (28.6)	7 (13.5)
	Compliance (% in those expected to complete questionnaires)[d]	12 (100.0)	7 (77.8)
	Not completed	0 (0.0)	2 (3.8)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	With visit, no record	0 (0.0)	1 (1.9)
	Missing by Design[e]	30 (71.4)	43 (82.7)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	9 (17.3)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-OES18	N[c] = 42 n (%)	N[c] = 52 n (%)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	18 (42.9)	27 (51.9)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
WEEK 60	Expected to Complete Questionnaires	12 (28.6)	7 (13.5)
	Completed	6 (14.3)	3 (5.8)
	Compliance (% in those expected to complete questionnaires)[d]	6 (50.0)	3 (42.9)
	Not completed	6 (14.3)	4 (7.7)
	With visit, no record	6 (14.3)	4 (7.7)
	Missing by Design[e]	30 (71.4)	45 (86.5)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	9 (17.3)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	18 (42.9)	29 (55.8)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
WEEK 69	Expected to Complete Questionnaires	11 (26.2)	4 (7.7)
	Completed	3 (7.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	3 (27.3)	0 (0.0)
	Not completed	8 (19.0)	4 (7.7)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	With visit, no record	8 (19.0)	3 (5.8)
	Missing by Design[e]	31 (73.8)	48 (92.3)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	10 (19.2)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	19 (45.2)	31 (59.6)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
WEEK 78	Expected to Complete Questionnaires	7 (16.7)	3 (5.8)
	Completed	0 (0.0)	1 (1.9)
	Compliance (% in those expected to complete questionnaires)[d]	0 (0.0)	1 (33.3)
	Not completed	7 (16.7)	2 (3.8)
	With visit, no record	7 (16.7)	2 (3.8)
	Missing by Design[e]	35 (83.3)	49 (94.2)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	10 (19.2)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	22 (52.4)	32 (61.5)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Visit not reached	1 (2.4)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires	7 (16.7)	2 (3.8)
	Not completed	7 (16.7)	2 (3.8)
	Not completed due to site staff error	0 (0.0)	1 (1.9)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	With visit, no record	7 (16.7)	0 (0.0)
	Missing by Design[e]	35 (83.3)	50 (96.2)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	10 (19.2)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	22 (52.4)	33 (63.5)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Visit not reached	1 (2.4)	0 (0.0)
WEEK 96	Expected to Complete Questionnaires	7 (16.7)	0 (0.0)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-OES18	N[c] = 42 n (%)	N[c] = 52 n (%)
	Not completed	7 (16.7)	0 (0.0)
	With visit, no record	7 (16.7)	0 (0.0)
	Missing by Design[e]	35 (83.3)	52 (100.0)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	10 (19.2)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	22 (52.4)	35 (67.3)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Visit not reached	1 (2.4)	0 (0.0)
WEEK 105	Expected to Complete Questionnaires	5 (11.9)	0 (0.0)
	Completed	2 (4.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	2 (40.0)	0 (0.0)
	Not completed	3 (7.1)	0 (0.0)
	With visit, no record	3 (7.1)	0 (0.0)
	Missing by Design[e]	37 (88.1)	52 (100.0)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	10 (19.2)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	22 (52.4)	35 (67.3)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Visit not reached	3 (7.1)	0 (0.0)
WEEK 114	Expected to Complete Questionnaires	2 (4.8)	0 (0.0)
	Completed	2 (4.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	2 (100.0)	0 (0.0)
	Missing by Design[e]	40 (95.2)	52 (100.0)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	10 (19.2)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	23 (54.8)	35 (67.3)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Completed study treatment	1 (2.4)	0 (0.0)
	Visit not reached	4 (9.5)	0 (0.0)

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10

d: Compliance is the proportion of participants who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design

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

CPS: Combined Proportion Score; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G3.3: Rücklaufquoten des EQ-5D VAS

Tabelle 4G-9: Gründe für das Fehlen von Werten in der EQ-5D VAS – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 42 n (%)	N[c] = 52 n (%)
BASELINE	Expected to Complete Questionnaires	42 (100.0)	52 (100.0)
	Completed	41 (97.6)	49 (94.2)
	Compliance (% in those expected to complete questionnaires)[d]	41 (97.6)	49 (94.2)
	Not completed	1 (2.4)	3 (5.8)
	Not completed due to site staff error	0 (0.0)	2 (3.8)
	Other	0 (0.0)	1 (1.9)
	With visit, no record	1 (2.4)	0 (0.0)
	Missing by Design[e]	0 (0.0)	0 (0.0)
WEEK 3	Expected to Complete Questionnaires	39 (92.9)	46 (88.5)
	Completed	36 (85.7)	40 (76.9)
	Compliance (% in those expected to complete questionnaires)[d]	36 (92.3)	40 (87.0)
	Not completed	3 (7.1)	6 (11.5)
	Not completed due to site staff error	1 (2.4)	4 (7.7)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	Subject did not complete due to side effects of treatment	1 (2.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	Other	1 (2.4)	0 (0.0)
	Missing by Design[e]	3 (7.1)	6 (11.5)
	Subject died	0 (0.0)	1 (1.9)
	Visit not scheduled	3 (7.1)	5 (9.6)
WEEK 6	Expected to Complete Questionnaires	39 (92.9)	47 (90.4)
	Completed	37 (88.1)	44 (84.6)
	Compliance (% in those expected to complete questionnaires)[d]	37 (94.9)	44 (93.6)
	Not completed	2 (4.8)	3 (5.8)
	Not completed due to site staff error	0 (0.0)	1 (1.9)
	Subject in hospital or hospice	1 (2.4)	1 (1.9)
	Subject was physically unable to complete	1 (2.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	Missing by Design[e]	3 (7.1)	5 (9.6)
	Discontinued due to adverse event	2 (4.8)	2 (3.8)
	Visit not scheduled	1 (2.4)	3 (5.8)
WEEK 9	Expected to Complete Questionnaires	32 (76.2)	47 (90.4)
	Completed	28 (66.7)	40 (76.9)
	Compliance (% in those expected to complete questionnaires)[d]	28 (87.5)	40 (85.1)
	Not completed	4 (9.5)	7 (13.5)
	Not completed due to site staff error	1 (2.4)	2 (3.8)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	Other	1 (2.4)	1 (1.9)
	With visit, no record	2 (4.8)	3 (5.8)
	Missing by Design[e]	10 (23.8)	5 (9.6)
	Discontinued due to adverse event	3 (7.1)	1 (1.9)
	Discontinued due to clinical progression	0 (0.0)	1 (1.9)
	Discontinued due to progressive disease	0 (0.0)	1 (1.9)
	Visit not scheduled	7 (16.7)	2 (3.8)
WEEK 12	Expected to Complete Questionnaires	29 (69.0)	44 (84.6)
	Completed	27 (64.3)	37 (71.2)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 42 n (%)	N[c] = 52 n (%)
	Compliance (% in those expected to complete questionnaires)[d]	27 (93.1)	37 (84.1)
	Not completed	2 (4.8)	7 (13.5)
	Not completed due to site staff error	0 (0.0)	1 (1.9)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	Other	2 (4.8)	0 (0.0)
	With visit, no record	0 (0.0)	4 (7.7)
	Missing by Design[e]	13 (31.0)	8 (15.4)
	Discontinued due to adverse event	3 (7.1)	2 (3.8)
	Discontinued due to clinical progression	0 (0.0)	3 (5.8)
	Discontinued due to progressive disease	1 (2.4)	1 (1.9)
	Subject died	1 (2.4)	0 (0.0)
	Visit not scheduled	8 (19.0)	2 (3.8)
WEEK 15	Expected to Complete Questionnaires	30 (71.4)	39 (75.0)
	Completed	29 (69.0)	38 (73.1)
	Compliance (% in those expected to complete questionnaires)[d]	29 (96.7)	38 (97.4)
	Not completed	1 (2.4)	1 (1.9)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	Other	1 (2.4)	0 (0.0)
	Missing by Design[e]	12 (28.6)	13 (25.0)
	Discontinued due to adverse event	3 (7.1)	2 (3.8)
	Discontinued due to clinical progression	1 (2.4)	4 (7.7)
	Discontinued due to progressive disease	2 (4.8)	1 (1.9)
	Subject died	0 (0.0)	3 (5.8)
	Visit not scheduled	6 (14.3)	3 (5.8)
WEEK 18	Expected to Complete Questionnaires	29 (69.0)	36 (69.2)
	Completed	27 (64.3)	34 (65.4)
	Compliance (% in those expected to complete questionnaires)[d]	27 (93.1)	34 (94.4)
	Not completed	2 (4.8)	2 (3.8)
	Subject did not complete due to disease under study	0 (0.0)	1 (1.9)
	Other	2 (4.8)	0 (0.0)
	With visit, no record	0 (0.0)	1 (1.9)
	Missing by Design[e]	13 (31.0)	16 (30.8)
	Discontinued due to adverse event	3 (7.1)	3 (5.8)
	Discontinued due to clinical progression	2 (4.8)	5 (9.6)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	4 (9.5)	4 (7.7)
	Visit not scheduled	4 (9.5)	2 (3.8)
WEEK 21	Expected to Complete Questionnaires	28 (66.7)	29 (55.8)
	Completed	24 (57.1)	28 (53.8)
	Compliance (% in those expected to complete questionnaires)[d]	24 (85.7)	28 (96.6)
	Not completed	4 (9.5)	1 (1.9)
	Not completed due to site staff error	0 (0.0)	1 (1.9)
	Other	1 (2.4)	0 (0.0)
	With visit, no record	3 (7.1)	0 (0.0)
	Missing by Design[e]	14 (33.3)	23 (44.2)
	Discontinued due to adverse event	3 (7.1)	3 (5.8)
	Discontinued due to clinical progression	2 (4.8)	6 (11.5)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	6 (14.3)	6 (11.5)
	Visit not scheduled	3 (7.1)	6 (11.5)
WEEK 24	Expected to Complete Questionnaires	26 (61.9)	34 (65.4)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 42 n (%)	N[c] = 52 n (%)
	Completed	25 (59.5)	28 (53.8)
	Compliance (% in those expected to complete questionnaires)[d]	25 (96.2)	28 (82.4)
	Not completed	1 (2.4)	6 (11.5)
	Not completed due to site staff error	0 (0.0)	3 (5.8)
	Subject was physically unable to complete	1 (2.4)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (1.9)
	Other	0 (0.0)	2 (3.8)
	Missing by Design[e]	16 (38.1)	18 (34.6)
	Discontinued due to adverse event	4 (9.5)	3 (5.8)
	Discontinued due to clinical progression	3 (7.1)	7 (13.5)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	8 (19.0)	6 (11.5)
	Visit not scheduled	1 (2.4)	0 (0.0)
WEEK 33	Expected to Complete Questionnaires	23 (54.8)	24 (46.2)
	Completed	19 (45.2)	22 (42.3)
	Compliance (% in those expected to complete questionnaires)[d]	19 (82.6)	22 (91.7)
	Not completed	4 (9.5)	2 (3.8)
	Not completed due to site staff error	1 (2.4)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	Other	2 (4.8)	0 (0.0)
	With visit, no record	1 (2.4)	1 (1.9)
	Missing by Design[e]	19 (45.2)	28 (53.8)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	3 (7.1)	7 (13.5)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	11 (26.2)	13 (25.0)
	Discontinued due to withdrawal by subject	0 (0.0)	2 (3.8)
	Subject died	0 (0.0)	1 (1.9)
WEEK 42	Expected to Complete Questionnaires	15 (35.7)	14 (26.9)
	Completed	13 (31.0)	11 (21.2)
	Compliance (% in those expected to complete questionnaires)[d]	13 (86.7)	11 (78.6)
	Not completed	2 (4.8)	3 (5.8)
	Not completed due to site staff error	0 (0.0)	1 (1.9)
	Subject was physically unable to complete	0 (0.0)	1 (1.9)
	With visit, no record	2 (4.8)	1 (1.9)
	Missing by Design[e]	27 (64.3)	38 (73.1)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	5 (11.9)	7 (13.5)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	16 (38.1)	23 (44.2)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Subject died	0 (0.0)	1 (1.9)
WEEK 51	Expected to Complete Questionnaires	12 (28.6)	9 (17.3)
	Completed	12 (28.6)	7 (13.5)
	Compliance (% in those expected to complete questionnaires)[d]	12 (100.0)	7 (77.8)
	Not completed	0 (0.0)	2 (3.8)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	With visit, no record	0 (0.0)	1 (1.9)
	Missing by Design[e]	30 (71.4)	43 (82.7)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	9 (17.3)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 42 n (%)	N[c] = 52 n (%)
	Discontinued due to progressive disease	18 (42.9)	27 (51.9)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
WEEK 60	Expected to Complete Questionnaires	12 (28.6)	7 (13.5)
	Completed	6 (14.3)	3 (5.8)
	Compliance (% in those expected to complete questionnaires)[d]	6 (50.0)	3 (42.9)
	Not completed	6 (14.3)	4 (7.7)
	With visit, no record	6 (14.3)	4 (7.7)
	Missing by Design[e]	30 (71.4)	45 (86.5)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	9 (17.3)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	18 (42.9)	29 (55.8)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
WEEK 69	Expected to Complete Questionnaires	11 (26.2)	4 (7.7)
	Completed	3 (7.1)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	3 (27.3)	0 (0.0)
	Not completed	8 (19.0)	4 (7.7)
	Subject refused for other reasons	0 (0.0)	1 (1.9)
	With visit, no record	8 (19.0)	3 (5.8)
	Missing by Design[e]	31 (73.8)	48 (92.3)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	10 (19.2)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	19 (45.2)	31 (59.6)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
WEEK 78	Expected to Complete Questionnaires	7 (16.7)	3 (5.8)
	Completed	0 (0.0)	1 (1.9)
	Compliance (% in those expected to complete questionnaires)[d]	0 (0.0)	1 (33.3)
	Not completed	7 (16.7)	2 (3.8)
	With visit, no record	7 (16.7)	2 (3.8)
	Missing by Design[e]	35 (83.3)	49 (94.2)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	10 (19.2)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	22 (52.4)	32 (61.5)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Visit not reached	1 (2.4)	0 (0.0)
WEEK 87	Expected to Complete Questionnaires	7 (16.7)	2 (3.8)
	Not completed	7 (16.7)	2 (3.8)
	Not completed due to site staff error	0 (0.0)	1 (1.9)
	Subject in hospital or hospice	0 (0.0)	1 (1.9)
	With visit, no record	7 (16.7)	0 (0.0)
	Missing by Design[e]	35 (83.3)	50 (96.2)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	10 (19.2)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	22 (52.4)	33 (63.5)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Visit not reached	1 (2.4)	0 (0.0)
WEEK 96	Expected to Complete Questionnaires	7 (16.7)	0 (0.0)
	Not completed	7 (16.7)	0 (0.0)

Study: KEYNOTE 590[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 42 n (%)	N[c] = 52 n (%)
	With visit, no record	7 (16.7)	0 (0.0)
	Missing by Design[e]	35 (83.3)	52 (100.0)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	10 (19.2)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	22 (52.4)	35 (67.3)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Visit not reached	1 (2.4)	0 (0.0)
WEEK 105	Expected to Complete Questionnaires	5 (11.9)	0 (0.0)
	Completed	2 (4.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	2 (40.0)	0 (0.0)
	Not completed	3 (7.1)	0 (0.0)
	With visit, no record	3 (7.1)	0 (0.0)
	Missing by Design[e]	37 (88.1)	52 (100.0)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	10 (19.2)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	22 (52.4)	35 (67.3)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Visit not reached	3 (7.1)	0 (0.0)
WEEK 114	Expected to Complete Questionnaires	2 (4.8)	0 (0.0)
	Completed	2 (4.8)	0 (0.0)
	Compliance (% in those expected to complete questionnaires)[d]	2 (100.0)	0 (0.0)
	Missing by Design[e]	40 (95.2)	52 (100.0)
	Discontinued due to adverse event	5 (11.9)	3 (5.8)
	Discontinued due to clinical progression	6 (14.3)	10 (19.2)
	Discontinued due to physician decision	0 (0.0)	2 (3.8)
	Discontinued due to progressive disease	23 (54.8)	35 (67.3)
	Discontinued due to withdrawal by subject	1 (2.4)	2 (3.8)
	Completed study treatment	1 (2.4)	0 (0.0)
	Visit not reached	4 (9.5)	0 (0.0)

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10

d: Compliance is the proportion of participants who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design

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

CPS: Combined Proportion Score; EQ-5D: European Quality of Life 5 Dimensions; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G4: Rücklaufquoten des EORTC QLQ-C30, des EORTC QLQ-STO22 und EQ-5D VAS – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.2.2 bzw. Abschnitt 4.3.1.3.1.3.1 die Rücklaufquoten des EORTC QLQ-C30, die Rücklaufquoten des EORTC QLQ-STO22 und die Rücklaufquoten des EQ-5D VAS dargestellt.

Alle Ergebnisse beziehen sich auf den finalen Datenschnitt (26. März 2019).

Anhang 4-G4.1: Rücklaufquoten des EORTC QLQ-C30

Tabelle 4G-10: Gründe für das Fehlen von Werten im EORTC QLQ-C30 – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 30 n (%)	N[c] = 20 n (%)
Baseline	Expected to Complete Questionnaires	30 (100.0)	20 (100.0)
	Completed	28 (93.3)	20 (100.0)
	Compliance (% in those expected to complete questionnaires)[d]	28 (93.3)	20 (100.0)
	Not completed	2 (6.7)	0 (0.0)
	Not completed due to site staff error	2 (6.7)	0 (0.0)
	Missing by Design[e]	0 (0.0)	0 (0.0)
Week 3	Expected to Complete Questionnaires	26 (86.7)	20 (100.0)
	Completed	23 (76.7)	19 (95.0)
	Compliance (% in those expected to complete questionnaires)[d]	23 (88.5)	19 (95.0)
	Not completed	3 (10.0)	1 (5.0)
	Not completed due to site staff error	2 (6.7)	0 (0.0)
	Subject refused for other reasons	1 (3.3)	1 (5.0)
	Missing by Design[e]	4 (13.3)	0 (0.0)
	Subject died	1 (3.3)	0 (0.0)
	No visit scheduled	3 (10.0)	0 (0.0)
Week 6	Expected to Complete Questionnaires	26 (86.7)	15 (75.0)
	Completed	24 (80.0)	15 (75.0)
	Compliance (% in those expected to complete questionnaires)[d]	24 (92.3)	15 (100.0)
	Not completed	2 (6.7)	0 (0.0)
	Not completed due to site staff error	1 (3.3)	0 (0.0)
	With visit, no record	1 (3.3)	0 (0.0)
	Missing by Design[e]	4 (13.3)	5 (25.0)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (5.0)
	No visit scheduled	4 (13.3)	4 (20.0)
Week 9	Expected to Complete Questionnaires	27 (90.0)	16 (80.0)
	Completed	24 (80.0)	16 (80.0)
	Compliance (% in those expected to complete questionnaires)[d]	24 (88.9)	16 (100.0)
	Not completed	3 (10.0)	0 (0.0)
	Not completed due to site staff error	1 (3.3)	0 (0.0)
	Other	1 (3.3)	0 (0.0)
	With visit, no record	1 (3.3)	0 (0.0)
	Missing by Design[e]	3 (10.0)	4 (20.0)
	Discontinued due to adverse event	1 (3.3)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (5.0)
	No visit scheduled	2 (6.7)	3 (15.0)
Week 12	Expected to Complete Questionnaires	28 (93.3)	18 (90.0)

Study: KEYNOTE 062[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 30 n (%)	N[c] = 20 n (%)
	Completed	27 (90.0)	17 (85.0)
	Compliance (% in those expected to complete questionnaires)[d]	27 (96.4)	17 (94.4)
	Not completed	1 (3.3)	1 (5.0)
	Other	1 (3.3)	0 (0.0)
	With visit, no record	0 (0.0)	1 (5.0)
	Missing by Design[e]	2 (6.7)	2 (10.0)
	Discontinued due to adverse event	2 (6.7)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (5.0)
	Subject died	0 (0.0)	1 (5.0)
Week 18	Expected to Complete Questionnaires	25 (83.3)	14 (70.0)
	Completed	19 (63.3)	10 (50.0)
	Compliance (% in those expected to complete questionnaires)[d]	19 (76.0)	10 (71.4)
	Not completed	6 (20.0)	4 (20.0)
	Subject did not complete due to disease under study	0 (0.0)	1 (5.0)
	Not completed due to site staff error	1 (3.3)	0 (0.0)
	Other	1 (3.3)	1 (5.0)
	With visit, no record	4 (13.3)	2 (10.0)
	Missing by Design[e]	5 (16.7)	6 (30.0)
	Discontinued due to adverse event	2 (6.7)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	1 (5.0)
	Discontinued due to progressive disease	2 (6.7)	1 (5.0)
	Discontinued due to withdrawal by subject	1 (3.3)	1 (5.0)
	No visit scheduled	0 (0.0)	3 (15.0)
Week 24	Expected to Complete Questionnaires	24 (80.0)	12 (60.0)
	Completed	17 (56.7)	10 (50.0)
	Compliance (% in those expected to complete questionnaires)[d]	17 (70.8)	10 (83.3)
	Not completed	7 (23.3)	2 (10.0)
	Subject did not complete due to disease under study	1 (3.3)	0 (0.0)
	Not completed due to site staff error	4 (13.3)	1 (5.0)
	Subject refused for other reasons	1 (3.3)	0 (0.0)
	Other	1 (3.3)	0 (0.0)
	With visit, no record	0 (0.0)	1 (5.0)
	Missing by Design[e]	6 (20.0)	8 (40.0)
	Discontinued due to adverse event	2 (6.7)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	1 (5.0)
	Discontinued due to progressive disease	3 (10.0)	6 (30.0)
	Discontinued due to withdrawal by subject	1 (3.3)	1 (5.0)
Week 30	Expected to Complete Questionnaires	18 (60.0)	10 (50.0)
	Completed	14 (46.7)	8 (40.0)
	Compliance (% in those expected to complete questionnaires)[d]	14 (77.8)	8 (80.0)
	Not completed	4 (13.3)	2 (10.0)
	Subject refused for other reasons	1 (3.3)	0 (0.0)
	Other	0 (0.0)	2 (10.0)
	With visit, no record	3 (10.0)	0 (0.0)
	Missing by Design[e]	12 (40.0)	10 (50.0)
	Discontinued due to adverse event	2 (6.7)	1 (5.0)
	Discontinued due to clinical progression	1 (3.3)	1 (5.0)
	Discontinued due to progressive disease	7 (23.3)	6 (30.0)
	Discontinued due to withdrawal by subject	2 (6.7)	1 (5.0)
	No visit scheduled	0 (0.0)	1 (5.0)
Week 36	Expected to Complete Questionnaires	15 (50.0)	9 (45.0)
	Completed	15 (50.0)	6 (30.0)

Study: KEYNOTE 062[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 30 n (%)	N[c] = 20 n (%)
	Compliance (% in those expected to complete questionnaires)[d]	15 (100.0)	6 (66.7)
	Not completed	0 (0.0)	3 (15.0)
	Subject refused for other reasons	0 (0.0)	1 (5.0)
	With visit, no record	0 (0.0)	2 (10.0)
	Missing by Design[e]	15 (50.0)	11 (55.0)
	Discontinued due to adverse event	2 (6.7)	1 (5.0)
	Discontinued due to clinical progression	3 (10.0)	1 (5.0)
	Discontinued due to progressive disease	7 (23.3)	8 (40.0)
	Discontinued due to withdrawal by subject	2 (6.7)	1 (5.0)
	No visit scheduled	1 (3.3)	0 (0.0)
Week 42	Expected to Complete Questionnaires	10 (33.3)	4 (20.0)
	Completed	8 (26.7)	2 (10.0)
	Compliance (% in those expected to complete questionnaires)[d]	8 (80.0)	2 (50.0)
	Not completed	2 (6.7)	2 (10.0)
	Subject did not complete due to disease under study	0 (0.0)	1 (5.0)
	Not completed due to site staff error	1 (3.3)	0 (0.0)
	With visit, no record	1 (3.3)	1 (5.0)
	Missing by Design[e]	20 (66.7)	16 (80.0)
	Discontinued due to adverse event	3 (10.0)	2 (10.0)
	Discontinued due to clinical progression	3 (10.0)	2 (10.0)
	Discontinued due to progressive disease	12 (40.0)	11 (55.0)
	Discontinued due to withdrawal by subject	2 (6.7)	1 (5.0)
Week 48	Expected to Complete Questionnaires	8 (26.7)	4 (20.0)
	Completed	7 (23.3)	2 (10.0)
	Compliance (% in those expected to complete questionnaires)[d]	7 (87.5)	2 (50.0)
	Not completed	1 (3.3)	2 (10.0)
	Other	1 (3.3)	1 (5.0)
	With visit, no record	0 (0.0)	1 (5.0)
	Missing by Design[e]	22 (73.3)	16 (80.0)
	Discontinued due to adverse event	3 (10.0)	2 (10.0)
	Discontinued due to clinical progression	3 (10.0)	2 (10.0)
	Discontinued due to progressive disease	13 (43.3)	11 (55.0)
	Discontinued due to withdrawal by subject	2 (6.7)	1 (5.0)
	No visit scheduled	1 (3.3)	0 (0.0)

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10

d: Compliance is the proportion of participants who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design

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

CPS: Combined Proportion 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

Anhang 4-G4.2: Rücklaufquoten des EORTC QLQ-STO22

Tabelle 4G-11: Gründe für das Fehlen von Werten im EORTC QLQ-STO22 – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-STO22	N[c] = 30 n (%)	N[c] = 20 n (%)
Baseline	Expected to Complete Questionnaires	30 (100.0)	20 (100.0)
	Completed	27 (90.0)	20 (100.0)
	Compliance (% in those expected to complete questionnaires)[d]	27 (90.0)	20 (100.0)
	Not completed	3 (10.0)	0 (0.0)
	Not completed due to site staff error	2 (6.7)	0 (0.0)
	Other	1 (3.3)	0 (0.0)
	Missing by Design[e]	0 (0.0)	0 (0.0)
Week 3	Expected to Complete Questionnaires	26 (86.7)	20 (100.0)
	Completed	23 (76.7)	19 (95.0)
	Compliance (% in those expected to complete questionnaires)[d]	23 (88.5)	19 (95.0)
	Not completed	3 (10.0)	1 (5.0)
	Not completed due to site staff error	2 (6.7)	0 (0.0)
	Subject refused for other reasons	1 (3.3)	1 (5.0)
	Missing by Design[e]	4 (13.3)	0 (0.0)
	Subject died	1 (3.3)	0 (0.0)
	No visit scheduled	3 (10.0)	0 (0.0)
Week 6	Expected to Complete Questionnaires	26 (86.7)	15 (75.0)
	Completed	24 (80.0)	15 (75.0)
	Compliance (% in those expected to complete questionnaires)[d]	24 (92.3)	15 (100.0)
	Not completed	2 (6.7)	0 (0.0)
	Not completed due to site staff error	1 (3.3)	0 (0.0)
	With visit, no record	1 (3.3)	0 (0.0)
	Missing by Design[e]	4 (13.3)	5 (25.0)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (5.0)
	No visit scheduled	4 (13.3)	4 (20.0)
Week 9	Expected to Complete Questionnaires	27 (90.0)	16 (80.0)
	Completed	24 (80.0)	16 (80.0)
	Compliance (% in those expected to complete questionnaires)[d]	24 (88.9)	16 (100.0)
	Not completed	3 (10.0)	0 (0.0)
	Not completed due to site staff error	1 (3.3)	0 (0.0)
	Other	1 (3.3)	0 (0.0)
	With visit, no record	1 (3.3)	0 (0.0)
	Missing by Design[e]	3 (10.0)	4 (20.0)
	Discontinued due to adverse event	1 (3.3)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (5.0)
	No visit scheduled	2 (6.7)	3 (15.0)
Week 12	Expected to Complete Questionnaires	28 (93.3)	18 (90.0)
	Completed	27 (90.0)	17 (85.0)
	Compliance (% in those expected to complete questionnaires)[d]	27 (96.4)	17 (94.4)
	Not completed	1 (3.3)	1 (5.0)
	Other	1 (3.3)	0 (0.0)
	With visit, no record	0 (0.0)	1 (5.0)
	Missing by Design[e]	2 (6.7)	2 (10.0)
	Discontinued due to adverse event	2 (6.7)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (5.0)
	Subject died	0 (0.0)	1 (5.0)

Study: KEYNOTE 062[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-STO22	N[c] = 30 n (%)	N[c] = 20 n (%)
Week 18	Expected to Complete Questionnaires	25 (83.3)	14 (70.0)
	Completed	20 (66.7)	10 (50.0)
	Compliance (% in those expected to complete questionnaires)[d]	20 (80.0)	10 (71.4)
	Not completed	5 (16.7)	4 (20.0)
	Subject did not complete due to disease under study	0 (0.0)	1 (5.0)
	Not completed due to site staff error	1 (3.3)	0 (0.0)
	Other	0 (0.0)	1 (5.0)
	With visit, no record	4 (13.3)	2 (10.0)
	Missing by Design[e]	5 (16.7)	6 (30.0)
	Discontinued due to adverse event	2 (6.7)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	1 (5.0)
	Discontinued due to progressive disease	2 (6.7)	1 (5.0)
	Discontinued due to withdrawal by subject	1 (3.3)	1 (5.0)
	No visit scheduled	0 (0.0)	3 (15.0)
Week 24	Expected to Complete Questionnaires	24 (80.0)	12 (60.0)
	Completed	17 (56.7)	10 (50.0)
	Compliance (% in those expected to complete questionnaires)[d]	17 (70.8)	10 (83.3)
	Not completed	7 (23.3)	2 (10.0)
	Subject did not complete due to disease under study	1 (3.3)	0 (0.0)
	Not completed due to site staff error	4 (13.3)	1 (5.0)
	Subject refused for other reasons	1 (3.3)	0 (0.0)
	Other	1 (3.3)	0 (0.0)
	With visit, no record	0 (0.0)	1 (5.0)
	Missing by Design[e]	6 (20.0)	8 (40.0)
	Discontinued due to adverse event	2 (6.7)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	1 (5.0)
	Discontinued due to progressive disease	3 (10.0)	6 (30.0)
	Discontinued due to withdrawal by subject	1 (3.3)	1 (5.0)
Week 30	Expected to Complete Questionnaires	18 (60.0)	10 (50.0)
	Completed	14 (46.7)	8 (40.0)
	Compliance (% in those expected to complete questionnaires)[d]	14 (77.8)	8 (80.0)
	Not completed	4 (13.3)	2 (10.0)
	Subject refused for other reasons	1 (3.3)	0 (0.0)
	Other	0 (0.0)	2 (10.0)
	With visit, no record	3 (10.0)	0 (0.0)
	Missing by Design[e]	12 (40.0)	10 (50.0)
	Discontinued due to adverse event	2 (6.7)	1 (5.0)
	Discontinued due to clinical progression	1 (3.3)	1 (5.0)
	Discontinued due to progressive disease	7 (23.3)	6 (30.0)
	Discontinued due to withdrawal by subject	2 (6.7)	1 (5.0)
	No visit scheduled	0 (0.0)	1 (5.0)
Week 36	Expected to Complete Questionnaires	15 (50.0)	9 (45.0)
	Completed	14 (46.7)	6 (30.0)
	Compliance (% in those expected to complete questionnaires)[d]	14 (93.3)	6 (66.7)
	Not completed	1 (3.3)	3 (15.0)
	Subject refused for other reasons	0 (0.0)	1 (5.0)
	Other	1 (3.3)	0 (0.0)
	With visit, no record	0 (0.0)	2 (10.0)
	Missing by Design[e]	15 (50.0)	11 (55.0)
	Discontinued due to adverse event	2 (6.7)	1 (5.0)
	Discontinued due to clinical progression	3 (10.0)	1 (5.0)
	Discontinued due to progressive disease	7 (23.3)	8 (40.0)

Study: KEYNOTE 062[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EORTC QLQ-STO22	N[c] = 30 n (%)	N[c] = 20 n (%)
	Discontinued due to withdrawal by subject	2 (6.7)	1 (5.0)
	No visit scheduled	1 (3.3)	0 (0.0)
Week 42	Expected to Complete Questionnaires	10 (33.3)	4 (20.0)
	Completed	8 (26.7)	2 (10.0)
	Compliance (% in those expected to complete questionnaires)[d]	8 (80.0)	2 (50.0)
	Not completed	2 (6.7)	2 (10.0)
	Subject did not complete due to disease under study	0 (0.0)	1 (5.0)
	Not completed due to site staff error	1 (3.3)	0 (0.0)
	With visit, no record	1 (3.3)	1 (5.0)
	Missing by Design[e]	20 (66.7)	16 (80.0)
	Discontinued due to adverse event	3 (10.0)	2 (10.0)
	Discontinued due to clinical progression	3 (10.0)	2 (10.0)
	Discontinued due to progressive disease	12 (40.0)	11 (55.0)
	Discontinued due to withdrawal by subject	2 (6.7)	1 (5.0)
Week 48	Expected to Complete Questionnaires	8 (26.7)	4 (20.0)
	Completed	6 (20.0)	2 (10.0)
	Compliance (% in those expected to complete questionnaires)[d]	6 (75.0)	2 (50.0)
	Not completed	2 (6.7)	2 (10.0)
	Other	2 (6.7)	1 (5.0)
	With visit, no record	0 (0.0)	1 (5.0)
	Missing by Design[e]	22 (73.3)	16 (80.0)
	Discontinued due to adverse event	3 (10.0)	2 (10.0)
	Discontinued due to clinical progression	3 (10.0)	2 (10.0)
	Discontinued due to progressive disease	13 (43.3)	11 (55.0)
	Discontinued due to withdrawal by subject	2 (6.7)	1 (5.0)
	No visit scheduled	1 (3.3)	0 (0.0)

a: Database Cutoff Date: 26MAR2019
b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine
c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10
d: Compliance is the proportion of participants who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design
e: Missing by design includes: death, discontinuation, translations not available, and no visit scheduled
CPS: Combined Proportion Score; EORTC QLQ-STO22: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Gastric Cancer 22 items; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G4.3: Rücklaufquoten des EQ-5D VAS

Tabelle 4G-12: Gründe für das Fehlen von Werten in der EQ-5D VAS – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 30 n (%)	N[c] = 20 n (%)
Baseline	Expected to Complete Questionnaires	30 (100.0)	20 (100.0)
	Completed	29 (96.7)	20 (100.0)
	Compliance (% in those expected to complete questionnaires)[d]	29 (96.7)	20 (100.0)
	Not completed	1 (3.3)	0 (0.0)
	Not completed due to site staff error	1 (3.3)	0 (0.0)
	Missing by Design[e]	0 (0.0)	0 (0.0)

Study: KEYNOTE 062[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 30 n (%)	N[c] = 20 n (%)
Week 3	Expected to Complete Questionnaires	26 (86.7)	20 (100.0)
	Completed	24 (80.0)	19 (95.0)
	Compliance (% in those expected to complete questionnaires)[d]	24 (92.3)	19 (95.0)
	Not completed	2 (6.7)	1 (5.0)
	Not completed due to site staff error	1 (3.3)	0 (0.0)
	Subject refused for other reasons	1 (3.3)	1 (5.0)
	Missing by Design[e]	4 (13.3)	0 (0.0)
	Subject died	1 (3.3)	0 (0.0)
	No visit scheduled	3 (10.0)	0 (0.0)
Week 6	Expected to Complete Questionnaires	26 (86.7)	15 (75.0)
	Completed	24 (80.0)	15 (75.0)
	Compliance (% in those expected to complete questionnaires)[d]	24 (92.3)	15 (100.0)
	Not completed	2 (6.7)	0 (0.0)
	Not completed due to site staff error	1 (3.3)	0 (0.0)
	With visit, no record	1 (3.3)	0 (0.0)
	Missing by Design[e]	4 (13.3)	5 (25.0)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (5.0)
	No visit scheduled	4 (13.3)	4 (20.0)
Week 9	Expected to Complete Questionnaires	27 (90.0)	16 (80.0)
	Completed	24 (80.0)	16 (80.0)
	Compliance (% in those expected to complete questionnaires)[d]	24 (88.9)	16 (100.0)
	Not completed	3 (10.0)	0 (0.0)
	Not completed due to site staff error	1 (3.3)	0 (0.0)
	Other	1 (3.3)	0 (0.0)
	With visit, no record	1 (3.3)	0 (0.0)
	Missing by Design[e]	3 (10.0)	4 (20.0)
	Discontinued due to adverse event	1 (3.3)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (5.0)
	No visit scheduled	2 (6.7)	3 (15.0)
Week 12	Expected to Complete Questionnaires	28 (93.3)	18 (90.0)
	Completed	27 (90.0)	17 (85.0)
	Compliance (% in those expected to complete questionnaires)[d]	27 (96.4)	17 (94.4)
	Not completed	1 (3.3)	1 (5.0)
	Other	1 (3.3)	0 (0.0)
	With visit, no record	0 (0.0)	1 (5.0)
	Missing by Design[e]	2 (6.7)	2 (10.0)
	Discontinued due to adverse event	2 (6.7)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (5.0)
	Subject died	0 (0.0)	1 (5.0)
Week 18	Expected to Complete Questionnaires	25 (83.3)	14 (70.0)
	Completed	20 (66.7)	11 (55.0)
	Compliance (% in those expected to complete questionnaires)[d]	20 (80.0)	11 (78.6)
	Not completed	5 (16.7)	3 (15.0)
	Not completed due to site staff error	1 (3.3)	0 (0.0)
	Other	0 (0.0)	1 (5.0)
	With visit, no record	4 (13.3)	2 (10.0)
	Missing by Design[e]	5 (16.7)	6 (30.0)
	Discontinued due to adverse event	2 (6.7)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	1 (5.0)
	Discontinued due to progressive disease	2 (6.7)	1 (5.0)
	Discontinued due to withdrawal by subject	1 (3.3)	1 (5.0)

Study: KEYNOTE 062[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 30 n (%)	N[c] = 20 n (%)
	No visit scheduled	0 (0.0)	3 (15.0)
Week 24	Expected to Complete Questionnaires	24 (80.0)	12 (60.0)
	Completed	17 (56.7)	10 (50.0)
	Compliance (% in those expected to complete questionnaires)[d]	17 (70.8)	10 (83.3)
	Not completed	7 (23.3)	2 (10.0)
	Subject did not complete due to disease under study	1 (3.3)	0 (0.0)
	Not completed due to site staff error	4 (13.3)	1 (5.0)
	Subject refused for other reasons	1 (3.3)	0 (0.0)
	Other	1 (3.3)	0 (0.0)
	With visit, no record	0 (0.0)	1 (5.0)
	Missing by Design[e]	6 (20.0)	8 (40.0)
	Discontinued due to adverse event	2 (6.7)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	1 (5.0)
	Discontinued due to progressive disease	3 (10.0)	6 (30.0)
	Discontinued due to withdrawal by subject	1 (3.3)	1 (5.0)
Week 30	Expected to Complete Questionnaires	18 (60.0)	10 (50.0)
	Completed	14 (46.7)	8 (40.0)
	Compliance (% in those expected to complete questionnaires)[d]	14 (77.8)	8 (80.0)
	Not completed	4 (13.3)	2 (10.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (5.0)
	Subject refused for other reasons	1 (3.3)	0 (0.0)
	Other	0 (0.0)	1 (5.0)
	With visit, no record	3 (10.0)	0 (0.0)
	Missing by Design[e]	12 (40.0)	10 (50.0)
	Discontinued due to adverse event	2 (6.7)	1 (5.0)
	Discontinued due to clinical progression	1 (3.3)	1 (5.0)
	Discontinued due to progressive disease	7 (23.3)	6 (30.0)
	Discontinued due to withdrawal by subject	2 (6.7)	1 (5.0)
	No visit scheduled	0 (0.0)	1 (5.0)
Week 36	Expected to Complete Questionnaires	15 (50.0)	9 (45.0)
	Completed	15 (50.0)	6 (30.0)
	Compliance (% in those expected to complete questionnaires)[d]	15 (100.0)	6 (66.7)
	Not completed	0 (0.0)	3 (15.0)
	Subject refused for other reasons	0 (0.0)	1 (5.0)
	With visit, no record	0 (0.0)	2 (10.0)
	Missing by Design[e]	15 (50.0)	11 (55.0)
	Discontinued due to adverse event	2 (6.7)	1 (5.0)
	Discontinued due to clinical progression	3 (10.0)	1 (5.0)
	Discontinued due to progressive disease	7 (23.3)	8 (40.0)
	Discontinued due to withdrawal by subject	2 (6.7)	1 (5.0)
	No visit scheduled	1 (3.3)	0 (0.0)
Week 42	Expected to Complete Questionnaires	10 (33.3)	4 (20.0)
	Completed	8 (26.7)	2 (10.0)
	Compliance (% in those expected to complete questionnaires)[d]	8 (80.0)	2 (50.0)
	Not completed	2 (6.7)	2 (10.0)
	Subject did not complete due to disease under study	0 (0.0)	1 (5.0)
	Not completed due to site staff error	1 (3.3)	0 (0.0)
	With visit, no record	1 (3.3)	1 (5.0)
	Missing by Design[e]	20 (66.7)	16 (80.0)
	Discontinued due to adverse event	3 (10.0)	2 (10.0)
	Discontinued due to clinical progression	3 (10.0)	2 (10.0)
	Discontinued due to progressive disease	12 (40.0)	11 (55.0)

Study: KEYNOTE 062[a]		Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]
Visit	EQ-5D	N[c] = 30 n (%)	N[c] = 20 n (%)
	Discontinued due to withdrawal by subject	2 (6.7)	1 (5.0)
Week 48	Expected to Complete Questionnaires	8 (26.7)	4 (20.0)
	Completed	7 (23.3)	2 (10.0)
	Compliance (% in those expected to complete questionnaires)[d]	7 (87.5)	2 (50.0)
	Not completed	1 (3.3)	2 (10.0)
	Other	1 (3.3)	1 (5.0)
	With visit, no record	0 (0.0)	1 (5.0)
	Missing by Design[e]	22 (73.3)	16 (80.0)
	Discontinued due to adverse event	3 (10.0)	2 (10.0)
	Discontinued due to clinical progression	3 (10.0)	2 (10.0)
	Discontinued due to progressive disease	13 (43.3)	11 (55.0)
	Discontinued due to withdrawal by subject	2 (6.7)	1 (5.0)
	No visit scheduled	1 (3.3)	0 (0.0)

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10

d: Compliance is the proportion of participants who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design

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

CPS: Combined Proportion Score; EQ-5D: European Quality of Life 5 Dimensions; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G5: Kaplan-Meier-Kurven der Subgruppen mit signifikantem Interaktionstest (p < 0,05) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

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 finalen Datenschnitt (02. Juli 2020).

Anhang 4-G5.1: Mortalität

Gesamtüberleben

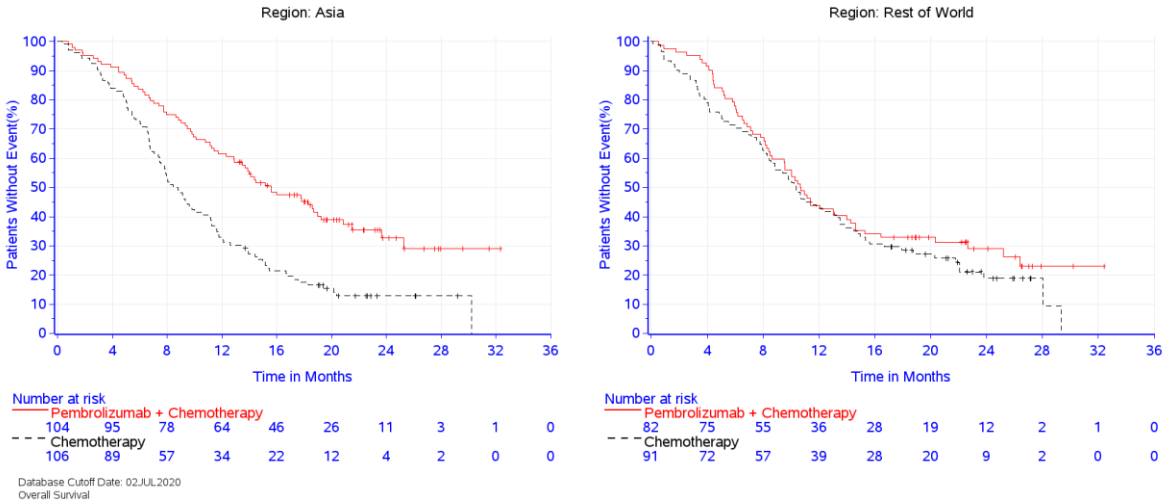

Abbildung 4G-1: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Gesamtüberleben nach Region – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G5.2: Morbidität

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30: Symptomskala Schmerzen

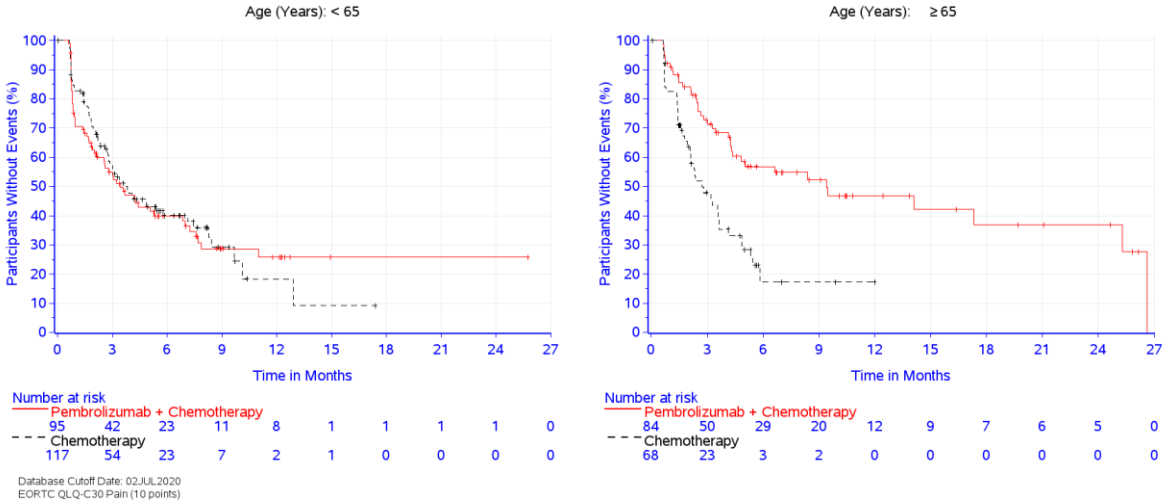

Abbildung 4G-2: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Alter für die Symptomskala Schmerzen des EORTC QLQ-C30 – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-C30: Symptomskala Dyspnoe

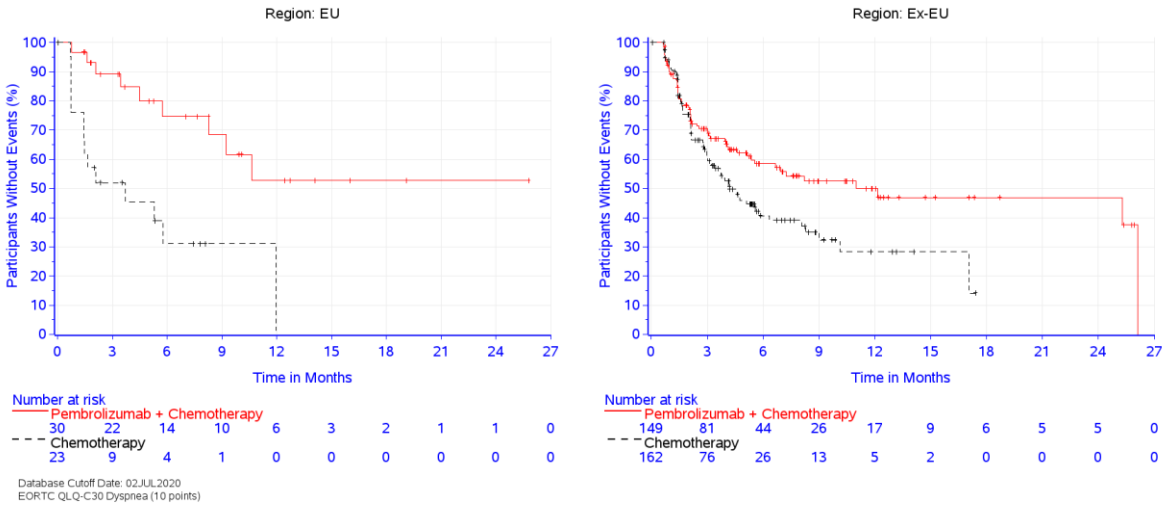

Abbildung 4G-3: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Dyspnoe des EORTC QLQ-C30 – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-OES18: Symptomskala Speichelschlucken

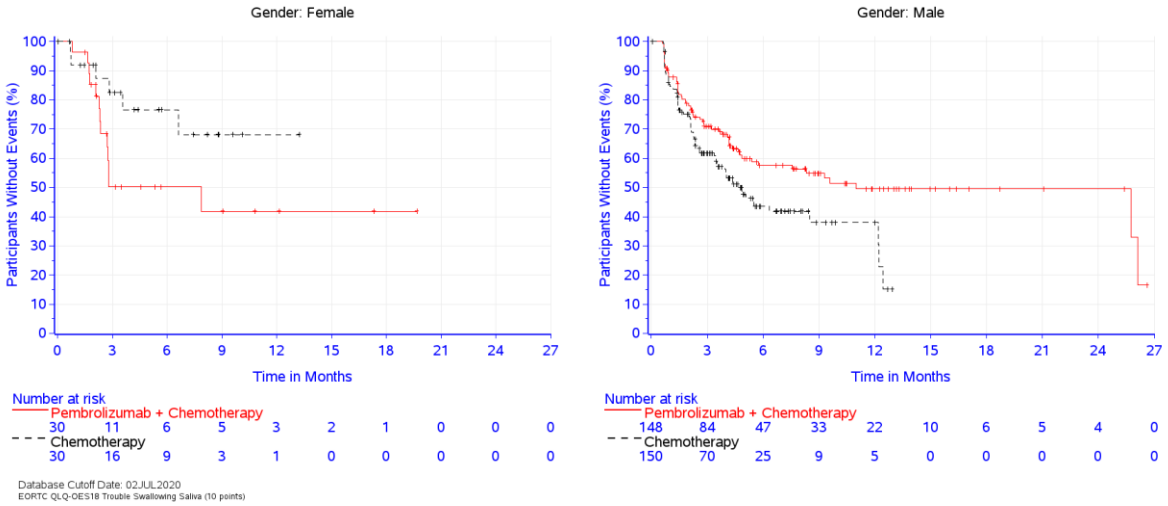

Abbildung 4G-4: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Geschlecht für die Symptomskala Speichelschlucken des EORTC QLQ-OES18 – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-OES18: Symptomskala Verschlucken

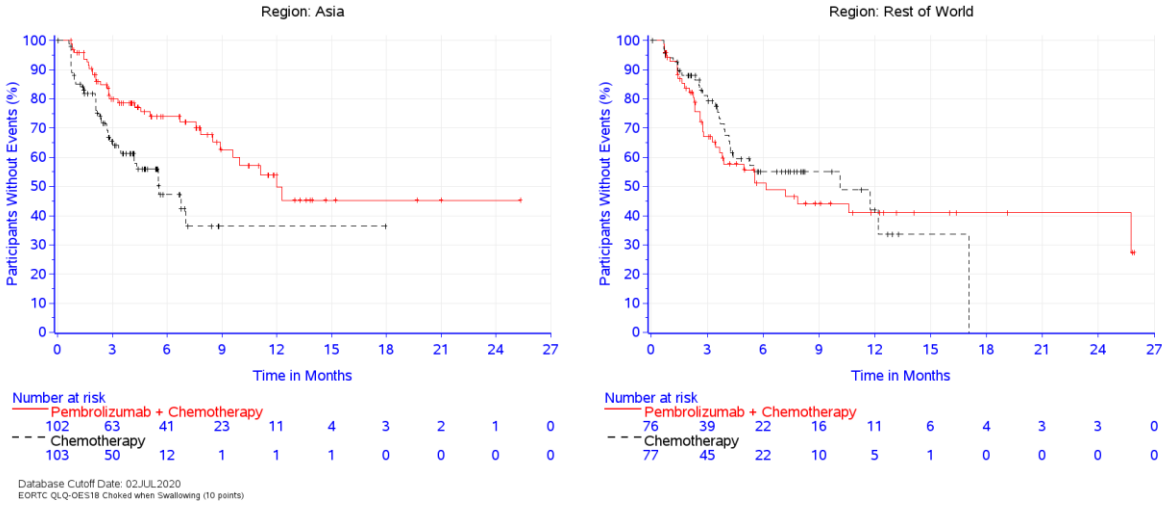

Abbildung 4G-5: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Verschlucken des EORTC QLQ-OES18 – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-OES18: Symptomskala Husten

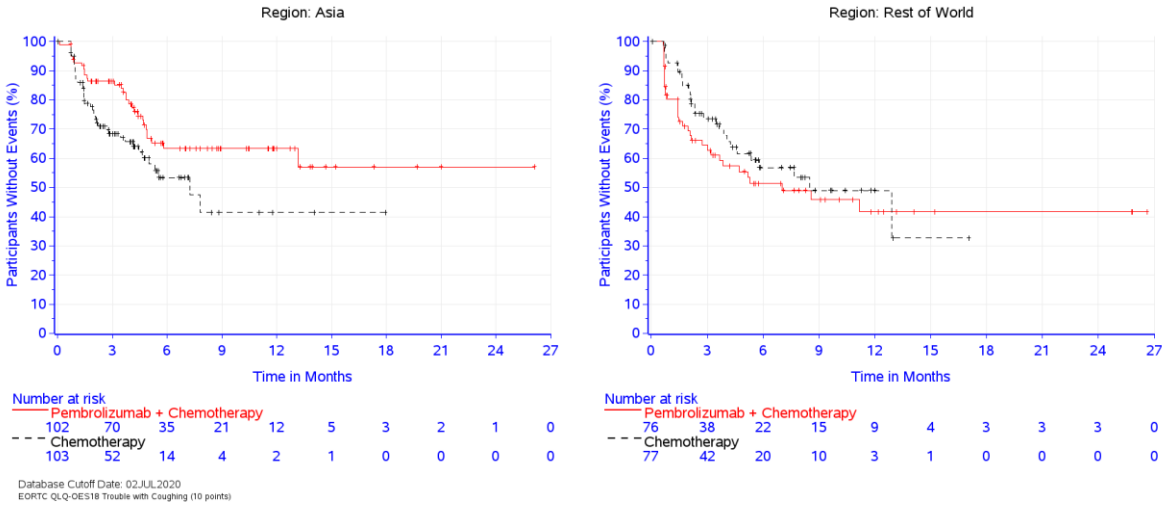

Abbildung 4G-6: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Husten des EORTC QLQ-OES18 – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-OES18: Symptomskala Dysphagie

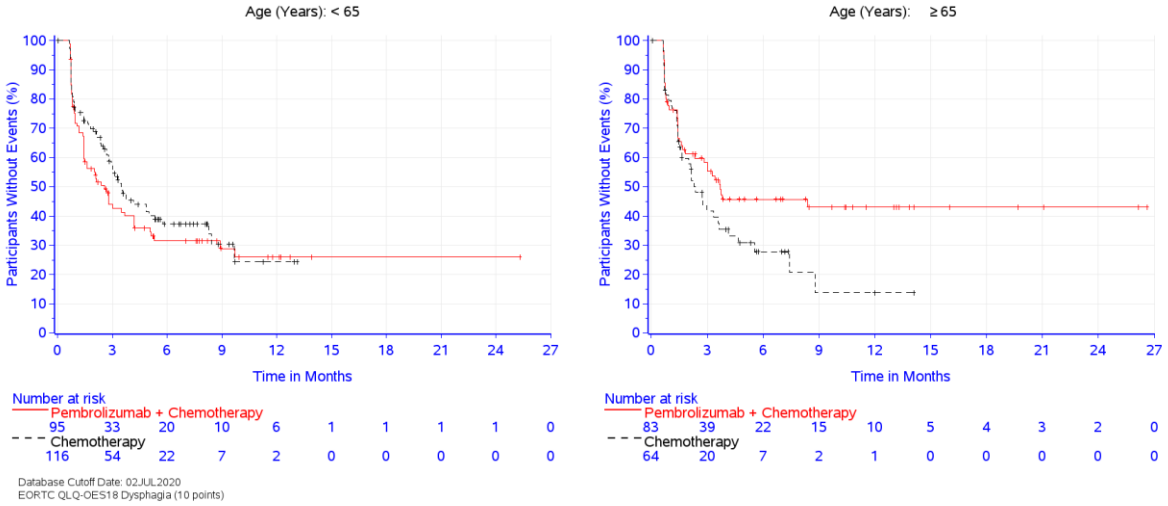

Abbildung 4G-7: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Dysphagie des EORTC QLQ-OES18 – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G5.3: Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

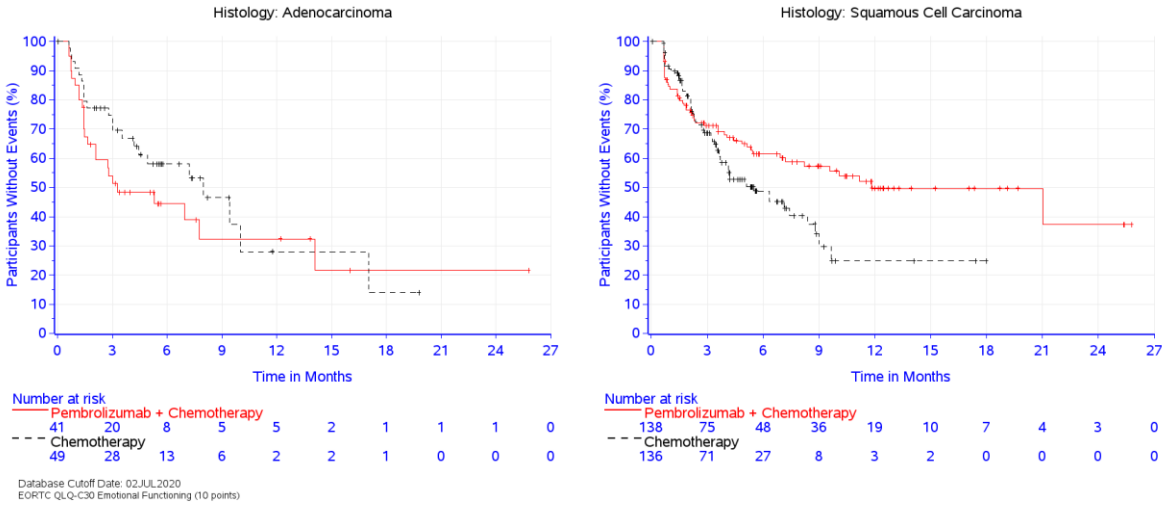

Abbildung 4G-8: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Histologie für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G5.4: Nebenwirkungen

Unerwünschte Ereignisse

Therapieabbruch wegen Unerwünschter Ereignisse

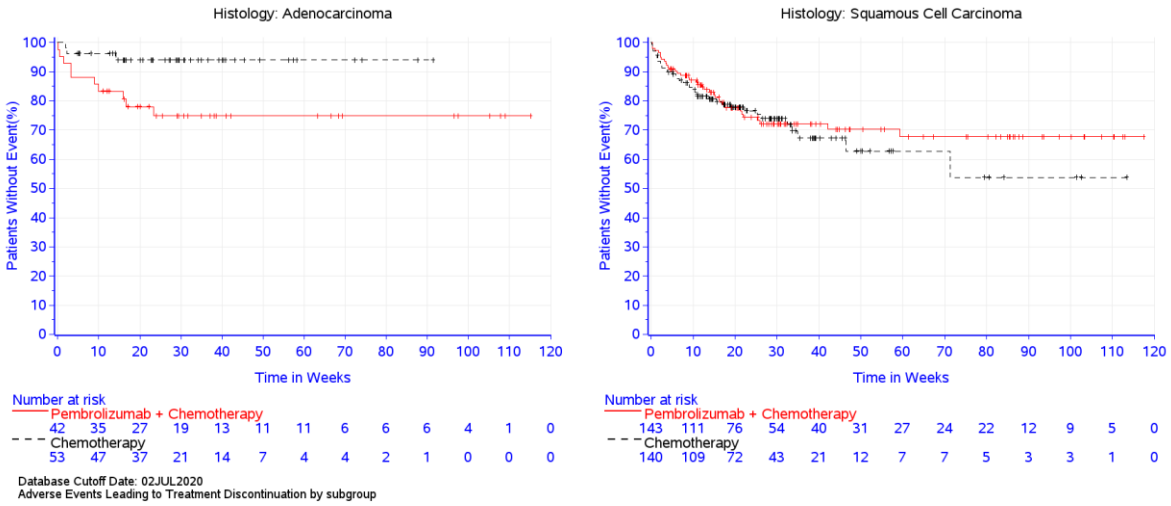

Abbildung 4G-9: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Histologie für den Endpunkt Therapieabbruch wegen Unerwünschter Ereignisse – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Unerwünschte Ereignisse (SOC und PT)

Unerwünschte Ereignisse (SOC und PT)

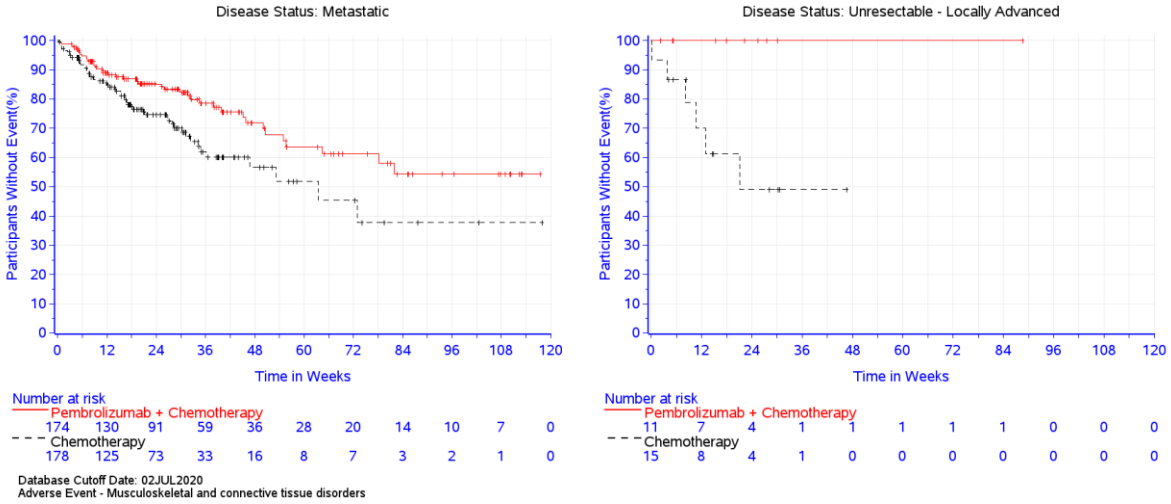

Abbildung 4G-10: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Krankheitsstatus für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC „Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen“ – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

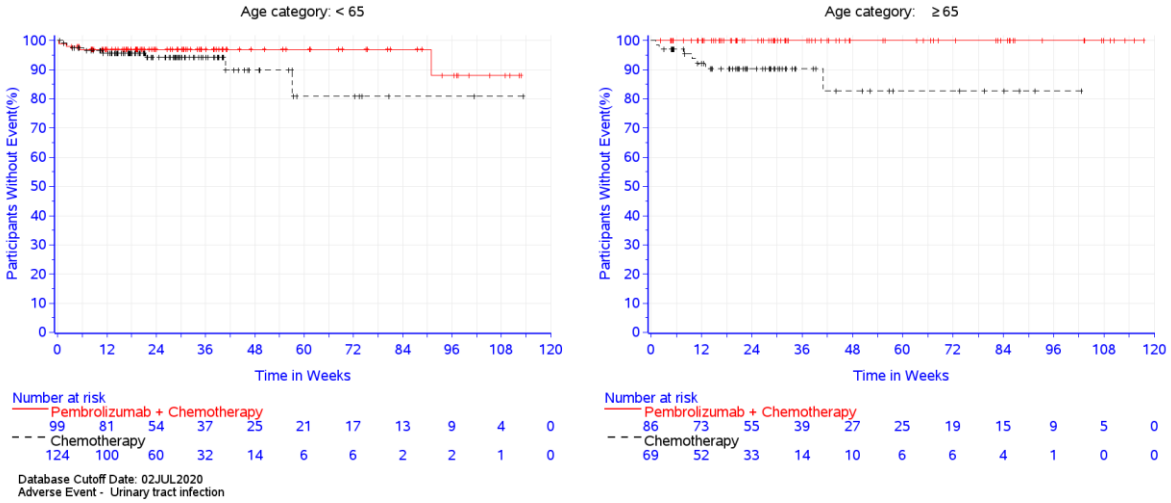

Abbildung 4G-11: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Harnwegsinfektion“ (der SOC „Infektionen und parasitaere Erkrankungen“) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

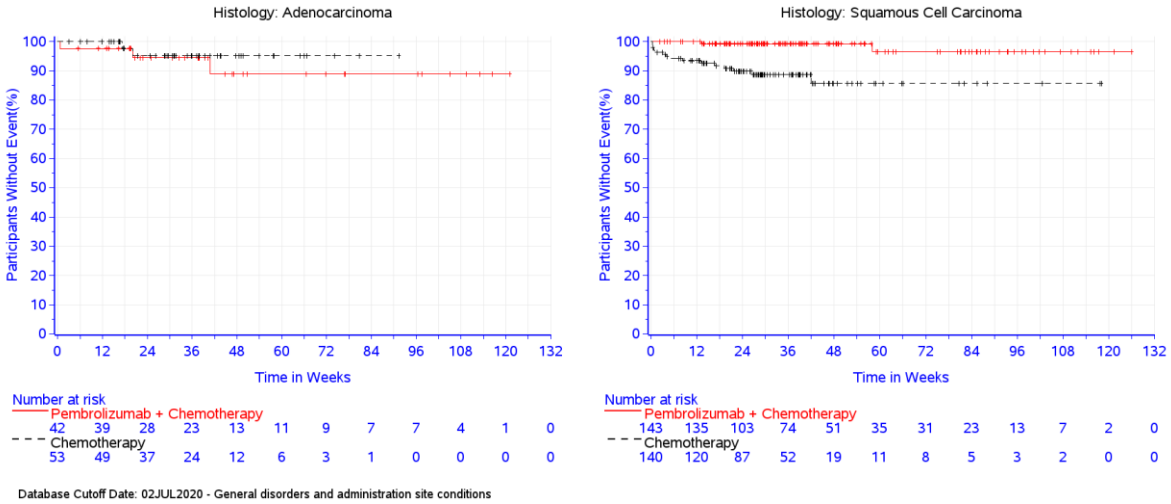

Abbildung 4G-12: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Histologie für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) für die SOC „Allgemeine Erkrankungen und Beschwerden am Verabreichungsort“ – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

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

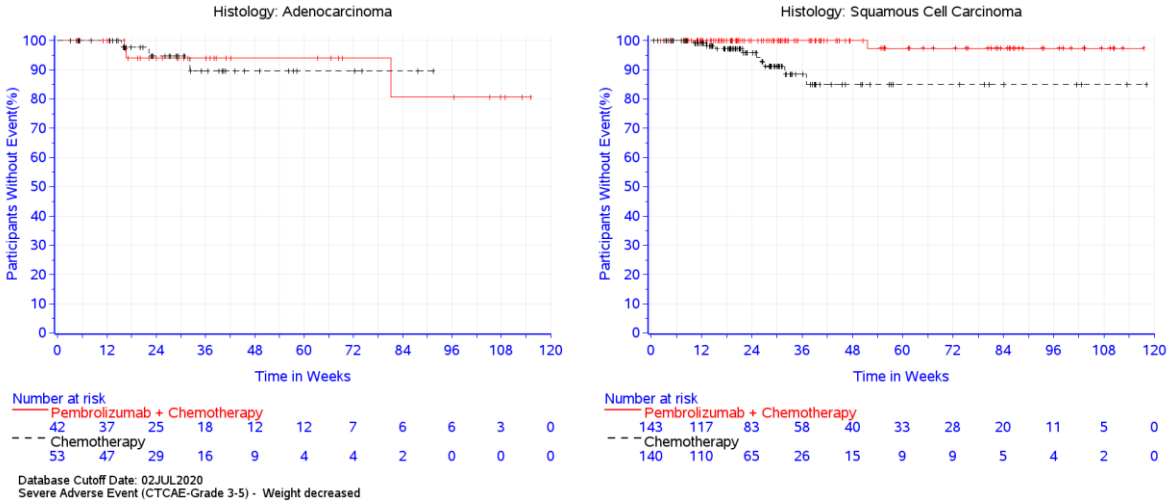

Abbildung 4G-13: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Histologie für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für den PT „Gewicht erniedrigt“ (der SOC „Untersuchungen“) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G6: Kaplan-Meier-Kurven der Subgruppen mit signifikantem Interaktionstest (p < 0,05) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

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 finalen Datenschnitt (02. Juli 2020).

Anhang 4-G6.1: Morbidität

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30: Symptomskala Schmerzen

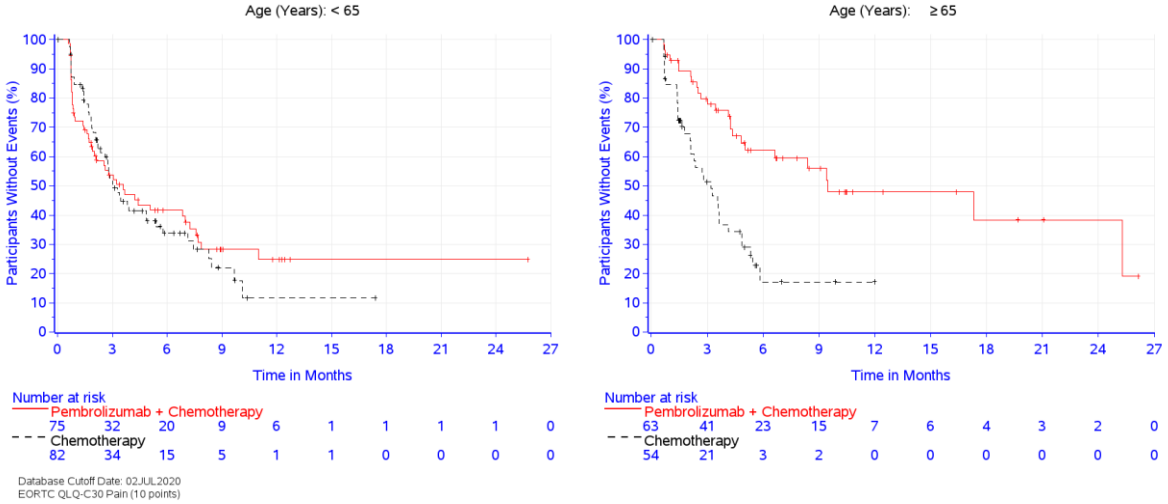

Abbildung 4G-14: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Alter für die Symptomskala Schmerzen des EORTC QLQ-C30– Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-C30: Symptomskala Dyspnoe

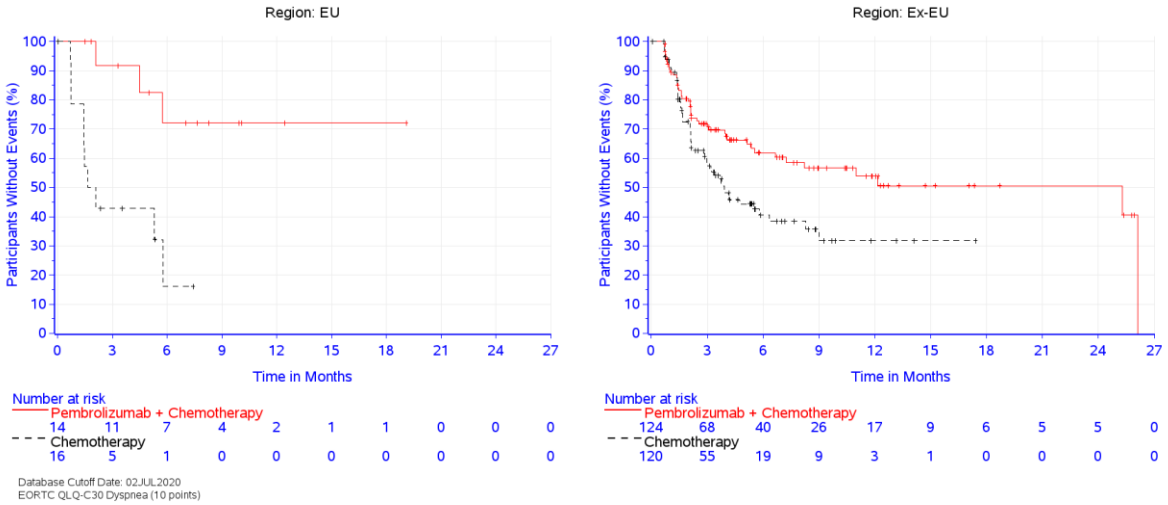

Abbildung 4G-15: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Dyspnoe des EORTC QLQ-C30 – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-OES18: Symptomskala Reflux

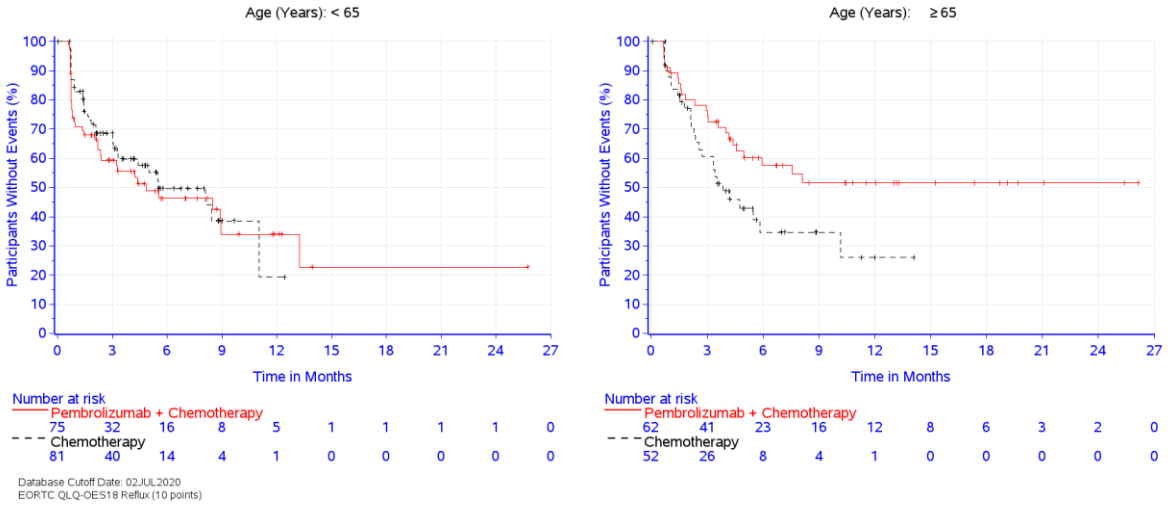

Abbildung 4G-16: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Alter für die Symptomskala Reflux des EORTC QLQ-OES18 – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

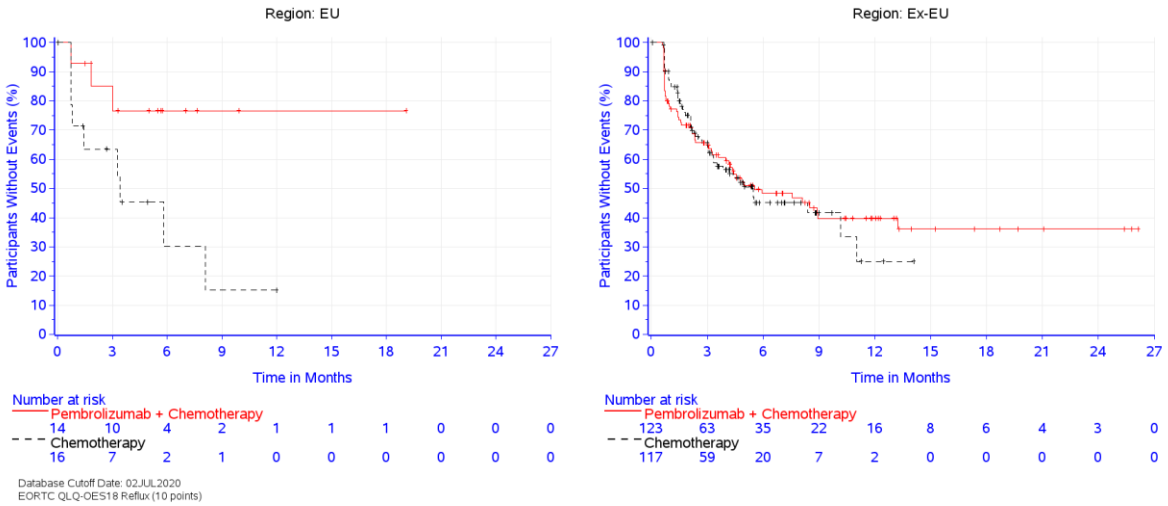

Abbildung 4G-17: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Reflux des EORTC QLQ-OES18 – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-OES18: Symptomskala Schmerzen

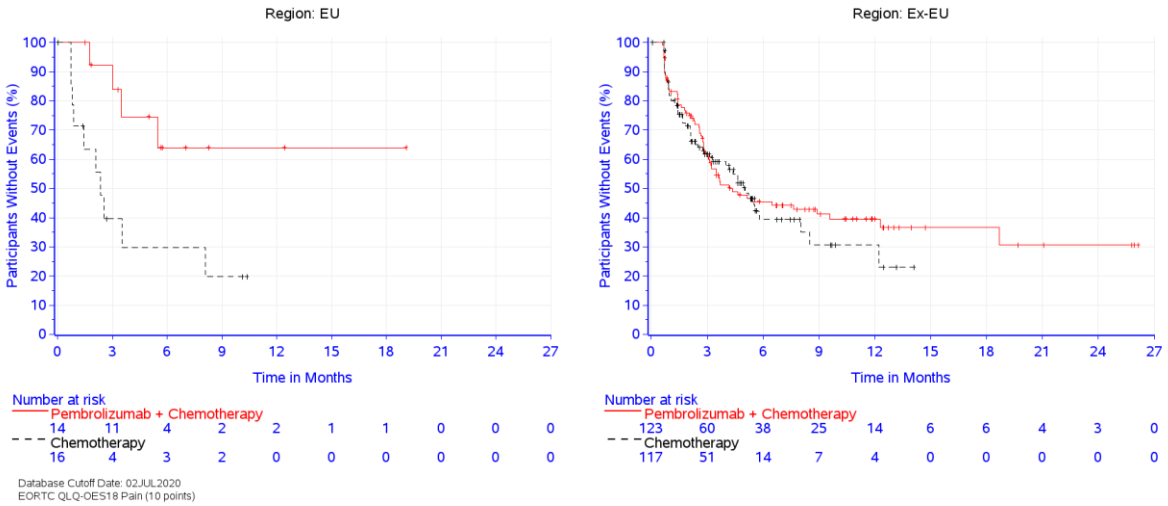

Abbildung 4G-18: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Schmerzen des EORTC QLQ-OES18 – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-OES18: Symptomskala Speichelschlucken

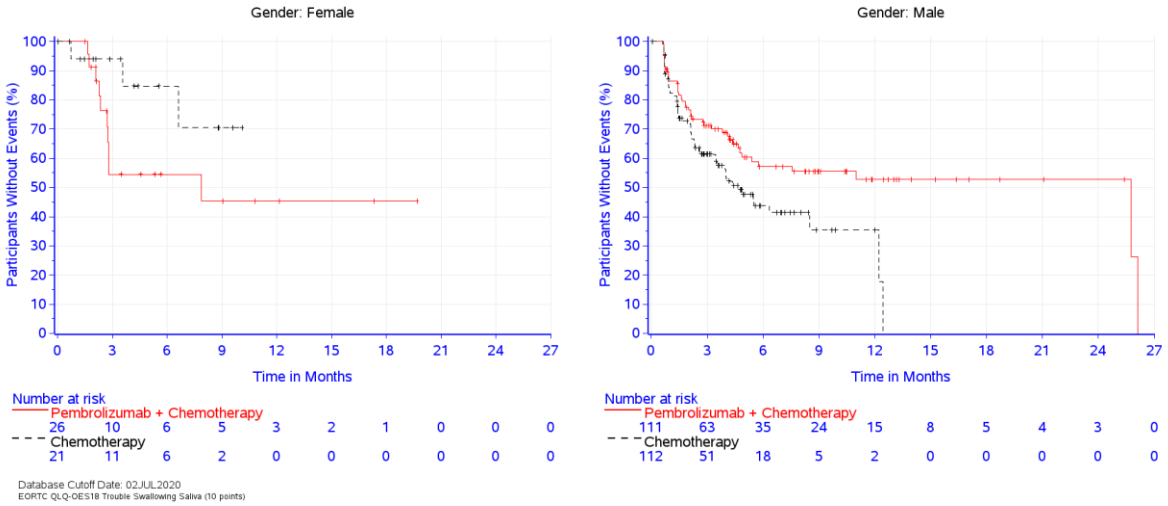

Abbildung 4G-19: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Geschlecht für die Symptomskala Speichelschlucken des EORTC QLQ-OES18 – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-OES18: Symptomskala Geschmackssinn

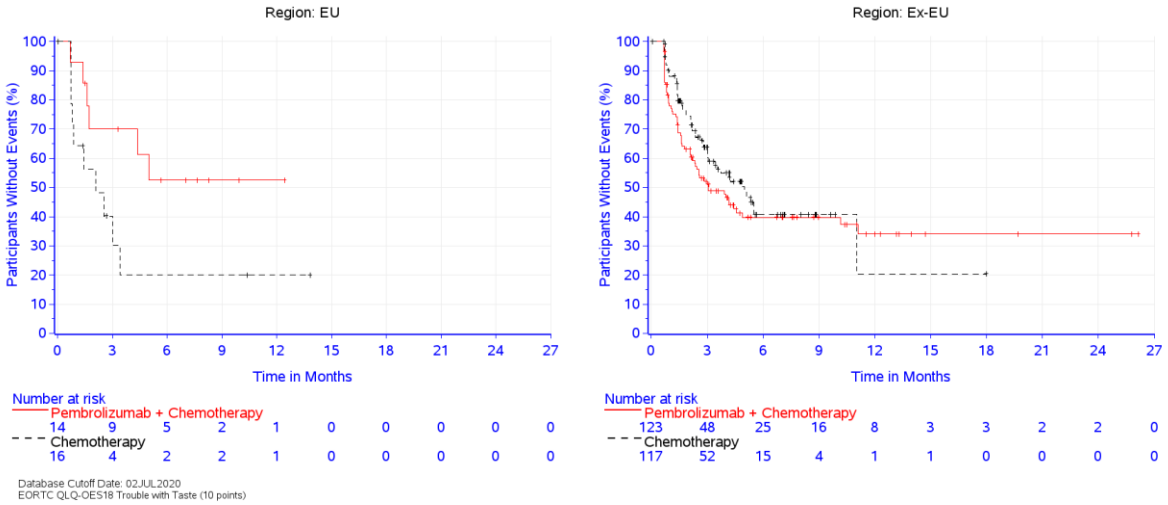

Abbildung 4G-20: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Geschmackssinn des EORTC QLQ-OES18 – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-OES18: Symptomskala Husten

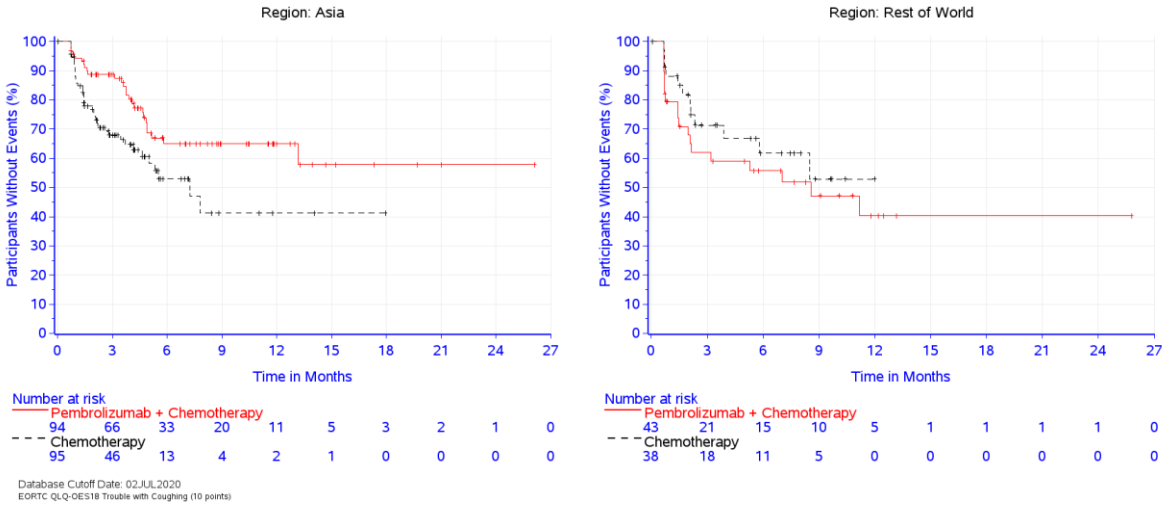

Abbildung 4G-21: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Husten des EORTC QLQ-OES18 – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-OES18: Symptomskala Dysphagie

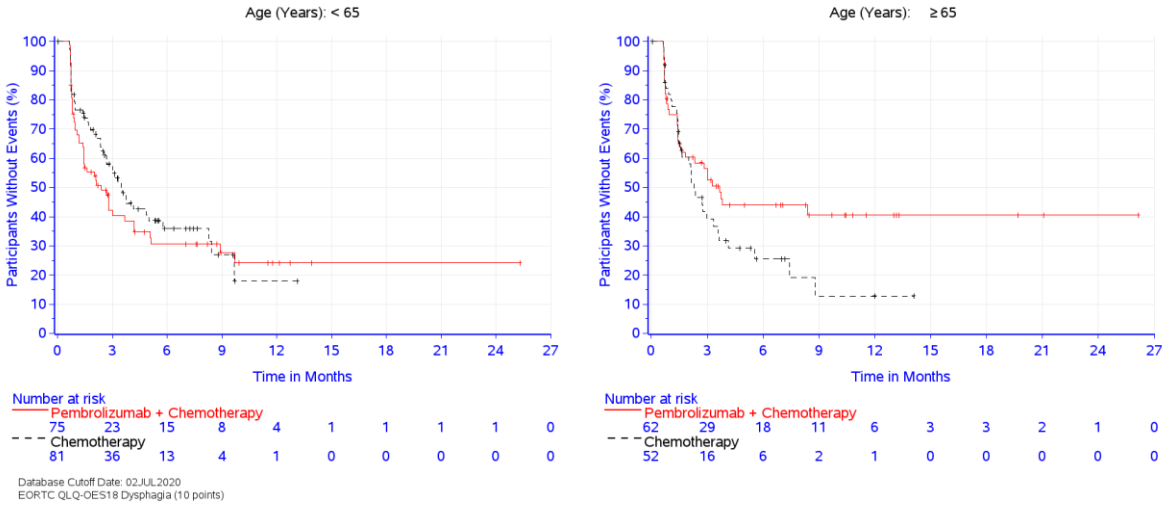

Abbildung 4G-22: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Alter für die Symptomskala Dysphagie des EORTC QLQ-OES18 – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G6.2: Nebenwirkungen

Unerwünschte Ereignisse (SOC und PT)

Unerwünschte Ereignisse (SOC und PT)

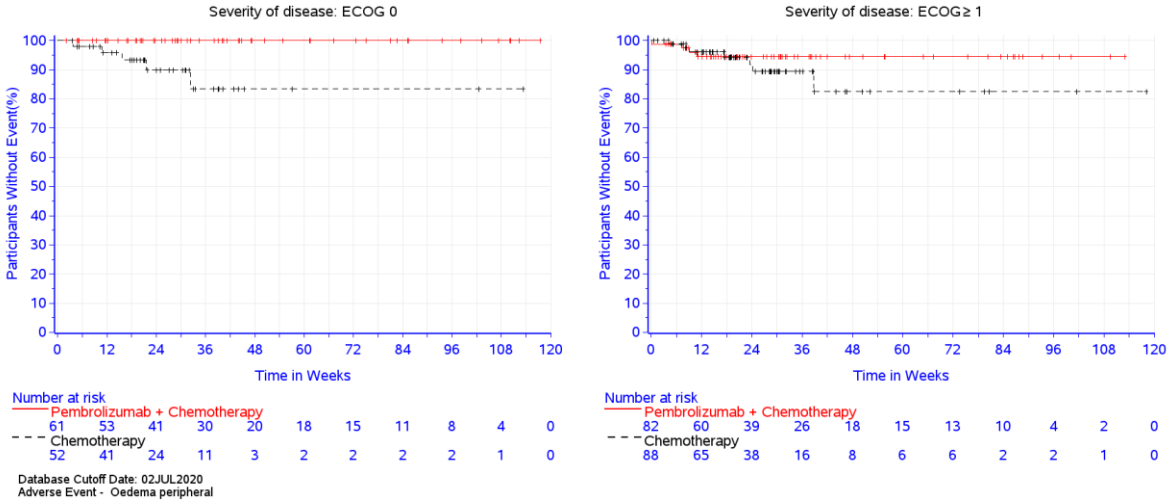

Abbildung 4G-23: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Ödem peripher“ (der SOC „Allgemeine Erkrankungen und Beschwerden am Verabreichungsort“) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

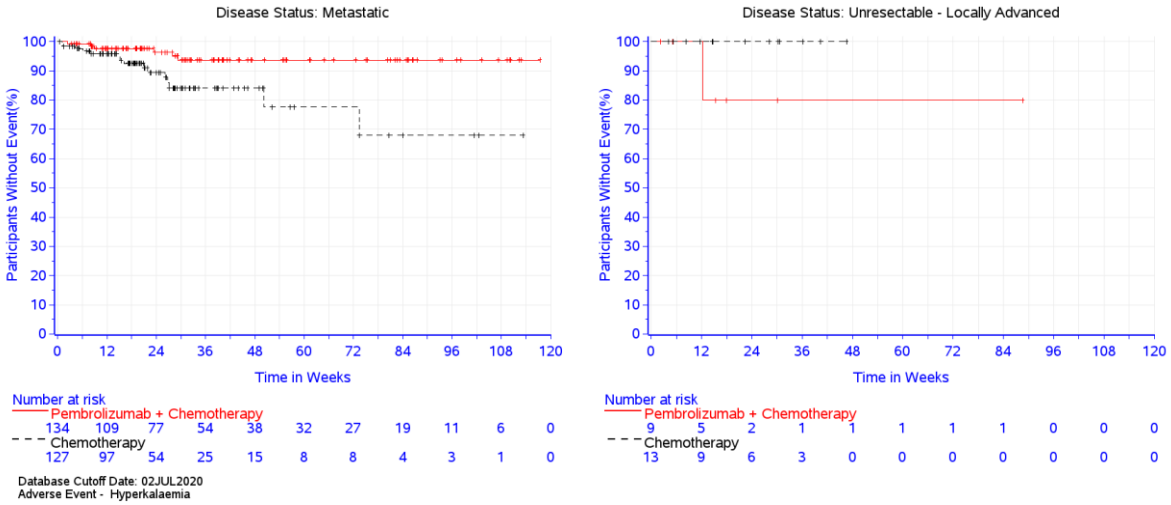

Abbildung 4G-24: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Krankheitsstatus für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Hyperkaliämie“ (der SOC „Stoffwechsel- und Ernährungsstörungen“) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G7: Kaplan-Meier-Kurven der Subgruppen mit signifikantem Interaktionstest (p < 0,05) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

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 finalen Datenschnitt (02. Juli 2020).

Anhang 4-G7.1: Mortalität

Gesamtüberleben

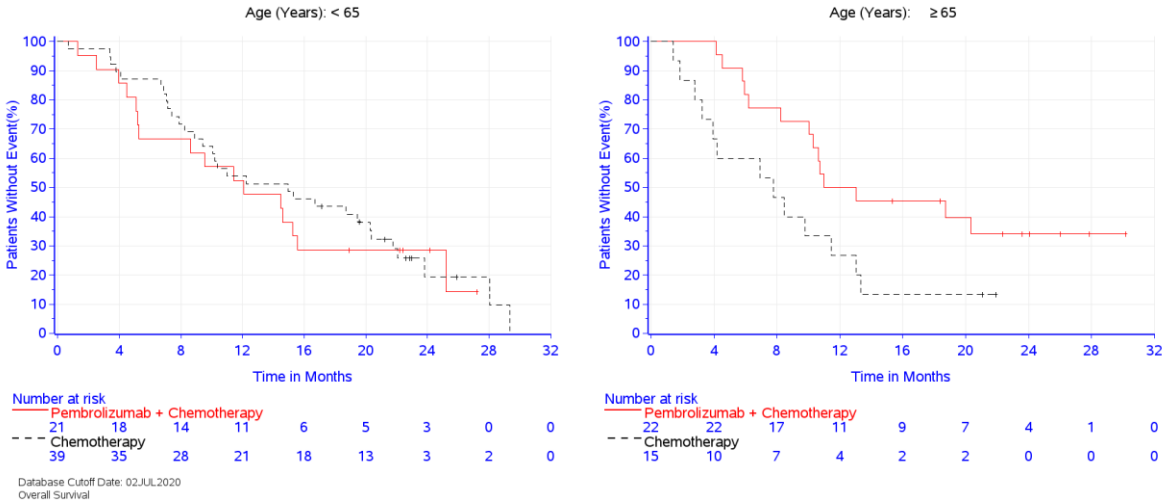

Abbildung 4G-25: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Gesamtüberleben nach Alter – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G7.2: Morbidität

Zeit bis zur ersten Folgetherapie (oder Tod)

Zeit bis zur ersten Folgetherapie oder Tod

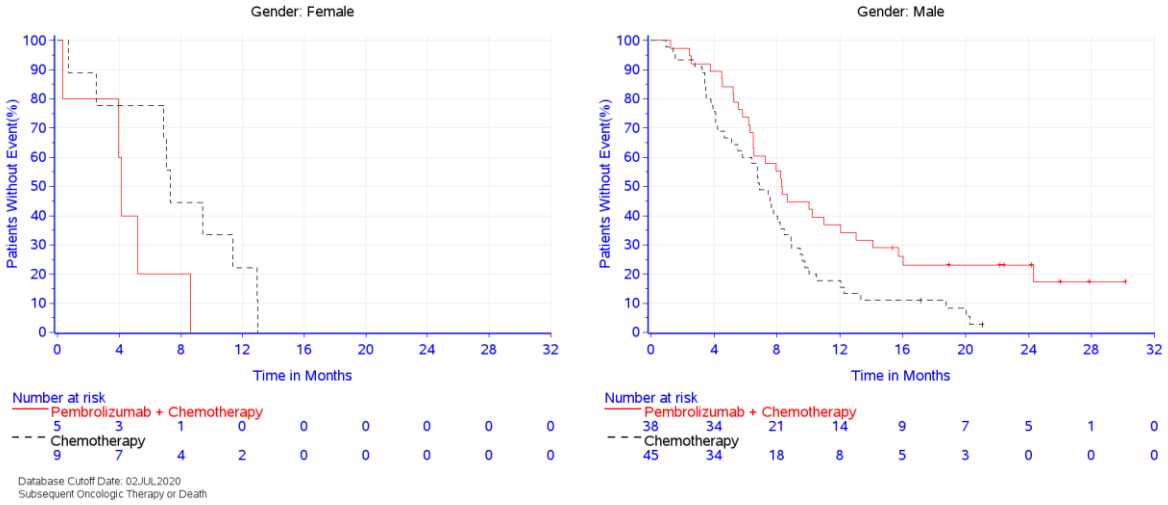

Abbildung 4G-26: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Folgetherapie (oder Tod) nach Geschlecht – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30: Symptomskala Schmerzen

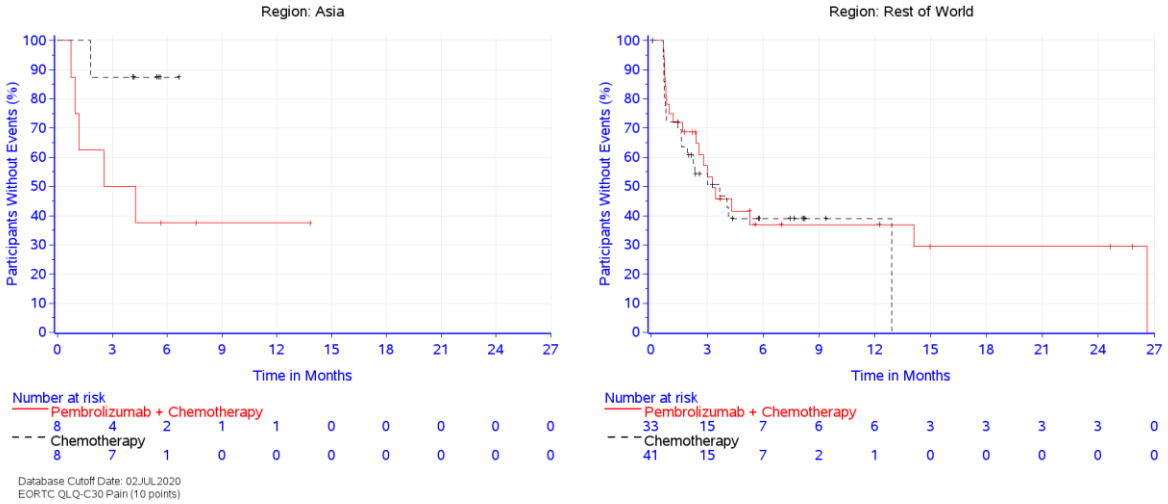

Abbildung 4G-27: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Schmerzen des EORTC QLQ-C30 – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-C30: Symptomskala Speichelschlucken

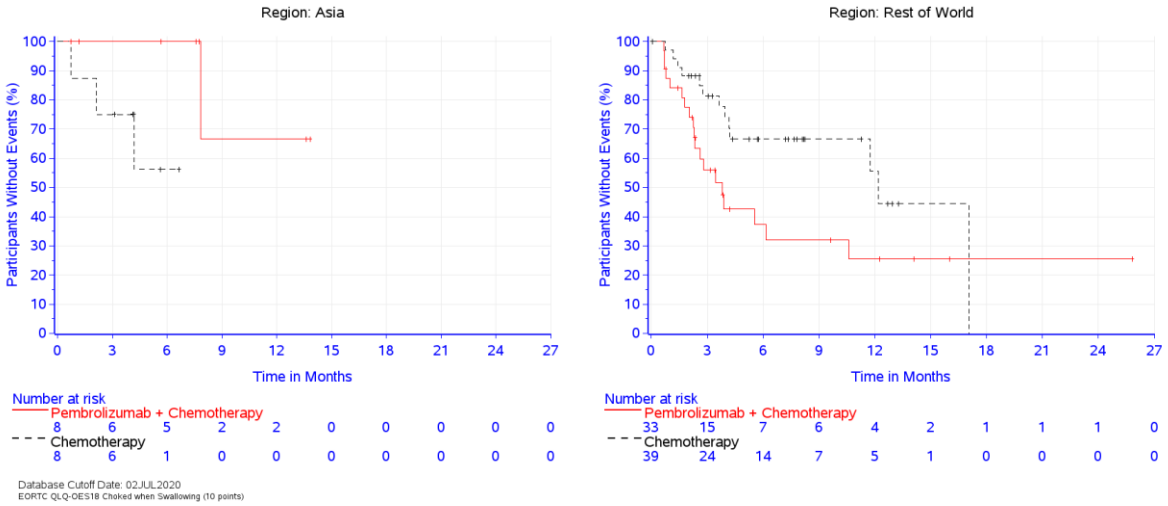

Abbildung 4G-28: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Speichelschlucken des EORTC QLQ-C30 – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-OES18: Symptomskala Mundtrockenheit

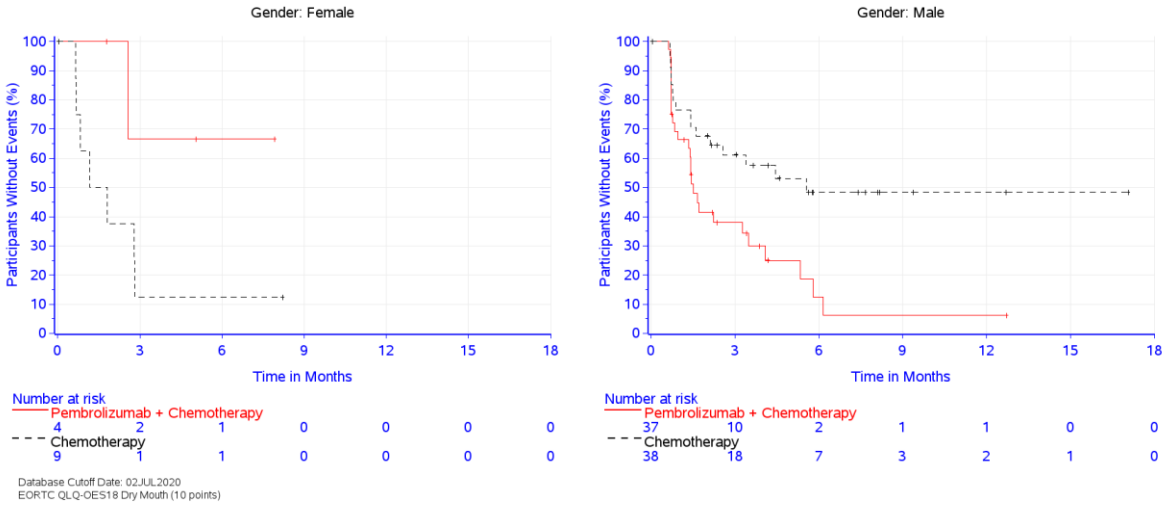

Abbildung 4G-29: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Geschlecht für die Symptomskala Mundtrockenheit des EORTC QLQ-OES18 – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

EORTC QLQ-OES18: Symptomskala Geschmackssinn

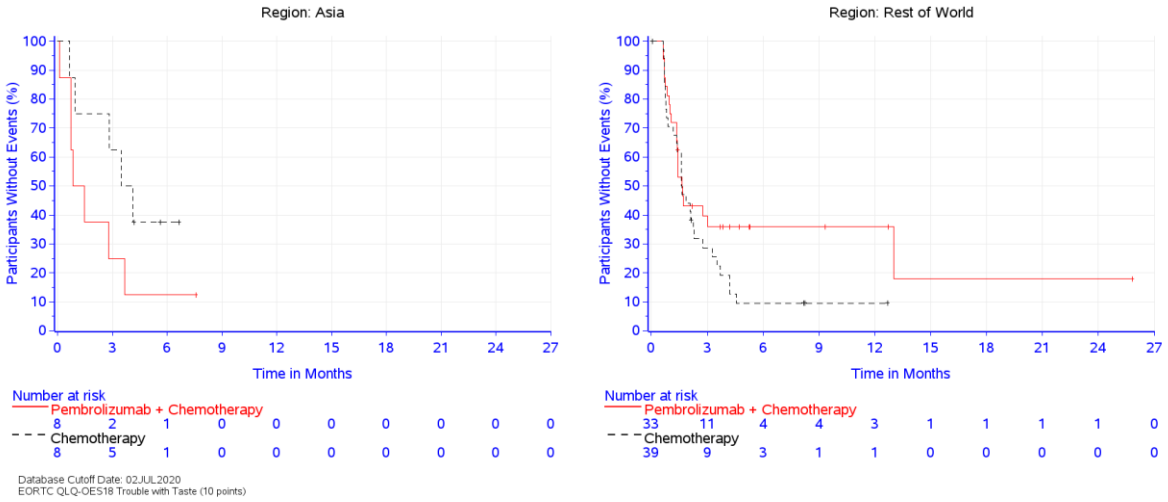

Abbildung 4G-30: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Geschmackssinn des EORTC QLQ-OES18 – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G8: Kaplan-Meier-Kurven der Subgruppen mit signifikantem Interaktionstest (p < 0,05) – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

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 finalen Datenschnitt (26. März 2019).

Anhang 4-G8.1: Morbidität

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

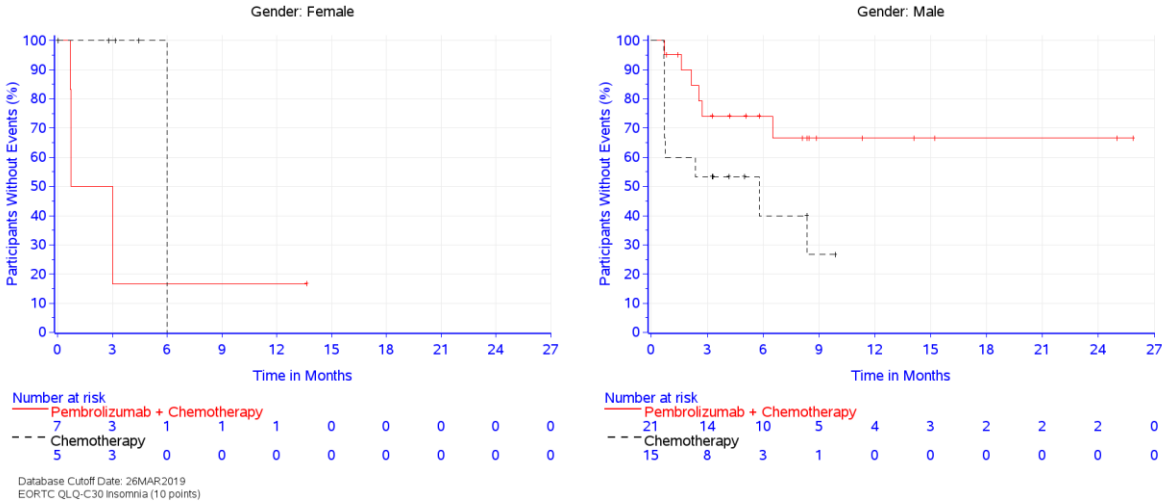

Abbildung 4G-31: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Geschlecht für die Symptomskala Schlaflosigkeit des EORTC QLQ-C30 – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

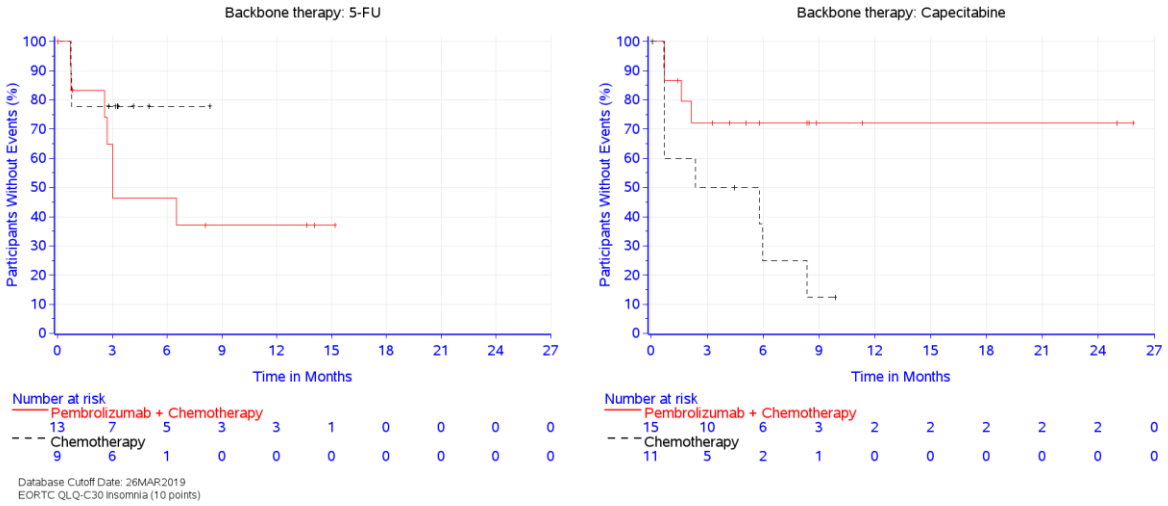

Abbildung 4G-32: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Chemotherapie-Backbone für die Symptomskala Schlaflosigkeit des EORTC QLQ-C30 – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

EORTC QLQ-C30: Symptomskala Appetitlosigkeit

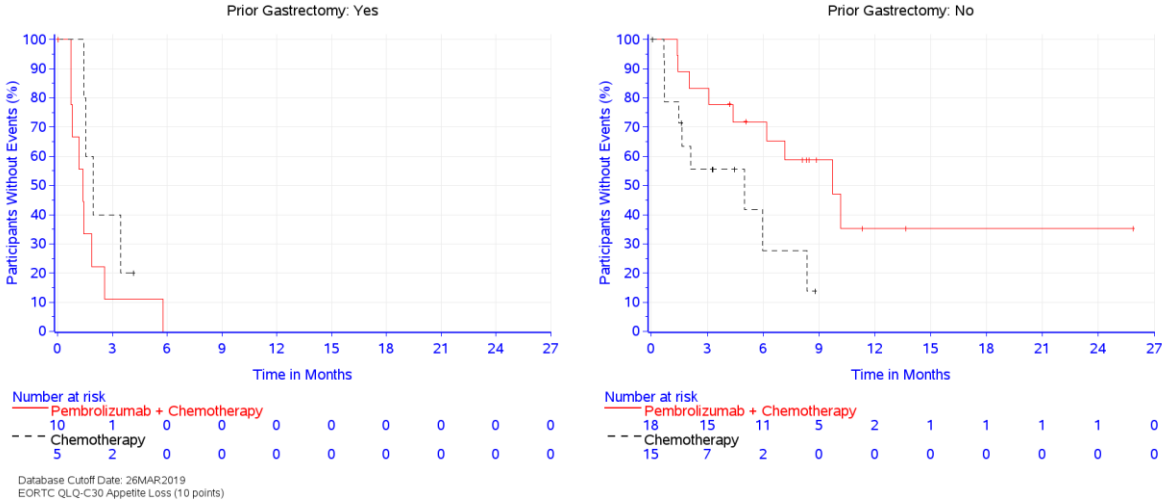

Abbildung 4G-33: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Vorangegangener Gastrektomie für die Symptomskala Appetitlosigkeit des EORTC QLQ-C30 – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

EORTC QLQ-C30: Symptomskala Reflux

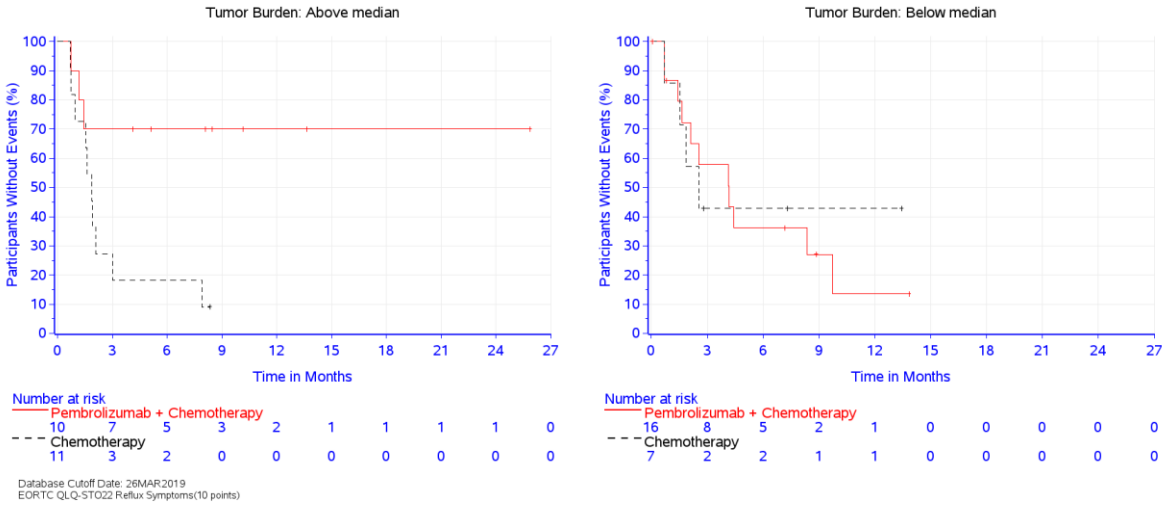

Abbildung 4G-34: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Tumorlast für die Symptomskala Reflux des EORTC QLQ-C30 – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

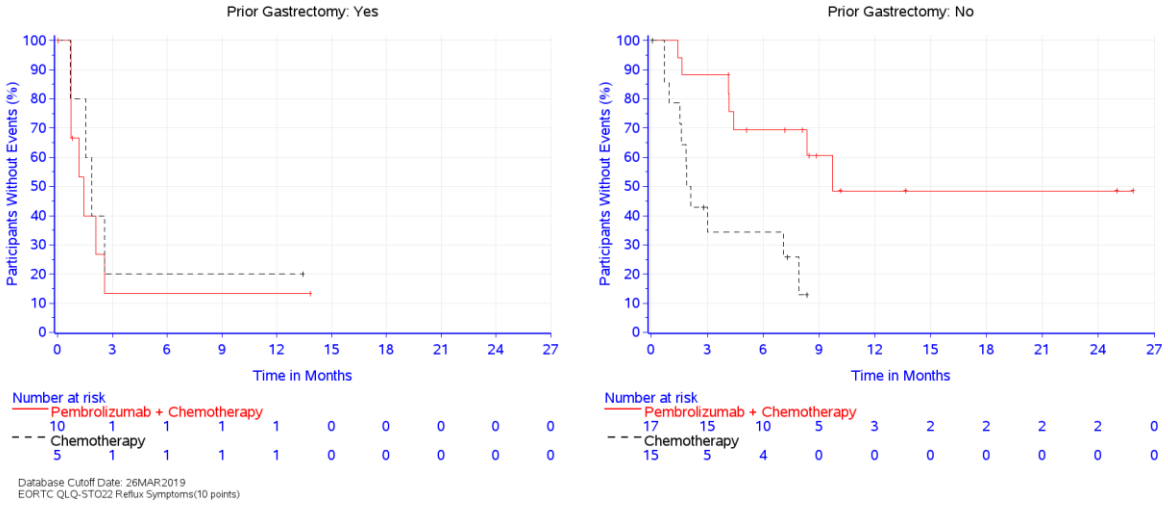

Abbildung 4G-35: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Vorangegangene Gastrektomie für die Symptomskala Reflux des EORTC QLQ-C30 – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

EQ-5D VAS (7 Punkte)

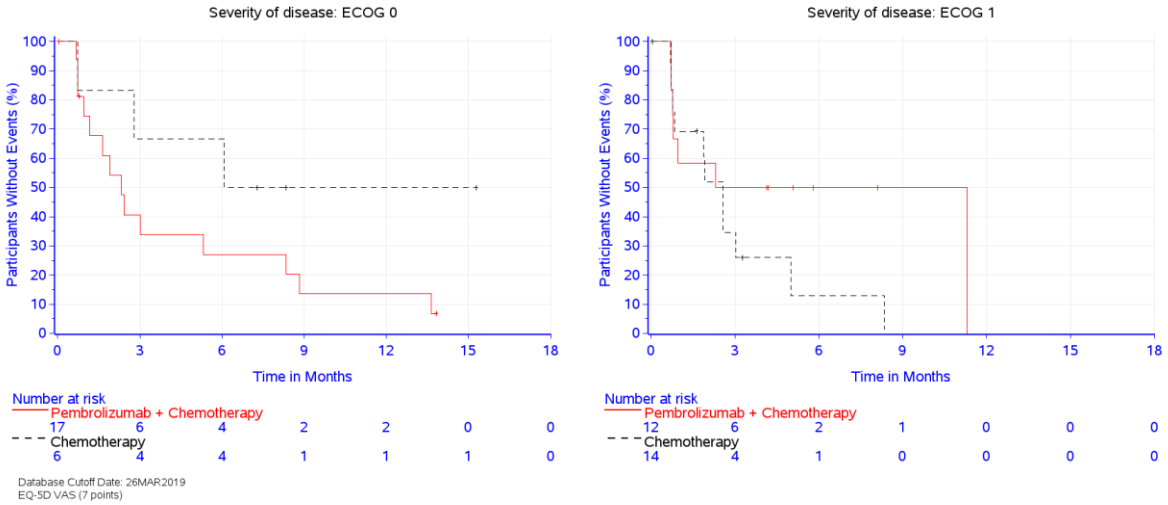

Abbildung 4G-36: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach ECOG-Leistungsstatus für die EQ-5D VAS (7 Punkte) – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

EQ-5D VAS (10 Punkte)

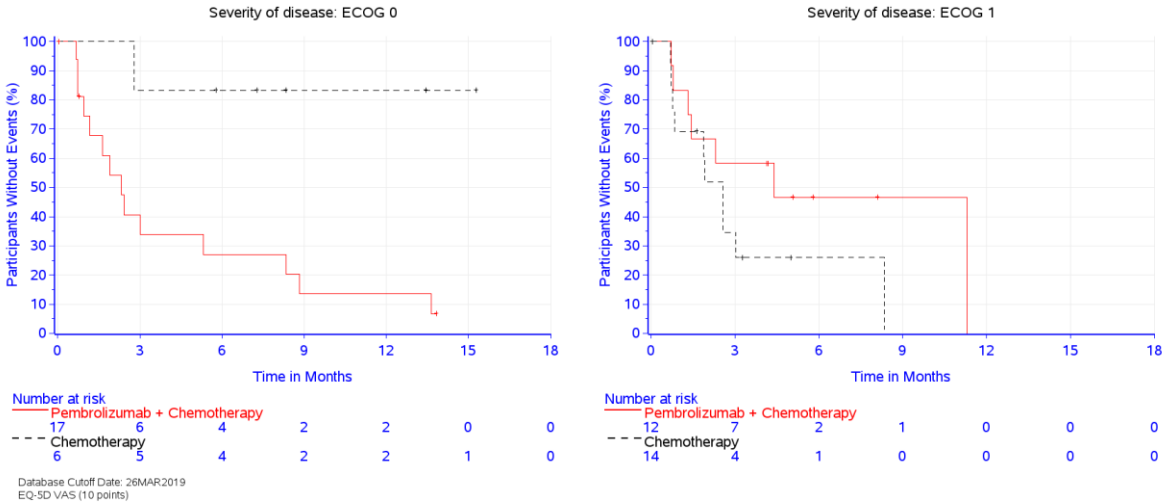

Abbildung 4G-37: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach ECOG-Leistungsstatus für die EQ-5D VAS (10 Punkte) – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Anhang 4-G8.2: Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30: Funktionsskala Rollenfunktion

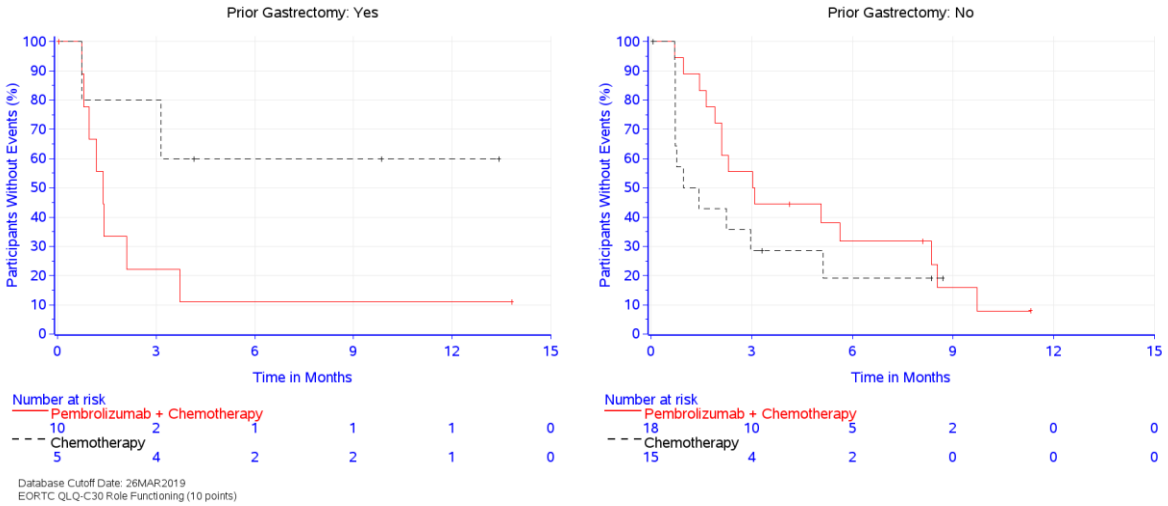

Abbildung 4G-38: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Vorangegangener Gastrektomie für die Funktionsskala Rollenfunktion des EORTC QLQ-C30 – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Anhang 4-G8.3: Nebenwirkungen

Unerwünschte Ereignisse

Schwerwiegende unerwünschte Ereignisse

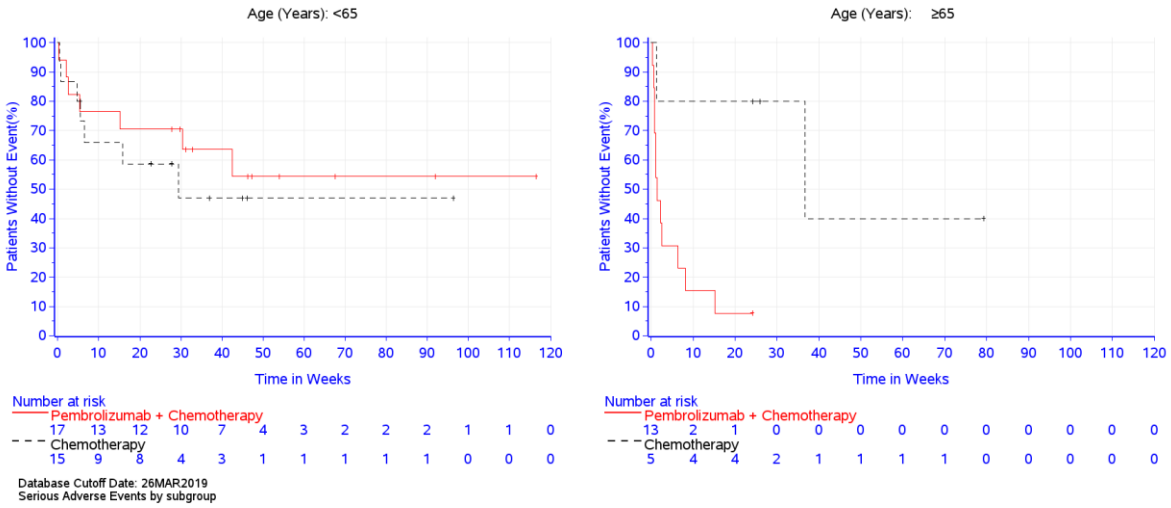

Abbildung 4G-39: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für den Endpunkt Schwerwiegende unerwünschte Ereignisse – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Schwere unerwünschte Ereignisse

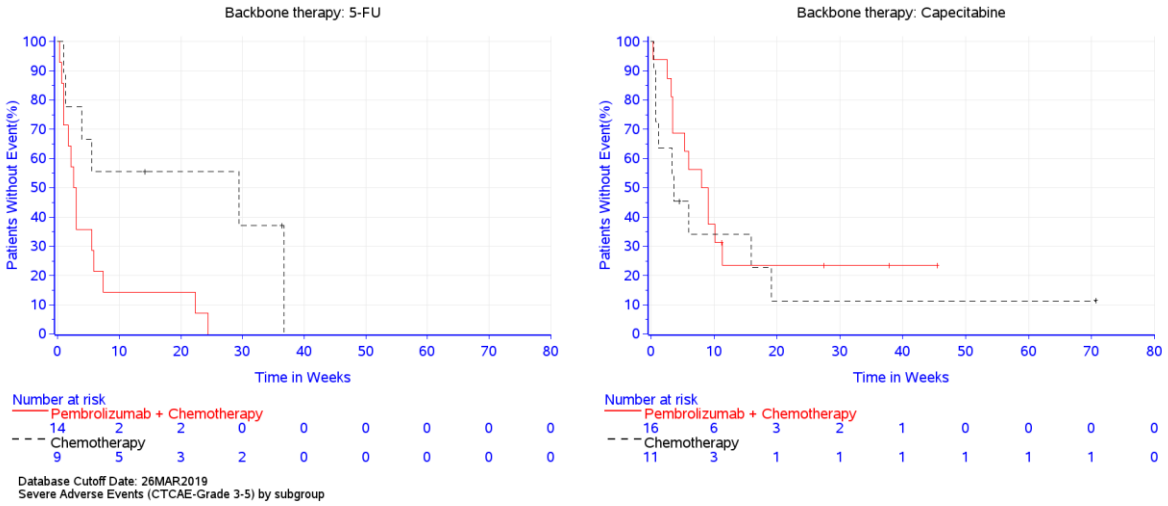

Abbildung 4G-40: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Chemotherapie-Backbone für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5) – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

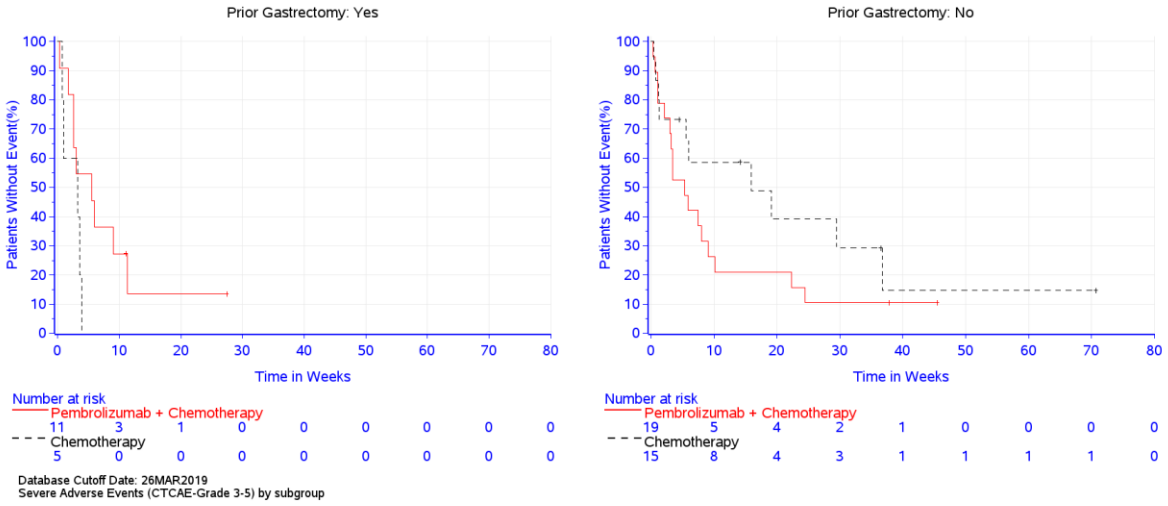

Abbildung 4G-41: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Vorangegangene Gastrektomie für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5) – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Anhang 4-G9: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest (p ≥ 0,05) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

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 finalen Datenschnitt (02. Juli 2020).

Anhang 4-G9.1: Mortalität

Gesamtüberleben

Tabelle 4G-13: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Overall Survival	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	34	22 (64.7)	11.6 [8.4; -]	36	29 (80.6)	9.4 [5.1; 13.8]	0.67 [0.39; 1.17]	0.159	0.870
Male	152	102 (67.1)	14.0 [11.0; 17.7]	161	136 (84.5)	9.3 [8.0; 11.0]	0.61 [0.47; 0.80]	< 0.001	
Age (Years)									
< 65	99	70 (70.7)	12.1 [9.5; 15.3]	127	108 (85.0)	9.1 [7.8; 11.0]	0.71 [0.52; 0.95]	0.024	0.338
≥ 65	87	54 (62.1)	14.4 [10.8; 22.6]	70	57 (81.4)	10.2 [7.9; 12.1]	0.56 [0.39; 0.82]	0.002	
Severity of disease									
ECOG 0	84	53 (63.1)	15.3 [12.1; 20.9]	80	65 (81.3)	10.8 [8.1; 13.5]	0.60 [0.42; 0.87]	0.006	0.880
ECOG ≥ 1	102	71 (69.6)	10.6 [8.6; 14.0]	117	100 (85.5)	8.4 [6.7; 9.8]	0.65 [0.48; 0.88]	0.005	
Region									
EU	31	22 (71.0)	11.4 [8.0; 22.6]	26	22 (84.6)	8.6 [4.1; 12.3]	0.56 [0.31; 1.03]	0.060	0.817
Ex-EU	155	102 (65.8)	13.7 [11.0; 16.0]	171	143 (83.6)	9.5 [8.0; 11.2]	0.63 [0.49; 0.81]	< 0.001	
Histology									
Adenocarcinoma	43	30 (69.8)	12.1 [9.6; 18.7]	54	44 (81.5)	10.7 [8.2; 15.3]	0.83 [0.52; 1.34]	0.447	0.251
Squamous Cell Carcinoma	143	94 (65.7)	13.9 [11.1; 17.7]	143	121 (84.6)	8.8 [7.8; 10.5]	0.57 [0.43; 0.75]	< 0.001	
Disease Status									
Metastatic	175	115 (65.7)	14.0 [11.4; 16.5]	180	151 (83.9)	9.5 [8.1; 11.2]	0.61 [0.48; 0.78]	< 0.001	0.361
Unresectable - Locally Advanced	11	9 (81.8)	8.2 [6.7; 11.4]	17	14 (82.4)	7.9 [2.8; 14.6]	0.89 [0.38; 2.06]	0.782	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: intention-to-treat population with PD-L1 CPS≥10

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

g: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G9.2: Morbidität

Zeit bis zur ersten Folgetherapie (oder Tod)

Zeit bis zur ersten Folgetherapie oder Tod

Tabelle 4G-14: 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 – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Time to Subsequent Oncologic Therapy or Death	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	34	25 (73.5)	9.3 [6.8; 14.3]	36	33 (91.7)	7.0 [4.2; 9.6]	0.60 [0.35; 1.00]	0.052	0.904
Male	152	128 (84.2)	8.2 [7.0; 8.9]	161	154 (95.7)	6.4 [5.6; 6.7]	0.55 [0.44; 0.71]	< 0.001	
Age (Years)									
< 65	99	81 (81.8)	7.9 [6.3; 8.5]	127	121 (95.3)	6.4 [5.2; 6.9]	0.63 [0.47; 0.84]	0.001	0.561
≥ 65	87	72 (82.8)	9.8 [7.3; 11.0]	70	66 (94.3)	6.6 [5.1; 7.1]	0.52 [0.37; 0.73]	< 0.001	
Severity of disease									
ECOG 0	84	66 (78.6)	9.1 [7.3; 11.8]	80	74 (92.5)	6.9 [5.8; 7.8]	0.57 [0.41; 0.80]	0.001	0.951
ECOG ≥ 1	102	87 (85.3)	7.9 [6.5; 8.8]	117	113 (96.6)	6.0 [5.0; 6.6]	0.57 [0.43; 0.76]	< 0.001	
Region									
EU	31	26 (83.9)	8.0 [6.5; 14.6]	26	25 (96.2)	7.0 [3.7; 10.4]	0.57 [0.32; 1.01]	0.054	0.668
Ex-EU	155	127 (81.9)	8.4 [7.1; 9.4]	171	162 (94.7)	6.3 [5.4; 6.7]	0.56 [0.44; 0.71]	< 0.001	
Region									
Asia	104	88 (84.6)	8.3 [6.9; 9.4]	106	103 (97.2)	5.7 [5.0; 6.3]	0.45 [0.33; 0.60]	< 0.001	0.055
Rest of World	82	65 (79.3)	8.4 [6.9; 11.0]	91	84 (92.3)	7.8 [6.7; 9.4]	0.67 [0.48; 0.93]	0.016	
Histology									
Adenocarcinoma	43	35 (81.4)	8.2 [6.2; 10.3]	54	52 (96.3)	7.2 [5.8; 8.2]	0.59 [0.37; 0.93]	0.024	0.568
Squamous Cell Carcinoma	143	118 (82.5)	8.5 [7.2; 9.7]	143	135 (94.4)	6.1 [5.1; 6.6]	0.53 [0.41; 0.68]	< 0.001	
Disease Status									
Metastatic	175	144 (82.3)	8.5 [7.3; 9.7]	180	170 (94.4)	6.4 [5.6; 6.8]	0.57 [0.46; 0.72]	< 0.001	0.897
Unresectable - Locally Advanced	11	9 (81.8)	7.2 [3.5; 10.0]	17	17 (100.0)	6.3 [2.8; 8.3]	0.63 [0.28; 1.43]	0.271	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: intention-to-treat population with PD-L1 CPS≥10

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other

subgroups

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

g: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30

EORTC QLQ-C30: Symptomskala Erschöpfung

Tabelle 4G-15: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Erschöpfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Fatigue	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	31	20 (64.5)	1.4 [0.9; 3.7]	32	17 (53.1)	1.6 [0.8; -]	1.02 [0.53; 1.95]	0.949	0.644
Male	148	105 (70.9)	1.8 [1.4; 2.8]	153	117 (76.5)	1.4 [1.4; 2.1]	0.82 [0.63; 1.07]	0.149	
Age (Years)									
< 65	95	70 (73.7)	1.6 [0.9; 2.8]	117	83 (70.9)	1.7 [1.4; 2.3]	1.05 [0.77; 1.45]	0.744	0.060
≥ 65	84	55 (65.5)	1.8 [1.2; 3.5]	68	51 (75.0)	1.4 [1.1; 1.8]	0.66 [0.45; 0.97]	0.035	
Severity of disease									
ECOG 0	82	63 (76.8)	1.4 [1.0; 2.4]	74	60 (81.1)	1.5 [1.2; 2.1]	0.87 [0.61; 1.24]	0.451	0.807
ECOG ≥ 1	97	62 (63.9)	2.0 [1.4; 3.5]	111	74 (66.7)	1.4 [1.3; 2.1]	0.82 [0.58; 1.15]	0.257	
Region									
EU	30	22 (73.3)	2.6 [1.0; 5.0]	23	17 (73.9)	1.4 [0.8; 4.9]	0.71 [0.38; 1.35]	0.301	0.582
Ex-EU	149	103 (69.1)	1.6 [1.1; 2.4]	162	117 (72.2)	1.4 [1.4; 2.1]	0.89 [0.68; 1.16]	0.383	
Region									
Asia	102	71 (69.6)	1.9 [1.1; 3.2]	103	78 (75.7)	1.4 [1.3; 2.1]	0.80 [0.58; 1.11]	0.179	0.632
Rest of World	77	54 (70.1)	1.5 [0.9; 2.8]	82	56 (68.3)	1.5 [1.0; 2.3]	0.93 [0.64; 1.36]	0.716	
Histology									
Adenocarcinoma	41	28 (68.3)	1.6 [1.0; 4.3]	49	34 (69.4)	2.0 [1.0; 2.8]	0.88 [0.53; 1.46]	0.627	0.947
Squamous Cell Carcinoma	138	97 (70.3)	1.7 [1.0; 2.6]	136	100 (73.5)	1.4 [1.3; 2.1]	0.87 [0.65; 1.15]	0.318	
Disease Status									
Metastatic	169	118 (69.8)	1.7 [1.1; 2.6]	170	122 (71.8)	1.4 [1.3; 2.1]	0.85 [0.66; 1.10]	0.218	0.602
Unresectable - Locally Advanced	10	7 (70.0)	1.7 [0.7; 3.5]	15	12 (80.0)	1.6 [0.9; 2.5]	0.92 [0.36; 2.36]	0.862	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other

subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; 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

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-16: 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 – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Nausea and Vomiting	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	31	22 (71.0)	2.6 [1.0; 4.6]	32	21 (65.6)	1.4 [0.8; 2.8]	0.76 [0.42; 1.39]	0.373	0.692
Male	148	87 (58.8)	3.0 [2.1; 4.1]	153	93 (60.8)	2.3 [2.1; 3.5]	0.87 [0.65; 1.17]	0.366	
Age (Years)									
< 65	95	61 (64.2)	2.3 [1.9; 3.5]	117	74 (63.2)	2.3 [1.6; 3.5]	0.95 [0.67; 1.33]	0.763	0.362
≥ 65	84	48 (57.1)	3.7 [2.3; 5.9]	68	40 (58.8)	2.1 [1.6; 3.6]	0.73 [0.47; 1.12]	0.148	
Severity of disease									
ECOG 0	82	55 (67.1)	3.3 [2.1; 4.4]	74	51 (68.9)	2.1 [1.5; 3.0]	0.79 [0.54; 1.16]	0.225	0.619
ECOG ≥ 1	97	54 (55.7)	2.6 [1.9; 4.6]	111	63 (56.8)	2.8 [1.7; 3.9]	0.87 [0.60; 1.26]	0.466	
Region									
EU	30	20 (66.7)	2.8 [1.4; 4.5]	23	19 (82.6)	1.4 [0.9; 3.1]	0.57 [0.30; 1.08]	0.083	0.197
Ex-EU	149	89 (59.7)	3.1 [2.1; 4.1]	162	95 (58.6)	2.3 [2.0; 3.5]	0.90 [0.67; 1.21]	0.478	
Region									
Asia	102	58 (56.9)	3.2 [2.1; 4.9]	103	58 (56.3)	3.0 [2.1; 5.5]	0.93 [0.64; 1.35]	0.708	0.409
Rest of World	77	51 (66.2)	2.8 [1.4; 4.2]	82	56 (68.3)	1.6 [1.4; 2.3]	0.75 [0.51; 1.10]	0.135	
Histology									
Adenocarcinoma	41	26 (63.4)	2.1 [1.4; 7.0]	49	30 (61.2)	2.3 [1.4; 4.1]	0.91 [0.53; 1.54]	0.712	0.749
Squamous Cell Carcinoma	138	83 (60.1)	3.1 [2.1; 4.2]	136	84 (61.8)	2.2 [1.8; 3.1]	0.79 [0.58; 1.08]	0.140	
Disease Status									
Metastatic	169	107 (63.3)	2.8 [2.1; 3.9]	170	107 (62.9)	2.2 [1.7; 3.0]	0.84 [0.64; 1.10]	0.199	0.615
Unresectable - Locally Advanced	10	2 (20.0)	Not reached [0.7; -]	15	7 (46.7)	3.4 [1.6; -]	0.61 [0.13; 2.97]	0.545	

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Nausea and Vomiting	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; 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

EORTC QLQ-C30: Symptomskala Schmerzen

Tabelle 4G-17: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schmerzen des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Pain	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	31	15 (48.4)	7.9 [2.7; -]	32	18 (56.3)	1.8 [0.8; 10.1]	0.53 [0.27; 1.06]	0.071	0.296
Male	148	81 (54.7)	4.4 [3.2; 7.6]	153	91 (59.5)	3.4 [2.8; 4.9]	0.76 [0.56; 1.03]	0.081	
Severity of disease									
ECOG 0	82	47 (57.3)	4.8 [2.7; 17.3]	74	46 (62.2)	3.5 [2.3; 5.8]	0.75 [0.49; 1.13]	0.166	0.918
ECOG ≥ 1	97	49 (50.5)	6.8 [3.3; 9.4]	111	63 (56.8)	3.3 [2.4; 4.9]	0.68 [0.47; 1.00]	0.051	
Region									
EU	30	17 (56.7)	4.4 [2.6; -]	23	12 (52.2)	2.3 [1.4; -]	0.75 [0.35; 1.60]	0.454	0.830
Ex-EU	149	79 (53.0)	5.0 [3.6; 7.7]	162	97 (59.9)	3.4 [2.8; 4.1]	0.71 [0.52; 0.96]	0.025	
Region									
Asia	102	55 (53.9)	5.0 [3.6; 7.7]	103	65 (63.1)	3.5 [2.8; 4.9]	0.66 [0.46; 0.96]	0.031	0.951
Rest of World	77	41 (53.2)	4.4 [2.6; 14.1]	82	44 (53.7)	3.0 [1.9; 9.7]	0.73 [0.47; 1.13]	0.160	
Histology									
Adenocarcinoma	41	25	3.3	49	22	4.1	1.11	0.723	0.151

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Pain	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
		(61.0)	[2.4; 14.1]		(44.9)	[1.9; -]	[0.62; 2.01]		
Squamous Cell Carcinoma	138	71 (51.4)	6.6 [4.1; 8.4]	136	87 (64.0)	3.2 [2.4; 3.8]	0.60 [0.44; 0.84]	0.002	
Disease Status									
Metastatic	169	92 (54.4)	5.1 [3.6; 7.9]	170	101 (59.4)	3.4 [2.4; 4.1]	0.70 [0.53; 0.93]	0.016	0.579
Unresectable - Locally Advanced	10	4 (40.0)	4.4 [0.7; -]	15	8 (53.3)	3.3 [2.2; -]	1.05 [0.31; 3.49]	0.941	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; 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

EORTC QLQ-C30: Symptomskala Dyspnoe

Tabelle 4G-18: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Dyspnoe des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Dyspnea	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	31	9 (29.0)	Not reached [4.5; -]	32	16 (50.0)	3.7 [1.7; -]	0.44 [0.19; 0.99]	0.048	0.421
Male	148	59 (39.9)	11.0 [7.0; -]	153	80 (52.3)	4.2 [3.0; 5.8]	0.59 [0.42; 0.83]	0.003	
Age (Years)									
< 65	95	36 (37.9)	9.2 [4.6; -]	117	59 (50.4)	5.3 [3.7; 8.1]	0.65 [0.43; 0.98]	0.040	0.224
≥ 65	84	32 (38.1)	12.2 [5.7; -]	68	37 (54.4)	2.1 [1.6; 4.1]	0.48 [0.30; 0.79]	0.004	
Severity of disease									
ECOG 0	82	38 (46.3)	8.3 [5.2; -]	74	39 (52.7)	4.6 [3.7; 8.1]	0.67 [0.42; 1.06]	0.087	0.288
ECOG ≥ 1	97	30 (30.9)	Not reached [11.0; -]	111	57 (51.4)	3.7 [2.2; 5.8]	0.48 [0.31; 0.76]	0.001	

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Dyspnea	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Region									
Asia	102	37 (36.3)	12.2 [7.2; -]	103	58 (56.3)	3.7 [2.2; 5.5]	0.47 [0.31; 0.72]	< 0.001	0.152
Rest of World	77	31 (40.3)	9.2 [4.6; -]	82	38 (46.3)	5.3 [3.2; 12.0]	0.72 [0.45; 1.17]	0.183	
Histology									
Adenocarcinoma	41	19 (46.3)	8.3 [3.2; -]	49	25 (51.0)	5.1 [3.0; 12.0]	0.96 [0.51; 1.78]	0.887	0.142
Squamous Cell Carcinoma	138	49 (35.5)	25.3 [7.2; -]	136	71 (52.2)	3.7 [2.9; 5.8]	0.50 [0.35; 0.74]	< 0.001	
Disease Status									
Metastatic	169	66 (39.1)	12.2 [7.2; -]	170	90 (52.9)	4.2 [3.0; 5.6]	0.56 [0.40; 0.77]	< 0.001	0.846
Unresectable - Locally Advanced	10	2 (20.0)	5.7 [1.0; -]	15	6 (40.0)	3.9 [2.1; -]	0.64 [0.13; 3.21]	0.590	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; 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

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

Tabelle 4G-19: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schlaflosigkeit des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Insomnia	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	31	15 (48.4)	4.5 [2.8; 12.5]	32	11 (34.4)	7.2 [2.8; -]	1.31 [0.59; 2.90]	0.501	0.210
Male	148	67 (45.3)	8.1 [4.0; 25.3]	153	74 (48.4)	4.6 [3.4; 7.1]	0.82 [0.59; 1.15]	0.257	
Age (Years)									
< 65	95	48 (50.5)	7.6 [2.8; 12.5]	117	51 (43.6)	7.0 [3.7; -]	1.08 [0.73; 1.62]	0.691	0.080

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Insomnia	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
≥ 65	84	34 (40.5)	25.3 [3.7; -]	68	34 (50.0)	4.0 [2.7; 7.4]	0.66 [0.41; 1.07]	0.090	
Severity of disease									
ECOG 0	82	43 (52.4)	7.6 [3.0; 25.3]	74	35 (47.3)	5.7 [3.2; -]	0.94 [0.60; 1.49]	0.805	0.655
ECOG ≥ 1	97	39 (40.2)	8.3 [3.0; -]	111	50 (45.0)	4.6 [3.0; 7.4]	0.85 [0.56; 1.29]	0.447	
Region									
EU	30	12 (40.0)	10.9 [4.1; -]	23	10 (43.5)	8.1 [2.3; -]	0.81 [0.35; 1.89]	0.630	0.691
Ex-EU	149	70 (47.0)	7.6 [3.0; 25.3]	162	75 (46.3)	4.8 [3.4; 7.1]	0.93 [0.66; 1.29]	0.648	
Region									
Asia	102	47 (46.1)	7.6 [2.5; -]	103	47 (45.6)	4.9 [3.7; 7.1]	0.96 [0.64; 1.45]	0.852	0.831
Rest of World	77	35 (45.5)	8.1 [4.0; 25.3]	82	38 (46.3)	4.6 [2.9; 8.5]	0.82 [0.51; 1.31]	0.402	
Histology									
Adenocarcinoma	41	15 (36.6)	Not reached [7.0; -]	49	24 (49.0)	4.6 [2.8; 12.9]	0.65 [0.34; 1.26]	0.204	0.151
Squamous Cell Carcinoma	138	67 (48.6)	4.5 [3.0; 25.3]	136	61 (44.9)	4.9 [3.7; 7.4]	1.01 [0.71; 1.43]	0.969	
Disease Status									
Metastatic	169	80 (47.3)	7.6 [3.7; 25.3]	170	78 (45.9)	5.6 [3.7; 7.4]	0.91 [0.66; 1.25]	0.556	0.433
Unresectable - Locally Advanced	10	2 (20.0)	5.1 [3.0; -]	15	7 (46.7)	4.6 [2.3; -]	0.50 [0.10; 2.41]	0.387	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; 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

EORTC QLQ-C30: Symptomskala Appetitverlust

Tabelle 4G-20: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Appetitverlust des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]	Chemotherapy[b]	Pembrolizumab + Chemotherapy[b] vs.	

							Chemotherapy[b]		
EORTC QLQ-C30 Appetite Loss	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	31	17 (54.8)	2.7 [1.1; -]	32	12 (37.5)	Not reached [0.8; -]	1.28 [0.61; 2.68]	0.515	0.204
Male	148	88 (59.5)	3.5 [2.5; 4.9]	153	99 (64.7)	2.8 [2.1; 3.5]	0.79 [0.59; 1.05]	0.106	
Age (Years)									
< 65	95	60 (63.2)	3.2 [1.9; 4.2]	117	74 (63.2)	2.9 [2.1; 3.7]	0.93 [0.66; 1.31]	0.687	0.598
≥ 65	84	45 (53.6)	4.2 [2.4; 9.5]	68	37 (54.4)	3.2 [2.0; 5.3]	0.82 [0.53; 1.27]	0.379	
Severity of disease									
ECOG 0	82	54 (65.9)	3.0 [1.7; 3.8]	74	46 (62.2)	3.5 [2.1; 4.1]	1.04 [0.70; 1.54]	0.850	0.239
ECOG ≥ 1	97	51 (52.6)	4.9 [2.6; 8.9]	111	65 (58.6)	2.7 [2.0; 3.9]	0.73 [0.50; 1.05]	0.091	
Region									
EU	30	16 (53.3)	4.2 [1.6; -]	23	13 (56.5)	2.0 [0.7; -]	0.82 [0.40; 1.72]	0.605	0.802
Ex-EU	149	89 (59.7)	3.5 [2.4; 4.7]	162	98 (60.5)	3.0 [2.2; 3.7]	0.86 [0.64; 1.15]	0.305	
Region									
Asia	102	62 (60.8)	3.5 [2.4; 4.9]	103	65 (63.1)	3.1 [2.3; 4.0]	0.80 [0.56; 1.14]	0.208	0.992
Rest of World	77	43 (55.8)	2.8 [1.6; 5.4]	82	46 (56.1)	2.8 [1.2; 3.9]	0.88 [0.58; 1.33]	0.539	
Histology									
Adenocarcinoma	41	24 (58.5)	2.7 [1.3; 14.9]	49	30 (61.2)	3.0 [1.4; 4.1]	0.83 [0.48; 1.44]	0.513	0.988
Squamous Cell Carcinoma	138	81 (58.7)	3.5 [2.7; 4.9]	136	81 (59.6)	2.9 [2.1; 3.7]	0.81 [0.59; 1.12]	0.202	
Disease Status									
Metastatic	169	101 (59.8)	3.5 [2.7; 4.7]	170	104 (61.2)	2.8 [2.1; 3.7]	0.82 [0.62; 1.08]	0.165	0.253
Unresectable - Locally Advanced	10	4 (40.0)	1.4 [0.7; -]	15	7 (46.7)	4.4 [1.1; -]	1.81 [0.51; 6.46]	0.362	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; 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

EORTC QLQ-C30: Symptomskala Verstopfung

Tabelle 4G-21: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Verstopfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Constipation	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	31	15 (48.4)	4.6 [1.6; -]	32	17 (53.1)	4.4 [0.8; -]	0.77 [0.39; 1.55]	0.472	0.776
Male	148	67 (45.3)	4.9 [3.0; -]	153	75 (49.0)	3.7 [3.0; 7.4]	0.87 [0.62; 1.21]	0.397	
Age (Years)									
< 65	95	41 (43.2)	13.2 [2.8; -]	117	64 (54.7)	3.5 [2.1; 4.9]	0.70 [0.47; 1.03]	0.073	0.132
≥ 65	84	41 (48.8)	4.7 [3.0; -]	68	28 (41.2)	7.4 [3.4; -]	1.16 [0.72; 1.88]	0.544	
Severity of disease									
ECOG 0	82	39 (47.6)	5.2 [2.7; -]	74	44 (59.5)	3.0 [1.9; 4.4]	0.67 [0.43; 1.03]	0.070	0.126
ECOG ≥ 1	97	43 (44.3)	4.6 [3.0; -]	111	48 (43.2)	5.8 [3.5; -]	1.01 [0.67; 1.53]	0.972	
Region									
EU	30	12 (40.0)	Not reached [1.6; -]	23	13 (56.5)	2.8 [0.8; -]	0.59 [0.27; 1.29]	0.185	0.256
Ex-EU	149	70 (47.0)	4.6 [3.0; -]	162	79 (48.8)	4.4 [3.1; 7.1]	0.90 [0.65; 1.24]	0.524	
Region									
Asia	102	48 (47.1)	4.2 [3.0; -]	103	50 (48.5)	4.4 [2.7; -]	0.87 [0.59; 1.30]	0.509	0.913
Rest of World	77	34 (44.2)	5.5 [2.3; -]	82	42 (51.2)	3.7 [2.3; 7.4]	0.82 [0.52; 1.29]	0.392	
Histology									
Adenocarcinoma	41	22 (53.7)	3.0 [1.4; -]	49	25 (51.0)	3.5 [2.1; -]	1.00 [0.56; 1.79]	0.993	0.491
Squamous Cell Carcinoma	138	60 (43.5)	5.2 [3.8; -]	136	67 (49.3)	4.4 [3.0; 7.1]	0.81 [0.57; 1.15]	0.228	
Disease Status									
Metastatic	169	78 (46.2)	4.9 [3.7; -]	170	83 (48.8)	4.1 [2.8; 7.4]	0.84 [0.62; 1.15]	0.276	0.713
Unresectable - Locally Advanced	10	4 (40.0)	5.1 [0.7; -]	15	9 (60.0)	4.4 [2.1; 5.8]	1.56 [0.45; 5.39]	0.479	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test

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

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; 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

EORTC QLQ-C30: Symptomskala Diarrhoe

Tabelle 4G-22: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Diarrhoe des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Diarrhea	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	31	13 (41.9)	Not reached [2.3; -]	32	9 (28.1)	Not reached [4.1; -]	1.45 [0.62; 3.39]	0.392	0.746
Male	148	68 (45.9)	5.0 [3.1; 24.9]	153	57 (37.3)	Not reached [3.9; -]	1.18 [0.83; 1.68]	0.359	
Age (Years)									
< 65	95	45 (47.4)	4.9 [2.6; -]	117	39 (33.3)	Not reached [4.1; -]	1.49 [0.97; 2.30]	0.069	0.123
≥ 65	84	36 (42.9)	10.6 [3.0; -]	68	27 (39.7)	5.7 [3.1; -]	0.91 [0.55; 1.50]	0.701	
Severity of disease									
ECOG 0	82	38 (46.3)	10.6 [3.0; -]	74	31 (41.9)	Not reached [3.4; -]	1.01 [0.63; 1.63]	0.959	0.289
ECOG ≥ 1	97	43 (44.3)	4.9 [2.6; -]	111	35 (31.5)	Not reached [4.4; -]	1.42 [0.91; 2.22]	0.127	
Region									
EU	30	17 (56.7)	4.1 [1.2; -]	23	7 (30.4)	Not reached [2.3; -]	1.87 [0.77; 4.54]	0.168	0.202
Ex-EU	149	64 (43.0)	6.9 [3.1; -]	162	59 (36.4)	Not reached [4.0; -]	1.11 [0.78; 1.59]	0.553	
Region									
Asia	102	44 (43.1)	6.9 [3.3; -]	103	37 (35.9)	Not reached [3.9; -]	1.17 [0.75; 1.81]	0.484	0.789
Rest of World	77	37 (48.1)	4.1 [2.3; -]	82	29 (35.4)	Not reached [2.7; -]	1.26 [0.77; 2.06]	0.355	
Histology									
Adenocarcinoma	41	24 (58.5)	3.0 [1.3; 10.6]	49	23 (46.9)	4.1 [1.8; -]	1.17 [0.65; 2.11]	0.591	0.952
Squamous Cell Carcinoma	138	57 (41.3)	12.2 [3.3; -]	136	43 (31.6)	Not reached [5.7; -]	1.23 [0.83; 1.84]	0.308	
Disease Status									
Metastatic	169	79 (46.7)	5.0 [3.0; -]	170	62 (36.5)	Not reached [4.0; -]	1.20 [0.86; 1.68]	0.281	0.897
Unresectable - Locally Advanced	10	2 (20.0)	Not reached [0.7; -]	15	4 (26.7)	Not reached [2.3; -]	1.04 [0.19; 5.71]	0.961	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; 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

EORTC QLQ-OES18

EORTC QLQ-OES18: Symptomskala Essen

Tabelle 4G-23: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Essen des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Eating	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	30	13 (43.3)	11.2 [2.3; -]	30	11 (36.7)	9.6 [2.8; -]	0.93 [0.41; 2.10]	0.868	0.695
Male	148	75 (50.7)	6.1 [4.1; 11.0]	150	81 (54.0)	3.6 [3.0; 5.2]	0.76 [0.55; 1.05]	0.097	
Age (Years)									
< 65	95	49 (51.6)	7.2 [3.3; 12.3]	116	58 (50.0)	4.4 [3.1; 7.1]	0.87 [0.59; 1.28]	0.487	0.292
≥ 65	83	39 (47.0)	6.1 [3.4; -]	64	34 (53.1)	3.5 [2.4; 5.1]	0.67 [0.42; 1.07]	0.096	
Severity of disease									
ECOG 0	82	44 (53.7)	5.3 [3.1; 13.0]	69	37 (53.6)	4.4 [2.8; 5.6]	0.82 [0.52; 1.28]	0.381	0.889
ECOG ≥ 1	96	44 (45.8)	7.6 [3.4; -]	111	55 (49.5)	3.6 [3.0; 7.1]	0.76 [0.51; 1.13]	0.173	
Region									
EU	30	13 (43.3)	13.0 [2.1; -]	23	13 (56.5)	3.1 [2.2; -]	0.61 [0.28; 1.33]	0.212	0.361
Ex-EU	148	75 (50.7)	5.5 [4.1; 11.0]	157	79 (50.3)	4.4 [3.4; 5.5]	0.82 [0.59; 1.12]	0.213	
Region									
Asia	102	51 (50.0)	7.2 [4.2; 12.3]	103	52 (50.5)	4.6 [2.9; 7.1]	0.75 [0.51; 1.12]	0.157	0.991
Rest of World	76	37 (48.7)	5.3 [2.8; 14.9]	77	40 (51.9)	3.5 [2.8; 5.1]	0.80 [0.51; 1.25]	0.327	
Histology									
Adenocarcinoma	41	21 (51.2)	5.3 [3.2; -]	47	23 (48.9)	4.4 [3.0; -]	0.88 [0.48; 1.60]	0.669	0.690
Squamous Cell	137	67	7.2	133	69	3.5	0.75	0.103	

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-OES18 Eating	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Carcinoma		(48.9)	[3.9; 11.2]		(51.9)	[2.9; 5.5]	[0.53; 1.06]		
Disease Status									
Metastatic	168	85 (50.6)	6.7 [4.2; 11.2]	165	84 (50.9)	3.9 [3.0; 5.5]	0.79 [0.58; 1.07]	0.134	0.987
Unresectable - Locally Advanced	10	3 (30.0)	Not reached [1.7; -]	15	8 (53.3)	3.5 [2.1; -]	0.92 [0.24; 3.50]	0.908	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Reflux

Tabelle 4G-24: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Reflux des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-OES18 Reflux	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	30	15 (50.0)	5.0 [3.0; -]	30	17 (56.7)	3.0 [1.4; 11.0]	0.58 [0.28; 1.18]	0.130	0.536
Male	148	65 (43.9)	8.5 [4.0; -]	150	74 (49.3)	4.8 [3.3; 8.4]	0.80 [0.57; 1.12]	0.195	
Age (Years)									
< 65	95	46 (48.4)	5.6 [2.4; 13.2]	116	57 (49.1)	5.5 [3.1; 10.2]	0.92 [0.62; 1.36]	0.681	0.097
≥ 65	83	34 (41.0)	12.7 [4.4; -]	64	34 (53.1)	3.4 [2.3; 5.8]	0.58 [0.36; 0.94]	0.027	
Severity of disease									
ECOG 0	82	38 (46.3)	8.1 [4.2; -]	69	29 (42.0)	8.4 [3.4; 12.0]	0.90 [0.55; 1.47]	0.675	0.470
ECOG ≥ 1	96	42 (43.8)	7.6 [3.0; -]	111	62 (55.9)	3.5 [2.1; 5.0]	0.72 [0.48; 1.06]	0.099	
Region									

EU	30	10 (33.3)	Not reached [3.0; -]	23	14 (60.9)	3.4 [1.4; 8.1]	0.38 [0.16; 0.88]	0.024	0.089
Ex-EU	148	70 (47.3)	5.6 [3.6; 13.2]	157	77 (49.0)	4.4 [3.1; 10.2]	0.86 [0.62; 1.19]	0.357	
Region									
Asia	102	44 (43.1)	8.5 [4.2; -]	103	48 (46.6)	5.5 [3.8; 10.2]	0.84 [0.55; 1.27]	0.408	0.428
Rest of World	76	36 (47.4)	4.9 [2.6; 13.2]	77	43 (55.8)	3.0 [1.4; 6.1]	0.64 [0.41; 1.01]	0.055	
Histology									
Adenocarcinoma	41	18 (43.9)	12.7 [2.3; -]	47	28 (59.6)	2.6 [1.4; 10.2]	0.50 [0.27; 0.92]	0.026	0.156
Squamous Cell Carcinoma	137	62 (45.3)	7.6 [4.2; -]	133	63 (47.4)	5.0 [3.4; 8.4]	0.89 [0.62; 1.27]	0.506	
Disease Status									
Metastatic	168	78 (46.4)	7.6 [4.2; 13.2]	165	83 (50.3)	4.8 [3.3; 8.1]	0.78 [0.57; 1.07]	0.121	0.359
Unresectable - Locally Advanced	10	2 (20.0)	Not reached [0.7; -]	15	8 (53.3)	2.7 [0.7; -]	0.50 [0.11; 2.37]	0.385	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Schmerzen

Tabelle 4G-25: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schmerzen des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Pain	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	30	14 (46.7)	4.2 [2.7; -]	30	15 (50.0)	4.4 [2.1; 8.1]	0.78 [0.38; 1.62]	0.511	0.812
Male	148	74 (50.0)	5.0 [3.2; 12.3]	150	78 (52.0)	4.6 [3.5; 5.6]	0.81 [0.59; 1.12]	0.204	
Age (Years)									
< 65	95	52 (54.7)	3.9 [3.2; 6.5]	116	63 (54.3)	4.4 [3.5; 5.5]	0.92 [0.64; 1.34]	0.669	0.283
≥ 65	83	36 (43.4)	9.6 [3.1; -]	64	30 (46.9)	5.2 [2.3; 8.5]	0.69 [0.42; 1.13]	0.142	

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-OES18 Pain	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Severity of disease									
ECOG 0	82	46 (56.1)	5.0 [3.0; 12.3]	69	36 (52.2)	4.9 [2.9; 8.0]	0.84 [0.54; 1.32]	0.457	0.605
ECOG ≥ 1	96	42 (43.8)	4.2 [3.5; -]	111	57 (51.4)	4.2 [3.0; 5.5]	0.77 [0.51; 1.15]	0.195	
Region									
EU	30	12 (40.0)	5.8 [3.4; -]	23	14 (60.9)	2.5 [1.4; 8.1]	0.47 [0.22; 1.03]	0.059	0.094
Ex-EU	148	76 (51.4)	4.4 [3.2; 8.9]	157	79 (50.3)	4.6 [4.1; 5.6]	0.88 [0.64; 1.21]	0.439	
Region									
Asia	102	52 (51.0)	5.0 [3.2; 12.3]	103	53 (51.5)	4.6 [3.1; 5.6]	0.80 [0.54; 1.17]	0.249	0.916
Rest of World	76	36 (47.4)	5.3 [3.1; -]	77	40 (51.9)	4.6 [3.0; 8.0]	0.83 [0.53; 1.31]	0.429	
Histology									
Adenocarcinoma	41	22 (53.7)	3.9 [2.9; 14.9]	47	27 (57.4)	4.4 [3.1; 8.0]	0.94 [0.53; 1.66]	0.827	0.693
Squamous Cell Carcinoma	137	66 (48.2)	5.2 [3.5; 12.3]	133	66 (49.6)	4.6 [2.9; 5.8]	0.79 [0.56; 1.13]	0.195	
Disease Status									
Metastatic	168	85 (50.6)	5.0 [3.5; 9.6]	165	85 (51.5)	4.6 [3.9; 5.5]	0.80 [0.59; 1.08]	0.146	0.836
Unresectable - Locally Advanced	10	3 (30.0)	Not reached [0.7; -]	15	8 (53.3)	4.6 [1.3; -]	1.07 [0.27; 4.15]	0.924	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Speichelschlucken

Tabelle 4G-26: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Speichelschlucken des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Trouble Swallowing Saliva	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Age (Years)									
< 65	95	39 (41.1)	11.0 [4.7; -]	116	50 (43.1)	5.5 [4.0; 12.5]	0.84 [0.55; 1.29]	0.428	0.297
≥ 65	83	33 (39.8)	9.6 [4.2; -]	64	30 (46.9)	4.4 [2.3; -]	0.62 [0.38; 1.03]	0.063	
Severity of disease									
ECOG 0	82	32 (39.0)	25.8 [5.4; -]	69	28 (40.6)	12.2 [3.9; -]	0.79 [0.47; 1.32]	0.366	0.905
ECOG ≥ 1	96	40 (41.7)	7.9 [3.6; -]	111	52 (46.8)	4.9 [3.4; 8.5]	0.77 [0.51; 1.16]	0.208	
Region									
EU	30	14 (46.7)	7.9 [3.6; -]	23	10 (43.5)	3.5 [2.1; -]	0.86 [0.38; 1.95]	0.721	0.835
Ex-EU	148	58 (39.2)	25.8 [4.9; -]	157	70 (44.6)	5.5 [4.0; 12.2]	0.72 [0.51; 1.03]	0.075	
Region									
Asia	102	36 (35.3)	26.1 [5.4; -]	103	49 (47.6)	5.5 [4.0; -]	0.58 [0.38; 0.91]	0.017	0.101
Rest of World	76	36 (47.4)	7.9 [2.8; -]	77	31 (40.3)	5.1 [3.5; -]	1.02 [0.63; 1.66]	0.922	
Histology									
Adenocarcinoma	41	19 (46.3)	8.3 [2.8; -]	47	21 (44.7)	5.1 [2.6; -]	0.93 [0.50; 1.75]	0.823	0.641
Squamous Cell Carcinoma	137	53 (38.7)	25.8 [4.9; -]	133	59 (44.4)	5.5 [4.0; -]	0.72 [0.49; 1.06]	0.093	
Disease Status									
Metastatic	168	68 (40.5)	11.0 [5.4; 26.1]	165	72 (43.6)	5.5 [4.0; 12.2]	0.76 [0.54; 1.06]	0.108	0.869
Unresectable - Locally Advanced	10	4 (40.0)	4.7 [1.4; -]	15	8 (53.3)	2.3 [0.9; -]	0.79 [0.24; 2.66]	0.707	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Verschlucken

Tabelle 4G-27: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Verschlucken des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Choked when Swallowing	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	30	14 (46.7)	7.2 [2.3; -]	30	14 (46.7)	4.2 [2.9; -]	0.85 [0.40; 1.79]	0.665	0.719
Male	148	52 (35.1)	12.3 [8.5; -]	150	58 (38.7)	7.0 [4.4; 17.1]	0.69 [0.47; 1.01]	0.057	
Age (Years)									
< 65	95	37 (38.9)	8.9 [5.6; 25.8]	116	45 (38.8)	10.1 [4.4; -]	0.85 [0.55; 1.33]	0.475	0.185
≥ 65	83	29 (34.9)	11.1 [7.6; -]	64	27 (42.2)	5.6 [3.4; -]	0.56 [0.33; 0.96]	0.034	
Severity of disease									
ECOG 0	82	30 (36.6)	12.3 [8.9; -]	69	24 (34.8)	10.1 [6.8; -]	0.86 [0.50; 1.49]	0.598	0.314
ECOG ≥ 1	96	36 (37.5)	8.5 [5.6; -]	111	48 (43.2)	4.4 [3.4; -]	0.65 [0.42; 1.00]	0.051	
Region									
EU	30	13 (43.3)	7.9 [3.3; -]	23	8 (34.8)	10.1 [3.5; -]	1.21 [0.50; 2.93]	0.677	0.231
Ex-EU	148	53 (35.8)	12.0 [7.8; -]	157	64 (40.8)	5.6 [4.2; 12.2]	0.64 [0.44; 0.94]	0.021	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Mundtrockenheit

Tabelle 4G-28: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Mundtrockenheit des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-OES18 Dry Mouth	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	30	16 (53.3)	4.2 [1.8; 8.9]	30	17 (56.7)	1.8 [0.8; 2.8]	0.64 [0.32; 1.28]	0.210	0.077
Male	148	86 (58.1)	3.3 [1.6; 5.1]	150	75 (50.0)	3.4 [2.7; -]	1.26 [0.92; 1.71]	0.150	
Age (Years)									
< 65	95	59 (62.1)	3.1 [1.4; 5.3]	116	59 (50.9)	2.8 [2.1; -]	1.23 [0.86; 1.77]	0.261	0.476
≥ 65	83	43 (51.8)	4.1 [1.7; 6.1]	64	33 (51.6)	3.0 [2.3; -]	0.99 [0.63; 1.56]	0.974	
Severity of disease									
ECOG 0	82	46 (56.1)	4.1 [1.5; 7.6]	69	35 (50.7)	3.9 [2.6; -]	1.18 [0.76; 1.83]	0.472	0.808
ECOG ≥ 1	96	56 (58.3)	3.1 [1.6; 4.9]	111	57 (51.4)	2.8 [1.8; 6.7]	1.11 [0.76; 1.60]	0.591	
Region									
EU	30	18 (60.0)	2.6 [1.7; 5.8]	23	11 (47.8)	3.1 [0.8; -]	1.16 [0.55; 2.45]	0.704	0.932
Ex-EU	148	84 (56.8)	3.5 [1.5; 6.1]	157	81 (51.6)	3.0 [2.3; 5.6]	1.12 [0.83; 1.53]	0.452	
Region									
Asia	102	53 (52.0)	4.0 [1.7; 9.9]	103	54 (52.4)	3.0 [2.2; -]	1.02 [0.70; 1.50]	0.906	0.367
Rest of World	76	49 (64.5)	2.6 [1.4; 4.8]	77	38 (49.4)	3.0 [1.6; -]	1.31 [0.86; 2.00]	0.216	
Histology									
Adenocarcinoma	41	28 (68.3)	1.7 [1.4; 3.5]	47	23 (48.9)	3.4 [1.6; -]	1.81 [1.00; 3.27]	0.048	0.176
Squamous Cell Carcinoma	137	74 (54.0)	4.0 [2.1; 8.1]	133	69 (51.9)	3.0 [2.3; 6.7]	1.03 [0.74; 1.44]	0.846	
Disease Status									
Metastatic	168	97 (57.7)	3.5 [1.8; 5.3]	165	83 (50.3)	3.0 [2.3; 5.6]	1.13 [0.84; 1.52]	0.411	0.700
Unresectable - Locally Advanced	10	5 (50.0)	3.3 [0.7; -]	15	9 (60.0)	3.9 [0.7; -]	1.68 [0.55; 5.19]	0.363	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test

for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Geschmackssinn

Tabelle 4G-29: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Geschmackssinn des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Trouble with Taste	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	30	19 (63.3)	2.6 [1.6; 4.6]	30	13 (43.3)	3.1 [1.4; -]	1.34 [0.66; 2.73]	0.415	0.312
Male	148	79 (53.4)	3.0 [2.1; 5.0]	150	85 (56.7)	3.3 [2.4; 4.2]	0.95 [0.70; 1.29]	0.726	
Age (Years)									
< 65	95	48 (50.5)	3.7 [1.7; -]	116	64 (55.2)	3.1 [2.3; 4.2]	0.89 [0.61; 1.30]	0.539	0.406
≥ 65	83	50 (60.2)	2.6 [1.6; 4.4]	64	34 (53.1)	3.4 [2.1; 5.3]	1.14 [0.74; 1.76]	0.555	
Severity of disease									
ECOG 0	82	50 (61.0)	2.4 [1.6; 4.0]	69	43 (62.3)	3.0 [2.1; 3.7]	0.97 [0.64; 1.46]	0.879	0.836
ECOG ≥ 1	96	48 (50.0)	4.2 [2.1; 10.2]	111	55 (49.5)	4.1 [2.7; 5.5]	1.01 [0.68; 1.48]	0.975	
Region									
EU	30	17 (56.7)	4.4 [1.6; -]	23	15 (65.2)	2.1 [0.9; 3.7]	0.63 [0.31; 1.27]	0.197	0.149
Ex-EU	148	81 (54.7)	2.8 [2.1; 4.2]	157	83 (52.9)	3.5 [2.8; 4.6]	1.08 [0.79; 1.47]	0.620	
Region									
Asia	102	55 (53.9)	3.1 [2.2; 10.2]	103	47 (45.6)	5.1 [3.4; -]	1.24 [0.84; 1.84]	0.275	0.062
Rest of World	76	43 (56.6)	2.1 [1.4; 4.6]	77	51 (66.2)	2.1 [1.6; 2.8]	0.75 [0.50; 1.13]	0.171	
Histology									
Adenocarcinoma	41	28 (68.3)	1.4 [1.3; 3.0]	47	35 (74.5)	2.0 [1.4; 2.8]	0.87 [0.52; 1.44]	0.576	0.415
Squamous Cell Carcinoma	137	70 (51.1)	4.0 [2.4; 10.2]	133	63 (47.4)	4.2 [3.0; 5.5]	1.07 [0.76; 1.51]	0.686	
Disease Status									
Metastatic	168	96 (57.1)	2.8 [2.1; 4.2]	165	89 (53.9)	3.4 [2.8; 4.2]	1.05 [0.79; 1.40]	0.738	0.112
Unresectable - Locally Advanced	10	2 (20.0)	Not reached [0.7; -]	15	9 (60.0)	2.1 [0.8; -]	0.36 [0.08; 1.69]	0.197	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Husten

Tabelle 4G-30: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Husten des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Trouble with Coughing	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	30	11 (36.7)	11.2 [3.7; -]	30	10 (33.3)	Not reached [3.5; -]	0.91 [0.38; 2.17]	0.835	0.844
Male	148	53 (35.8)	Not reached [5.2; -]	150	58 (38.7)	7.7 [5.3; -]	0.83 [0.57; 1.21]	0.331	
Age (Years)									
< 65	95	36 (37.9)	Not reached [4.4; -]	116	42 (36.2)	12.9 [5.0; -]	1.05 [0.67; 1.64]	0.842	0.199
≥ 65	83	28 (33.7)	Not reached [5.8; -]	64	26 (40.6)	7.8 [3.9; -]	0.63 [0.37; 1.08]	0.095	
Severity of disease									
ECOG 0	82	29 (35.4)	Not reached [5.2; -]	69	29 (42.0)	7.7 [3.7; -]	0.69 [0.41; 1.16]	0.161	0.298
ECOG ≥ 1	96	35 (36.5)	11.2 [4.9; -]	111	39 (35.1)	7.8 [5.4; -]	0.99 [0.62; 1.57]	0.963	
Region									
EU	30	11 (36.7)	Not reached [5.2; -]	23	10 (43.5)	4.2 [2.0; -]	0.74 [0.31; 1.74]	0.482	0.618
Ex-EU	148	53 (35.8)	13.2 [5.2; -]	157	58 (36.9)	7.8 [5.4; -]	0.87 [0.59; 1.26]	0.450	
Histology									
Adenocarcinoma	41	19 (46.3)	4.7 [2.7; -]	47	19 (40.4)	7.7 [4.2; -]	1.32 [0.70; 2.52]	0.393	0.147
Squamous Cell Carcinoma	137	45 (32.8)	Not reached [8.6; -]	133	49 (36.8)	7.8 [5.3; -]	0.73 [0.48; 1.10]	0.131	
Disease Status									
Metastatic	168	61 (36.3)	Not reached [7.0; -]	165	62 (37.6)	7.8 [5.3; -]	0.85 [0.60; 1.22]	0.375	0.885
Unresectable - Locally Advanced	10	3 (30.0)	4.7 [1.7; -]	15	6 (40.0)	5.8 [0.9; -]	1.11 [0.26; 4.65]	0.890	
a: Database Cutoff Date: 02JUL2020									

b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Sprechen

Tabelle 4G-31: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Sprechen des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Trouble Talking	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	30	10 (33.3)	13.2 [5.9; -]	30	8 (26.7)	10.1 [3.0; -]	0.84 [0.32; 2.22]	0.725	0.812
Male	148	50 (33.8)	24.3 [9.3; -]	150	51 (34.0)	Not reached [5.5; -]	0.96 [0.65; 1.43]	0.841	
Age (Years)									
< 65	95	35 (36.8)	13.2 [7.6; 25.3]	116	36 (31.0)	Not reached [10.1; -]	1.10 [0.68; 1.78]	0.687	0.233
≥ 65	83	25 (30.1)	Not reached [11.1; -]	64	23 (35.9)	6.7 [4.7; -]	0.76 [0.43; 1.35]	0.352	
Severity of disease									
ECOG 0	82	29 (35.4)	24.3 [9.3; -]	69	23 (33.3)	10.1 [5.3; -]	0.89 [0.51; 1.56]	0.681	0.798
ECOG ≥ 1	96	31 (32.3)	Not reached [5.1; -]	111	36 (32.4)	Not reached [5.3; -]	1.03 [0.64; 1.67]	0.901	
Region									
EU	30	9 (30.0)	24.3 [5.0; -]	23	7 (30.4)	Not reached [2.3; -]	0.84 [0.30; 2.31]	0.734	0.756
Ex-EU	148	51 (34.5)	25.3 [9.3; -]	157	52 (33.1)	Not reached [5.5; -]	0.98 [0.67; 1.46]	0.937	
Region									
Asia	102	36 (35.3)	25.3 [7.6; -]	103	36 (35.0)	7.0 [5.5; -]	0.89 [0.56; 1.43]	0.643	0.801
Rest of World	76	24 (31.6)	24.3 [9.3; -]	77	23 (29.9)	Not reached [4.7; -]	0.98 [0.55; 1.76]	0.944	
Histology									
Adenocarcinoma	41	15 (36.6)	24.3 [2.8; -]	47	13 (27.7)	Not reached [4.7; -]	1.33 [0.62; 2.84]	0.461	0.377
Squamous Cell	137	45	25.3	133	46	10.1	0.83	0.384	

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-OES18 Trouble Talking	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Carcinoma		(32.8)	[11.1; -]		(34.6)	[5.5; -]	[0.54; 1.26]		
Disease Status									
Metastatic	168	57 (33.9)	24.3 [11.1; -]	165	54 (32.7)	Not reached [5.6; -]	0.94 [0.64; 1.37]	0.735	0.601
Unresectable - Locally Advanced	10	3 (30.0)	Not reached [1.0; -]	15	5 (33.3)	Not reached [3.6; -]	1.39 [0.33; 5.83]	0.655	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Dysphagie

Tabelle 4G-32: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Dysphagie des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-OES18 Dysphagia	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	30	16 (53.3)	3.0 [1.4; -]	30	14 (46.7)	3.5 [0.8; -]	1.02 [0.50; 2.10]	0.955	0.872
Male	148	85 (57.4)	3.0 [1.7; 4.2]	150	91 (60.7)	3.1 [2.5; 4.1]	0.93 [0.69; 1.25]	0.619	
Severity of disease									
ECOG 0	82	50 (61.0)	3.0 [1.7; 4.2]	69	43 (62.3)	2.9 [1.6; 5.3]	0.96 [0.64; 1.45]	0.853	0.935
ECOG ≥ 1	96	51 (53.1)	2.8 [1.4; 8.4]	111	62 (55.9)	3.3 [2.5; 4.9]	0.92 [0.63; 1.33]	0.644	
Region									
EU	30	16 (53.3)	3.7 [1.4; -]	23	15 (65.2)	2.3 [0.7; 7.4]	0.65 [0.32; 1.32]	0.238	0.276
Ex-EU	148	85 (57.4)	3.0 [1.6; 4.2]	157	90 (57.3)	3.3 [2.7; 4.1]	1.00 [0.74; 1.35]	0.990	
Region									

Asia	102	59 (57.8)	3.0 [1.6; 5.1]	103	63 (61.2)	3.1 [2.4; 4.1]	0.89 [0.62; 1.27]	0.508	0.706
Rest of World	76	42 (55.3)	2.6 [1.4; 5.3]	77	42 (54.5)	3.0 [1.7; 7.4]	0.99 [0.65; 1.53]	0.980	
Histology									
Adenocarcinoma	41	22 (53.7)	3.7 [1.6; -]	47	24 (51.1)	3.5 [2.1; -]	0.98 [0.55; 1.76]	0.942	0.981
Squamous Cell Carcinoma	137	79 (57.7)	2.8 [1.6; 3.8]	133	81 (60.9)	3.0 [2.3; 3.7]	0.92 [0.67; 1.26]	0.593	
Disease Status									
Metastatic	168	97 (57.7)	3.0 [2.0; 4.2]	165	96 (58.2)	3.3 [2.7; 4.1]	0.94 [0.71; 1.25]	0.674	0.802
Unresectable - Locally Advanced	10	4 (40.0)	1.7 [0.7; -]	15	9 (60.0)	2.5 [1.1; -]	1.14 [0.35; 3.71]	0.832	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EQ-5D VAS

EQ-5D VAS (7 Punkte)

Tabelle 4G-33: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS (7 Punkte) aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EQ-5D VAS (7 Points)	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	31	20 (64.5)	3.5 [0.9; 5.9]	31	17 (54.8)	4.1 [1.4; 10.1]	1.13 [0.59; 2.17]	0.704	0.667
Male	149	100 (67.1)	3.2 [2.3; 4.1]	152	98 (64.5)	3.0 [2.3; 4.1]	0.99 [0.75; 1.31]	0.939	
Age (Years)									
< 65	96	66 (68.8)	3.2 [2.5; 4.1]	118	71 (60.2)	3.6 [2.8; 4.9]	1.09 [0.78; 1.53]	0.603	0.359
≥ 65	84	54 (64.3)	3.2 [2.0; 4.4]	65	44 (67.7)	2.7 [1.7; 4.4]	0.88 [0.59; 1.31]	0.537	
Severity of disease									
ECOG 0	82	59 (72.0)	2.4 [1.4; 4.1]	71	51 (71.8)	3.5 [2.8; 4.6]	1.13 [0.78; 1.64]	0.528	0.398

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EQ-5D VAS (7 Points)	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
ECOG ≥ 1	98	61 (62.2)	3.5 [2.7; 4.7]	112	64 (57.1)	2.8 [2.0; 4.7]	0.91 [0.64; 1.29]	0.600	
Region									
EU	30	22 (73.3)	3.7 [2.0; 4.9]	24	18 (75.0)	2.8 [1.4; 4.9]	0.90 [0.48; 1.69]	0.741	0.601
Ex-EU	150	98 (65.3)	3.0 [2.2; 3.9]	159	97 (61.0)	3.0 [2.6; 4.6]	1.05 [0.79; 1.39]	0.754	
Region									
Asia	103	71 (68.9)	2.7 [1.8; 3.9]	103	67 (65.0)	3.0 [2.3; 3.7]	1.05 [0.75; 1.48]	0.762	0.911
Rest of World	77	49 (63.6)	3.7 [2.5; 4.6]	80	48 (60.0)	3.7 [2.0; 7.2]	1.00 [0.67; 1.49]	0.994	
Histology									
Adenocarcinoma	41	24 (58.5)	4.8 [3.2; 9.3]	49	27 (55.1)	4.5 [2.8; 8.1]	0.83 [0.47; 1.48]	0.529	0.708
Squamous Cell Carcinoma	139	96 (69.1)	2.7 [2.0; 3.5]	134	88 (65.7)	2.8 [2.1; 3.5]	1.08 [0.80; 1.44]	0.626	
Disease Status									
Metastatic	169	115 (68.0)	3.1 [2.3; 4.1]	168	107 (63.7)	3.0 [2.2; 4.4]	1.00 [0.77; 1.31]	0.986	0.999
Unresectable - Locally Advanced	11	5 (45.5)	3.9 [1.4; -]	15	8 (53.3)	3.5 [2.1; -]	0.97 [0.31; 3.00]	0.960	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 7 points or more decrease from baseline

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; EQ-5D: European Quality of Life 5 Dimensions; PD-L1: Programmed Cell Death - Ligand 1; VAS: Visual Analog Scale

EQ-5D VAS (10 Punkte)

Tabelle 4G-34: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS (10 Punkte) aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EQ-5D VAS (10 Points)	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EQ-5D VAS (10 Points)	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Female	31	19 (61.3)	4.6 [1.0; 12.4]	31	16 (51.6)	4.1 [2.1; 10.1]	1.06 [0.54; 2.08]	0.856	0.746
Male	149	96 (64.4)	3.3 [2.4; 4.1]	152	96 (63.2)	3.3 [2.6; 4.6]	0.96 [0.72; 1.27]	0.762	
Age (Years)									
< 65	96	63 (65.6)	3.3 [2.7; 4.2]	118	70 (59.3)	4.1 [2.8; 4.9]	1.05 [0.74; 1.47]	0.794	0.399
≥ 65	84	52 (61.9)	3.5 [2.1; 4.7]	65	42 (64.6)	2.8 [1.7; 4.5]	0.86 [0.57; 1.30]	0.476	
Severity of disease									
ECOG 0	82	58 (70.7)	3.3 [1.6; 4.1]	71	48 (67.6)	4.1 [2.9; 4.7]	1.14 [0.78; 1.67]	0.511	0.269
ECOG ≥ 1	98	57 (58.2)	3.6 [2.7; 4.9]	112	64 (57.1)	2.8 [2.1; 4.7]	0.85 [0.59; 1.22]	0.377	
Region									
EU	30	21 (70.0)	4.1 [2.0; 5.5]	24	16 (66.7)	4.4 [1.4; 7.4]	0.97 [0.50; 1.86]	0.920	0.870
Ex-EU	150	94 (62.7)	3.2 [2.4; 4.2]	159	96 (60.4)	3.3 [2.7; 4.7]	0.99 [0.74; 1.32]	0.943	
Region									
Asia	103	68 (66.0)	3.2 [2.0; 4.2]	103	66 (64.1)	3.0 [2.3; 4.1]	1.00 [0.71; 1.40]	0.982	0.924
Rest of World	77	47 (61.0)	3.9 [2.7; 4.9]	80	46 (57.5)	4.5 [2.1; 7.4]	0.99 [0.66; 1.50]	0.977	
Histology									
Adenocarcinoma	41	22 (53.7)	7.8 [3.6; 13.8]	49	27 (55.1)	4.9 [3.0; 8.1]	0.78 [0.43; 1.41]	0.410	0.632
Squamous Cell Carcinoma	139	93 (66.9)	2.8 [2.1; 3.9]	134	85 (63.4)	2.9 [2.2; 3.6]	1.03 [0.76; 1.38]	0.857	
Disease Status									
Metastatic	169	110 (65.1)	3.2 [2.5; 4.2]	168	105 (62.5)	3.0 [2.6; 4.6]	0.96 [0.73; 1.25]	0.748	0.765
Unresectable - Locally Advanced	11	5 (45.5)	3.9 [1.4; -]	15	7 (46.7)	4.7 [2.1; -]	1.13 [0.36; 3.62]	0.831	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; EQ-5D: European Quality of Life 5 Dimensions; PD-L1: Programmed Cell Death - Ligand 1; VAS: Visual Analog Scale

Anhang 4-G9.3: Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-35: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den globalen Gesundheitsstatus des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Global Health Status	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	31	19 (61.3)	3.6 [2.1; 9.9]	32	13 (40.6)	3.7 [2.1; -]	1.21 [0.59; 2.45]	0.604	0.531
Male	148	87 (58.8)	2.9 [2.1; 4.5]	153	92 (60.1)	3.5 [2.8; 4.7]	0.99 [0.74; 1.33]	0.956	
Age (Years)									
< 65	95	55 (57.9)	3.6 [2.1; 5.3]	117	63 (53.8)	4.1 [3.0; 8.3]	1.07 [0.75; 1.54]	0.704	0.471
≥ 65	84	51 (60.7)	2.8 [1.9; 4.7]	68	42 (61.8)	2.9 [2.0; 4.6]	0.91 [0.61; 1.37]	0.655	
Severity of disease									
ECOG 0	82	53 (64.6)	2.9 [2.1; 4.7]	74	47 (63.5)	3.7 [2.3; 4.8]	1.06 [0.72; 1.57]	0.771	0.784
ECOG ≥ 1	97	53 (54.6)	3.6 [1.9; 7.0]	111	58 (52.3)	3.5 [2.7; 5.7]	0.98 [0.68; 1.43]	0.935	
Region									
EU	30	20 (66.7)	2.8 [1.4; 9.9]	23	13 (56.5)	3.5 [1.4; 10.1]	1.13 [0.56; 2.27]	0.739	0.788
Ex-EU	149	86 (57.7)	3.5 [2.1; 4.6]	162	92 (56.8)	3.7 [2.9; 4.8]	1.00 [0.75; 1.35]	0.977	
Region									
Asia	102	58 (56.9)	3.6 [2.1; 5.3]	103	65 (63.1)	3.4 [2.1; 4.0]	0.86 [0.60; 1.22]	0.399	0.127
Rest of World	77	48 (62.3)	3.3 [1.6; 5.1]	82	40 (48.8)	4.7 [3.1; 10.2]	1.29 [0.85; 1.96]	0.236	
Histology									
Adenocarcinoma	41	24 (58.5)	3.7 [1.6; 7.8]	49	24 (49.0)	5.6 [4.1; 12.2]	1.14 [0.63; 2.04]	0.665	0.454
Squamous Cell Carcinoma	138	82 (59.4)	3.2 [2.1; 4.2]	136	81 (59.6)	3.4 [2.1; 3.7]	0.97 [0.72; 1.33]	0.868	
Disease Status									
Metastatic	169	99 (58.6)	3.5 [2.2; 4.7]	170	97 (57.1)	3.7 [2.8; 4.8]	0.97 [0.73; 1.28]	0.809	0.062
Unresectable - Locally Advanced	10	7 (70.0)	1.5 [0.7; 3.5]	15	8 (53.3)	3.7 [2.1; -]	3.42 [1.17; 9.98]	0.025	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Global Health Status	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]

ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; 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

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-36: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Physical Functioning	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	31	17 (54.8)	4.3 [1.5; 7.2]	32	18 (56.3)	2.2 [1.7; -]	0.75 [0.38; 1.46]	0.394	0.445
Male	148	91 (61.5)	3.6 [2.8; 4.4]	153	93 (60.8)	3.4 [2.8; 4.2]	0.94 [0.70; 1.26]	0.699	
Age (Years)									
< 65	95	60 (63.2)	4.0 [2.2; 4.5]	117	70 (59.8)	3.1 [2.8; 4.6]	1.01 [0.71; 1.43]	0.948	0.323
≥ 65	84	48 (57.1)	3.6 [3.0; 5.9]	68	41 (60.3)	3.0 [2.1; 4.2]	0.81 [0.53; 1.23]	0.318	
Severity of disease									
ECOG 0	82	52 (63.4)	4.1 [2.6; 5.5]	74	51 (68.9)	3.0 [2.5; 4.2]	0.79 [0.53; 1.16]	0.230	0.354
ECOG ≥ 1	97	56 (57.7)	3.4 [2.1; 4.5]	111	60 (54.1)	3.0 [2.3; 4.6]	1.03 [0.71; 1.49]	0.881	
Region									
EU	30	18 (60.0)	4.1 [1.7; 10.9]	23	15 (65.2)	3.1 [1.4; 8.1]	0.90 [0.45; 1.79]	0.759	0.907
Ex-EU	149	90 (60.4)	3.6 [2.8; 4.4]	162	96 (59.3)	3.0 [2.8; 3.7]	0.91 [0.68; 1.22]	0.538	
Region									
Asia	102	56 (54.9)	4.3 [3.5; 6.0]	103	60 (58.3)	3.2 [2.8; 4.6]	0.80 [0.55; 1.16]	0.241	0.243
Rest of World	77	52 (67.5)	3.2 [1.4; 4.1]	82	51 (62.2)	3.0 [2.1; 4.3]	1.10 [0.74; 1.62]	0.642	
Histology									
Adenocarcinoma	41	25 (61.0)	4.1 [1.4; 10.9]	49	29 (59.2)	3.7 [2.8; 8.0]	1.16 [0.66; 2.02]	0.608	0.531

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Physical Functioning	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Squamous Cell Carcinoma	138	83 (60.1)	3.6 [2.8; 4.4]	136	82 (60.3)	2.9 [2.5; 3.6]	0.89 [0.65; 1.22]	0.474	
Disease Status									
Metastatic	169	103 (60.9)	3.6 [3.0; 4.4]	170	99 (58.2)	3.4 [2.8; 4.3]	0.93 [0.71; 1.23]	0.627	0.884
Unresectable - Locally Advanced	10	5 (50.0)	2.6 [0.7; -]	15	12 (80.0)	2.5 [1.5; 3.0]	0.81 [0.28; 2.31]	0.692	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; 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

EORTC QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-37: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Rollenfunktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Role Functioning	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	31	20 (64.5)	2.8 [1.4; 6.8]	32	21 (65.6)	2.1 [1.2; 2.9]	0.76 [0.41; 1.41]	0.388	0.328
Male	148	97 (65.5)	2.4 [1.4; 4.0]	153	93 (60.8)	2.7 [2.1; 4.4]	1.08 [0.81; 1.43]	0.611	
Age (Years)									
< 65	95	59 (62.1)	3.6 [1.6; 5.5]	117	70 (59.8)	2.8 [2.1; 4.8]	0.98 [0.69; 1.38]	0.890	0.927
≥ 65	84	58 (69.0)	2.1 [1.2; 3.3]	68	44 (64.7)	2.1 [1.5; 2.8]	1.05 [0.71; 1.56]	0.805	
Severity of disease									
ECOG 0	82	58 (70.7)	2.4 [1.5; 4.1]	74	50 (67.6)	2.8 [1.6; 3.4]	0.97 [0.66; 1.42]	0.873	0.788
ECOG ≥ 1	97	59 (60.8)	3.0 [1.3; 3.6]	111	64 (57.7)	2.3 [1.8; 4.8]	1.07 [0.75; 1.52]	0.718	

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Role Functioning	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Region									
EU	30	19 (63.3)	2.4 [1.4; 10.6]	23	13 (56.5)	2.8 [1.4; -]	1.11 [0.55; 2.26]	0.773	0.868
Ex-EU	149	98 (65.8)	2.6 [1.4; 3.6]	162	101 (62.3)	2.4 [2.1; 3.1]	1.01 [0.76; 1.33]	0.961	
Region									
Asia	102	66 (64.7)	2.7 [1.6; 4.4]	103	64 (62.1)	2.4 [2.1; 3.1]	0.96 [0.68; 1.35]	0.801	0.507
Rest of World	77	51 (66.2)	2.4 [1.2; 4.0]	82	50 (61.0)	2.8 [1.5; 5.0]	1.12 [0.76; 1.66]	0.565	
Histology									
Adenocarcinoma	41	28 (68.3)	3.0 [1.2; 5.5]	49	29 (59.2)	2.8 [1.2; 8.0]	1.05 [0.61; 1.81]	0.847	0.844
Squamous Cell Carcinoma	138	89 (64.5)	2.4 [1.4; 3.6]	136	85 (62.5)	2.3 [2.1; 3.0]	1.03 [0.76; 1.39]	0.868	
Disease Status									
Metastatic	169	111 (65.7)	2.7 [1.6; 4.0]	170	104 (61.2)	2.8 [2.1; 3.4]	1.00 [0.76; 1.31]	0.987	0.346
Unresectable - Locally Advanced	10	6 (60.0)	1.5 [0.7; 3.3]	15	10 (66.7)	1.8 [0.9; -]	1.61 [0.57; 4.54]	0.367	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; 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

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-38: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Emotional Functioning	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Patients with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	31	9 (29.0)	Not reached [6.9; -]	32	11 (34.4)	10.0 [1.6; -]	0.57 [0.23; 1.40]	0.222	0.475

Male	148	68 (45.9)	8.2 [4.1; 21.0]	153	74 (48.4)	5.5 [4.1; 8.0]	0.87 [0.62; 1.21]	0.400	
Age (Years)									
< 65	95	41 (43.2)	8.2 [3.9; -]	117	58 (49.6)	5.5 [4.0; 8.0]	0.78 [0.52; 1.17]	0.234	0.777
≥ 65	84	36 (42.9)	10.1 [5.2; -]	68	27 (39.7)	7.4 [3.2; -]	0.90 [0.54; 1.50]	0.698	
Severity of disease									
ECOG 0	82	40 (48.8)	7.8 [4.4; -]	74	29 (39.2)	9.4 [7.2; 10.0]	1.12 [0.69; 1.82]	0.656	0.121
ECOG ≥ 1	97	37 (38.1)	14.1 [6.9; -]	111	56 (50.5)	4.2 [3.5; 6.3]	0.65 [0.43; 1.00]	0.051	
Region									
EU	30	12 (40.0)	14.1 [2.1; -]	23	12 (52.2)	3.7 [1.6; -]	0.62 [0.27; 1.39]	0.244	0.433
Ex-EU	149	65 (43.6)	8.2 [5.2; -]	162	73 (45.1)	7.1 [4.2; 9.0]	0.85 [0.60; 1.19]	0.343	
Region									
Asia	102	40 (39.2)	21.0 [5.4; -]	103	46 (44.7)	6.3 [4.1; 9.0]	0.72 [0.47; 1.12]	0.147	0.323
Rest of World	77	37 (48.1)	7.0 [2.3; 14.1]	82	39 (47.6)	7.2 [3.5; 9.7]	0.97 [0.61; 1.52]	0.886	
Disease Status									
Metastatic	169	75 (44.4)	10.1 [5.4; -]	170	77 (45.3)	7.1 [4.2; 8.8]	0.84 [0.61; 1.16]	0.298	0.340
Unresectable - Locally Advanced	10	2 (20.0)	Not reached [1.4; -]	15	8 (53.3)	3.5 [2.1; -]	0.42 [0.09; 1.99]	0.276	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; 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

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-39: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Kognitive Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Cognitive Functioning	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Patients with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	31	18 (58.1)	2.8 [1.5; -]	32	20 (62.5)	1.8 [0.8; 3.7]	0.67 [0.35; 1.26]	0.214	0.146
Male	148	88	3.3	153	89	4.1	0.97	0.849	

		(59.5)	[2.6; 4.3]		(58.2)	[3.2; 4.9]	[0.72; 1.31]		
Age (Years)									
< 65	95	59 (62.1)	2.8 [2.1; 3.5]	117	70 (59.8)	3.9 [3.2; 4.7]	1.11 [0.78; 1.58]	0.563	0.112
≥ 65	84	47 (56.0)	3.7 [2.8; 5.5]	68	39 (57.4)	2.7 [1.6; 5.8]	0.73 [0.47; 1.12]	0.150	
Severity of disease									
ECOG 0	82	56 (68.3)	2.8 [2.3; 3.7]	74	43 (58.1)	3.9 [3.0; 7.0]	1.19 [0.79; 1.78]	0.399	0.071
ECOG ≥ 1	97	50 (51.5)	3.1 [2.6; 12.7]	111	66 (59.5)	3.2 [2.3; 4.2]	0.73 [0.50; 1.06]	0.103	
Region									
EU	30	18 (60.0)	4.9 [1.7; 12.5]	23	13 (56.5)	4.2 [1.4; 7.4]	0.83 [0.40; 1.71]	0.608	0.708
Ex-EU	149	88 (59.1)	3.1 [2.6; 3.7]	162	96 (59.3)	3.7 [2.8; 4.4]	0.95 [0.70; 1.27]	0.707	
Region									
Asia	102	58 (56.9)	3.5 [2.6; 8.2]	103	60 (58.3)	3.7 [2.8; 4.9]	0.87 [0.60; 1.26]	0.468	0.659
Rest of World	77	48 (62.3)	2.9 [2.0; 3.5]	82	49 (59.8)	3.7 [2.3; 4.3]	1.02 [0.68; 1.52]	0.936	
Histology									
Adenocarcinoma	41	27 (65.9)	2.8 [1.6; 4.3]	49	31 (63.3)	3.7 [2.3; 5.3]	0.94 [0.55; 1.61]	0.832	0.814
Squamous Cell Carcinoma	138	79 (57.2)	3.3 [2.7; 4.6]	136	78 (57.4)	3.7 [2.8; 4.9]	0.92 [0.67; 1.27]	0.609	
Disease Status									
Metastatic	169	102 (60.4)	3.1 [2.7; 4.1]	170	101 (59.4)	3.7 [2.9; 4.4]	0.91 [0.69; 1.20]	0.506	0.818
Unresectable - Locally Advanced	10	4 (40.0)	2.6 [1.0; -]	15	8 (53.3)	2.3 [1.5; -]	1.11 [0.32; 3.80]	0.869	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; 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

EORTC QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-40: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Soziale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**		**Chemotherapy[b]**		**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**	
	Patients	**Median**	**Patients**	**Median**		

EORTC QLQ-C30 Social Functioning	N[c]	with Event[d] n (%)	Time[e] in Months [95 %-CI]	N[c]	with Event[d] n (%)	Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	31	19 (61.3)	3.6 [1.7; -]	32	15 (46.9)	2.1 [1.1; -]	0.85 [0.43; 1.70]	0.651	0.928
Male	148	82 (55.4)	4.7 [2.8; 5.7]	153	85 (55.6)	3.6 [2.6; 4.6]	0.88 [0.65; 1.20]	0.409	
Age (Years)									
< 65	95	53 (55.8)	3.6 [2.1; 5.7]	117	62 (53.0)	3.7 [2.8; 5.0]	1.02 [0.71; 1.48]	0.900	0.242
≥ 65	84	48 (57.1)	4.7 [3.2; 15.5]	68	38 (55.9)	2.6 [1.7; 5.3]	0.73 [0.47; 1.13]	0.156	
Severity of disease									
ECOG 0	82	50 (61.0)	3.7 [2.1; 4.9]	74	45 (60.8)	2.9 [2.2; 4.2]	0.87 [0.58; 1.31]	0.516	0.792
ECOG ≥ 1	97	51 (52.6)	4.9 [2.6; 13.1]	111	55 (49.5)	3.9 [2.3; 5.5]	0.89 [0.60; 1.30]	0.540	
Region									
EU	30	18 (60.0)	2.6 [1.5; -]	23	13 (56.5)	2.3 [0.9; -]	0.93 [0.45; 1.89]	0.835	0.937
Ex-EU	149	83 (55.7)	4.4 [3.0; 5.4]	162	87 (53.7)	3.6 [2.4; 4.2]	0.88 [0.64; 1.19]	0.397	
Region									
Asia	102	56 (54.9)	4.7 [3.5; 15.5]	103	58 (56.3)	3.0 [2.2; 5.2]	0.77 [0.53; 1.12]	0.176	0.391
Rest of World	77	45 (58.4)	3.2 [1.6; 5.3]	82	42 (51.2)	3.7 [2.3; 5.0]	1.06 [0.70; 1.62]	0.786	
Histology									
Adenocarcinoma	41	25 (61.0)	3.2 [1.6; 7.1]	49	28 (57.1)	3.7 [1.6; 4.2]	0.94 [0.54; 1.62]	0.811	0.931
Squamous Cell Carcinoma	138	76 (55.1)	4.4 [3.0; 5.7]	136	72 (52.9)	3.2 [2.3; 5.2]	0.84 [0.61; 1.17]	0.312	
Disease Status									
Metastatic	169	97 (57.4)	4.2 [3.0; 5.3]	170	96 (56.5)	3.0 [2.3; 4.2]	0.82 [0.62; 1.10]	0.185	0.099
Unresectable - Locally Advanced	10	4 (40.0)	1.7 [0.7; -]	15	4 (26.7)	Not reached [2.3; -]	3.47 [0.77; 15.64]	0.105	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with PD-L1 CPS≥10, participants with baseline

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

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

f: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) for histology. Based on Cox regression model with treatment as a covariate for other subgroups

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

h: Based on Cox regression model with treatment, histology, geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1) as covariates, and treatment-by-histology interaction for histology (p-value of likelihood ratio test for interaction term). Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction for other subgroups (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; 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

Anhang 4-G9.4: Nebenwirkungen

Unerwünschte Ereignisse

Unerwünschte Ereignisse gesamt

Tabelle 4G-41: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	33	33 (100.0)	0.6 [0.4; 0.9]	35	35 (100.0)	0.4 [0.3; 0.7]	0.86 [0.53; 1.39]	0.535	0.071
Male	152	152 (100.0)	0.4 [0.3; 0.4]	158	157 (99.4)	0.4 [0.4; 0.6]	1.40 [1.12; 1.77]	0.004	
Age category									
< 65	99	99 (100.0)	0.4 [0.3; 0.4]	124	124 (100.0)	0.5 [0.3; 0.6]	1.28 [0.98; 1.67]	0.073	0.761
≥ 65	86	86 (100.0)	0.4 [0.3; 0.4]	69	68 (98.6)	0.4 [0.3; 0.6]	1.23 [0.89; 1.70]	0.208	
Severity of disease									
ECOG 0	84	84 (100.0)	0.4 [0.3; 0.4]	78	78 (100.0)	0.4 [0.3; 0.6]	1.15 [0.84; 1.57]	0.373	0.399
ECOG ≥ 1	101	101 (100.0)	0.4 [0.4; 0.6]	115	114 (99.1)	0.6 [0.4; 0.7]	1.37 [1.04; 1.81]	0.025	
Region									
EU	30	30 (100.0)	0.4 [0.3; 0.6]	24	24 (100.0)	0.4 [0.3; 1.0]	1.48 [0.85; 2.59]	0.163	0.707
Ex-EU	155	155 (100.0)	0.4 [0.3; 0.4]	169	168 (99.4)	0.4 [0.4; 0.6]	1.26 [1.01; 1.57]	0.041	
Region									
Asia	104	104 (100.0)	0.4 [0.3; 0.4]	104	104 (100.0)	0.4 [0.4; 0.6]	1.45 [1.09; 1.92]	0.010	0.149
Rest of World	81	81 (100.0)	0.4 [0.3; 0.6]	89	88 (98.9)	0.4 [0.3; 0.7]	1.09 [0.80; 1.48]	0.575	
Histology									
Adenocarcinoma	42	42 (100.0)	0.4 [0.3; 0.4]	53	52 (98.1)	0.3 [0.3; 0.7]	1.33 [0.88; 2.02]	0.174	0.670
Squamous Cell Carcinoma	143	143 (100.0)	0.4 [0.3; 0.4]	140	140 (100.0)	0.4 [0.4; 0.6]	1.28 [1.01; 1.62]	0.042	
Disease Status									
Metastatic	174	174 (100.0)	0.4 [0.3; 0.4]	178	177 (99.4)	0.4 [0.3; 0.6]	1.28 [1.03; 1.58]	0.023	0.827
Unresectable - Locally Advanced	11	11 (100.0)	0.7 [0.1; 1.3]	15	15 (100.0)	0.6 [0.3; 1.1]	1.22 [0.55; 2.73]	0.625	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: all-participants-as-treated population with PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-42: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Serious Adverse Events	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	33	20 (60.6)	35.9 [6.9; 62.1]	35	23 (65.7)	21.7 [3.0; 49.7]	0.84 [0.46; 1.54]	0.575	0.611
Male	152	86 (56.6)	27.1 [16.3; 58.0]	158	86 (54.4)	29.6 [20.1; 48.0]	1.01 [0.75; 1.36]	0.961	
Age category									
< 65	99	52 (52.5)	35.9 [16.1; -]	124	66 (53.2)	31.1 [23.0; 55.1]	0.97 [0.67; 1.40]	0.871	0.677
≥ 65	86	54 (62.8)	21.3 [12.3; 39.3]	69	43 (62.3)	19.1 [10.7; 48.0]	0.91 [0.61; 1.37]	0.662	
Severity of disease									
ECOG 0	84	45 (53.6)	35.6 [17.1; 106.7]	78	43 (55.1)	30.6 [22.1; 60.3]	0.90 [0.59; 1.38]	0.638	0.601
ECOG ≥ 1	101	61 (60.4)	17.7 [12.3; 39.3]	115	66 (57.4)	24.3 [14.6; 48.0]	1.04 [0.73; 1.47]	0.841	
Region									
EU	30	21 (70.0)	16.3 [8.3; 42.6]	24	15 (62.5)	31.1 [4.7; 49.7]	1.22 [0.62; 2.38]	0.568	0.513
Ex-EU	155	85 (54.8)	34.0 [16.4; 58.0]	169	94 (55.6)	25.7 [18.3; 55.1]	0.92 [0.69; 1.24]	0.598	
Region									
Asia	104	50 (48.1)	45.9 [17.6; -]	104	57 (54.8)	25.3 [15.6; 71.3]	0.80 [0.54; 1.17]	0.254	0.083
Rest of World	81	56 (69.1)	16.4 [13.0; 27.9]	89	52 (58.4)	31.1 [19.1; 49.7]	1.25 [0.85; 1.83]	0.251	
Histology									
Adenocarcinoma	42	28 (66.7)	15.6 [8.0; 27.9]	53	30 (56.6)	31.1 [17.1; 60.3]	1.34 [0.80; 2.26]	0.266	0.195
Squamous Cell Carcinoma	143	78 (54.5)	35.6 [16.4; 62.1]	140	79 (56.4)	25.7 [16.7; 48.0]	0.87 [0.64; 1.20]	0.405	
Disease Status									
Metastatic	174	96 (55.2)	34.0 [17.1; 58.0]	178	97 (54.5)	29.6 [20.1; 55.1]	0.95 [0.71; 1.26]	0.724	0.205
Unresectable - Locally Advanced	11	10 (90.9)	3.1 [1.0; 16.6]	15	12 (80.0)	14.6 [1.1; 42.0]	2.31 [0.89; 5.97]	0.084	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: all-participants-as-treated population with PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5)

Tabelle 4G-43: 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 – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	33	31 (93.9)	3.7 [2.9; 6.9]	35	32 (91.4)	5.6 [2.1; 8.9]	0.99 [0.60; 1.64]	0.981	0.865
Male	152	132 (86.8)	4.4 [3.1; 6.9]	158	131 (82.9)	6.1 [3.9; 9.1]	1.06 [0.83; 1.36]	0.626	
Age category									
< 65	99	86 (86.9)	6.1 [4.0; 9.3]	124	101 (81.5)	8.1 [5.9; 10.6]	1.06 [0.79; 1.42]	0.687	0.510
≥ 65	86	77 (89.5)	3.3 [3.0; 5.1]	69	62 (89.9)	3.4 [2.9; 6.1]	0.96 [0.68; 1.34]	0.802	
Severity of disease									
ECOG 0	84	73 (86.9)	6.1 [3.3; 9.0]	78	61 (78.2)	8.4 [3.4; 13.9]	1.17 [0.83; 1.64]	0.383	0.509
ECOG ≥ 1	101	90 (89.1)	3.3 [3.0; 4.6]	115	102 (88.7)	5.1 [3.3; 7.1]	1.00 [0.75; 1.32]	0.978	
Region									
EU	30	28 (93.3)	6.3 [2.6; 9.6]	24	21 (87.5)	6.1 [2.7; 12.7]	0.97 [0.55; 1.73]	0.922	0.856
Ex-EU	155	135 (87.1)	4.0 [3.0; 6.1]	169	142 (84.0)	6.1 [3.6; 8.9]	1.06 [0.84; 1.35]	0.608	
Region									
Asia	104	88 (84.6)	3.3 [3.0; 6.9]	104	86 (82.7)	4.7 [3.1; 8.9]	0.97 [0.72; 1.31]	0.846	0.295
Rest of World	81	75 (92.6)	6.0 [3.3; 7.0]	89	77 (86.5)	6.1 [3.6; 9.3]	1.21 [0.88; 1.66]	0.249	
Histology									
Adenocarcinoma	42	37 (88.1)	4.7 [2.4; 7.4]	53	44 (83.0)	6.3 [3.9; 11.6]	1.14 [0.73; 1.77]	0.567	0.625
Squamous Cell Carcinoma	143	126 (88.1)	4.4 [3.1; 6.3]	140	119 (85.0)	5.0 [3.3; 8.9]	1.01 [0.78; 1.30]	0.952	
Disease Status									
Metastatic	174	153 (87.9)	4.3 [3.1; 6.6]	178	149 (83.7)	6.1 [3.9; 9.0]	1.06 [0.84; 1.33]	0.641	0.935
Unresectable - Locally Advanced	11	10 (90.9)	4.6 [1.7; 10.4]	15	14 (93.3)	4.7 [1.0; 8.1]	1.22 [0.53; 2.80]	0.646	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: all-participants-as-treated population with PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; CPS: Combined Proportion Score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-44: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Adverse Events Leading to Treatment Discontinuation	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	33	9 (27.3)	Not reached [25.3; -]	35	9 (25.7)	Not reached [-; -]	1.00 [0.40; 2.52]	0.998	0.702
Male	152	37 (24.3)	Not reached [-; -]	158	31 (19.6)	Not reached [71.3; -]	1.19 [0.74; 1.92]	0.475	
Age category									
< 65	99	19 (19.2)	Not reached [-; -]	124	19 (15.3)	Not reached [-; -]	1.23 [0.65; 2.34]	0.516	0.547
≥ 65	86	27 (31.4)	Not reached [59.3; -]	69	21 (30.4)	Not reached [71.3; -]	0.95 [0.54; 1.69]	0.867	
Severity of disease									
ECOG 0	84	19 (22.6)	Not reached [-; -]	78	17 (21.8)	Not reached [-; -]	0.99 [0.51; 1.91]	0.978	0.518
ECOG ≥ 1	101	27 (26.7)	Not reached [-; -]	115	23 (20.0)	Not reached [46.4; -]	1.28 [0.73; 2.24]	0.383	
Region									
EU	30	8 (26.7)	Not reached [-; -]	24	6 (25.0)	Not reached [15.6; -]	1.07 [0.37; 3.08]	0.901	0.845
Ex-EU	155	38 (24.5)	Not reached [-; -]	169	34 (20.1)	Not reached [71.3; -]	1.15 [0.72; 1.82]	0.568	
Region									
Asia	104	21 (20.2)	Not reached [-; -]	104	21 (20.2)	Not reached [71.3; -]	0.94 [0.51; 1.72]	0.837	0.297
Rest of World	81	25 (30.9)	Not reached [59.3; -]	89	19 (21.3)	Not reached [-; -]	1.43 [0.79; 2.60]	0.243	
Disease Status									
Metastatic	174	42 (24.1)	Not reached [-; -]	178	33 (18.5)	Not reached [-; -]	1.25 [0.79; 1.98]	0.333	0.514
Unresectable - Locally Advanced	11	4 (36.4)	Not reached [1.7; -]	15	7 (46.7)	34.9 [3.9; -]	0.80 [0.23; 2.74]	0.720	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: all-participants-as-treated population with PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-45: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
SOC[h]: Endocrine disorders									
Gender									
Female	33	4 (12.1)	Not reached [-; -]	35	3 (8.6)	Not reached [-; -]	1.35 [0.30; 6.03]	0.696	0.473
Male	152	29 (19.1)	Not reached [107.4; -]	158	12 (7.6)	Not reached [-; -]	2.15 [1.09; 4.25]	0.027	
Age category									
< 65	99	16 (16.2)	107.4 [107.4; -]	124	9 (7.3)	Not reached [-; -]	1.91 [0.84; 4.35]	0.125	0.936
≥ 65	86	17 (19.8)	Not reached [-; -]	69	6 (8.7)	Not reached [-; -]	2.02 [0.79; 5.14]	0.140	
Severity of disease									
ECOG 0	84	15 (17.9)	Not reached [107.4; -]	78	4 (5.1)	Not reached [-; -]	3.05 [1.00; 9.27]	0.049	0.359
ECOG ≥ 1	101	18 (17.8)	Not reached [77.1; -]	115	11 (9.6)	Not reached [-; -]	1.62 [0.76; 3.44]	0.212	
Region									
EU	30	4 (13.3)	Not reached [-; -]	24	1 (4.2)	Not reached [-; -]	2.86 [0.32; 25.66]	0.347	0.804
Ex-EU	155	29 (18.7)	Not reached [107.4; -]	169	14 (8.3)	Not reached [-; -]	1.95 [1.02; 3.71]	0.043	
Region									
Asia	104	20 (19.2)	Not reached [77.1; -]	104	9 (8.7)	Not reached [-; -]	1.81 [0.81; 4.01]	0.147	0.874
Rest of World	81	13 (16.0)	Not reached [107.4; -]	89	6 (6.7)	Not reached [-; -]	2.18 [0.82; 5.80]	0.117	
Histology									
Adenocarcinoma	42	8 (19.0)	Not reached [-; -]	53	2 (3.8)	Not reached [-; -]	4.96 [1.05; 23.35]	0.043	0.218
Squamous Cell Carcinoma	143	25 (17.5)	Not reached [107.4; -]	140	13 (9.3)	Not reached [-; -]	1.56 [0.79; 3.07]	0.198	
Disease Status									
Metastatic	174	32 (18.4)	Not reached [107.4; -]	178	14 (7.9)	Not reached [-; -]	2.00 [1.06; 3.77]	0.032	0.855
Unresectable - Locally Advanced	11	1 (9.1)	Not reached [8.9; -]	15	1 (6.7)	Not reached [-; -]	1.85 [0.12; 29.66]	0.663	
SOC[h]: General disorders and administration site conditions									
Gender									
Female	33	25 (75.8)	3.7 [0.9; 12.6]	35	21 (60.0)	8.3 [2.3; 12.0]	1.30 [0.73; 2.33]	0.371	0.914
Male	152	123 (80.9)	2.0 [1.0; 4.9]	158	115 (72.8)	6.7 [3.1; 9.1]	1.36 [1.05; 1.75]	0.019	

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Age category									
< 65	99	77 (77.8)	4.3 [1.9; 7.0]	124	83 (66.9)	8.3 [6.0; 10.3]	1.33 [0.97; 1.82]	0.072	0.935
≥ 65	86	71 (82.6)	1.0 [0.7; 3.3]	69	53 (76.8)	3.3 [1.4; 9.0]	1.30 [0.91; 1.86]	0.149	
Severity of disease									
ECOG 0	84	65 (77.4)	2.0 [0.9; 6.3]	78	57 (73.1)	3.6 [1.4; 9.7]	1.22 [0.85; 1.74]	0.279	0.422
ECOG ≥ 1	101	83 (82.2)	3.1 [0.9; 5.4]	115	79 (68.7)	8.1 [5.1; 9.4]	1.46 [1.07; 1.99]	0.017	
Region									
EU	30	27 (90.0)	2.1 [0.7; 6.1]	24	18 (75.0)	1.9 [0.7; 10.4]	1.33 [0.73; 2.43]	0.345	0.989
Ex-EU	155	121 (78.1)	3.1 [1.0; 5.9]	169	118 (69.8)	7.9 [3.9; 9.4]	1.33 [1.03; 1.72]	0.027	
Region									
Asia	104	79 (76.0)	1.6 [0.9; 6.1]	104	69 (66.3)	8.4 [4.3; 10.3]	1.42 [1.03; 1.97]	0.034	0.749
Rest of World	81	69 (85.2)	3.3 [1.0; 6.0]	89	67 (75.3)	6.0 [2.0; 9.7]	1.33 [0.95; 1.87]	0.094	
Histology									
Adenocarcinoma	42	36 (85.7)	2.6 [0.7; 4.9]	53	39 (73.6)	3.1 [1.1; 12.1]	1.48 [0.94; 2.34]	0.091	0.659
Squamous Cell Carcinoma	143	112 (78.3)	3.0 [1.0; 6.0]	140	97 (69.3)	7.9 [5.1; 9.1]	1.32 [1.01; 1.74]	0.045	
Disease Status									
Metastatic	174	141 (81.0)	1.9 [1.0; 4.7]	178	126 (70.8)	7.3 [3.9; 9.3]	1.36 [1.07; 1.73]	0.012	0.730
Unresectable - Locally Advanced	11	7 (63.6)	7.4 [0.3; -]	15	10 (66.7)	2.7 [1.0; -]	1.02 [0.39; 2.71]	0.963	
SOC[h]: Musculoskeletal and connective tissue disorders									
Gender									
Female	33	9 (27.3)	55.6 [39.9; -]	35	11 (31.4)	53.1 [17.9; -]	0.70 [0.29; 1.70]	0.434	0.572
Male	152	31 (20.4)	Not reached [78.1; -]	158	47 (29.7)	63.4 [34.9; -]	0.50 [0.31; 0.79]	0.003	
Age category									
< 65	99	21 (21.2)	Not reached [50.6; -]	124	37 (29.8)	63.4 [34.1; -]	0.55 [0.32; 0.95]	0.031	0.909
≥ 65	86	19 (22.1)	Not reached [55.6; -]	69	21 (30.4)	73.0 [27.9; -]	0.51 [0.27; 0.97]	0.039	
Severity of disease									
ECOG 0	84	19 (22.6)	Not reached [78.1; -]	78	24 (30.8)	53.1 [34.1; -]	0.52 [0.28; 0.97]	0.039	0.982
ECOG ≥ 1	101	21 (20.8)	Not reached [50.0; -]	115	34 (29.6)	63.4 [31.3; -]	0.53 [0.31; 0.92]	0.025	
Region									
EU	30	7 (23.3)	Not reached [37.9; -]	24	9 (37.5)	Not reached [8.1; -]	0.49 [0.18; 1.31]	0.156	0.779

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Ex-EU	155	33 (21.3)	Not reached [55.6; -]	169	49 (29.0)	53.1 [34.9; -]	0.53 [0.33; 0.83]	0.006	
Region									
Asia	104	16 (15.4)	Not reached [78.1; -]	104	27 (26.0)	73.0 [32.3; -]	0.35 [0.18; 0.67]	0.002	0.142
Rest of World	81	24 (29.6)	82.0 [45.7; -]	89	31 (34.8)	63.4 [31.3; -]	0.73 [0.43; 1.25]	0.247	
Histology									
Adenocarcinoma	42	13 (31.0)	78.1 [45.7; -]	53	14 (26.4)	Not reached [31.3; -]	0.98 [0.45; 2.11]	0.957	0.083
Squamous Cell Carcinoma	143	27 (18.9)	Not reached [55.6; -]	140	44 (31.4)	53.1 [34.1; -]	0.41 [0.25; 0.67]	< 0.001	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: all-participants-as-treated population with PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
h: A system organ class appears on this report only if its incidence ≥10% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05 or rule of 10 is not met
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1; SOC: System Organ Class

Tabelle 4G-46: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (PT) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC: Endocrine disorders, PT[h]: Hyperthyroidism									
Gender									
Female	33	3 (9.1)	Not reached [-; -]	35	1 (2.9)	Not reached [-; -]	3.25 [0.34; 31.38]	0.308	0.461
Male	152	11 (7.2)	Not reached [-; -]	158	1 (0.6)	Not reached [-; -]	10.15 [1.31; 78.79]	0.027	
Age category									
< 65	99	9 (9.1)	Not reached [-; -]	124	1 (0.8)	Not reached [-; -]	10.28 [1.30; 81.28]	0.027	0.467
≥ 65	86	5 (5.8)	Not reached [-; -]	69	1 (1.4)	Not reached [-; -]	3.81 [0.44; 32.62]	0.222	
Severity of disease									
ECOG 0	84	5 (6.0)	Not reached [-; -]	78	1 (1.3)	Not reached [-; -]	4.32 [0.50; 36.97]	0.182	0.580
ECOG ≥ 1	101	9	Not reached	115	1	Not reached	9.36	0.034	

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
		(8.9)	[-; -]		(0.9)	[-; -]	[1.18; 74.06]		
Region									
EU	30	2 (6.7)	Not reached [-; -]	24	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.232	0.505
Ex-EU	155	12 (7.7)	Not reached [-; -]	169	2 (1.2)	Not reached [-; -]	5.85 [1.31; 26.21]	0.021	
Region									
Asia	104	7 (6.7)	n.c.	104	1 (1.0)	n.c.	n.c.	n.c.	n.c.
Rest of World	81	7 (8.6)	n.c.	89	1 (1.1)	n.c.	n.c.	n.c.	
Histology									
Adenocarcinoma	42	6 (14.3)	Not reached [-; -]	53	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.006	0.101
Squamous Cell Carcinoma	143	8 (5.6)	Not reached [-; -]	140	2 (1.4)	Not reached [-; -]	3.28 [0.69; 15.54]	0.134	
Disease Status									
Metastatic	174	14 (8.0)	Not reached [-; -]	178	2 (1.1)	Not reached [-; -]	6.41 [1.46; 28.26]	0.014	0.997
Unresectable - Locally Advanced	11	0 (0.0)	Not reached [-; -]	15	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
SOC: General disorders and administration site conditions, PT[h]: Oedema peripheral									
Gender									
Female	33	1 (3.0)	Not reached [-; -]	35	5 (14.3)	Not reached [52.6; -]	0.18 [0.02; 1.56]	0.121	0.526
Male	152	5 (3.3)	Not reached [-; -]	158	11 (7.0)	Not reached [-; -]	0.38 [0.13; 1.12]	0.080	
Age category									
< 65	99	1 (1.0)	Not reached [-; -]	124	8 (6.5)	Not reached [-; -]	0.09 [0.01; 0.77]	0.028	0.333
≥ 65	86	5 (5.8)	Not reached [-; -]	69	8 (11.6)	Not reached [-; -]	0.46 [0.15; 1.41]	0.175	
Severity of disease									
ECOG 0	84	1 (1.2)	Not reached [-; -]	78	6 (7.7)	Not reached [52.6; -]	0.08 [0.01; 0.73]	0.025	0.228
ECOG ≥ 1	101	5 (5.0)	Not reached [-; -]	115	10 (8.7)	Not reached [-; -]	0.52 [0.18; 1.51]	0.229	
Region									
EU	30	1 (3.3)	Not reached [-; -]	24	3 (12.5)	Not reached [-; -]	0.25 [0.03; 2.37]	0.225	0.724
Ex-EU	155	5 (3.2)	Not reached [-; -]	169	13 (7.7)	Not reached [-; -]	0.31 [0.11; 0.88]	0.029	
Region									
Asia	104	2 (1.9)	Not reached [-; -]	104	6 (5.8)	Not reached [-; -]	0.24 [0.05; 1.24]	0.089	0.677
Rest of World	81	4 (4.9)	Not reached [-; -]	89	10 (11.2)	Not reached [-; -]	0.37 [0.11; 1.19]	0.094	
Histology									
Adenocarcinoma	42	2	Not reached	53	4	Not reached	0.41	0.323	0.502

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
		(4.8)	[84.1; -]		(7.5)	[52.6; -]	[0.07; 2.40]		
Squamous Cell Carcinoma	143	4 (2.8)	Not reached [-; -]	140	12 (8.6)	Not reached [-; -]	0.27 [0.09; 0.86]	0.026	
Disease Status									
Metastatic	174	5 (2.9)	Not reached [-; -]	178	14 (7.9)	Not reached [-; -]	0.27 [0.10; 0.77]	0.014	0.512
Unresectable - Locally Advanced	11	1 (9.1)	Not reached [14.0; -]	15	2 (13.3)	Not reached [-; -]	0.75 [0.07; 8.27]	0.814	
SOC: Infections and infestations, PT[h]: Urinary tract infection									
Gender									
Female	33	2 (6.1)	Not reached [-; -]	35	7 (20.0)	Not reached [57.1; -]	0.25 [0.05; 1.20]	0.082	0.873
Male	152	2 (1.3)	Not reached [-; -]	158	8 (5.1)	Not reached [-; -]	0.18 [0.04; 0.89]	0.036	
Severity of disease									
ECOG 0	84	1 (1.2)	Not reached [-; -]	78	5 (6.4)	Not reached [-; -]	0.11 [0.01; 1.04]	0.054	0.578
ECOG ≥ 1	101	3 (3.0)	Not reached [-; -]	115	10 (8.7)	Not reached [57.1; -]	0.29 [0.08; 1.06]	0.061	
Region									
EU	30	2 (6.7)	Not reached [91.0; -]	24	4 (16.7)	Not reached [-; -]	0.29 [0.05; 1.70]	0.172	0.590
Ex-EU	155	2 (1.3)	Not reached [-; -]	169	11 (6.5)	Not reached [-; -]	0.16 [0.03; 0.71]	0.017	
Region									
Asia	104	0 (0.0)	Not reached [-; -]	104	3 (2.9)	Not reached [40.9; -]	n.a. [n.a.; n.a.]	0.022	0.183
Rest of World	81	4 (4.9)	Not reached [-; -]	89	12 (13.5)	Not reached [-; -]	0.29 [0.09; 0.93]	0.038	
Histology									
Adenocarcinoma	42	0 (0.0)	Not reached [-; -]	53	6 (11.3)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.020	0.081
Squamous Cell Carcinoma	143	4 (2.8)	Not reached [-; -]	140	9 (6.4)	Not reached [-; -]	0.31 [0.09; 1.06]	0.061	
Disease Status									
Metastatic	174	4 (2.3)	Not reached [-; -]	178	12 (6.7)	Not reached [-; -]	0.24 [0.08; 0.78]	0.018	0.338
Unresectable - Locally Advanced	11	0 (0.0)	Not reached [-; -]	15	3 (20.0)	Not reached [13.0; -]	n.a. [n.a.; n.a.]	0.163	
SOC: Investigations, PT[h]: Blood alkaline phosphatase increased									
Gender									
Female	33	1 (3.0)	Not reached [-; -]	35	2 (5.7)	Not reached [-; -]	0.50 [0.05; 5.49]	0.569	0.536
Male	152	2 (1.3)	Not reached [-; -]	158	8 (5.1)	Not reached [-; -]	0.20 [0.04; 0.96]	0.044	
Age category									
< 65	99	3 (3.0)	Not reached [-; -]	124	8 (6.5)	Not reached [-; -]	0.41 [0.11; 1.55]	0.189	0.185
≥ 65	86	0	Not reached	69	2	Not reached	n.a.	0.066	

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
		(0.0)	[-; -]		(2.9)	[-; -]	[n.a.; n.a.]		
Severity of disease									
ECOG 0	84	1 (1.2)	n.c.	78	4 (5.1)	n.c.	n.c.	n.c.	n.c.
ECOG ≥ 1	101	2 (2.0)	n.c.	115	6 (5.2)	n.c.	n.c.	n.c.	
Region									
EU	30	2 (6.7)	n.c.	24	2 (8.3)	n.c.	n.c.	n.c.	n.c.
Ex-EU	155	1 (0.6)	n.c.	169	8 (4.7)	n.c.	n.c.	n.c.	
Region									
Asia	104	1 (1.0)	Not reached [-; -]	104	1 (1.0)	Not reached [-; -]	0.84 [0.05; 13.53]	0.901	0.494
Rest of World	81	2 (2.5)	Not reached [-; -]	89	9 (10.1)	Not reached [-; -]	0.24 [0.05; 1.10]	0.066	
Histology									
Adenocarcinoma	42	0 (0.0)	n.c.	53	4 (7.5)	n.c.	n.c.	n.c.	n.c.
Squamous Cell Carcinoma	143	3 (2.1)	n.c.	140	6 (4.3)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	174	3 (1.7)	Not reached [-; -]	178	7 (3.9)	Not reached [-; -]	0.37 [0.10; 1.45]	0.155	0.291
Unresectable - Locally Advanced	11	0 (0.0)	Not reached [-; -]	15	3 (20.0)	40.9 [19.0; -]	n.a. [n.a.; n.a.]	0.132	
SOC: Musculoskeletal and connective tissue disorders, PT[h]: Back pain									
Gender									
Female	33	1 (3.0)	Not reached [-; -]	35	7 (20.0)	Not reached [53.1; -]	0.12 [0.01; 0.98]	0.048	0.295
Male	152	5 (3.3)	Not reached [-; -]	158	11 (7.0)	Not reached [-; -]	0.36 [0.12; 1.05]	0.061	
Age category									
< 65	99	4 (4.0)	Not reached [-; -]	124	9 (7.3)	Not reached [-; -]	0.43 [0.13; 1.41]	0.161	0.182
≥ 65	86	2 (2.3)	Not reached [-; -]	69	9 (13.0)	Not reached [73.0; -]	0.14 [0.03; 0.65]	0.012	
Severity of disease									
ECOG 0	84	4 (4.8)	Not reached [-; -]	78	9 (11.5)	73.0 [53.1; -]	0.28 [0.08; 0.95]	0.042	0.650
ECOG ≥ 1	101	2 (2.0)	Not reached [-; -]	115	9 (7.8)	Not reached [-; -]	0.21 [0.04; 0.96]	0.045	
Region									
EU	30	1 (3.3)	Not reached [-; -]	24	5 (20.8)	Not reached [27.9; -]	0.14 [0.02; 1.23]	0.076	0.397
Ex-EU	155	5 (3.2)	Not reached [-; -]	169	13 (7.7)	Not reached [73.0; -]	0.30 [0.10; 0.85]	0.024	
Region									
Asia	104	4	Not reached	104	8	Not reached	0.31	0.073	0.508

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
		(3.8)	[-; -]		(7.7)	[73.0; -]	[0.09; 1.11]		
Rest of World	81	2 (2.5)	Not reached [-; -]	89	10 (11.2)	Not reached [-; -]	0.19 [0.04; 0.88]	0.034	
Histology									
Adenocarcinoma	42	1 (2.4)	Not reached [-; -]	53	2 (3.8)	Not reached [-; -]	0.57 [0.05; 6.32]	0.649	0.545
Squamous Cell Carcinoma	143	5 (3.5)	Not reached [-; -]	140	16 (11.4)	Not reached [53.1; -]	0.21 [0.08; 0.60]	0.003	
Disease Status									
Metastatic	174	6 (3.4)	Not reached [-; -]	178	16 (9.0)	Not reached [-; -]	0.29 [0.11; 0.74]	0.010	0.398
Unresectable - Locally Advanced	11	0 (0.0)	Not reached [-; -]	15	2 (13.3)	Not reached [25.0; -]	n.a. [n.a.; n.a.]	0.292	
SOC: Respiratory, thoracic and mediastinal disorders, PT[h]: Pneumonitis									
Gender									
Female	33	2 (6.1)	n.c.	35	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Male	152	9 (5.9)	n.c.	158	0 (0.0)	n.c.	n.c.	n.c.	
Age category									
< 65	99	5 (5.1)	n.c.	124	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	86	6 (7.0)	n.c.	69	0 (0.0)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	84	7 (8.3)	n.c.	78	0 (0.0)	n.c.	n.c.	n.c.	n.c.
ECOG ≥ 1	101	4 (4.0)	n.c.	115	0 (0.0)	n.c.	n.c.	n.c.	
Region									
EU	30	1 (3.3)	Not reached [-; -]	24	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.383	0.997
Ex-EU	155	10 (6.5)	Not reached [-; -]	169	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	
Region									
Asia	104	4 (3.8)	n.c.	104	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Rest of World	81	7 (8.6)	n.c.	89	0 (0.0)	n.c.	n.c.	n.c.	
Histology									
Adenocarcinoma	42	4 (9.5)	n.c.	53	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Squamous Cell Carcinoma	143	7 (4.9)	n.c.	140	0 (0.0)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	174	10 (5.7)	Not reached [-; -]	178	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.003	0.997
Unresectable - Locally Advanced	11	1 (9.1)	Not reached [23.3; -]	15	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.237	
a: Database Cutoff Date: 02JUL2020									

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
b: Chemotherapy: Cisplatin and 5-Fluorouracil									
c: Number of participants: all-participants-as-treated population with PD-L1 CPS≥10									
d: From product-limit (Kaplan-Meier) method for censored data									
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval									
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)									
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
h: A specific adverse event appears on this report only if its incidence ≥10% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05 or rule of 10 is not met									
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term; SOC: System Organ Class									

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-47: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Serious Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC[h]: General disorders and administration site conditions									
Gender									
Female	33	0 (0.0)	Not reached [-; -]	35	4 (11.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.046	0.136
Male	152	5 (3.3)	Not reached [-; -]	158	13 (8.2)	Not reached [-; -]	0.34 [0.12; 0.96]	0.042	
Age category									
< 65	99	2 (2.0)	Not reached [-; -]	124	9 (7.3)	Not reached [-; -]	0.27 [0.06; 1.23]	0.090	0.995
≥ 65	86	3 (3.5)	Not reached [-; -]	69	8 (11.6)	Not reached [-; -]	0.22 [0.06; 0.84]	0.027	
Severity of disease									
ECOG 0	84	2 (2.4)	Not reached [-; -]	78	3 (3.8)	Not reached [-; -]	0.56 [0.09; 3.38]	0.528	0.380
ECOG ≥ 1	101	3 (3.0)	Not reached [-; -]	115	14 (12.2)	Not reached [-; -]	0.20 [0.06; 0.70]	0.012	
Region									
EU	30	0 (0.0)	Not reached [-; -]	24	4 (16.7)	Not reached [42.0; -]	n.a. [n.a.; n.a.]	0.015	0.076
Ex-EU	155	5 (3.2)	Not reached [-; -]	169	13 (7.7)	Not reached [-; -]	0.37 [0.13; 1.03]	0.058	
Region									
Asia	104	2 (1.9)	Not reached [-; -]	104	8 (7.7)	Not reached [-; -]	0.20 [0.04; 0.95]	0.044	0.626
Rest of World	81	3	Not reached	89	9	Not reached	0.35	0.113	

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Serious Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
		(3.7)	[-; -]		(10.1)	[-; -]	[0.09; 1.28]		
Disease Status									
Metastatic	174	5 (2.9)	Not reached [-; -]	178	14 (7.9)	Not reached [-; -]	0.32 [0.11; 0.88]	0.028	0.280
Unresectable - Locally Advanced	11	0 (0.0)	Not reached [-; -]	15	3 (20.0)	42.0 [42.0; -]	n.a. [n.a.; n.a.]	0.171	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: all-participants-as-treated population with PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
h: A system organ class appears on this report only if its incidence ≥5% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05 or rule of 10 not met
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); PD-L1: Programmed Cell Death - Ligand 1; SOC: System Organ Class

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

Tabelle 4G-48: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5) (PT) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Severe Adverse Events (CTCAE-Grade 3-5)	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC: Investigations, PT[h]: Weight decreased									
Gender									
Female	33	2 (6.1)	Not reached [51.6; -]	35	4 (11.4)	Not reached [-; -]	0.48 [0.09; 2.62]	0.394	0.443
Male	152	2 (1.3)	Not reached [-; -]	158	8 (5.1)	Not reached [-; -]	0.17 [0.03; 0.83]	0.028	
Age category									
< 65	99	4 (4.0)	n.c.	124	5 (4.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	86	0 (0.0)	n.c.	69	7 (10.1)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	84	1 (1.2)	Not reached [-; -]	78	5 (6.4)	Not reached [-; -]	0.12 [0.01; 1.05]	0.055	0.414
ECOG ≥ 1	101	3 (3.0)	Not reached [-; -]	115	7 (6.1)	Not reached [-; -]	0.37 [0.09; 1.44]	0.151	
Region									
EU	30	0 (0.0)	Not reached [-; -]	24	1 (4.2)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.244	0.403

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Severe Adverse Events (CTCAE-Grade 3-5)	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Ex-EU	155	4 (2.6)	Not reached [-; -]	169	11 (6.5)	Not reached [-; -]	0.26 [0.08; 0.85]	0.026	
Region									
Asia	104	0 (0.0)	Not reached [-; -]	104	3 (2.9)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.061	0.102
Rest of World	81	4 (4.9)	Not reached [-; -]	89	9 (10.1)	Not reached [-; -]	0.40 [0.12; 1.32]	0.133	
Disease Status									
Metastatic	174	4 (2.3)	Not reached [-; -]	178	10 (5.6)	Not reached [-; -]	0.28 [0.09; 0.91]	0.035	0.353
Unresectable - Locally Advanced	11	0 (0.0)	Not reached [-; -]	15	2 (13.3)	Not reached [21.9; -]	n.a. [n.a.; n.a.]	0.256	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: all-participants-as-treated population with PD-L1 CPS≥10

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

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

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

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

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

CI: Confidence Interval; CPS: Combined Proportion Score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term; SOC: System Organ Class

Anhang 4-G10: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest (p ≥ 0,05) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

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 finalen Datenschnitt (02. Juli 2020).

Anhang 4-G10.1: Mortalität

Gesamtüberleben

Tabelle 4G-49: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Overall Survival	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	29	17 (58.6)	13.5 [10.1; -]	27	21 (77.8)	9.5 [3.7; 15.6]	0.58 [0.31; 1.10]	0.095	0.933
Male	114	77 (67.5)	13.9 [9.9; 17.8]	116	100 (86.2)	8.8 [7.6; 10.6]	0.57 [0.42; 0.77]	< 0.001	
Age (Years)									
< 65	78	54 (69.2)	11.9 [9.0; 16.0]	88	77 (87.5)	8.0 [6.5; 9.5]	0.57 [0.40; 0.81]	0.002	0.838
≥ 65	65	40 (61.5)	14.6 [11.4; 23.7]	55	44 (80.0)	10.6 [8.0; 13.9]	0.59 [0.39; 0.91]	0.018	
Severity of disease									
ECOG 0	61	39 (63.9)	15.6 [11.7; 20.9]	54	43 (79.6)	9.5 [7.9; 11.2]	0.55 [0.36; 0.85]	0.008	0.967
ECOG ≥ 1	82	55 (67.1)	10.6 [8.5; 16.0]	89	78 (87.6)	8.4 [6.0; 10.7]	0.59 [0.42; 0.83]	0.003	
Region									
EU	14	11 (78.6)	11.3 [6.6; 22.6]	18	15 (83.3)	6.3 [3.2; 10.6]	0.57 [0.26; 1.25]	0.161	0.932
Ex-EU	129	83 (64.3)	14.0 [10.8; 18.3]	125	106 (84.8)	9.1 [7.9; 11.2]	0.57 [0.42; 0.76]	< 0.001	
Region									
Asia	96	61 (63.5)	14.4 [11.4; 19.0]	98	86 (87.8)	8.6 [7.4; 10.5]	0.48 [0.35; 0.67]	< 0.001	0.126
Rest of World	47	33 (70.2)	10.5 [8.0; 14.6]	45	35 (77.8)	9.8 [6.0; 13.5]	0.79 [0.49; 1.28]	0.338	
Disease Status									
Metastatic	134	87 (64.9)	14.0 [11.2; 18.3]	128	109 (85.2)	9.0 [7.8; 10.6]	0.55 [0.41; 0.73]	< 0.001	0.305
Unresectable - Locally Advanced	9	7 (77.8)	7.9 [0.5; -]	15	12 (80.0)	7.9 [1.7; 14.6]	0.90 [0.35; 2.29]	0.825	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: intention-to-treat population with squamous cell carcinoma and PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G10.2: Morbidität

Zeit bis zur ersten Folgetherapie (oder Tod)

Zeit bis zur ersten Folgetherapie oder Tod

Tabelle 4G-50: 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 – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Time to Subsequent Oncologic Therapy or Death	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio[e] [95 %-CI]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	29	20 (69.0)	10.5 [7.1; 25.6]	27	24 (88.9)	5.1 [3.2; 10.4]	0.51 [0.28; 0.93]	0.028	0.750
Male	114	98 (86.0)	8.0 [6.9; 9.4]	116	111 (95.7)	6.2 [5.2; 6.6]	0.55 [0.41; 0.73]	< 0.001	
Age (Years)									
< 65	78	64 (82.1)	7.9 [6.0; 8.7]	88	83 (94.3)	5.7 [4.9; 6.5]	0.60 [0.43; 0.84]	0.003	0.607
≥ 65	65	54 (83.1)	9.9 [7.5; 14.6]	55	52 (94.5)	6.6 [5.0; 7.0]	0.47 [0.32; 0.71]	< 0.001	
Severity of disease									
ECOG 0	61	48 (78.7)	9.4 [7.3; 12.9]	54	49 (90.7)	6.6 [5.1; 7.7]	0.55 [0.36; 0.82]	0.003	0.977
ECOG ≥ 1	82	70 (85.4)	8.0 [6.6; 9.4]	89	86 (96.6)	5.7 [4.8; 6.5]	0.55 [0.40; 0.77]	< 0.001	
Region									
EU	14	12 (85.7)	9.6 [6.5; 19.6]	18	17 (94.4)	6.2 [3.2; 8.0]	0.47 [0.22; 1.00]	0.051	0.828
Ex-EU	129	106 (82.2)	8.5 [7.1; 9.7]	125	118 (94.4)	6.1 [5.1; 6.6]	0.56 [0.43; 0.73]	< 0.001	
Region									
Asia	96	82 (85.4)	8.2 [6.7; 9.4]	98	95 (96.9)	5.6 [4.7; 6.3]	0.46 [0.34; 0.63]	< 0.001	0.166
Rest of World	47	36 (76.6)	9.6 [7.1; 14.3]	45	40 (88.9)	8.0 [5.5; 10.4]	0.68 [0.43; 1.06]	0.090	
Disease Status									
Metastatic	134	111 (82.8)	8.6 [7.3; 9.9]	128	120 (93.8)	6.1 [5.0; 6.6]	0.55 [0.42; 0.72]	< 0.001	0.834
Unresectable - Locally Advanced	9	7 (77.8)	7.1 [0.5; -]	15	15 (100.0)	6.3 [1.7; 7.9]	0.64 [0.26; 1.59]	0.340	
a: Database Cutoff Date: 02JUL2020									

b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: intention-to-treat population with squamous cell carcinoma and PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30

EORTC QLQ-C30: Symptomskala Erschöpfung

Tabelle 4G-51: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Erschöpfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Fatigue	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	16 (59.3)	1.4 [0.9; -]	23	11 (47.8)	2.1 [0.7; -]	1.06 [0.49; 2.29]	0.878	0.666
Male	111	81 (73.0)	1.8 [1.0; 2.6]	113	89 (78.8)	1.4 [1.3; 1.8]	0.81 [0.59; 1.10]	0.173	
Age (Years)									
< 65	75	55 (73.3)	1.4 [0.8; 2.1]	82	57 (69.5)	1.5 [1.1; 2.3]	1.07 [0.74; 1.55]	0.714	0.068
≥ 65	63	42 (66.7)	2.4 [1.0; 4.4]	54	43 (79.6)	1.4 [1.0; 1.8]	0.61 [0.39; 0.95]	0.029	
Severity of disease									
ECOG 0	60	49 (81.7)	1.1 [0.9; 2.4]	51	41 (80.4)	1.5 [1.3; 2.1]	0.99 [0.65; 1.51]	0.964	0.240
ECOG ≥ 1	78	48 (61.5)	2.1 [1.4; 4.9]	85	59 (69.4)	1.4 [1.0; 2.1]	0.73 [0.49; 1.07]	0.108	
Region									
EU	14	11 (78.6)	2.8 [1.0; 5.0]	16	11 (68.8)	1.4 [0.7; 2.3]	0.43 [0.17; 1.05]	0.065	0.336
Ex-EU	124	86 (69.4)	1.4 [1.0; 2.1]	120	89 (74.2)	1.4 [1.3; 2.1]	0.91 [0.67; 1.22]	0.515	
Region									
Asia	94	66 (70.2)	1.9 [1.0; 3.2]	95	74 (77.9)	1.4 [1.3; 2.1]	0.76 [0.54; 1.07]	0.118	0.316
Rest of World	44	31 (70.5)	1.4 [0.8; 2.6]	41	26 (63.4)	1.5 [0.8; 2.5]	1.07 [0.63; 1.80]	0.806	
Disease Status									
Metastatic	130	92 (70.8)	1.7 [1.0; 2.6]	123	89 (72.4)	1.4 [1.3; 2.1]	0.86 [0.64; 1.16]	0.329	0.977
Unresectable - Locally Advanced	8	5 (62.5)	1.7 [1.4; -]	13	11 (84.6)	1.5 [0.9; 2.1]	0.67 [0.23; 1.96]	0.464	
a: Database Cutoff Date: 02JUL2020									

b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-52: 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 – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Nausea and Vomiting	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	18 (66.7)	3.9 [2.0; 5.9]	23	15 (65.2)	1.5 [0.7; 2.8]	0.67 [0.34; 1.35]	0.265	0.528
Male	111	65 (58.6)	3.1 [2.1; 4.4]	113	69 (61.1)	2.3 [1.9; 3.5]	0.87 [0.62; 1.23]	0.430	
Age (Years)									
< 65	75	46 (61.3)	2.8 [2.0; 4.1]	82	51 (62.2)	2.3 [1.6; 3.5]	0.91 [0.61; 1.36]	0.652	0.459
≥ 65	63	37 (58.7)	3.7 [2.3; 4.6]	54	33 (61.1)	2.1 [1.4; 3.4]	0.71 [0.44; 1.15]	0.163	
Severity of disease									
ECOG 0	60	40 (66.7)	3.5 [2.1; 4.4]	51	35 (68.6)	2.1 [1.4; 3.4]	0.74 [0.47; 1.18]	0.207	0.550
ECOG ≥ 1	78	43 (55.1)	2.8 [2.0; 4.6]	85	49 (57.6)	2.3 [1.7; 3.9]	0.86 [0.56; 1.30]	0.472	
Region									
EU	14	10 (71.4)	3.3 [0.7; -]	16	14 (87.5)	1.4 [0.7; 2.2]	0.46 [0.20; 1.07]	0.071	0.117
Ex-EU	124	73 (58.9)	3.1 [2.1; 4.2]	120	70 (58.3)	2.3 [2.1; 3.6]	0.91 [0.65; 1.27]	0.569	
Region									
Asia	94	53 (56.4)	3.3 [2.1; 4.9]	95	53 (55.8)	3.0 [2.1; 5.5]	0.91 [0.62; 1.34]	0.646	0.250
Rest of World	44	30 (68.2)	2.8 [1.3; 4.4]	41	31 (75.6)	1.4 [0.8; 2.2]	0.63 [0.38; 1.05]	0.077	
Disease Status									
Metastatic	130	81 (62.3)	3.1 [2.1; 4.2]	123	78 (63.4)	2.1 [1.6; 3.0]	0.79 [0.58; 1.09]	0.154	0.809
Unresectable - Locally Advanced	8	2 (25.0)	Not reached [0.7; -]	13	6 (46.2)	3.5 [1.1; -]	1.17 [0.24; 5.85]	0.845	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Schmerzen

Tabelle 4G-53: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schmerzen des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Pain	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	12 (44.4)	9.4 [4.2; -]	23	13 (56.5)	1.7 [0.7; 10.1]	0.44 [0.20; 0.98]	0.044	0.220
Male	111	59 (53.2)	4.4 [3.2; 7.7]	113	74 (65.5)	3.3 [2.8; 3.9]	0.68 [0.48; 0.96]	0.030	
Severity of disease									
ECOG 0	60	33 (55.0)	5.1 [3.0; 25.3]	51	32 (62.7)	3.5 [2.1; 7.4]	0.69 [0.42; 1.12]	0.135	0.683
ECOG ≥ 1	78	38 (48.7)	7.0 [3.4; 9.4]	85	55 (64.7)	2.8 [2.2; 3.6]	0.57 [0.38; 0.88]	0.010	
Region									
EU	14	7 (50.0)	7.9 [1.8; -]	16	8 (50.0)	5.8 [0.8; -]	0.79 [0.28; 2.19]	0.645	0.694
Ex-EU	124	64 (51.6)	6.6 [3.7; 9.4]	120	79 (65.8)	3.0 [2.4; 3.6]	0.60 [0.43; 0.84]	0.003	
Region									
Asia	94	50 (53.2)	5.1 [3.6; 8.4]	95	64 (67.4)	3.3 [2.7; 3.9]	0.58 [0.39; 0.85]	0.005	0.987
Rest of World	44	21 (47.7)	7.9 [2.1; -]	41	23 (56.1)	2.3 [0.8; 10.1]	0.66 [0.36; 1.20]	0.173	
Disease Status									
Metastatic	130	69 (53.1)	6.6 [3.7; 8.4]	123	80 (65.0)	3.0 [2.3; 3.9]	0.61 [0.44; 0.85]	0.004	0.943
Unresectable - Locally Advanced	8	2 (25.0)	4.4 [0.7; -]	13	7 (53.8)	3.3 [2.1; -]	0.64 [0.13; 3.09]	0.575	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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; PD-L1: Programmed Cell Death

- Ligand 1

EORTC QLQ-C30: Symptomskala Dyspnoe

Tabelle 4G-54: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Dyspnoe des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Dyspnea	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	8 (29.6)	Not reached [3.1; -]	23	11 (47.8)	3.2 [1.6; -]	0.41 [0.17; 1.03]	0.059	0.565
Male	111	41 (36.9)	25.3 [7.2; -]	113	60 (53.1)	3.9 [2.9; 5.8]	0.53 [0.35; 0.80]	0.002	
Age (Years)									
< 65	75	27 (36.0)	Not reached [4.5; -]	82	39 (47.6)	5.3 [3.7; 8.3]	0.65 [0.39; 1.06]	0.086	0.142
≥ 65	63	22 (34.9)	25.3 [5.7; -]	54	32 (59.3)	2.1 [1.6; 3.9]	0.39 [0.22; 0.68]	0.001	
Severity of disease									
ECOG 0	60	26 (43.3)	25.3 [5.2; -]	51	26 (51.0)	3.9 [2.1; -]	0.59 [0.34; 1.03]	0.064	0.568
ECOG ≥ 1	78	23 (29.5)	12.2 [11.0; -]	85	45 (52.9)	3.7 [2.1; 6.3]	0.45 [0.27; 0.75]	0.002	
Region									
Asia	94	34 (36.2)	12.2 [7.2; -]	95	54 (56.8)	3.7 [2.1; 5.5]	0.44 [0.28; 0.68]	< 0.001	0.297
Rest of World	44	15 (34.1)	25.3 [4.5; -]	41	17 (41.5)	5.8 [2.1; -]	0.72 [0.36; 1.46]	0.367	
Disease Status									
Metastatic	130	47 (36.2)	25.3 [8.2; -]	123	66 (53.7)	3.7 [2.2; 5.8]	0.49 [0.34; 0.72]	< 0.001	0.378
Unresectable - Locally Advanced	8	2 (25.0)	5.7 [1.0; -]	13	5 (38.5)	3.9 [1.6; -]	1.01 [0.20; 5.23]	0.990	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

Tabelle 4G-55: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schlaflosigkeit des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Insomnia	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	14 (51.9)	3.0 [2.0; 12.5]	23	6 (26.1)	Not reached [2.3; -]	1.69 [0.64; 4.46]	0.286	0.166
Male	111	53 (47.7)	5.0 [2.8; 25.3]	113	55 (48.7)	4.8 [3.5; 7.1]	0.91 [0.62; 1.34]	0.634	
Age (Years)									
< 65	75	38 (50.7)	4.0 [2.2; -]	82	33 (40.2)	7.0 [3.7; -]	1.23 [0.77; 1.97]	0.394	0.192
≥ 65	63	29 (46.0)	5.1 [3.0; -]	54	28 (51.9)	4.2 [2.7; 7.4]	0.77 [0.45; 1.30]	0.330	
Severity of disease									
ECOG 0	60	31 (51.7)	7.6 [2.9; 25.3]	51	22 (43.1)	5.6 [3.0; -]	1.01 [0.58; 1.77]	0.967	0.931
ECOG ≥ 1	78	36 (46.2)	4.2 [2.5; -]	85	39 (45.9)	4.8 [3.4; 7.4]	1.03 [0.66; 1.63]	0.885	
Region									
EU	14	6 (42.9)	5.1 [2.9; -]	16	6 (37.5)	7.4 [2.1; -]	0.98 [0.32; 3.05]	0.973	0.890
Ex-EU	124	61 (49.2)	4.2 [2.5; 25.3]	120	55 (45.8)	4.8 [3.4; 7.1]	1.02 [0.71; 1.48]	0.902	
Region									
Asia	94	45 (47.9)	4.5 [2.4; -]	95	44 (46.3)	4.9 [3.4; 7.1]	0.97 [0.64; 1.49]	0.904	0.589
Rest of World	44	22 (50.0)	5.0 [2.8; -]	41	17 (41.5)	7.4 [2.9; -]	1.10 [0.58; 2.09]	0.779	
Disease Status									
Metastatic	130	65 (50.0)	4.2 [2.8; 25.3]	123	56 (45.5)	5.6 [3.4; 8.5]	1.00 [0.70; 1.44]	> 0.999	0.888
Unresectable - Locally Advanced	8	2 (25.0)	5.1 [3.0; -]	13	5 (38.5)	4.6 [3.2; -]	0.99 [0.19; 5.15]	0.993	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Appetitverlust

Tabelle 4G-56: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Appetitverlust des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Appetite Loss	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	14 (51.9)	3.7 [1.1; -]	23	6 (26.1)	Not reached [0.8; -]	1.76 [0.68; 4.59]	0.245	0.079
Male	111	67 (60.4)	3.5 [2.5; 5.0]	113	75 (66.4)	2.7 [2.1; 3.4]	0.74 [0.53; 1.03]	0.076	
Age (Years)									
< 65	75	46 (61.3)	3.2 [1.9; 4.7]	82	49 (59.8)	2.3 [1.8; 4.4]	0.90 [0.60; 1.35]	0.626	0.529
≥ 65	63	35 (55.6)	4.2 [2.1; 9.5]	54	32 (59.3)	3.2 [2.1; 4.2]	0.76 [0.46; 1.23]	0.263	
Severity of disease									
ECOG 0	60	40 (66.7)	3.0 [1.7; 4.0]	51	30 (58.8)	3.4 [1.8; 5.3]	1.15 [0.72; 1.84]	0.567	0.077
ECOG ≥ 1	78	41 (52.6)	5.0 [2.8; 9.5]	85	51 (60.0)	2.7 [1.8; 4.0]	0.64 [0.42; 0.98]	0.041	
Region									
EU	14	9 (64.3)	2.5 [0.7; -]	16	9 (56.3)	1.4 [0.7; -]	0.96 [0.38; 2.45]	0.939	0.707
Ex-EU	124	72 (58.1)	3.5 [2.8; 5.1]	120	72 (60.0)	3.0 [2.2; 3.7]	0.82 [0.59; 1.14]	0.232	
Region									
Asia	94	57 (60.6)	3.5 [2.7; 5.1]	95	60 (63.2)	3.1 [2.3; 3.7]	0.78 [0.54; 1.13]	0.188	0.791
Rest of World	44	24 (54.5)	3.7 [1.4; 5.4]	41	21 (51.2)	1.7 [0.7; -]	0.89 [0.50; 1.61]	0.709	
Disease Status									
Metastatic	130	78 (60.0)	3.7 [2.8; 4.9]	123	75 (61.0)	2.9 [2.1; 3.6]	0.80 [0.58; 1.10]	0.169	0.213
Unresectable - Locally Advanced	8	3 (37.5)	1.4 [0.7; -]	13	6 (46.2)	4.4 [1.1; -]	1.97 [0.46; 8.33]	0.358	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Verstopfung

Tabelle 4G-57: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Verstopfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Constipation	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	13 (48.1)	5.5 [1.0; -]	23	13 (56.5)	2.1 [0.8; 4.9]	0.67 [0.31; 1.45]	0.308	0.594
Male	111	47 (42.3)	5.2 [3.8; -]	113	54 (47.8)	4.8 [3.1; -]	0.83 [0.56; 1.23]	0.346	
Age (Years)									
< 65	75	30 (40.0)	13.2 [3.0; -]	82	43 (52.4)	4.8 [1.6; 7.1]	0.66 [0.41; 1.05]	0.079	0.248
≥ 65	63	30 (47.6)	4.8 [3.0; -]	54	24 (44.4)	4.4 [3.2; -]	1.06 [0.62; 1.81]	0.831	
Severity of disease									
ECOG 0	60	25 (41.7)	Not reached [3.8; -]	51	30 (58.8)	3.2 [1.6; 4.4]	0.54 [0.32; 0.92]	0.024	0.057
ECOG ≥ 1	78	35 (44.9)	4.6 [2.6; -]	85	37 (43.5)	5.8 [2.7; -]	1.04 [0.65; 1.65]	0.881	
Region									
EU	14	5 (35.7)	Not reached [4.8; -]	16	9 (56.3)	2.2 [0.7; -]	0.40 [0.13; 1.21]	0.105	0.162
Ex-EU	124	55 (44.4)	4.7 [3.0; -]	120	58 (48.3)	4.8 [3.1; -]	0.87 [0.60; 1.26]	0.461	
Region									
Asia	94	42 (44.7)	4.9 [3.0; -]	95	46 (48.4)	3.6 [2.3; -]	0.82 [0.54; 1.24]	0.346	> 0.999
Rest of World	44	18 (40.9)	13.2 [1.4; -]	41	21 (51.2)	4.4 [1.6; -]	0.79 [0.42; 1.49]	0.461	
Disease Status									
Metastatic	130	57 (43.8)	5.5 [4.1; -]	123	59 (48.0)	4.8 [2.3; -]	0.81 [0.56; 1.16]	0.250	0.770
Unresectable - Locally Advanced	8	3 (37.5)	4.0 [2.6; -]	13	8 (61.5)	4.4 [2.1; 5.8]	1.60 [0.39; 6.55]	0.510	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Diarrhoe

Tabelle 4G-58: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Diarrhoe des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Diarrhea	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	9 (33.3)	Not reached [2.7; -]	23	3 (13.0)	Not reached [-; -]	2.32 [0.63; 8.56]	0.208	0.362
Male	111	48 (43.2)	6.9 [3.1; -]	113	40 (35.4)	Not reached [3.9; -]	1.19 [0.78; 1.81]	0.426	
Age (Years)									
< 65	75	32 (42.7)	6.9 [3.1; -]	82	22 (26.8)	Not reached [-; -]	1.60 [0.93; 2.77]	0.091	0.146
≥ 65	63	25 (39.7)	12.2 [2.8; -]	54	21 (38.9)	Not reached [3.5; -]	0.91 [0.51; 1.64]	0.758	
Severity of disease									
ECOG 0	60	26 (43.3)	24.9 [3.0; -]	51	21 (41.2)	Not reached [2.7; -]	0.91 [0.51; 1.63]	0.751	0.140
ECOG ≥ 1	78	31 (39.7)	12.2 [2.8; -]	85	22 (25.9)	Not reached [-; -]	1.61 [0.93; 2.79]	0.088	
Region									
EU	14	8 (57.1)	2.5 [0.7; -]	16	5 (31.3)	Not reached [0.8; -]	1.86 [0.61; 5.69]	0.278	0.428
Ex-EU	124	49 (39.5)	24.9 [3.5; -]	120	38 (31.7)	Not reached [5.7; -]	1.19 [0.78; 1.82]	0.425	
Region									
Asia	94	39 (41.5)	12.2 [3.3; -]	95	32 (33.7)	Not reached [3.9; -]	1.19 [0.74; 1.90]	0.472	0.686
Rest of World	44	18 (40.9)	24.9 [2.5; -]	41	11 (26.8)	Not reached [3.1; -]	1.41 [0.66; 3.01]	0.375	
Disease Status									
Metastatic	130	56 (43.1)	12.2 [3.3; -]	123	40 (32.5)	Not reached [5.7; -]	1.24 [0.82; 1.86]	0.302	0.710
Unresectable - Locally Advanced	8	1 (12.5)	Not reached [2.6; -]	13	3 (23.1)	Not reached [2.3; -]	0.81 [0.08; 7.84]	0.857	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18

EORTC QLQ-OES18: Symptomskala Essen

Tabelle 4G-59: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Essen des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Eating	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	26	10 (38.5)	11.2 [2.7; -]	21	6 (28.6)	9.6 [1.4; -]	0.98 [0.35; 2.73]	0.973	0.632
Male	111	57 (51.4)	6.7 [3.1; 11.0]	112	63 (56.3)	3.4 [2.7; 5.2]	0.74 [0.51; 1.06]	0.103	
Age (Years)									
< 65	75	36 (48.0)	7.6 [3.1; 12.3]	81	40 (49.4)	4.4 [2.9; 7.1]	0.78 [0.49; 1.24]	0.292	0.651
≥ 65	62	31 (50.0)	5.5 [3.0; -]	52	29 (55.8)	3.4 [2.4; 5.2]	0.70 [0.42; 1.16]	0.168	
Severity of disease									
ECOG 0	60	33 (55.0)	5.1 [2.8; 12.3]	48	25 (52.1)	4.6 [2.3; 5.8]	0.87 [0.51; 1.47]	0.599	0.518
ECOG ≥ 1	77	34 (44.2)	9.6 [3.3; -]	85	44 (51.8)	3.5 [2.7; 7.1]	0.67 [0.42; 1.06]	0.084	
Region									
EU	14	5 (35.7)	Not reached [2.1; -]	16	9 (56.3)	3.1 [1.4; -]	0.45 [0.15; 1.35]	0.156	0.350
Ex-EU	123	62 (50.4)	6.7 [3.3; 11.0]	117	60 (51.3)	4.4 [2.9; 5.5]	0.79 [0.55; 1.13]	0.197	
Region									
Asia	94	48 (51.1)	6.7 [4.1; 11.0]	95	50 (52.6)	3.6 [2.7; 5.8]	0.72 [0.48; 1.07]	0.105	0.924
Rest of World	43	19 (44.2)	11.2 [1.4; -]	38	19 (50.0)	3.3 [2.2; 9.6]	0.83 [0.43; 1.57]	0.559	
Disease Status									
Metastatic	129	65 (50.4)	7.2 [3.9; 11.2]	120	63 (52.5)	3.5 [2.7; 5.5]	0.75 [0.53; 1.07]	0.111	0.889
Unresectable - Locally Advanced	8	2 (25.0)	Not reached [1.7; -]	13	6 (46.2)	3.5 [2.1; -]	1.09 [0.22; 5.45]	0.916	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Reflux

Tabelle 4G-60: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Reflux des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Reflux	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	26	13 (50.0)	5.0 [3.0; -]	21	11 (52.4)	4.4 [0.8; -]	0.62 [0.27; 1.42]	0.263	0.505
Male	111	49 (44.1)	8.1 [4.0; -]	112	52 (46.4)	5.5 [3.4; 10.2]	0.91 [0.61; 1.34]	0.622	
Severity of disease									
ECOG 0	60	26 (43.3)	8.9 [4.6; -]	48	17 (35.4)	8.4 [3.4; -]	0.98 [0.53; 1.82]	0.949	0.765
ECOG ≥ 1	77	36 (46.8)	7.6 [2.3; 13.2]	85	46 (54.1)	4.2 [2.3; 5.5]	0.87 [0.56; 1.35]	0.523	
Region									
Asia	94	40 (42.6)	8.5 [4.4; -]	95	44 (46.3)	5.5 [3.5; 11.0]	0.82 [0.53; 1.26]	0.368	0.928
Rest of World	43	22 (51.2)	4.6 [2.3; -]	38	19 (50.0)	3.3 [1.4; -]	0.87 [0.47; 1.62]	0.663	
Disease Status									
Metastatic	129	61 (47.3)	7.6 [4.2; 13.2]	120	56 (46.7)	5.5 [3.4; 10.2]	0.90 [0.63; 1.30]	0.582	0.190
Unresectable - Locally Advanced	8	1 (12.5)	Not reached [0.7; -]	13	7 (53.8)	2.7 [0.7; -]	0.35 [0.04; 2.85]	0.326	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Schmerzen

Tabelle 4G-61: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schmerzen des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Pain	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**

Gender									
Female	26	12 (46.2)	4.8 [2.7; -]	21	9 (42.9)	4.6 [1.4; -]	0.78 [0.33; 1.85]	0.568	0.904
Male	111	54 (48.6)	5.2 [3.1; 18.7]	112	57 (50.9)	5.0 [2.8; 5.8]	0.80 [0.55; 1.17]	0.249	
Age (Years)									
< 65	75	40 (53.3)	3.7 [2.9; 8.9]	81	41 (50.6)	4.4 [2.8; 5.6]	0.92 [0.60; 1.43]	0.721	0.341
≥ 65	62	26 (41.9)	9.6 [3.1; -]	52	25 (48.1)	5.2 [2.1; 12.2]	0.64 [0.36; 1.12]	0.115	
Severity of disease									
ECOG 0	60	34 (56.7)	4.6 [3.0; 12.3]	48	24 (50.0)	4.6 [2.1; 8.1]	0.79 [0.46; 1.35]	0.393	0.673
ECOG ≥ 1	77	32 (41.6)	6.5 [3.1; -]	85	42 (49.4)	4.6 [2.5; 8.5]	0.76 [0.48; 1.21]	0.252	
Region									
Asia	94	48 (51.1)	4.6 [3.2; 12.3]	95	48 (50.5)	4.6 [2.9; 5.6]	0.79 [0.52; 1.19]	0.255	0.899
Rest of World	43	18 (41.9)	6.5 [2.6; -]	38	18 (47.4)	4.6 [2.1; -]	0.79 [0.41; 1.53]	0.491	
Disease Status									
Metastatic	129	64 (49.6)	5.2 [3.5; 12.3]	120	59 (49.2)	5.0 [2.8; 5.8]	0.79 [0.55; 1.13]	0.198	0.931
Unresectable - Locally Advanced	8	2 (25.0)	Not reached [0.7; -]	13	7 (53.8)	4.6 [1.3; -]	1.06 [0.21; 5.34]	0.942	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Speichelschlucken

Tabelle 4G-62: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Speichelschlucken des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Trouble Swallowing Saliva	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Age (Years)									
< 65	75	31 (41.3)	11.0 [4.4; -]	81	34 (42.0)	6.3 [3.9; -]	0.83 [0.51; 1.37]	0.466	0.221
≥ 65	62	22 (35.5)	26.1 [4.8; -]	52	25 (48.1)	4.4 [2.3; -]	0.55 [0.30; 0.98]	0.044	
Severity of disease									

ECOG 0	60	23 (38.3)	25.8 [4.9; -]	48	19 (39.6)	5.5 [3.5; -]	0.76 [0.40; 1.41]	0.379	0.848
ECOG ≥ 1	77	30 (39.0)	7.9 [4.1; -]	85	40 (47.1)	5.5 [3.5; 12.2]	0.71 [0.44; 1.15]	0.166	
Region									
EU	14	7 (50.0)	5.7 [1.7; -]	16	7 (43.8)	3.5 [1.4; -]	0.79 [0.27; 2.28]	0.660	0.789
Ex-EU	123	46 (37.4)	25.8 [4.9; -]	117	52 (44.4)	6.3 [4.0; -]	0.69 [0.46; 1.04]	0.073	
Region									
Asia	94	35 (37.2)	26.1 [4.9; -]	95	47 (49.5)	4.9 [3.5; 12.2]	0.59 [0.37; 0.92]	0.019	0.119
Rest of World	43	18 (41.9)	7.9 [2.8; -]	38	12 (31.6)	Not reached [3.5; -]	1.16 [0.55; 2.43]	0.692	
Disease Status									
Metastatic	129	50 (38.8)	25.8 [5.4; -]	120	53 (44.2)	5.5 [4.0; -]	0.69 [0.47; 1.03]	0.070	0.548
Unresectable - Locally Advanced	8	3 (37.5)	4.7 [1.4; -]	13	6 (46.2)	3.5 [0.9; -]	1.08 [0.27; 4.34]	0.914	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Verschlucken

Tabelle 4G-63: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Verschlucken des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Choked when Swallowing	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	26	11 (42.3)	7.9 [2.8; -]	21	11 (52.4)	3.9 [2.9; -]	0.52 [0.22; 1.23]	0.138	0.968
Male	111	35 (31.5)	25.8 [9.6; -]	112	45 (40.2)	5.6 [4.3; -]	0.53 [0.33; 0.84]	0.007	
Age (Years)									
< 65	75	25 (33.3)	12.0 [7.9; -]	81	32 (39.5)	5.5 [4.2; -]	0.54 [0.31; 0.94]	0.030	0.529
≥ 65	62	21 (33.9)	Not reached [7.6; -]	52	24 (46.2)	4.3 [2.9; -]	0.49 [0.27; 0.89]	0.020	
Severity of disease									
ECOG 0	60	21 (35.0)	12.3 [8.9; -]	48	17 (35.4)	7.0 [4.2; -]	0.65 [0.33; 1.29]	0.219	0.291

ECOG ≥ 1	77	25 (32.5)	12.0 [7.2; -]	85	39 (45.9)	4.4 [2.8; -]	0.47 [0.28; 0.79]	0.005	
Region									
EU	14	5 (35.7)	Not reached [3.3; -]	16	7 (43.8)	4.2 [2.6; -]	0.52 [0.16; 1.67]	0.272	0.829
Ex-EU	123	41 (33.3)	12.3 [8.9; -]	117	49 (41.9)	5.5 [3.9; -]	0.52 [0.34; 0.81]	0.003	
Region									
Asia	94	31 (33.0)	12.0 [8.9; -]	95	40 (42.1)	5.5 [3.4; -]	0.49 [0.30; 0.80]	0.005	0.768
Rest of World	43	15 (34.9)	25.8 [5.0; -]	38	16 (42.1)	5.3 [3.5; -]	0.62 [0.30; 1.27]	0.190	
Disease Status									
Metastatic	129	44 (34.1)	12.3 [8.9; -]	120	54 (45.0)	5.5 [3.5; 7.0]	0.47 [0.31; 0.72]	< 0.001	0.055
Unresectable - Locally Advanced	8	2 (25.0)	Not reached [1.4; -]	13	2 (15.4)	Not reached [3.7; -]	2.97 [0.40; 22.02]	0.287	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Mundtrockenheit

Tabelle 4G-64: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Mundtrockenheit des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Dry Mouth	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	26	15 (57.7)	4.2 [0.9; 8.9]	21	10 (47.6)	2.1 [0.8; -]	0.88 [0.39; 1.97]	0.753	0.692
Male	111	59 (53.2)	4.0 [1.8; 9.7]	112	59 (52.7)	3.0 [2.4; 6.7]	1.04 [0.72; 1.49]	0.837	
Age (Years)									
< 65	75	45 (60.0)	3.3 [1.4; 8.1]	81	39 (48.1)	3.0 [2.1; -]	1.18 [0.76; 1.82]	0.457	0.261
≥ 65	62	29 (46.8)	4.9 [1.7; -]	52	30 (57.7)	2.9 [2.1; 5.0]	0.81 [0.49; 1.36]	0.428	
Severity of disease									
ECOG 0	60	31 (51.7)	5.1 [1.4; -]	48	22 (45.8)	5.0 [2.7; -]	1.20 [0.69; 2.07]	0.524	0.495
ECOG ≥ 1	77	43	3.9	85	47	2.6	0.94	0.778	

		(55.8)	[1.7; 8.9]		(55.3)	[1.6; 4.9]	[0.62; 1.43]		
Region									
EU	14	7 (50.0)	4.8 [2.1; -]	16	8 (50.0)	2.7 [0.7; -]	0.66 [0.24; 1.85]	0.433	0.479
Ex-EU	123	67 (54.5)	4.0 [1.6; 8.3]	117	61 (52.1)	3.0 [2.2; 6.7]	1.07 [0.75; 1.51]	0.711	
Region									
Asia	94	47 (50.0)	5.1 [2.4; -]	95	49 (51.6)	3.0 [2.2; -]	0.95 [0.63; 1.42]	0.790	0.476
Rest of World	43	27 (62.8)	2.8 [0.8; 7.2]	38	20 (52.6)	2.7 [1.4; -]	1.18 [0.66; 2.11]	0.568	
Disease Status									
Metastatic	129	71 (55.0)	4.2 [1.9; 8.3]	120	60 (50.0)	3.0 [2.3; -]	1.06 [0.75; 1.50]	0.733	0.832
Unresectable - Locally Advanced	8	3 (37.5)	4.0 [0.7; -]	13	9 (69.2)	2.7 [0.7; 6.7]	1.15 [0.30; 4.34]	0.839	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Geschmackssinn

Tabelle 4G-65: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Geschmackssinn des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Trouble with Taste	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	26	15 (57.7)	4.2 [1.6; 11.1]	21	6 (28.6)	11.0 [3.0; -]	2.06 [0.80; 5.32]	0.136	0.128
Male	111	55 (49.5)	4.0 [2.3; -]	112	57 (50.9)	3.5 [2.7; 5.3]	1.00 [0.69; 1.45]	0.989	
Age (Years)									
< 65	75	36 (48.0)	3.9 [1.6; -]	81	36 (44.4)	5.0 [3.0; -]	1.15 [0.72; 1.83]	0.561	0.739
≥ 65	62	34 (54.8)	4.2 [2.4; 10.2]	52	27 (51.9)	3.4 [2.4; 5.5]	1.00 [0.60; 1.66]	> 0.999	
Severity of disease									
ECOG 0	60	34 (56.7)	2.6 [1.4; 11.1]	48	26 (54.2)	3.0 [2.1; -]	1.10 [0.66; 1.84]	0.707	0.954
ECOG ≥ 1	77	36 (46.8)	4.4 [2.6; -]	85	37 (43.5)	5.0 [3.0; -]	1.06 [0.67; 1.69]	0.794	

Region									
Asia	94	48 (51.1)	4.0 [2.4; 11.1]	95	42 (44.2)	5.1 [3.1; -]	1.17 [0.77; 1.78]	0.464	0.392
Rest of World	43	22 (51.2)	4.2 [1.6; -]	38	21 (55.3)	2.5 [1.9; 4.2]	0.88 [0.48; 1.60]	0.674	
Disease Status									
Metastatic	129	69 (53.5)	3.9 [2.3; 5.0]	120	56 (46.7)	4.2 [3.0; 11.0]	1.16 [0.81; 1.65]	0.412	0.105
Unresectable - Locally Advanced	8	1 (12.5)	Not reached [0.7; -]	13	7 (53.8)	2.1 [0.8; -]	0.30 [0.04; 2.48]	0.265	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Husten

Tabelle 4G-66: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Husten des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Trouble with Coughing	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	26	10 (38.5)	11.2 [2.1; -]	21	5 (23.8)	Not reached [3.7; -]	1.19 [0.40; 3.55]	0.759	0.330
Male	111	35 (31.5)	Not reached [8.6; -]	112	44 (39.3)	7.8 [5.0; -]	0.66 [0.42; 1.04]	0.073	
Age (Years)									
< 65	75	25 (33.3)	Not reached [4.7; -]	81	27 (33.3)	Not reached [5.5; -]	0.89 [0.52; 1.55]	0.692	0.368
≥ 65	62	20 (32.3)	Not reached [7.0; -]	52	22 (42.3)	7.8 [3.4; -]	0.56 [0.30; 1.04]	0.066	
Severity of disease									
ECOG 0	60	18 (30.0)	Not reached [13.2; -]	48	20 (41.7)	4.6 [2.7; -]	0.50 [0.26; 0.96]	0.037	0.120
ECOG ≥ 1	77	27 (35.1)	11.2 [4.9; -]	85	29 (34.1)	7.8 [5.5; -]	0.96 [0.56; 1.62]	0.866	
Region									
EU	14	5 (35.7)	8.6 [1.5; -]	16	5 (31.3)	Not reached [0.8; -]	0.86 [0.25; 2.99]	0.813	0.943
Ex-EU	123	40 (32.5)	Not reached [5.8; -]	117	44 (37.6)	7.8 [5.0; -]	0.73 [0.47; 1.13]	0.154	
Disease Status									

Metastatic	129	44 (34.1)	Not reached [8.6; -]	120	43 (35.8)	8.5 [5.3; -]	0.78 [0.51; 1.19]	0.241	0.442
Unresectable - Locally Advanced	8	1 (12.5)	Not reached [4.7; -]	13	6 (46.2)	5.8 [0.9; -]	0.41 [0.05; 3.48]	0.410	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Sprechen

Tabelle 4G-67: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Sprechen des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Trouble Talking	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	26	9 (34.6)	13.2 [5.9; -]	21	6 (28.6)	10.1 [3.0; -]	0.67 [0.22; 2.02]	0.475	0.983
Male	111	36 (32.4)	25.3 [7.6; -]	112	40 (35.7)	Not reached [5.3; -]	0.88 [0.56; 1.39]	0.576	
Age (Years)									
< 65	75	27 (36.0)	13.2 [5.1; -]	81	24 (29.6)	10.1 [5.5; -]	1.14 [0.65; 2.00]	0.645	0.098
≥ 65	62	18 (29.0)	Not reached [11.1; -]	52	22 (42.3)	5.6 [3.9; -]	0.57 [0.30; 1.07]	0.080	
Severity of disease									
ECOG 0	60	21 (35.0)	25.3 [7.6; -]	48	18 (37.5)	7.0 [4.2; -]	0.70 [0.37; 1.34]	0.283	0.557
ECOG ≥ 1	77	24 (31.2)	13.2 [5.0; -]	85	28 (32.9)	Not reached [5.5; -]	0.98 [0.57; 1.70]	0.944	
Region									
EU	14	4 (28.6)	Not reached [1.5; -]	16	5 (31.3)	10.1 [2.3; -]	0.81 [0.22; 3.06]	0.760	0.813
Ex-EU	123	41 (33.3)	25.3 [11.1; -]	117	41 (35.0)	Not reached [5.5; -]	0.87 [0.56; 1.36]	0.552	
Region									
Asia	94	34 (36.2)	25.3 [7.5; -]	95	34 (35.8)	7.0 [5.3; -]	0.88 [0.54; 1.43]	0.609	0.729
Rest of World	43	11 (25.6)	13.2 [13.2; -]	38	12 (31.6)	10.1 [3.9; -]	0.70 [0.30; 1.63]	0.409	
Disease Status									
Metastatic	129	43 (33.3)	25.3 [11.1; -]	120	41 (34.2)	10.1 [5.5; -]	0.85 [0.55; 1.32]	0.477	0.861

Unresectable - Locally Advanced	8	2 (25.0)	Not reached [1.4; -]	13	5 (38.5)	5.3 [3.6; -]	1.07 [0.21; 5.52]	0.938	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Dysphagie

Tabelle 4G-68: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Dysphagie des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Dysphagia	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	26	14 (53.8)	3.0 [0.9; -]	21	10 (47.6)	1.4 [0.7; -]	0.91 [0.40; 2.04]	0.811	0.778
Male	111	65 (58.6)	2.8 [1.5; 4.2]	112	71 (63.4)	3.0 [2.3; 3.7]	0.94 [0.67; 1.32]	0.705	
Severity of disease									
ECOG 0	60	37 (61.7)	3.0 [1.6; 3.8]	48	32 (66.7)	2.8 [1.6; 4.1]	0.91 [0.56; 1.46]	0.691	0.813
ECOG ≥ 1	77	42 (54.5)	2.8 [1.4; 8.4]	85	49 (57.6)	3.1 [2.4; 4.9]	0.95 [0.63; 1.44]	0.800	
Region									
EU	14	7 (50.0)	2.4 [0.8; -]	16	12 (75.0)	1.6 [0.7; 3.5]	0.48 [0.19; 1.24]	0.129	0.124
Ex-EU	123	72 (58.5)	2.8 [1.5; 3.8]	117	69 (59.0)	3.1 [2.3; 4.1]	1.02 [0.73; 1.42]	0.916	
Region									
Asia	94	56 (59.6)	3.0 [1.6; 5.1]	95	60 (63.2)	3.0 [2.1; 3.7]	0.86 [0.60; 1.25]	0.436	0.490
Rest of World	43	23 (53.5)	2.3 [1.1; -]	38	21 (55.3)	3.5 [1.1; 9.7]	1.05 [0.58; 1.90]	0.871	
Disease Status									
Metastatic	129	76 (58.9)	2.8 [1.6; 4.2]	120	73 (60.8)	3.1 [2.3; 4.1]	0.94 [0.68; 1.29]	0.684	0.656
Unresectable - Locally Advanced	8	3 (37.5)	1.4 [0.7; -]	13	8 (61.5)	2.1 [1.1; -]	1.45 [0.37; 5.66]	0.595	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data

f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; PD-L1: Programmed Cell Death - Ligand 1

EQ-5D VAS

EQ-5D VAS (7 Punkte)

Tabelle 4G-69: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS (7 Punkte) aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EQ-5D VAS (7 Points)	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	18 (66.7)	3.5 [0.9; 5.9]	22	12 (54.5)	3.0 [1.4; -]	1.09 [0.52; 2.27]	0.821	0.885
Male	112	78 (69.6)	2.4 [1.8; 3.3]	112	76 (67.9)	2.7 [2.1; 3.5]	1.05 [0.76; 1.44]	0.768	
Age (Years)									
< 65	76	55 (72.4)	2.7 [1.4; 3.7]	82	50 (61.0)	3.0 [2.3; 4.7]	1.21 [0.82; 1.77]	0.339	0.207
≥ 65	63	41 (65.1)	2.4 [1.4; 4.4]	52	38 (73.1)	2.1 [1.5; 3.4]	0.86 [0.55; 1.34]	0.503	
Severity of disease									
ECOG 0	60	46 (76.7)	1.4 [1.0; 3.3]	48	36 (75.0)	3.0 [2.2; 4.6]	1.33 [0.86; 2.06]	0.204	0.133
ECOG ≥ 1	79	50 (63.3)	3.1 [2.3; 4.4]	86	52 (60.5)	2.3 [1.7; 4.1]	0.85 [0.58; 1.26]	0.425	
Region									
EU	14	11 (78.6)	3.3 [1.0; 5.5]	17	11 (64.7)	3.0 [1.4; 10.1]	1.45 [0.59; 3.57]	0.413	0.789
Ex-EU	125	85 (68.0)	2.5 [1.8; 3.5]	117	77 (65.8)	2.8 [2.1; 3.5]	1.05 [0.77; 1.43]	0.773	
Region									
Asia	95	66 (69.5)	2.4 [1.5; 3.5]	95	65 (68.4)	2.9 [2.1; 3.5]	1.04 [0.74; 1.47]	0.822	0.768
Rest of World	44	30 (68.2)	2.8 [1.4; 4.4]	39	23 (59.0)	2.2 [1.4; 8.3]	1.13 [0.65; 1.95]	0.667	
Disease Status									
Metastatic	130	92 (70.8)	2.5 [1.8; 3.5]	121	81 (66.9)	2.7 [2.1; 3.4]	1.03 [0.76; 1.39]	0.840	0.988
Unresectable - Locally Advanced	9	4 (44.4)	3.5 [1.4; -]	13	7 (53.8)	3.5 [1.4; -]	1.08 [0.32; 3.71]	0.899	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 7 points or more decrease from baseline
e: From product-limit (Kaplan-Meier) method for censored data

f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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; EQ-5D: European Quality of Life 5 Dimensions; PD-L1: Programmed Cell Death - Ligand 1; VAS: Visual Analog Scale

EQ-5D VAS (10 Punkte)

Tabelle 4G-70: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS (10 Punkte) aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EQ-5D VAS (10 Points)	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	17 (63.0)	4.6 [1.0; 12.4]	22	11 (50.0)	3.0 [2.1; -]	1.02 [0.47; 2.19]	0.964	0.931
Male	112	76 (67.9)	2.5 [2.0; 3.7]	112	74 (66.1)	2.8 [2.1; 3.6]	1.02 [0.74; 1.41]	0.884	
Age (Years)									
< 65	76	53 (69.7)	2.8 [1.8; 3.9]	82	49 (59.8)	3.0 [2.3; 4.7]	1.16 [0.79; 1.72]	0.452	0.228
≥ 65	63	40 (63.5)	2.5 [1.9; 4.4]	52	36 (69.2)	2.2 [1.5; 3.4]	0.84 [0.54; 1.33]	0.460	
Severity of disease									
ECOG 0	60	45 (75.0)	2.1 [1.0; 3.7]	48	33 (68.8)	3.4 [2.3; 4.7]	1.32 [0.84; 2.06]	0.232	0.121
ECOG ≥ 1	79	48 (60.8)	3.1 [2.4; 4.7]	86	52 (60.5)	2.6 [2.0; 4.1]	0.82 [0.55; 1.21]	0.319	
Region									
EU	14	11 (78.6)	3.3 [1.0; 5.5]	17	9 (52.9)	3.0 [1.4; -]	1.64 [0.65; 4.14]	0.299	0.448
Ex-EU	125	82 (65.6)	2.8 [2.1; 3.9]	117	76 (65.0)	2.8 [2.1; 3.6]	0.99 [0.72; 1.35]	0.934	
Region									
Asia	95	63 (66.3)	2.8 [2.0; 3.9]	95	64 (67.4)	2.9 [2.3; 3.6]	0.97 [0.69; 1.38]	0.884	0.510
Rest of World	44	30 (68.2)	2.8 [1.4; 4.4]	39	21 (53.8)	2.2 [1.4; 8.3]	1.19 [0.68; 2.09]	0.538	
Disease Status									
Metastatic	130	89 (68.5)	2.7 [2.0; 3.9]	121	79 (65.3)	2.8 [2.1; 3.4]	0.99 [0.73; 1.34]	0.953	0.763
Unresectable - Locally Advanced	9	4 (44.4)	3.5 [1.4; -]	13	6 (46.2)	4.7 [1.4; -]	1.26 [0.35; 4.48]	0.723	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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; EQ-5D: European Quality of Life 5 Dimensions; PD-L1: Programmed Cell Death - Ligand 1; VAS: Visual Analog Scale

Anhang 4-G10.3: Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-71: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den globalen Gesundheitsstatus des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		p-Value for Interaction Test[h]
EORTC QLQ-C30 Global Health Status	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	
Gender									
Female	27	16 (59.3)	3.6 [2.1; 9.9]	23	9 (39.1)	3.7 [2.1; -]	1.10 [0.48; 2.51]	0.817	0.581
Male	111	66 (59.5)	2.8 [1.7; 4.2]	113	72 (63.7)	3.0 [2.1; 3.7]	0.96 [0.69; 1.34]	0.799	
Age (Years)									
< 65	75	43 (57.3)	3.6 [2.1; 5.5]	82	46 (56.1)	3.7 [2.3; 5.0]	0.96 [0.63; 1.46]	0.857	0.852
≥ 65	63	39 (61.9)	2.3 [1.6; 4.6]	54	35 (64.8)	2.7 [1.5; 3.6]	0.94 [0.59; 1.48]	0.785	
Severity of disease									
ECOG 0	60	40 (66.7)	2.8 [2.1; 4.0]	51	34 (66.7)	3.5 [2.1; 4.8]	1.03 [0.65; 1.63]	0.905	0.681
ECOG ≥ 1	78	42 (53.8)	3.5 [1.8; 7.2]	85	47 (55.3)	3.4 [2.1; 4.8]	0.90 [0.59; 1.37]	0.619	
Region									
EU	14	11 (78.6)	1.7 [0.8; 9.9]	16	8 (50.0)	3.5 [1.5; -]	1.96 [0.76; 5.08]	0.166	0.181
Ex-EU	124	71 (57.3)	3.3 [2.1; 4.5]	120	73 (60.8)	3.0 [2.1; 3.7]	0.90 [0.65; 1.25]	0.547	
Region									
Asia	94	54 (57.4)	3.5 [2.1; 4.7]	95	63 (66.3)	3.0 [2.1; 3.7]	0.81 [0.56; 1.17]	0.264	0.075
Rest of World	44	28 (63.6)	2.1 [1.2; 5.5]	41	18 (43.9)	7.4 [1.9; -]	1.50 [0.83; 2.71]	0.184	
Disease Status									
Metastatic	130	77 (59.2)	3.3 [2.1; 4.6]	123	75 (61.0)	3.0 [2.1; 4.0]	0.90 [0.65; 1.23]	0.498	0.085
Unresectable - Locally Advanced	8	5 (62.5)	1.5 [1.0; -]	13	6 (46.2)	3.7 [1.3; -]	2.95 [0.88; 9.87]	0.079	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline
e: From product-limit (Kaplan-Meier) method for censored data

f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-72: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Physical Functioning	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	15 (55.6)	4.3 [2.1; -]	23	12 (52.2)	2.3 [0.8; -]	0.77 [0.36; 1.65]	0.496	0.663
Male	111	68 (61.3)	3.6 [2.4; 4.4]	113	70 (61.9)	3.0 [2.5; 4.2]	0.91 [0.65; 1.28]	0.605	
Age (Years)									
< 65	75	48 (64.0)	3.5 [2.1; 4.5]	82	47 (57.3)	3.0 [2.5; 5.8]	1.11 [0.74; 1.67]	0.612	0.114
≥ 65	63	35 (55.6)	4.1 [3.0; 21.0]	54	35 (64.8)	2.8 [2.0; 3.7]	0.67 [0.41; 1.08]	0.101	
Severity of disease									
ECOG 0	60	37 (61.7)	4.1 [2.4; 5.9]	51	35 (68.6)	3.0 [2.3; 4.8]	0.76 [0.47; 1.21]	0.242	0.373
ECOG ≥ 1	78	46 (59.0)	3.6 [2.1; 4.5]	85	47 (55.3)	2.9 [2.1; 4.6]	1.00 [0.66; 1.51]	0.994	
Region									
EU	14	9 (64.3)	4.1 [1.0; 7.7]	16	10 (62.5)	3.1 [0.8; 10.1]	0.95 [0.38; 2.40]	0.914	0.992
Ex-EU	124	74 (59.7)	3.6 [2.6; 4.4]	120	72 (60.0)	2.9 [2.3; 3.7]	0.89 [0.64; 1.24]	0.508	
Region									
Asia	94	53 (56.4)	4.1 [3.0; 5.9]	95	55 (57.9)	3.2 [2.4; 4.8]	0.84 [0.58; 1.24]	0.385	0.731
Rest of World	44	30 (68.2)	2.8 [0.9; 4.4]	41	27 (65.9)	2.5 [1.6; 3.5]	0.97 [0.57; 1.64]	0.899	
Disease Status									
Metastatic	130	80 (61.5)	3.6 [2.8; 4.4]	123	72 (58.5)	3.1 [2.5; 4.6]	0.92 [0.67; 1.27]	0.618	0.562
Unresectable - Locally Advanced	8	3 (37.5)	2.6 [1.4; -]	13	10 (76.9)	2.5 [1.5; 3.0]	0.62 [0.17; 2.26]	0.467	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate

g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-73: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Rollenfunktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Role Functioning	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	16 (59.3)	3.3 [2.1; 7.2]	23	15 (65.2)	2.1 [0.8; 3.1]	0.64 [0.31; 1.29]	0.212	0.171
Male	111	73 (65.8)	2.1 [1.4; 3.6]	113	70 (61.9)	2.3 [2.1; 3.5]	1.13 [0.81; 1.57]	0.483	
Age (Years)									
< 65	75	46 (61.3)	3.5 [1.4; 4.5]	82	48 (58.5)	2.9 [2.1; 4.9]	1.00 [0.66; 1.50]	0.992	0.824
≥ 65	63	43 (68.3)	2.2 [1.1; 3.3]	54	37 (68.5)	2.1 [1.5; 2.8]	0.99 [0.63; 1.54]	0.948	
Severity of disease									
ECOG 0	60	42 (70.0)	2.4 [1.4; 4.0]	51	33 (64.7)	2.4 [1.6; 3.5]	1.04 [0.66; 1.66]	0.855	0.845
ECOG ≥ 1	78	47 (60.3)	3.2 [1.3; 4.5]	85	52 (61.2)	2.1 [1.8; 4.2]	1.00 [0.67; 1.48]	0.988	
Region									
EU	14	8 (57.1)	2.4 [1.0; -]	16	9 (56.3)	3.4 [1.0; -]	1.04 [0.39; 2.78]	0.931	0.914
Ex-EU	124	81 (65.3)	2.4 [1.4; 3.6]	120	76 (63.3)	2.3 [2.0; 2.9]	1.01 [0.74; 1.39]	0.941	
Region									
Asia	94	61 (64.9)	2.6 [1.4; 4.0]	95	61 (64.2)	2.3 [2.1; 3.0]	0.94 [0.66; 1.35]	0.752	0.514
Rest of World	44	28 (63.6)	2.4 [0.9; 6.8]	41	24 (58.5)	2.1 [1.5; 8.3]	1.18 [0.68; 2.04]	0.564	
Disease Status									
Metastatic	130	85 (65.4)	2.6 [1.4; 4.0]	123	77 (62.6)	2.4 [2.1; 3.1]	0.98 [0.72; 1.33]	0.888	0.375
Unresectable - Locally Advanced	8	4 (50.0)	1.5 [0.7; -]	13	8 (61.5)	1.8 [0.9; -]	1.56 [0.47; 5.22]	0.472	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-74: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Emotional Functioning	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	8 (29.6)	Not reached [6.9; -]	23	6 (26.1)	Not reached [1.6; -]	0.74 [0.25; 2.17]	0.586	0.913
Male	111	45 (40.5)	11.8 [5.2; -]	113	57 (50.4)	5.0 [3.6; 7.4]	0.69 [0.46; 1.03]	0.068	
Age (Years)									
< 65	75	29 (38.7)	11.8 [4.9; -]	82	40 (48.8)	5.1 [3.7; 8.4]	0.66 [0.41; 1.08]	0.102	0.914
≥ 65	63	24 (38.1)	21.0 [5.4; -]	54	23 (42.6)	7.4 [3.2; -]	0.71 [0.39; 1.28]	0.251	
Severity of disease									
ECOG 0	60	25 (41.7)	11.8 [5.2; -]	51	18 (35.3)	9.7 [3.7; -]	0.96 [0.51; 1.77]	0.885	0.252
ECOG ≥ 1	78	28 (35.9)	21.0 [6.9; -]	85	45 (52.9)	4.2 [3.5; 6.3]	0.56 [0.34; 0.91]	0.020	
Region									
EU	14	4 (28.6)	Not reached [1.7; -]	16	9 (56.3)	3.5 [1.4; 7.4]	0.26 [0.07; 0.96]	0.043	0.137
Ex-EU	124	49 (39.5)	11.8 [5.4; -]	120	54 (45.0)	6.3 [4.0; 8.8]	0.75 [0.50; 1.11]	0.154	
Region									
Asia	94	35 (37.2)	21.0 [5.4; -]	95	43 (45.3)	5.5 [4.1; 8.4]	0.66 [0.41; 1.04]	0.074	0.837
Rest of World	44	18 (40.9)	10.1 [2.1; -]	41	20 (48.8)	3.6 [2.1; 9.7]	0.71 [0.37; 1.36]	0.297	
Disease Status									
Metastatic	130	52 (40.0)	11.8 [6.9; -]	123	57 (46.3)	5.5 [4.0; 8.4]	0.69 [0.47; 1.02]	0.060	0.464
Unresectable - Locally Advanced	8	1 (12.5)	Not reached [1.4; -]	13	6 (46.2)	3.6 [2.1; -]	0.41 [0.05; 3.42]	0.410	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more decrease from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-75: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Kognitive Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Cognitive Functioning	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	14 (51.9)	3.1 [2.0; -]	23	14 (60.9)	2.3 [0.7; 3.8]	0.59 [0.28; 1.25]	0.166	0.119
Male	111	65 (58.6)	3.4 [2.6; 4.9]	113	64 (56.6)	4.1 [2.8; 5.1]	0.99 [0.70; 1.41]	0.951	
Age (Years)									
< 65	75	47 (62.7)	2.8 [2.0; 3.5]	82	47 (57.3)	3.9 [2.9; 4.8]	1.18 [0.78; 1.77]	0.431	0.072
≥ 65	63	32 (50.8)	5.0 [2.8; -]	54	31 (57.4)	2.8 [1.6; 7.4]	0.67 [0.40; 1.11]	0.123	
Severity of disease									
ECOG 0	60	41 (68.3)	3.1 [2.3; 3.7]	51	28 (54.9)	3.8 [2.3; 7.0]	1.23 [0.76; 1.99]	0.409	0.099
ECOG ≥ 1	78	38 (48.7)	3.5 [2.7; -]	85	50 (58.8)	3.6 [2.1; 4.9]	0.72 [0.46; 1.10]	0.130	
Region									
EU	14	8 (57.1)	5.0 [1.5; -]	16	8 (50.0)	5.8 [0.8; -]	0.75 [0.28; 2.01]	0.562	0.700
Ex-EU	124	71 (57.3)	3.1 [2.6; 3.7]	120	70 (58.3)	3.7 [2.7; 4.8]	0.94 [0.67; 1.32]	0.735	
Region									
Asia	94	53 (56.4)	3.5 [2.6; 9.6]	95	57 (60.0)	3.6 [2.3; 4.8]	0.80 [0.55; 1.18]	0.259	0.260
Rest of World	44	26 (59.1)	3.1 [2.0; 4.9]	41	21 (51.2)	3.8 [2.1; 7.4]	1.27 [0.71; 2.26]	0.418	
Disease Status									
Metastatic	130	77 (59.2)	3.3 [2.7; 4.6]	123	72 (58.5)	3.7 [2.8; 4.8]	0.91 [0.66; 1.26]	0.580	0.778
Unresectable - Locally Advanced	8	2 (25.0)	Not reached [1.5; -]	13	6 (46.2)	6.7 [1.1; -]	0.76 [0.15; 3.93]	0.744	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-76: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Soziale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Social Functioning	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	27	16 (59.3)	3.7 [2.1; -]	23	11 (47.8)	2.1 [0.7; -]	0.69 [0.31; 1.52]	0.354	0.685
Male	111	60 (54.1)	4.7 [2.8; 13.1]	113	61 (54.0)	3.3 [2.6; 5.3]	0.89 [0.61; 1.28]	0.517	
Age (Years)									
< 65	75	41 (54.7)	3.6 [1.8; 13.1]	82	42 (51.2)	3.3 [2.2; 5.5]	1.03 [0.67; 1.58]	0.903	0.305
≥ 65	63	35 (55.6)	4.7 [3.6; 18.7]	54	30 (55.6)	3.2 [2.1; 5.3]	0.70 [0.42; 1.17]	0.176	
Severity of disease									
ECOG 0	60	35 (58.3)	4.4 [2.8; 18.7]	51	31 (60.8)	2.9 [2.1; 4.2]	0.76 [0.46; 1.23]	0.263	0.356
ECOG ≥ 1	78	41 (52.6)	4.9 [2.1; 15.5]	85	41 (48.2)	4.6 [2.4; 7.4]	0.93 [0.60; 1.45]	0.750	
Region									
EU	14	7 (50.0)	5.7 [1.0; -]	16	8 (50.0)	2.1 [0.7; -]	0.68 [0.24; 1.90]	0.458	0.399
Ex-EU	124	69 (55.6)	4.1 [2.9; 5.4]	120	64 (53.3)	3.3 [2.4; 5.2]	0.91 [0.65; 1.29]	0.606	
Region									
Asia	94	51 (54.3)	4.7 [3.5; 18.7]	95	54 (56.8)	3.0 [2.2; 5.2]	0.74 [0.50; 1.10]	0.142	0.252
Rest of World	44	25 (56.8)	3.6 [1.4; 13.1]	41	18 (43.9)	5.0 [2.1; -]	1.24 [0.67; 2.28]	0.488	
Disease Status									
Metastatic	130	73 (56.2)	4.4 [3.5; 5.7]	123	69 (56.1)	3.0 [2.2; 4.2]	0.78 [0.56; 1.10]	0.159	0.066
Unresectable - Locally Advanced	8	3 (37.5)	1.7 [0.7; -]	13	3 (23.1)	Not reached [2.1; -]	4.66 [0.77; 28.18]	0.093	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with squamous cell carcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G10.4: Nebenwirkungen

Unerwünschte Ereignisse

Unerwünschte Ereignisse gesamt

Tabelle 4G-77: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	29	29 (100.0)	0.4 [0.3; 0.9]	26	26 (100.0)	0.4 [0.3; 0.7]	0.94 [0.55; 1.61]	0.825	0.176
Male	114	114 (100.0)	0.4 [0.3; 0.4]	114	114 (100.0)	0.4 [0.4; 0.6]	1.40 [1.07; 1.83]	0.014	
Age category									
< 65	78	78 (100.0)	0.4 [0.3; 0.6]	85	85 (100.0)	0.6 [0.4; 0.7]	1.28 [0.94; 1.75]	0.119	0.778
≥ 65	65	65 (100.0)	0.4 [0.3; 0.4]	55	55 (100.0)	0.4 [0.3; 0.6]	1.23 [0.85; 1.77]	0.270	
Severity of disease									
ECOG 0	61	61 (100.0)	0.4 [0.3; 0.6]	52	52 (100.0)	0.4 [0.3; 0.6]	1.00 [0.69; 1.45]	0.984	0.122
ECOG ≥ 1	82	82 (100.0)	0.4 [0.3; 0.6]	88	88 (100.0)	0.6 [0.4; 0.7]	1.52 [1.11; 2.08]	0.009	
Region									
EU	14	14 (100.0)	0.5 [0.3; 0.9]	17	17 (100.0)	0.3 [0.3; 1.4]	1.13 [0.55; 2.33]	0.742	0.651
Ex-EU	129	129 (100.0)	0.4 [0.3; 0.4]	123	123 (100.0)	0.4 [0.4; 0.6]	1.31 [1.02; 1.68]	0.037	
Region									
Asia	96	96 (100.0)	0.4 [0.3; 0.4]	96	96 (100.0)	0.4 [0.4; 0.6]	1.41 [1.05; 1.89]	0.021	0.238
Rest of World	47	47 (100.0)	0.4 [0.3; 0.7]	44	44 (100.0)	0.6 [0.3; 0.7]	1.05 [0.70; 1.59]	0.804	
Disease Status									
Metastatic	134	134 (100.0)	0.4 [0.3; 0.4]	127	127 (100.0)	0.4 [0.4; 0.6]	1.26 [0.99; 1.61]	0.065	0.970
Unresectable - Locally Advanced	9	9 (100.0)	0.7 [0.1; 1.3]	13	13 (100.0)	0.6 [0.3; 1.1]	1.30 [0.54; 3.15]	0.562	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: all-participants-as-treated population with squamous cell carcinoma and PD-L1 CPS≥10

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

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

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

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

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-78: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Serious Adverse Events	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	29	17 (58.6)	36.7 [6.9; 62.1]	26	15 (57.7)	21.7 [1.4; -]	0.90 [0.44; 1.81]	0.760	0.954
Male	114	61 (53.5)	34.0 [16.3; -]	114	64 (56.1)	25.7 [16.7; 48.0]	0.87 [0.61; 1.25]	0.457	
Age category									
< 65	78	38 (48.7)	42.6 [16.3; -]	85	45 (52.9)	29.6 [19.0; 60.3]	0.83 [0.54; 1.29]	0.408	0.816
≥ 65	65	40 (61.5)	27.1 [13.0; 62.1]	55	34 (61.8)	20.1 [9.1; 71.3]	0.91 [0.57; 1.43]	0.672	
Severity of disease									
ECOG 0	61	29 (47.5)	58.0 [21.3; -]	52	27 (51.9)	29.6 [22.1; -]	0.76 [0.45; 1.29]	0.307	0.368
ECOG ≥ 1	82	49 (59.8)	21.4 [11.1; 45.9]	88	52 (59.1)	21.7 [14.6; 55.1]	1.00 [0.67; 1.48]	0.991	
Region									
EU	14	9 (64.3)	16.5 [4.1; -]	17	9 (52.9)	26.6 [1.4; -]	1.21 [0.48; 3.05]	0.691	0.437
Ex-EU	129	69 (53.5)	35.9 [17.1; 101.9]	123	70 (56.9)	25.4 [15.6; 55.1]	0.84 [0.60; 1.17]	0.298	
Region									
Asia	96	45 (46.9)	58.0 [21.4; -]	96	54 (56.3)	24.9 [14.6; 71.3]	0.73 [0.49; 1.09]	0.127	0.078
Rest of World	47	33 (70.2)	16.4 [13.0; 36.7]	44	25 (56.8)	42.0 [10.4; 60.3]	1.30 [0.77; 2.19]	0.330	
Disease Status									
Metastatic	134	70 (52.2)	39.3 [21.3; 101.9]	127	68 (53.5)	26.6 [19.0; 60.3]	0.87 [0.62; 1.22]	0.410	0.166
Unresectable - Locally Advanced	9	8 (88.9)	3.0 [0.9; -]	13	11 (84.6)	5.0 [1.1; 42.0]	2.20 [0.78; 6.18]	0.135	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: all-participants-as-treated population with squamous cell carcinoma and PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5)

Tabelle 4G-79: 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 – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	29	27 (93.1)	5.9 [3.0; 9.1]	26	23 (88.5)	4.6 [1.3; 9.7]	0.94 [0.54; 1.66]	0.835	0.826
Male	114	99 (86.8)	4.1 [3.1; 6.9]	114	96 (84.2)	5.0 [3.3; 9.1]	1.03 [0.77; 1.36]	0.854	
Age category									
< 65	78	67 (85.9)	6.4 [4.0; 10.4]	85	69 (81.2)	8.1 [3.3; 11.0]	0.96 [0.69; 1.35]	0.830	0.782
≥ 65	65	59 (90.8)	3.3 [3.0; 5.1]	55	50 (90.9)	3.6 [2.9; 8.1]	1.04 [0.71; 1.52]	0.845	
Severity of disease									
ECOG 0	61	52 (85.2)	6.0 [3.3; 9.1]	52	40 (76.9)	7.3 [3.1; 12.9]	1.04 [0.69; 1.58]	0.848	0.941
ECOG ≥ 1	82	74 (90.2)	3.6 [3.0; 5.1]	88	79 (89.8)	4.6 [3.1; 8.9]	1.03 [0.75; 1.41]	0.879	
Region									
EU	14	14 (100.0)	5.9 [0.7; 13.7]	17	14 (82.4)	8.1 [1.4; 15.6]	1.18 [0.55; 2.52]	0.672	0.529
Ex-EU	129	112 (86.8)	4.0 [3.0; 6.9]	123	105 (85.4)	4.7 [3.1; 8.9]	0.99 [0.75; 1.29]	0.919	
Region									
Asia	96	81 (84.4)	3.4 [3.0; 7.0]	96	82 (85.4)	4.6 [3.1; 8.9]	0.89 [0.65; 1.22]	0.466	0.089
Rest of World	47	45 (95.7)	5.9 [3.6; 8.0]	44	37 (84.1)	7.1 [3.0; 12.7]	1.45 [0.93; 2.26]	0.103	
Disease Status									
Metastatic	134	118 (88.1)	4.4 [3.1; 6.9]	127	107 (84.3)	5.9 [3.3; 9.0]	1.00 [0.77; 1.30]	0.983	0.477
Unresectable - Locally Advanced	9	8 (88.9)	4.0 [0.6; 6.0]	13	12 (92.3)	4.7 [1.1; 12.7]	1.59 [0.60; 4.18]	0.349	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: all-participants-as-treated population with squamous cell carcinoma and PD-L1 CPS≥10

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

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

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

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

CI: Confidence Interval; CPS: Combined Proportion Score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-80: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Adverse Events Leading to Treatment Discontinuation	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	29	9 (31.0)	Not reached [25.3; -]	26	8 (30.8)	Not reached [7.6; -]	0.88 [0.34; 2.28]	0.788	0.974
Male	114	27 (23.7)	Not reached [-; -]	114	29 (25.4)	71.3 [46.4; -]	0.86 [0.51; 1.46]	0.583	
Age category									
< 65	78	16 (20.5)	Not reached [-; -]	85	16 (18.8)	Not reached [46.4; -]	1.05 [0.52; 2.10]	0.894	0.425
≥ 65	65	20 (30.8)	Not reached [59.3; -]	55	21 (38.2)	71.3 [22.3; -]	0.72 [0.39; 1.34]	0.305	
Severity of disease									
ECOG 0	61	13 (21.3)	Not reached [-; -]	52	15 (28.8)	Not reached [32.4; -]	0.65 [0.31; 1.37]	0.258	0.272
ECOG ≥ 1	82	23 (28.0)	Not reached [42.1; -]	88	22 (25.0)	71.3 [46.4; -]	1.07 [0.59; 1.93]	0.821	
Region									
EU	14	4 (28.6)	Not reached [4.1; -]	17	6 (35.3)	Not reached [6.1; -]	0.76 [0.21; 2.69]	0.665	0.699
Ex-EU	129	32 (24.8)	Not reached [-; -]	123	31 (25.2)	Not reached [46.4; -]	0.90 [0.55; 1.49]	0.694	
Region									
Asia	96	19 (19.8)	Not reached [-; -]	96	21 (21.9)	Not reached [71.3; -]	0.84 [0.45; 1.57]	0.587	0.726
Rest of World	47	17 (36.2)	Not reached [21.3; -]	44	16 (36.4)	Not reached [22.3; -]	0.95 [0.48; 1.88]	0.877	
Disease Status									
Metastatic	134	33 (24.6)	Not reached [-; -]	127	30 (23.6)	Not reached [71.3; -]	0.96 [0.59; 1.59]	0.886	0.638
Unresectable - Locally Advanced	9	3 (33.3)	Not reached [0.9; -]	13	7 (53.8)	34.9 [3.9; -]	0.67 [0.17; 2.59]	0.559	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: all-participants-as-treated population with squamous cell carcinoma and PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-81: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
SOC[h]: General disorders and administration site conditions									
Gender									
Female	29	21 (72.4)	3.0 [0.7; 19.1]	26	15 (57.7)	9.1 [6.0; 16.3]	1.40 [0.72; 2.73]	0.318	0.878
Male	114	91 (79.8)	2.6 [0.9; 6.1]	114	82 (71.9)	7.1 [3.3; 9.1]	1.31 [0.97; 1.77]	0.077	
Age category									
< 65	78	60 (76.9)	5.4 [1.7; 7.1]	85	55 (64.7)	8.1 [6.0; 10.3]	1.30 [0.90; 1.88]	0.165	0.894
≥ 65	65	52 (80.0)	0.9 [0.6; 3.3]	55	42 (76.4)	4.3 [1.7; 9.3]	1.32 [0.87; 1.98]	0.189	
Severity of disease									
ECOG 0	61	45 (73.8)	3.7 [1.0; 8.1]	52	34 (65.4)	7.3 [2.3; 12.0]	1.21 [0.77; 1.89]	0.407	0.444
ECOG ≥ 1	82	67 (81.7)	1.8 [0.7; 6.0]	88	63 (71.6)	7.9 [5.1; 9.1]	1.45 [1.03; 2.05]	0.035	
Region									
EU	14	11 (78.6)	5.3 [0.4; 11.9]	17	13 (76.5)	6.0 [0.7; 12.0]	0.93 [0.41; 2.09]	0.863	0.361
Ex-EU	129	101 (78.3)	1.9 [0.9; 6.0]	123	84 (68.3)	7.9 [5.1; 9.4]	1.39 [1.04; 1.86]	0.027	
Region									
Asia	96	76 (79.2)	1.6 [0.7; 5.4]	96	65 (67.7)	8.4 [3.9; 9.6]	1.46 [1.04; 2.03]	0.027	0.381
Rest of World	47	36 (76.6)	5.9 [0.9; 8.1]	44	32 (72.7)	6.4 [2.3; 10.6]	1.14 [0.71; 1.83]	0.593	
Disease Status									
Metastatic	134	107 (79.9)	1.9 [1.0; 5.4]	127	88 (69.3)	8.1 [6.0; 9.3]	1.35 [1.02; 1.79]	0.039	0.577
Unresectable - Locally Advanced	9	5 (55.6)	10.6 [0.1; -]	13	9 (69.2)	2.7 [1.0; -]	0.85 [0.29; 2.56]	0.778	
SOC[h]: Musculoskeletal and connective tissue disorders									
Gender									
Female	29	8 (27.6)	55.6 [39.9; -]	26	8 (30.8)	53.1 [15.3; -]	0.54 [0.20; 1.47]	0.227	0.430
Male	114	19 (16.7)	Not reached [82.0; -]	114	36 (31.6)	63.4 [32.3; -]	0.36 [0.20; 0.64]	< 0.001	
Age category									
< 65	78	14 (17.9)	Not reached [50.6; -]	85	27 (31.8)	53.1 [32.3; -]	0.40 [0.21; 0.77]	0.006	0.855
≥ 65	65	13	Not reached	55	17	73.0	0.44	0.028	

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
		(20.0)	[55.6; -]		(30.9)	[26.9; -]	[0.21; 0.91]		
Severity of disease									
ECOG 0	61	11 (18.0)	Not reached [82.0; -]	52	16 (30.8)	53.1 [32.3; -]	0.38 [0.17; 0.85]	0.019	0.660
ECOG ≥ 1	82	16 (19.5)	Not reached [45.1; -]	88	28 (31.8)	63.4 [27.9; -]	0.44 [0.24; 0.83]	0.011	
Region									
EU	14	3 (21.4)	Not reached [37.9; -]	17	7 (41.2)	27.9 [8.1; -]	0.41 [0.11; 1.62]	0.204	0.929
Ex-EU	129	24 (18.6)	Not reached [55.6; -]	123	37 (30.1)	53.1 [34.1; 73.0]	0.41 [0.24; 0.69]	< 0.001	
Region									
Asia	96	15 (15.6)	Not reached [-; -]	96	26 (27.1)	73.0 [32.3; -]	0.36 [0.19; 0.70]	0.003	0.476
Rest of World	47	12 (25.5)	55.6 [39.9; -]	44	18 (40.9)	53.1 [21.1; -]	0.52 [0.25; 1.08]	0.078	
Disease Status									
Metastatic	134	27 (20.1)	Not reached [55.6; -]	127	39 (30.7)	53.1 [34.1; -]	0.44 [0.27; 0.73]	0.002	0.077
Unresectable - Locally Advanced	9	0 (0.0)	Not reached [-; -]	13	5 (38.5)	21.1 [8.1; -]	n.a. [n.a.; n.a.]	0.081	
SOC[h]: Skin and subcutaneous tissue disorders									
Gender									
Female	29	15 (51.7)	20.4 [3.1; -]	26	7 (26.9)	Not reached [16.1; -]	2.07 [0.84; 5.09]	0.112	0.568
Male	114	48 (42.1)	38.4 [20.1; -]	114	35 (30.7)	89.4 [29.3; -]	1.54 [0.99; 2.39]	0.055	
Age category									
< 65	78	28 (35.9)	Not reached [25.1; -]	85	22 (25.9)	89.4 [89.4; -]	1.43 [0.82; 2.49]	0.214	0.548
≥ 65	65	35 (53.8)	19.9 [6.0; 49.7]	55	20 (36.4)	Not reached [22.9; -]	1.81 [1.04; 3.14]	0.035	
Severity of disease									
ECOG 0	61	34 (55.7)	19.9 [7.1; 38.4]	52	22 (42.3)	28.3 [13.1; -]	1.38 [0.81; 2.37]	0.240	0.609
ECOG ≥ 1	82	29 (35.4)	Not reached [25.1; -]	88	20 (22.7)	89.4 [89.4; -]	1.72 [0.98; 3.05]	0.061	
Region									
EU	14	6 (42.9)	Not reached [2.3; -]	17	3 (17.6)	Not reached [22.9; -]	2.60 [0.65; 10.41]	0.178	0.445
Ex-EU	129	57 (44.2)	36.0 [19.9; -]	123	39 (31.7)	89.4 [29.3; -]	1.53 [1.01; 2.29]	0.042	
Region									
Asia	96	48 (50.0)	28.7 [11.9; 49.7]	96	33 (34.4)	89.4 [23.7; -]	1.61 [1.03; 2.53]	0.038	0.869
Rest of World	47	15 (31.9)	Not reached [20.4; -]	44	9 (20.5)	Not reached [-; -]	1.73 [0.76; 3.96]	0.193	
Disease Status									

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Metastatic	134	59 (44.0)	38.4 [19.9; -]	127	39 (30.7)	89.4 [29.3; -]	1.53 [1.02; 2.29]	0.041	0.334
Unresectable - Locally Advanced	9	4 (44.4)	Not reached [2.1; -]	13	3 (23.1)	Not reached [6.9; -]	3.47 [0.75; 16.00]	0.111	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: all-participants-as-treated population with squamous cell carcinoma and PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
h: A system organ class appears on this report only if its incidence ≥10% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05 or rule of 10 is not met
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); PD-L1: Programmed Cell Death - Ligand 1; SOC: System Organ Class

Tabelle 4G-82: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (PT) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC: General disorders and administration site conditions, PT[h]: Oedema peripheral									
Gender									
Female	29	1 (3.4)	Not reached [-; -]	26	3 (11.5)	Not reached [38.7; -]	0.26 [0.03; 2.50]	0.242	0.924
Male	114	3 (2.6)	Not reached [-; -]	114	9 (7.9)	Not reached [-; -]	0.29 [0.08; 1.09]	0.067	
Age category									
< 65	78	0 (0.0)	Not reached [-; -]	85	6 (7.1)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.008	0.051
≥ 65	65	4 (6.2)	Not reached [-; -]	55	6 (10.9)	Not reached [-; -]	0.53 [0.15; 1.89]	0.329	
Region									
EU	14	1 (7.1)	Not reached [-; -]	17	2 (11.8)	Not reached [21.6; -]	0.51 [0.05; 5.69]	0.585	0.645
Ex-EU	129	3 (2.3)	Not reached [-; -]	123	10 (8.1)	Not reached [-; -]	0.24 [0.06; 0.87]	0.030	
Region									
Asia	96	2 (2.1)	n.c.	96	6 (6.3)	n.c.	n.c.	n.c.	n.c.
Rest of World	47	2 (4.3)	n.c.	44	6 (13.6)	n.c.	n.c.	n.c.	
Disease Status									

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Metastatic	134	4 (3.0)	Not reached [-; -]	127	10 (7.9)	Not reached [-; -]	0.31 [0.10; 0.99]	0.048	0.431
Unresectable - Locally Advanced	9	0 (0.0)	Not reached [-; -]	13	2 (15.4)	Not reached [10.7; -]	n.a. [n.a.; n.a.]	0.279	
SOC: Metabolism and nutrition disorders, PT[h]: Hyperkalaemia									
Gender									
Female	29	1 (3.4)	Not reached [-; -]	26	2 (7.7)	73.4 [73.4; -]	0.22 [0.02; 2.60]	0.232	0.944
Male	114	6 (5.3)	Not reached [-; -]	114	13 (11.4)	Not reached [-; -]	0.38 [0.14; 1.00]	0.049	
Age category									
< 65	78	5 (6.4)	Not reached [-; -]	85	9 (10.6)	Not reached [73.4; -]	0.50 [0.17; 1.50]	0.215	0.401
≥ 65	65	2 (3.1)	Not reached [-; -]	55	6 (10.9)	Not reached [50.1; -]	0.21 [0.04; 1.06]	0.059	
Severity of disease									
ECOG 0	61	2 (3.3)	Not reached [-; -]	52	7 (13.5)	Not reached [-; -]	0.19 [0.04; 0.91]	0.038	0.198
ECOG ≥ 1	82	5 (6.1)	Not reached [-; -]	88	8 (9.1)	Not reached [73.4; -]	0.55 [0.18; 1.70]	0.298	
Region									
EU	14	1 (7.1)	Not reached [29.3; -]	17	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.378	0.100
Ex-EU	129	6 (4.7)	Not reached [-; -]	123	15 (12.2)	Not reached [73.4; -]	0.30 [0.11; 0.77]	0.013	
Region									
Asia	96	5 (5.2)	Not reached [-; -]	96	13 (13.5)	Not reached [50.1; -]	0.29 [0.10; 0.84]	0.022	0.305
Rest of World	47	2 (4.3)	Not reached [-; -]	44	2 (4.5)	Not reached [73.4; -]	0.83 [0.11; 5.99]	0.851	
SOC: Musculoskeletal and connective tissue disorders, PT[h]: Back pain									
Gender									
Female	29	1 (3.4)	Not reached [-; -]	26	6 (23.1)	53.1 [17.1; -]	0.09 [0.01; 0.79]	0.030	0.311
Male	114	4 (3.5)	Not reached [-; -]	114	10 (8.8)	Not reached [73.0; -]	0.28 [0.09; 0.92]	0.036	
Age category									
< 65	78	4 (5.1)	Not reached [-; -]	85	7 (8.2)	Not reached [53.1; -]	0.44 [0.13; 1.56]	0.205	0.062
≥ 65	65	1 (1.5)	Not reached [-; -]	55	9 (16.4)	Not reached [73.0; -]	0.07 [0.01; 0.55]	0.012	
Severity of disease									
ECOG 0	61	3 (4.9)	Not reached [-; -]	52	8 (15.4)	53.1 [34.1; -]	0.18 [0.04; 0.72]	0.016	0.986
ECOG ≥ 1	82	2 (2.4)	Not reached [-; -]	88	8 (9.1)	Not reached [-; -]	0.22 [0.05; 1.06]	0.059	
Region									
EU	14	1 (7.1)	Not reached [-; -]	17	5 (29.4)	Not reached [9.1; -]	0.19 [0.02; 1.61]	0.127	0.788

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Ex-EU	129	4 (3.1)	Not reached [-; -]	123	11 (8.9)	Not reached [53.1; -]	0.22 [0.07; 0.73]	0.013	
Region									
Asia	96	4 (4.2)	Not reached [-; -]	96	8 (8.3)	Not reached [73.0; -]	0.32 [0.09; 1.12]	0.076	0.257
Rest of World	47	1 (2.1)	Not reached [-; -]	44	8 (18.2)	Not reached [53.1; -]	0.10 [0.01; 0.80]	0.030	
Disease Status									
Metastatic	134	5 (3.7)	Not reached [-; -]	127	14 (11.0)	Not reached [53.1; -]	0.23 [0.08; 0.66]	0.006	0.444
Unresectable - Locally Advanced	9	0 (0.0)	Not reached [-; -]	13	2 (15.4)	Not reached [25.0; -]	n.a. [n.a.; n.a.]	0.329	
SOC: Respiratory, thoracic and mediastinal disorders, PT[h]: Oropharyngeal pain									
Gender									
Female	29	2 (6.9)	Not reached [-; -]	26	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.181	0.425
Male	114	9 (7.9)	Not reached [-; -]	114	2 (1.8)	Not reached [-; -]	4.07 [0.87; 18.92]	0.074	
Age category									
< 65	78	3 (3.8)	n.c.	85	1 (1.2)	n.c.	n.c.	n.c.	n.c.
≥ 65	65	8 (12.3)	n.c.	55	1 (1.8)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	61	8 (13.1)	Not reached [-; -]	52	2 (3.8)	Not reached [-; -]	2.96 [0.62; 14.04]	0.172	0.232
ECOG ≥ 1	82	3 (3.7)	Not reached [-; -]	88	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.078	
Region									
EU	14	0 (0.0)	Not reached [-; -]	17	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	0.997
Ex-EU	129	11 (8.5)	Not reached [-; -]	123	2 (1.6)	Not reached [-; -]	4.78 [1.06; 21.64]	0.042	
Region									
Asia	96	8 (8.3)	Not reached [-; -]	96	2 (2.1)	Not reached [-; -]	3.33 [0.70; 15.87]	0.130	0.259
Rest of World	47	3 (6.4)	Not reached [-; -]	44	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.088	
Disease Status									
Metastatic	134	11 (8.2)	Not reached [-; -]	127	1 (0.8)	Not reached [-; -]	9.30 [1.20; 72.19]	0.033	0.080
Unresectable - Locally Advanced	9	0 (0.0)	Not reached [-; -]	13	1 (7.7)	Not reached [22.7; -]	n.a. [n.a.; n.a.]	0.480	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: all-participants-as-treated population with squamous cell carcinoma and PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
test for interaction term)									

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

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term; SOC: System Organ Class

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-83: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Serious Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC[h]: General disorders and administration site conditions									
Gender									
Female	29	0 (0.0)	Not reached [-; -]	26	4 (15.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.026	0.251
Male	114	2 (1.8)	Not reached [-; -]	114	11 (9.6)	Not reached [-; -]	0.15 [0.03; 0.70]	0.016	
Age category									
< 65	78	0 (0.0)	n.c.	85	8 (9.4)	n.c.	n.c.	n.c.	n.c.
≥ 65	65	2 (3.1)	n.c.	55	7 (12.7)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	61	0 (0.0)	Not reached [-; -]	52	3 (5.8)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.035	0.313
ECOG ≥ 1	82	2 (2.4)	Not reached [-; -]	88	12 (13.6)	Not reached [-; -]	0.15 [0.03; 0.69]	0.014	
Region									
EU	14	0 (0.0)	Not reached [-; -]	17	3 (17.6)	Not reached [42.0; -]	n.a. [n.a.; n.a.]	0.090	0.387
Ex-EU	129	2 (1.6)	Not reached [-; -]	123	12 (9.8)	Not reached [-; -]	0.14 [0.03; 0.61]	0.009	
Region									
Asia	96	2 (2.1)	Not reached [-; -]	96	8 (8.3)	Not reached [-; -]	0.20 [0.04; 0.95]	0.043	0.129
Rest of World	47	0 (0.0)	Not reached [-; -]	44	7 (15.9)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.005	
Disease Status									
Metastatic	134	2 (1.5)	Not reached [-; -]	127	12 (9.4)	Not reached [-; -]	0.13 [0.03; 0.60]	0.009	0.486
Unresectable - Locally Advanced	9	0 (0.0)	Not reached [-; -]	13	3 (23.1)	42.0 [42.0; -]	n.a. [n.a.; n.a.]	0.182	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: all-participants-as-treated population with squamous cell carcinoma and PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
h: A system organ class appears on this report only if its incidence ≥ 5% or (incidence ≥ 1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05 or rule of 10 not met
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; SOC: System Organ Class

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

Tabelle 4G-84: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5) (PT) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
SOC: Investigations, PT[h]: Platelet count decreased									
Gender									
Female	29	0 (0.0)	Not reached [-; -]	26	1 (3.8)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.281	0.440
Male	114	3 (2.6)	Not reached [-; -]	114	10 (8.8)	Not reached [-; -]	0.28 [0.08; 1.04]	0.057	
Age category									
< 65	78	3 (3.8)	n.c.	85	4 (4.7)	n.c.	n.c.	n.c.	n.c.
≥ 65	65	0 (0.0)	n.c.	55	7 (12.7)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	61	0 (0.0)	Not reached [-; -]	52	3 (5.8)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.052	0.157
ECOG ≥ 1	82	3 (3.7)	Not reached [-; -]	88	8 (9.1)	Not reached [-; -]	0.38 [0.10; 1.44]	0.155	
Region									
EU	14	0 (0.0)	Not reached [-; -]	17	1 (5.9)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.364	0.503
Ex-EU	129	3 (2.3)	Not reached [-; -]	123	10 (8.1)	Not reached [-; -]	0.27 [0.07; 0.98]	0.047	
Region									
Asia	96	3 (3.1)	Not reached [-; -]	96	8 (8.3)	Not reached [-; -]	0.34 [0.09; 1.30]	0.116	0.189
Rest of World	47	0 (0.0)	Not reached [-; -]	44	3 (6.8)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.068	
Disease Status									
Metastatic	134	3 (2.2)	Not reached [-; -]	127	10 (7.9)	Not reached [-; -]	0.26 [0.07; 0.96]	0.043	0.591
Unresectable -	9	0	Not reached	13	1	Not reached	n.a.	0.500	

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Severe Adverse Events (CTCAE-Grade 3-5)	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Locally Advanced		(0.0)	[-; -]		(7.7)	[-; -]	[n.a.; n.a.]		
SOC: Investigations, PT[h]: Weight decreased									
Gender									
Female	29	1 (3.4)	n.c.	26	3 (11.5)	n.c.	n.c.	n.c.	n.c.
Male	114	0 (0.0)	n.c.	114	6 (5.3)	n.c.	n.c.	n.c.	
Age category									
< 65	78	1 (1.3)	n.c.	85	4 (4.7)	n.c.	n.c.	n.c.	n.c.
≥ 65	65	0 (0.0)	n.c.	55	5 (9.1)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	61	0 (0.0)	n.c.	52	3 (5.8)	n.c.	n.c.	n.c.	n.c.
ECOG ≥ 1	82	1 (1.2)	n.c.	88	6 (6.8)	n.c.	n.c.	n.c.	
Region									
EU	14	0 (0.0)	n.c.	17	1 (5.9)	n.c.	n.c.	n.c.	n.c.
Ex-EU	129	1 (0.8)	n.c.	123	8 (6.5)	n.c.	n.c.	n.c.	
Region									
Asia	96	0 (0.0)	n.c.	96	3 (3.1)	n.c.	n.c.	n.c.	n.c.
Rest of World	47	1 (2.1)	n.c.	44	6 (13.6)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	134	1 (0.7)	n.c.	127	7 (5.5)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	9	0 (0.0)	n.c.	13	2 (15.4)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: all-participants-as-treated population with squamous cell carcinoma and PD-L1 CPS≥10

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

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

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

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

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

CI: Confidence Interval; CPS: Combined Proportion Score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term; SOC: System Organ Class

Anhang 4-G11: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest (p ≥ 0,05) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

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

Alle Ergebnisse beziehen sich auf den finalen Datenschnitt (02. Juli 2020).

Anhang 4-G11.1: Mortalität

Gesamtüberleben

Tabelle 4G-85: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Overall Survival	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	5	5 (100.0)	5.9 [3.9; -]	9	8 (88.9)	9.4 [0.7; -]	2.35 [0.71; 7.85]	0.163	0.114
Male	38	25 (65.8)	14.5 [10.3; 25.2]	45	36 (80.0)	11.5 [8.2; 18.7]	0.73 [0.44; 1.22]	0.225	
Severity of disease									
ECOG 0	23	14 (60.9)	15.3 [10.3; -]	26	22 (84.6)	15.1 [10.1; 20.3]	0.70 [0.36; 1.39]	0.310	0.569
ECOG ≥ 1	20	16 (80.0)	10.3 [5.8; 15.6]	28	22 (78.6)	8.7 [6.9; 12.3]	0.89 [0.47; 1.70]	0.734	
Region									
EU	17	11 (64.7)	15.3 [5.1; -]	8	7 (87.5)	11.6 [3.2; 21.8]	0.65 [0.25; 1.72]	0.388	0.601
Ex-EU	26	19 (73.1)	11.7 [8.6; 15.6]	46	37 (80.4)	10.3 [7.4; 18.7]	0.87 [0.50; 1.51]	0.609	
Region									
Asia	8	4 (50.0)	18.7 [1.3; -]	8	6 (75.0)	13.4 [6.7; -]	0.61 [0.17; 2.18]	0.446	0.466
Rest of World	35	26 (74.3)	10.7 [8.2; 14.6]	46	38 (82.6)	10.7 [8.2; 15.3]	0.86 [0.52; 1.41]	0.544	
Disease Status									
Metastatic	41	28 (68.3)	n.c.	52	42 (80.8)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	2 (100.0)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: intention-to-treat population with adenocarcinoma and PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G11.2: Morbidität

Zeit bis zur ersten Folgetherapie (oder Tod)

Zeit bis zur ersten Folgetherapie oder Tod

Tabelle 4G-86: 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 – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Time to Subsequent Oncologic Therapy or Death	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Age (Years)									
< 65	21	17 (81.0)	8.3 [5.2; 12.1]	39	38 (97.4)	7.1 [5.8; 8.9]	0.62 [0.34; 1.12]	0.114	0.991
≥ 65	22	18 (81.8)	8.1 [5.8; 13.0]	15	14 (93.3)	7.6 [2.8; 9.5]	0.66 [0.33; 1.33]	0.248	
Severity of disease									
ECOG 0	23	18 (78.3)	8.3 [5.6; 15.7]	26	25 (96.2)	7.6 [5.8; 10.1]	0.62 [0.33; 1.16]	0.134	0.991
ECOG ≥ 1	20	17 (85.0)	7.2 [5.2; 11.0]	28	27 (96.4)	6.9 [3.5; 8.2]	0.67 [0.36; 1.23]	0.198	
Region									
EU	17	14 (82.4)	7.9 [3.7; 16.0]	8	8 (100.0)	11.2 [3.2; 13.3]	0.78 [0.32; 1.93]	0.596	0.425
Ex-EU	26	21 (80.8)	8.3 [5.8; 10.3]	46	44 (95.7)	6.9 [4.7; 7.8]	0.60 [0.36; 1.01]	0.056	
Region									
Asia	8	6 (75.0)	8.5 [1.2; -]	8	8 (100.0)	6.1 [2.5; 7.1]	0.18 [0.05; 0.73]	0.016	0.155
Rest of World	35	29 (82.9)	7.9 [5.6; 11.0]	46	44 (95.7)	7.7 [5.1; 9.4]	0.68 [0.42; 1.10]	0.116	
Disease Status									
Metastatic	41	33 (80.5)	n.c.	52	50 (96.2)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	2 (100.0)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: intention-to-treat population with adenocarcinoma and PD-L1 CPS≥10

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

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

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

g: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30

EORTC QLQ-C30: Symptomskala Erschöpfung

Tabelle 4G-87: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Erschöpfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Fatigue	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	4 (100.0)	1.4 [0.8; -]	9	6 (66.7)	1.1 [0.7; -]	1.21 [0.34; 4.33]	0.766	0.540
Male	37	24 (64.9)	1.6 [1.0; 4.6]	40	28 (70.0)	2.0 [1.0; 4.3]	0.83 [0.48; 1.43]	0.499	
Age (Years)									
< 65	20	15 (75.0)	3.0 [0.7; 4.6]	35	26 (74.3)	2.0 [0.9; 4.3]	0.97 [0.51; 1.85]	0.930	0.737
≥ 65	21	13 (61.9)	1.4 [0.9; -]	14	8 (57.1)	1.3 [0.6; -]	0.84 [0.35; 2.03]	0.696	
Severity of disease									
ECOG 0	22	14 (63.6)	1.6 [0.7; -]	23	19 (82.6)	1.3 [0.7; 2.8]	0.60 [0.30; 1.21]	0.155	0.143
ECOG ≥ 1	19	14 (73.7)	1.7 [0.9; 3.5]	26	15 (57.7)	2.0 [1.0; 17.1]	1.25 [0.60; 2.60]	0.546	
Region									
EU	16	11 (68.8)	1.2 [0.7; -]	7	6 (85.7)	2.3 [0.7; 8.1]	0.98 [0.36; 2.66]	0.966	0.670
Ex-EU	25	17 (68.0)	3.0 [1.2; 4.3]	42	28 (66.7)	2.0 [1.0; 2.8]	0.79 [0.43; 1.44]	0.434	
Region									
Asia	8	5 (62.5)	1.6 [0.7; -]	8	4 (50.0)	Not reached [0.7; -]	1.36 [0.36; 5.08]	0.650	0.443
Rest of World	33	23 (69.7)	1.6 [0.8; 3.7]	41	30 (73.2)	1.7 [0.8; 2.8]	0.78 [0.46; 1.35]	0.383	
Disease Status									
Metastatic	39	26 (66.7)	n.c.	47	33 (70.2)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	2 (100.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-88: 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 – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Nausea and Vomiting	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	4 (100.0)	1.4 [0.8; -]	9	6 (66.7)	0.9 [0.7; -]	1.32 [0.35; 4.95]	0.685	0.487
Male	37	22 (59.5)	2.3 [1.4; -]	40	24 (60.0)	3.4 [1.6; 4.7]	0.90 [0.50; 1.61]	0.721	
Age (Years)									
< 65	20	15 (75.0)	1.5 [0.7; 2.8]	35	23 (65.7)	2.1 [0.8; 4.1]	1.16 [0.60; 2.23]	0.655	0.630
≥ 65	21	11 (52.4)	4.1 [1.1; -]	14	7 (50.0)	3.6 [1.6; -]	0.89 [0.34; 2.34]	0.821	
Severity of disease									
ECOG 0	22	15 (68.2)	2.3 [1.3; 7.0]	23	16 (69.6)	2.1 [1.3; 4.1]	0.92 [0.46; 1.87]	0.823	0.973
ECOG ≥ 1	19	11 (57.9)	1.7 [0.8; -]	26	14 (53.8)	3.6 [0.8; 8.1]	0.95 [0.43; 2.10]	0.896	
Region									
EU	16	10 (62.5)	1.6 [0.7; -]	7	5 (71.4)	3.6 [0.7; -]	1.01 [0.34; 2.99]	0.979	0.855
Ex-EU	25	16 (64.0)	2.3 [1.1; 7.0]	42	25 (59.5)	2.1 [1.4; 4.1]	0.91 [0.48; 1.70]	0.760	
Region									
Asia	8	5 (62.5)	1.5 [0.7; -]	8	5 (62.5)	3.5 [1.0; -]	1.13 [0.32; 3.90]	0.851	0.821
Rest of World	33	21 (63.6)	2.3 [1.0; 7.0]	41	25 (61.0)	2.1 [1.3; 4.7]	0.91 [0.51; 1.62]	0.743	
Disease Status									
Metastatic	39	26 (66.7)	n.c.	47	29 (61.7)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	0 (0.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Schmerzen

Tabelle 4G-89: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schmerzen des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Pain	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	3 (75.0)	1.8 [0.8; -]	9	5 (55.6)	2.9 [0.7; -]	1.70 [0.37; 7.84]	0.496	0.550
Male	37	22 (59.5)	4.3 [2.4; -]	40	17 (42.5)	12.9 [2.3; -]	1.09 [0.57; 2.10]	0.788	
Age (Years)									
< 65	20	12 (60.0)	3.4 [0.8; -]	35	15 (42.9)	12.9 [3.0; -]	1.44 [0.67; 3.09]	0.347	0.129
≥ 65	21	13 (61.9)	3.3 [1.2; -]	14	7 (50.0)	1.9 [0.6; -]	0.57 [0.22; 1.50]	0.253	
Severity of disease									
ECOG 0	22	14 (63.6)	3.4 [1.1; -]	23	14 (60.9)	3.7 [1.4; -]	0.90 [0.42; 1.93]	0.795	0.369
ECOG ≥ 1	19	11 (57.9)	3.3 [1.0; -]	26	8 (30.8)	Not reached [1.6; -]	1.45 [0.57; 3.68]	0.431	
Region									
EU	16	10 (62.5)	3.0 [2.4; -]	7	4 (57.1)	2.3 [0.7; -]	0.63 [0.19; 2.10]	0.450	0.505
Ex-EU	25	15 (60.0)	3.3 [1.0; -]	42	18 (42.9)	12.9 [1.8; -]	1.24 [0.62; 2.47]	0.545	
Disease Status									
Metastatic	39	23 (59.0)	n.c.	47	21 (44.7)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	2 (100.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Dyspnoe

Tabelle 4G-90: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Dyspnoe des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Dyspnea	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	1 (25.0)	Not reached [1.6; -]	9	5 (55.6)	8.5 [0.7; -]	0.57 [0.06; 5.21]	0.616	0.639
Male	37	18 (48.6)	7.0 [3.2; -]	40	20 (50.0)	4.6 [3.0; 10.1]	0.85 [0.45; 1.62]	0.625	
Age (Years)									
< 65	20	9 (45.0)	8.3 [3.4; -]	35	20 (57.1)	5.1 [2.8; 12.0]	0.81 [0.36; 1.79]	0.594	0.866
≥ 65	21	10 (47.6)	7.0 [1.4; -]	14	5 (35.7)	4.6 [1.3; -]	1.04 [0.35; 3.07]	0.948	
Severity of disease									
ECOG 0	22	12 (54.5)	7.0 [2.0; 10.6]	23	13 (56.5)	5.1 [4.1; 12.0]	1.11 [0.50; 2.43]	0.801	0.359
ECOG ≥ 1	19	7 (36.8)	Not reached [1.6; -]	26	12 (46.2)	5.6 [1.6; -]	0.70 [0.27; 1.80]	0.456	
Region									
EU	16	6 (37.5)	10.6 [3.4; -]	7	4 (57.1)	12.0 [0.7; -]	0.44 [0.12; 1.61]	0.218	0.158
Ex-EU	25	13 (52.0)	4.1 [1.4; -]	42	21 (50.0)	4.6 [2.8; 10.1]	1.29 [0.63; 2.63]	0.488	
Region									
Asia	8	3 (37.5)	Not reached [1.0; -]	8	4 (50.0)	4.1 [1.0; -]	1.15 [0.25; 5.18]	0.860	0.826
Rest of World	33	16 (48.5)	8.3 [3.4; -]	41	21 (51.2)	5.1 [3.0; 12.0]	0.80 [0.42; 1.53]	0.496	
Disease Status									
Metastatic	39	19 (48.7)	n.c.	47	24 (51.1)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	0 (0.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

Tabelle 4G-91: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schlaflosigkeit des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Insomnia	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	1 (25.0)	Not reached [2.1; -]	9	5 (55.6)	5.7 [0.7; -]	0.76 [0.08; 7.36]	0.814	0.937
Male	37	14 (37.8)	Not reached [4.6; -]	40	19 (47.5)	3.4 [2.8; 12.9]	0.60 [0.30; 1.21]	0.151	
Age (Years)									
< 65	20	10 (50.0)	8.1 [1.4; -]	35	18 (51.4)	5.7 [2.8; -]	0.77 [0.35; 1.69]	0.513	0.192
≥ 65	21	5 (23.8)	Not reached [7.0; -]	14	6 (42.9)	2.3 [1.0; -]	0.37 [0.11; 1.24]	0.108	
Severity of disease									
ECOG 0	22	12 (54.5)	8.1 [1.4; -]	23	13 (56.5)	5.7 [2.8; -]	0.87 [0.39; 1.93]	0.735	0.075
ECOG ≥ 1	19	3 (15.8)	Not reached [4.6; -]	26	11 (42.3)	3.3 [2.3; -]	0.26 [0.07; 0.94]	0.040	
Region									
EU	16	6 (37.5)	10.9 [1.4; -]	7	4 (57.1)	8.1 [0.7; -]	0.57 [0.16; 2.03]	0.383	0.992
Ex-EU	25	9 (36.0)	8.1 [3.0; -]	42	20 (47.6)	4.6 [2.8; -]	0.56 [0.25; 1.25]	0.156	
Region									
Asia	8	2 (25.0)	Not reached [0.7; -]	8	3 (37.5)	Not reached [1.8; -]	0.86 [0.14; 5.17]	0.868	0.973
Rest of World	33	13 (39.4)	10.9 [4.6; -]	41	21 (51.2)	3.3 [2.8; 12.9]	0.59 [0.30; 1.19]	0.143	
Disease Status									
Metastatic	39	15 (38.5)	n.c.	47	22 (46.8)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	0 (0.0)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Appetitverlust

Tabelle 4G-92: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Appetitverlust des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Appetite Loss	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	3 (75.0)	1.8 [0.8; -]	9	6 (66.7)	1.5 [0.7; -]	1.24 [0.29; 5.28]	0.769	0.613
Male	37	21 (56.8)	3.7 [1.3; -]	40	24 (60.0)	3.5 [2.0; 5.6]	0.90 [0.50; 1.62]	0.722	
Age (Years)									
< 65	20	14 (70.0)	2.6 [0.7; -]	35	25 (71.4)	3.0 [1.4; 3.9]	1.01 [0.52; 1.96]	0.977	0.839
≥ 65	21	10 (47.6)	4.9 [1.2; -]	14	5 (35.7)	Not reached [1.0; -]	1.19 [0.41; 3.48]	0.754	
Severity of disease									
ECOG 0	22	14 (63.6)	2.7 [1.3; 14.9]	23	16 (69.6)	3.5 [1.2; 4.1]	0.81 [0.39; 1.69]	0.579	0.696
ECOG ≥ 1	19	10 (52.6)	2.6 [0.8; -]	26	14 (53.8)	2.6 [1.0; -]	1.01 [0.44; 2.31]	0.977	
Region									
EU	16	7 (43.8)	Not reached [0.8; -]	7	4 (57.1)	2.8 [0.7; -]	0.81 [0.24; 2.78]	0.739	0.696
Ex-EU	25	17 (68.0)	1.4 [1.0; 4.9]	42	26 (61.9)	3.5 [1.4; 4.1]	1.08 [0.58; 2.01]	0.798	
Region									
Asia	8	5 (62.5)	2.4 [0.7; -]	8	5 (62.5)	3.9 [1.0; -]	1.03 [0.30; 3.57]	0.964	0.702
Rest of World	33	19 (57.6)	2.7 [1.0; -]	41	25 (61.0)	3.0 [1.2; 3.9]	0.85 [0.47; 1.55]	0.597	
Disease Status									
Metastatic	39	23 (59.0)	n.c.	47	29 (61.7)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Verstopfung

Tabelle 4G-93: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Verstopfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Constipation	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	2 (50.0)	3.0 [1.6; -]	9	4 (44.4)	Not reached [0.7; -]	1.00 [0.18; 5.66]	0.996	0.928
Male	37	20 (54.1)	2.3 [0.9; -]	40	21 (52.5)	3.0 [2.1; 7.4]	0.99 [0.54; 1.83]	0.981	
Age (Years)									
< 65	20	11 (55.0)	2.3 [0.7; -]	35	21 (60.0)	3.0 [1.6; 4.4]	0.92 [0.44; 1.91]	0.821	0.349
≥ 65	21	11 (52.4)	4.2 [0.7; -]	14	4 (28.6)	7.4 [0.7; -]	1.77 [0.56; 5.62]	0.330	
Severity of disease									
ECOG 0	22	14 (63.6)	1.6 [0.7; -]	23	14 (60.9)	2.3 [0.7; -]	1.09 [0.52; 2.29]	0.822	0.812
ECOG ≥ 1	19	8 (42.1)	Not reached [1.4; -]	26	11 (42.3)	4.4 [1.0; -]	0.93 [0.37; 2.32]	0.877	
Region									
EU	16	7 (43.8)	Not reached [0.7; -]	7	4 (57.1)	2.8 [0.7; -]	0.86 [0.25; 2.96]	0.817	0.689
Ex-EU	25	15 (60.0)	2.3 [0.8; -]	42	21 (50.0)	4.1 [1.6; -]	1.13 [0.58; 2.19]	0.718	
Region									
Asia	8	6 (75.0)	1.9 [0.1; -]	8	4 (50.0)	4.4 [0.6; -]	1.47 [0.41; 5.23]	0.552	0.426
Rest of World	33	16 (48.5)	7.0 [0.9; -]	41	21 (51.2)	3.0 [2.1; -]	0.91 [0.47; 1.74]	0.771	
Disease Status									
Metastatic	39	21 (53.8)	n.c.	47	24 (51.1)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Diarrhoe

Tabelle 4G-94: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Diarrhoe des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Diarrhea	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	4 (100.0)	1.0 [0.8; -]	9	6 (66.7)	3.8 [0.8; -]	3.96 [0.86; 18.31]	0.078	0.367
Male	37	20 (54.1)	4.9 [1.6; 10.6]	40	17 (42.5)	Not reached [1.6; -]	1.23 [0.64; 2.36]	0.528	
Age (Years)									
< 65	20	13 (65.0)	2.1 [0.8; -]	35	17 (48.6)	4.1 [2.1; -]	1.72 [0.83; 3.56]	0.142	0.253
≥ 65	21	11 (52.4)	5.0 [1.0; -]	14	6 (42.9)	1.8 [0.7; -]	0.87 [0.32; 2.39]	0.792	
Severity of disease									
ECOG 0	22	12 (54.5)	3.0 [1.0; -]	23	10 (43.5)	Not reached [1.6; -]	1.42 [0.61; 3.29]	0.416	0.713
ECOG ≥ 1	19	12 (63.2)	2.1 [0.8; 10.6]	26	13 (50.0)	2.3 [1.4; -]	1.13 [0.51; 2.49]	0.759	
Region									
EU	16	9 (56.3)	10.6 [1.0; -]	7	2 (28.6)	Not reached [2.3; -]	2.23 [0.48; 10.44]	0.309	0.428
Ex-EU	25	15 (60.0)	2.1 [1.0; -]	42	21 (50.0)	2.3 [1.6; -]	1.23 [0.63; 2.38]	0.548	
Region									
Asia	8	5 (62.5)	4.9 [0.7; -]	8	5 (62.5)	3.1 [0.7; -]	1.10 [0.31; 3.82]	0.885	0.888
Rest of World	33	19 (57.6)	2.6 [1.0; -]	41	18 (43.9)	3.4 [2.1; -]	1.28 [0.67; 2.44]	0.456	
Disease Status									
Metastatic	39	23 (59.0)	n.c.	47	22 (46.8)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18

EORTC QLQ-OES18: Symptomskala Essen

Tabelle 4G-95: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Essen des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Eating	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	3 (75.0)	2.3 [1.0; -]	9	5 (55.6)	3.2 [0.7; -]	2.36 [0.51; 10.86]	0.271	0.261
Male	37	18 (48.6)	6.1 [3.2; -]	38	18 (47.4)	4.4 [3.0; -]	0.81 [0.42; 1.57]	0.530	
Age (Years)									
< 65	20	13 (65.0)	4.9 [1.4; -]	35	18 (51.4)	3.9 [2.8; -]	1.18 [0.57; 2.46]	0.654	0.272
≥ 65	21	8 (38.1)	Not reached [1.7; -]	12	5 (41.7)	4.4 [2.0; -]	0.69 [0.22; 2.14]	0.518	
Severity of disease									
ECOG 0	22	11 (50.0)	13.0 [1.7; -]	21	12 (57.1)	3.5 [2.3; -]	0.68 [0.29; 1.63]	0.389	0.358
ECOG ≥ 1	19	10 (52.6)	4.9 [2.3; -]	26	11 (42.3)	4.7 [3.0; -]	1.21 [0.50; 2.92]	0.670	
Region									
EU	16	8 (50.0)	13.0 [1.3; -]	7	4 (57.1)	4.4 [0.7; -]	0.79 [0.23; 2.72]	0.709	0.698
Ex-EU	25	13 (52.0)	5.3 [3.2; -]	40	19 (47.5)	3.9 [3.0; -]	0.95 [0.46; 1.93]	0.878	
Region									
Asia	8	3 (37.5)	Not reached [0.7; -]	8	2 (25.0)	Not reached [2.1; -]	1.51 [0.25; 9.27]	0.658	0.448
Rest of World	33	18 (54.5)	5.3 [3.0; 14.9]	39	21 (53.8)	3.5 [2.8; -]	0.77 [0.40; 1.45]	0.416	
Disease Status									
Metastatic	39	20 (51.3)	n.c.	45	21 (46.7)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Reflux

Tabelle 4G-96: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Reflux des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Reflux	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	2 (50.0)	3.0 [2.6; -]	9	6 (66.7)	2.6 [0.7; -]	0.70 [0.14; 3.64]	0.675	0.858
Male	37	16 (43.2)	12.7 [2.0; -]	38	22 (57.9)	2.6 [1.4; 10.2]	0.55 [0.28; 1.06]	0.075	
Age (Years)									
< 65	20	8 (40.0)	Not reached [2.1; -]	35	22 (62.9)	3.7 [1.4; 10.2]	0.57 [0.25; 1.28]	0.173	0.624
≥ 65	21	10 (47.6)	12.7 [1.6; -]	12	6 (50.0)	1.6 [0.7; -]	0.50 [0.18; 1.43]	0.198	
Severity of disease									
ECOG 0	22	12 (54.5)	3.1 [1.6; -]	21	12 (57.1)	10.2 [0.7; -]	0.71 [0.31; 1.62]	0.418	0.199
ECOG ≥ 1	19	6 (31.6)	Not reached [2.6; -]	26	16 (61.5)	2.1 [1.4; 4.2]	0.32 [0.12; 0.84]	0.021	
Region									
EU	16	7 (43.8)	12.7 [1.6; -]	7	5 (71.4)	6.1 [0.7; -]	0.51 [0.15; 1.68]	0.268	0.780
Ex-EU	25	11 (44.0)	Not reached [2.0; -]	40	23 (57.5)	2.6 [1.4; 10.2]	0.61 [0.30; 1.26]	0.183	
Region									
Asia	8	4 (50.0)	3.1 [0.1; -]	8	4 (50.0)	4.2 [0.7; -]	1.25 [0.31; 5.04]	0.750	0.319
Rest of World	33	14 (42.4)	12.7 [2.3; -]	39	24 (61.5)	2.1 [1.4; 10.2]	0.45 [0.23; 0.90]	0.023	
Disease Status									
Metastatic	39	17 (43.6)	n.c.	45	27 (60.0)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Schmerzen

Tabelle 4G-97: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schmerzen des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Pain	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	2 (50.0)	3.7 [0.8; -]	9	6 (66.7)	3.8 [0.8; -]	1.24 [0.22; 6.83]	0.809	0.705
Male	37	20 (54.1)	5.0 [2.3; -]	38	21 (55.3)	4.6 [3.9; 8.1]	0.90 [0.48; 1.67]	0.731	
Age (Years)									
< 65	20	12 (60.0)	5.0 [1.4; 14.9]	35	22 (62.9)	4.4 [3.9; 8.1]	0.96 [0.47; 1.96]	0.914	0.565
≥ 65	21	10 (47.6)	3.8 [1.4; -]	12	5 (41.7)	5.2 [1.0; -]	0.89 [0.30; 2.62]	0.834	
Severity of disease									
ECOG 0	22	12 (54.5)	5.0 [1.4; -]	21	12 (57.1)	5.5 [2.3; 8.1]	0.94 [0.41; 2.13]	0.873	0.970
ECOG ≥ 1	19	10 (52.6)	3.8 [1.4; -]	26	15 (57.7)	4.2 [2.5; 5.2]	0.93 [0.41; 2.11]	0.871	
Region									
EU	16	8 (50.0)	3.9 [2.3; -]	7	4 (57.1)	5.2 [0.7; -]	1.02 [0.30; 3.39]	0.980	0.903
Ex-EU	25	14 (56.0)	5.0 [1.3; -]	40	23 (57.5)	4.4 [3.1; 8.0]	0.98 [0.50; 1.92]	0.946	
Region									
Asia	8	4 (50.0)	5.0 [0.1; -]	8	5 (62.5)	4.4 [0.7; -]	0.78 [0.21; 2.93]	0.707	0.896
Rest of World	33	18 (54.5)	3.9 [2.9; 14.9]	39	22 (56.4)	4.2 [3.0; 8.0]	0.92 [0.49; 1.74]	0.805	
Disease Status									
Metastatic	39	21 (53.8)	n.c.	45	26 (57.8)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Speichelschlucken

Tabelle 4G-98: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Speichelschlucken des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Trouble Swallowing Saliva	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	3 (75.0)	2.0 [0.8; -]	9	3 (33.3)	Not reached [0.7; -]	2.82 [0.55; 14.43]	0.213	0.074
Male	37	16 (43.2)	9.3 [3.6; -]	38	18 (47.4)	4.9 [2.3; -]	0.75 [0.38; 1.47]	0.401	
Age (Years)									
< 65	20	8 (40.0)	9.3 [2.3; -]	35	16 (45.7)	5.1 [2.8; -]	0.82 [0.35; 1.93]	0.648	0.973
≥ 65	21	11 (52.4)	4.2 [1.8; -]	12	5 (41.7)	2.6 [0.7; -]	0.80 [0.28; 2.32]	0.680	
Severity of disease									
ECOG 0	22	9 (40.9)	9.3 [2.6; -]	21	9 (42.9)	12.2 [2.0; -]	0.93 [0.37; 2.36]	0.881	0.977
ECOG ≥ 1	19	10 (52.6)	3.6 [2.2; -]	26	12 (46.2)	3.5 [2.3; -]	0.93 [0.40; 2.17]	0.865	
Region									
EU	16	7 (43.8)	8.3 [1.8; -]	7	3 (42.9)	Not reached [0.7; -]	0.98 [0.25; 3.79]	0.971	0.934
Ex-EU	25	12 (48.0)	9.3 [2.3; -]	40	18 (45.0)	4.9 [2.3; -]	0.93 [0.45; 1.95]	0.852	
Region									
Asia	8	1 (12.5)	Not reached [1.4; -]	8	2 (25.0)	Not reached [0.7; -]	0.59 [0.05; 6.51]	0.664	0.546
Rest of World	33	18 (54.5)	4.2 [2.3; 9.6]	39	19 (48.7)	4.3 [2.3; -]	0.99 [0.52; 1.88]	0.965	
Disease Status									
Metastatic	39	18 (46.2)	n.c.	45	19 (42.2)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Verschlucken

Tabelle 4G-99: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Verschlucken des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Choked when Swallowing	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	3 (75.0)	2.0 [0.8; -]	9	3 (33.3)	Not reached [1.2; -]	3.03 [0.60; 15.36]	0.181	0.186
Male	37	17 (45.9)	6.1 [2.8; -]	38	13 (34.2)	12.2 [4.2; -]	1.41 [0.68; 2.91]	0.350	
Age (Years)									
< 65	20	12 (60.0)	2.8 [1.6; -]	35	13 (37.1)	12.2 [4.2; -]	2.44 [1.09; 5.47]	0.031	0.359
≥ 65	21	8 (38.1)	10.6 [3.8; -]	12	3 (25.0)	11.8 [2.6; -]	1.18 [0.31; 4.47]	0.806	
Severity of disease									
ECOG 0	22	9 (40.9)	10.6 [2.6; -]	21	7 (33.3)	12.2 [3.6; -]	1.35 [0.50; 3.64]	0.549	0.687
ECOG ≥ 1	19	11 (57.9)	3.9 [1.8; -]	26	9 (34.6)	17.1 [3.9; -]	1.98 [0.79; 4.95]	0.144	
Region									
EU	16	8 (50.0)	3.9 [1.8; -]	7	1 (14.3)	Not reached [2.8; -]	4.80 [0.59; 38.87]	0.142	0.186
Ex-EU	25	12 (48.0)	6.1 [2.3; -]	40	15 (37.5)	11.8 [4.2; -]	1.35 [0.62; 2.92]	0.445	
Disease Status									
Metastatic	39	18 (46.2)	n.c.	45	16 (35.6)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	2 (100.0)	n.c.	2	0 (0.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Mundtrockenheit

Tabelle 4G-100: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Mundtrockenheit des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Dry Mouth	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Age (Years)									
< 65	20	14 (70.0)	1.4 [0.7; 5.3]	35	20 (57.1)	2.8 [1.4; -]	1.57 [0.79; 3.12]	0.202	0.538
≥ 65	21	14 (66.7)	2.2 [0.8; 5.8]	12	3 (25.0)	Not reached [0.7; -]	2.59 [0.73; 9.23]	0.143	
Severity of disease									
ECOG 0	22	15 (68.2)	1.7 [1.0; 5.3]	21	13 (61.9)	2.6 [0.7; -]	1.41 [0.66; 3.02]	0.380	0.427
ECOG ≥ 1	19	13 (68.4)	1.8 [0.8; 6.1]	26	10 (38.5)	Not reached [1.4; -]	1.97 [0.86; 4.49]	0.109	
Region									
EU	16	11 (68.8)	1.7 [0.7; 5.8]	7	3 (42.9)	Not reached [0.7; -]	1.83 [0.50; 6.71]	0.359	0.624
Ex-EU	25	17 (68.0)	1.6 [1.0; 5.3]	40	20 (50.0)	3.4 [1.6; -]	1.56 [0.81; 2.98]	0.183	
Region									
Asia	8	6 (75.0)	1.0 [0.7; -]	8	5 (62.5)	4.2 [0.7; -]	12.49 [1.37; 114.04]	0.025	0.237
Rest of World	33	22 (66.7)	2.6 [1.4; 5.3]	39	18 (46.2)	3.4 [1.2; -]	1.44 [0.77; 2.69]	0.257	
Disease Status									
Metastatic	39	26 (66.7)	n.c.	45	23 (51.1)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	2 (100.0)	n.c.	2	0 (0.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Geschmackssinn

Tabelle 4G-101: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Geschmackssinn des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Trouble with Taste	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	4 (100.0)	1.0 [1.0; -]	9	7 (77.8)	1.1 [0.7; 2.8]	1.23 [0.34; 4.44]	0.750	0.341
Male	37	24 (64.9)	1.7 [1.3; 3.7]	38	28 (73.7)	2.2 [1.6; 3.5]	0.84 [0.48; 1.45]	0.523	
Age (Years)									
< 65	20	12 (60.0)	3.0 [1.0; -]	35	28 (80.0)	1.9 [1.0; 2.8]	0.55 [0.27; 1.11]	0.097	0.143
≥ 65	21	16 (76.2)	1.4 [0.8; 1.7]	12	7 (58.3)	2.1 [0.6; 4.1]	1.45 [0.59; 3.54]	0.414	
Severity of disease									
ECOG 0	22	16 (72.7)	1.7 [1.3; 3.7]	21	17 (81.0)	2.0 [0.8; 3.5]	0.81 [0.40; 1.62]	0.544	0.722
ECOG ≥ 1	19	12 (63.2)	1.4 [0.9; -]	26	18 (69.2)	2.0 [1.2; 3.3]	1.00 [0.48; 2.09]	0.997	
Region									
EU	16	11 (68.8)	1.6 [1.0; 13.0]	7	5 (71.4)	1.4 [0.7; -]	0.87 [0.29; 2.55]	0.794	0.995
Ex-EU	25	17 (68.0)	1.4 [0.8; 3.7]	40	30 (75.0)	2.1 [1.6; 2.8]	0.89 [0.49; 1.62]	0.714	
Disease Status									
Metastatic	39	27 (69.2)	n.c.	45	33 (73.3)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Husten

Tabelle 4G-102: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Husten des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Trouble with Coughing	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	1 (25.0)	Not reached [3.7; -]	9	5 (55.6)	4.3 [1.8; -]	0.61 [0.07; 5.27]	0.654	0.275
Male	37	18 (48.6)	4.7 [1.7; -]	38	14 (36.8)	7.7 [4.2; -]	1.51 [0.75; 3.04]	0.252	
Age (Years)									
< 65	20	11 (55.0)	3.7 [0.8; -]	35	15 (42.9)	7.7 [4.1; -]	1.91 [0.87; 4.17]	0.105	0.309
≥ 65	21	8 (38.1)	Not reached [3.0; -]	12	4 (33.3)	5.4 [2.0; -]	0.93 [0.28; 3.11]	0.911	
Severity of disease									
ECOG 0	22	11 (50.0)	4.4 [1.4; -]	21	9 (42.9)	12.9 [3.5; -]	1.48 [0.61; 3.60]	0.382	0.690
ECOG ≥ 1	19	8 (42.1)	4.7 [1.4; -]	26	10 (38.5)	5.4 [2.1; -]	1.19 [0.47; 3.03]	0.712	
Region									
EU	16	6 (37.5)	Not reached [1.4; -]	7	5 (71.4)	3.6 [0.9; -]	0.64 [0.20; 2.12]	0.470	0.160
Ex-EU	25	13 (52.0)	4.4 [1.4; -]	40	14 (35.0)	12.9 [4.4; -]	1.72 [0.81; 3.66]	0.160	
Region									
Asia	8	4 (50.0)	4.4 [0.1; -]	8	3 (37.5)	Not reached [1.4; -]	1.73 [0.38; 7.77]	0.477	0.716
Rest of World	33	15 (45.5)	4.7 [2.7; -]	39	16 (41.0)	7.7 [4.1; -]	1.26 [0.62; 2.54]	0.527	
Disease Status									
Metastatic	39	17 (43.6)	n.c.	45	19 (42.2)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	2 (100.0)	n.c.	2	0 (0.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Sprechen

Tabelle 4G-103: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Sprechen des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Trouble Talking	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	1 (25.0)	Not reached [0.8; -]	9	2 (22.2)	Not reached [1.4; -]	1.31 [0.12; 14.70]	0.824	0.873
Male	37	14 (37.8)	24.3 [2.8; -]	38	11 (28.9)	Not reached [4.6; -]	1.26 [0.56; 2.83]	0.572	
Age (Years)									
< 65	20	8 (40.0)	24.3 [1.6; -]	35	12 (34.3)	Not reached [3.7; -]	1.02 [0.40; 2.61]	0.965	0.231
≥ 65	21	7 (33.3)	Not reached [1.2; -]	12	1 (8.3)	Not reached [4.7; -]	4.01 [0.49; 32.72]	0.194	
Severity of disease									
ECOG 0	22	8 (36.4)	24.3 [1.7; -]	21	5 (23.8)	Not reached [5.1; -]	1.53 [0.48; 4.84]	0.469	0.803
ECOG ≥ 1	19	7 (36.8)	Not reached [1.0; -]	26	8 (30.8)	Not reached [3.5; -]	1.28 [0.46; 3.52]	0.639	
Region									
EU	16	5 (31.3)	24.3 [1.7; -]	7	2 (28.6)	Not reached [1.4; -]	0.87 [0.16; 4.76]	0.873	0.588
Ex-EU	25	10 (40.0)	9.3 [1.4; -]	40	11 (27.5)	Not reached [4.6; -]	1.58 [0.67; 3.73]	0.301	
Region									
Asia	8	2 (25.0)	Not reached [0.7; -]	8	2 (25.0)	Not reached [1.8; -]	1.31 [0.18; 9.40]	0.785	0.876
Rest of World	33	13 (39.4)	24.3 [1.7; -]	39	11 (28.2)	Not reached [4.6; -]	1.38 [0.61; 3.12]	0.446	
Disease Status									
Metastatic	39	14 (35.9)	n.c.	45	13 (28.9)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	0 (0.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-OES18: Symptomskala Dysphagie

Tabelle 4G-104: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Dysphagie des EORTC QLQ-OES18 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-OES18 Dysphagia	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	2 (50.0)	2.6 [1.6; -]	9	4 (44.4)	3.5 [0.8; -]	1.29 [0.23; 7.33]	0.774	0.844
Male	37	20 (54.1)	3.7 [1.4; -]	38	20 (52.6)	3.4 [1.3; -]	0.92 [0.49; 1.71]	0.788	
Age (Years)									
< 65	20	13 (65.0)	3.0 [1.4; -]	35	19 (54.3)	3.5 [2.1; -]	1.15 [0.57; 2.33]	0.703	0.501
≥ 65	21	9 (42.9)	Not reached [1.4; -]	12	5 (41.7)	4.7 [0.6; -]	0.74 [0.25; 2.20]	0.586	
Severity of disease									
ECOG 0	22	13 (59.1)	3.7 [1.4; -]	21	11 (52.4)	2.9 [0.8; -]	1.11 [0.49; 2.48]	0.803	0.629
ECOG ≥ 1	19	9 (47.4)	3.5 [1.4; -]	26	13 (50.0)	3.5 [0.8; -]	0.82 [0.35; 1.93]	0.654	
Region									
EU	16	9 (56.3)	3.7 [1.4; -]	7	3 (42.9)	Not reached [0.7; -]	1.33 [0.36; 4.92]	0.674	0.500
Ex-EU	25	13 (52.0)	3.5 [1.4; -]	40	21 (52.5)	3.4 [2.1; -]	0.88 [0.44; 1.76]	0.723	
Region									
Asia	8	3 (37.5)	Not reached [0.7; -]	8	3 (37.5)	Not reached [0.7; -]	1.18 [0.24; 5.90]	0.842	0.826
Rest of World	33	19 (57.6)	3.5 [1.4; -]	39	21 (53.8)	3.0 [0.9; -]	0.94 [0.50; 1.74]	0.834	
Disease Status									
Metastatic	39	21 (53.8)	n.c.	45	23 (51.1)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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-OES18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer 18 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EQ-5D VAS

EQ-5D VAS (7 Punkte)

Tabelle 4G-105: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS (7 Punkte) aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EQ-5D VAS (7 Points)	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	2 (50.0)	3.2 [0.8; -]	9	5 (55.6)	5.6 [0.7; -]	1.19 [0.21; 6.60]	0.845	0.800
Male	37	22 (59.5)	4.8 [3.6; 9.3]	40	22 (55.0)	4.5 [2.8; 8.1]	0.90 [0.50; 1.63]	0.734	
Age (Years)									
< 65	20	11 (55.0)	4.9 [3.2; -]	36	21 (58.3)	4.9 [2.0; 8.1]	0.72 [0.35; 1.50]	0.382	0.423
≥ 65	21	13 (61.9)	3.9 [0.8; 13.8]	13	6 (46.2)	4.5 [0.6; -]	1.22 [0.46; 3.28]	0.690	
Severity of disease									
ECOG 0	22	13 (59.1)	7.8 [2.0; 9.3]	23	15 (65.2)	4.4 [0.9; 8.1]	0.79 [0.38; 1.67]	0.544	0.500
ECOG ≥ 1	19	11 (57.9)	4.3 [3.0; -]	26	12 (46.2)	4.9 [1.3; -]	1.11 [0.49; 2.52]	0.802	
Region									
EU	16	11 (68.8)	3.7 [1.6; 9.2]	7	7 (100.0)	2.8 [0.7; 4.5]	0.57 [0.21; 1.50]	0.253	0.341
Ex-EU	25	13 (52.0)	7.8 [3.0; -]	42	20 (47.6)	7.2 [3.0; 9.4]	0.94 [0.47; 1.90]	0.872	
Region									
Asia	8	5 (62.5)	9.3 [0.1; -]	8	2 (25.0)	Not reached [0.7; -]	1.03 [0.15; 7.35]	0.973	0.359
Rest of World	33	19 (57.6)	4.1 [3.0; 9.2]	41	25 (61.0)	4.4 [2.0; 7.2]	0.85 [0.47; 1.54]	0.589	
Disease Status									
Metastatic	39	23 (59.0)	n.c.	47	26 (55.3)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 7 points or more decrease from baseline

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EQ-5D: European Quality of Life 5 Dimensions; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; VAS: Visual Analog Scale

EQ-5D VAS (10 Punkte)

Tabelle 4G-106: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS (10 Punkte) aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EQ-5D VAS (10 Points)	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	2 (50.0)	3.2 [0.8; -]	9	5 (55.6)	5.6 [0.7; -]	1.19 [0.21; 6.60]	0.845	0.723
Male	37	20 (54.1)	7.8 [3.7; 13.8]	40	22 (55.0)	4.9 [3.0; 8.1]	0.83 [0.45; 1.52]	0.541	
Age (Years)									
< 65	20	10 (50.0)	7.8 [3.2; -]	36	21 (58.3)	4.9 [2.0; 8.1]	0.67 [0.31; 1.42]	0.297	0.463
≥ 65	21	12 (57.1)	5.2 [0.8; 13.8]	13	6 (46.2)	4.7 [0.6; -]	1.08 [0.40; 2.93]	0.884	
Severity of disease									
ECOG 0	22	13 (59.1)	5.2 [2.7; 9.3]	23	15 (65.2)	7.2 [0.9; 9.4]	0.86 [0.41; 1.80]	0.680	0.901
ECOG ≥ 1	19	9 (47.4)	13.8 [3.0; -]	26	12 (46.2)	4.7 [2.0; -]	0.91 [0.38; 2.17]	0.834	
Region									
EU	16	10 (62.5)	4.1 [1.6; -]	7	7 (100.0)	4.4 [0.7; 4.9]	0.53 [0.20; 1.45]	0.219	0.339
Ex-EU	25	12 (48.0)	9.3 [3.0; -]	42	20 (47.6)	7.2 [3.0; 10.2]	0.90 [0.44; 1.84]	0.764	
Region									
Asia	8	5 (62.5)	9.3 [0.1; -]	8	2 (25.0)	Not reached [1.0; -]	1.17 [0.16; 8.30]	0.878	0.289
Rest of World	33	17 (51.5)	4.8 [3.2; -]	41	25 (61.0)	4.6 [3.0; 8.0]	0.76 [0.41; 1.41]	0.383	
Disease Status									
Metastatic	39	21 (53.8)	n.c.	47	26 (55.3)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EQ-5D: European Quality of Life 5 Dimensions; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; VAS: Visual Analog Scale

Anhang 4-G11.3: Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-107: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den globalen Gesundheitsstatus des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Global Health Status	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	4	3 (75.0)	2.7 [1.0; -]	9	4 (44.4)	Not reached [0.7; -]	1.54 [0.34; 6.93]	0.574	0.576
Male	37	21 (56.8)	4.3 [1.4; -]	40	20 (50.0)	5.6 [4.1; 12.2]	1.11 [0.60; 2.05]	0.744	
Age (Years)									
< 65	20	12 (60.0)	3.7 [1.4; -]	35	17 (48.6)	10.2 [2.8; -]	1.52 [0.72; 3.22]	0.277	0.426
≥ 65	21	12 (57.1)	4.3 [1.3; -]	14	7 (50.0)	4.6 [0.6; -]	0.89 [0.35; 2.26]	0.799	
Severity of disease									
ECOG 0	22	13 (59.1)	3.5 [1.4; -]	23	13 (56.5)	4.6 [2.0; 12.2]	1.08 [0.50; 2.34]	0.846	0.713
ECOG ≥ 1	19	11 (57.9)	4.0 [1.6; -]	26	11 (42.3)	5.7 [2.3; -]	1.34 [0.58; 3.10]	0.490	
Region									
EU	16	9 (56.3)	3.5 [1.4; -]	7	5 (71.4)	1.4 [0.7; -]	0.66 [0.22; 1.97]	0.454	0.276
Ex-EU	25	15 (60.0)	5.3 [1.4; 7.8]	42	19 (45.2)	5.7 [4.1; -]	1.36 [0.69; 2.68]	0.380	
Region									
Asia	8	4 (50.0)	7.8 [1.0; -]	8	2 (25.0)	Not reached [1.0; -]	1.69 [0.27; 10.46]	0.573	0.415
Rest of World	33	20 (60.6)	3.5 [1.4; -]	41	22 (53.7)	4.7 [3.0; 12.2]	1.09 [0.59; 2.00]	0.786	
Disease Status									
Metastatic	39	22 (56.4)	n.c.	47	22 (46.8)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	2 (100.0)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand

1

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-108: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Physical Functioning	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	2 (50.0)	Not reached [0.8; -]	9	6 (66.7)	2.0 [0.8; -]	1.08 [0.21; 5.45]	0.925	0.778
Male	37	23 (62.2)	4.1 [1.4; 10.9]	40	23 (57.5)	4.2 [2.8; 8.1]	1.12 [0.62; 1.99]	0.710	
Age (Years)									
< 65	20	12 (60.0)	5.3 [0.8; -]	35	23 (65.7)	3.5 [2.8; 8.0]	0.81 [0.40; 1.65]	0.564	0.250
≥ 65	21	13 (61.9)	3.2 [1.2; 6.0]	14	6 (42.9)	7.4 [0.6; -]	1.61 [0.60; 4.29]	0.342	
Severity of disease									
ECOG 0	22	15 (68.2)	4.3 [1.2; 10.9]	23	16 (69.6)	3.5 [2.0; 8.1]	0.88 [0.43; 1.81]	0.724	0.659
ECOG ≥ 1	19	10 (52.6)	3.3 [1.0; -]	26	13 (50.0)	4.3 [2.0; 17.1]	1.19 [0.51; 2.76]	0.683	
Region									
EU	16	9 (56.3)	4.1 [1.0; -]	7	5 (71.4)	2.1 [0.9; -]	0.92 [0.31; 2.78]	0.889	0.934
Ex-EU	25	16 (64.0)	3.3 [1.2; -]	42	24 (57.1)	3.7 [2.8; 8.0]	1.10 [0.58; 2.09]	0.776	
Region									
Asia	8	3 (37.5)	Not reached [0.7; -]	8	5 (62.5)	3.1 [1.8; -]	0.32 [0.06; 1.73]	0.187	0.158
Rest of World	33	22 (66.7)	3.2 [1.2; 5.3]	41	24 (58.5)	3.7 [2.1; 8.1]	1.29 [0.72; 2.30]	0.397	
Disease Status									
Metastatic	39	23 (59.0)	n.c.	47	27 (57.4)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	2 (100.0)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-109: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Rollenfunktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Role Functioning	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	4 (100.0)	1.0 [0.8; -]	9	6 (66.7)	2.3 [0.7; -]	4.93 [0.86; 28.14]	0.073	0.203
Male	37	24 (64.9)	3.6 [1.4; 7.8]	40	23 (57.5)	4.6 [1.2; 8.0]	1.04 [0.58; 1.84]	0.900	
Age (Years)									
< 65	20	13 (65.0)	4.6 [1.0; -]	35	22 (62.9)	2.8 [0.9; 8.0]	1.00 [0.49; 2.00]	0.990	0.535
≥ 65	21	15 (71.4)	1.6 [0.7; 4.8]	14	7 (50.0)	4.7 [0.6; -]	1.35 [0.55; 3.32]	0.513	
Severity of disease									
ECOG 0	22	16 (72.7)	4.6 [1.2; 7.8]	23	17 (73.9)	2.8 [0.7; 4.6]	0.87 [0.44; 1.73]	0.699	0.362
ECOG ≥ 1	19	12 (63.2)	2.2 [0.8; -]	26	12 (46.2)	5.7 [0.8; -]	1.42 [0.63; 3.17]	0.398	
Region									
EU	16	11 (68.8)	2.1 [1.1; 10.6]	7	4 (57.1)	2.8 [0.7; -]	1.14 [0.36; 3.58]	0.823	0.700
Ex-EU	25	17 (68.0)	3.3 [0.8; 7.8]	42	25 (59.5)	3.4 [1.2; 8.0]	1.04 [0.56; 1.94]	0.892	
Region									
Asia	8	5 (62.5)	6.3 [0.7; -]	8	3 (37.5)	Not reached [0.6; -]	1.14 [0.25; 5.19]	0.864	0.892
Rest of World	33	23 (69.7)	2.1 [1.0; 5.5]	41	26 (63.4)	2.8 [1.2; 5.7]	1.10 [0.62; 1.93]	0.749	
Disease Status									
Metastatic	39	26 (66.7)	n.c.	47	27 (57.4)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	2 (100.0)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-110: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Emotional Functioning	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	1 (25.0)	Not reached [2.1; -]	9	5 (55.6)	7.2 [0.7; -]	0.57 [0.06; 5.51]	0.629	0.251
Male	37	23 (62.2)	3.0 [1.4; 7.8]	40	17 (42.5)	8.0 [3.5; 17.1]	1.61 [0.86; 3.03]	0.136	
Age (Years)									
< 65	20	12 (60.0)	3.0 [1.4; -]	35	18 (51.4)	7.2 [3.0; -]	1.48 [0.70; 3.10]	0.305	0.626
≥ 65	21	12 (57.1)	3.3 [1.2; -]	14	4 (28.6)	9.4 [1.3; -]	1.83 [0.59; 5.70]	0.297	
Severity of disease									
ECOG 0	22	15 (68.2)	2.8 [1.3; 7.8]	23	11 (47.8)	8.0 [3.5; 10.0]	1.78 [0.81; 3.91]	0.149	0.512
ECOG ≥ 1	19	9 (47.4)	14.1 [1.4; -]	26	11 (42.3)	4.9 [1.4; -]	1.19 [0.48; 2.94]	0.704	
Region									
EU	16	8 (50.0)	14.1 [1.4; -]	7	3 (42.9)	Not reached [0.7; -]	1.38 [0.36; 5.28]	0.635	0.892
Ex-EU	25	16 (64.0)	3.1 [1.4; 7.8]	42	19 (45.2)	8.0 [3.5; 10.0]	1.63 [0.83; 3.21]	0.154	
Region									
Asia	8	5 (62.5)	4.6 [0.7; -]	8	3 (37.5)	Not reached [1.0; -]	1.58 [0.35; 7.06]	0.551	0.763
Rest of World	33	19 (57.6)	3.3 [1.6; 14.1]	41	19 (46.3)	8.0 [3.0; 17.1]	1.35 [0.71; 2.57]	0.356	
Disease Status									
Metastatic	39	23 (59.0)	n.c.	47	20 (42.6)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-111: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Kognitive Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Cognitive Functioning	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	4 (100.0)	1.4 [0.8; -]	9	6 (66.7)	1.0 [0.7; -]	1.16 [0.32; 4.13]	0.823	0.495
Male	37	23 (62.2)	2.9 [1.6; 5.3]	40	25 (62.5)	3.9 [2.8; 5.3]	0.96 [0.54; 1.71]	0.893	
Age (Years)									
< 65	20	12 (60.0)	3.0 [1.0; -]	35	23 (65.7)	3.9 [2.3; 7.7]	1.01 [0.50; 2.03]	0.982	0.690
≥ 65	21	15 (71.4)	2.0 [1.4; 4.9]	14	8 (57.1)	2.3 [0.7; -]	0.76 [0.32; 1.83]	0.540	
Severity of disease									
ECOG 0	22	15 (68.2)	2.8 [1.6; 5.3]	23	15 (65.2)	4.1 [1.4; 8.1]	1.12 [0.53; 2.35]	0.764	0.620
ECOG ≥ 1	19	12 (63.2)	2.6 [1.0; -]	26	16 (61.5)	2.3 [1.0; 4.2]	0.86 [0.40; 1.84]	0.690	
Region									
EU	16	10 (62.5)	2.9 [1.0; -]	7	5 (71.4)	4.2 [0.7; -]	0.78 [0.26; 2.36]	0.665	0.683
Ex-EU	25	17 (68.0)	2.8 [1.4; 4.9]	42	26 (61.9)	3.7 [2.3; 5.3]	1.09 [0.59; 2.01]	0.785	
Region									
Asia	8	5 (62.5)	4.3 [0.7; -]	8	3 (37.5)	Not reached [0.7; -]	2.55 [0.60; 10.85]	0.206	0.156
Rest of World	33	22 (66.7)	2.8 [1.6; 5.3]	41	28 (68.3)	3.6 [1.4; 4.2]	0.84 [0.47; 1.48]	0.539	
Disease Status									
Metastatic	39	25 (64.1)	n.c.	47	29 (61.7)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	2 (100.0)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-112: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Soziale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Social Functioning	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	4	3 (75.0)	2.0 [1.1; -]	9	4 (44.4)	Not reached [0.7; -]	1.57 [0.35; 7.04]	0.554	0.395
Male	37	22 (59.5)	4.2 [1.6; 7.1]	40	24 (60.0)	3.7 [1.6; 4.2]	0.85 [0.48; 1.53]	0.591	
Age (Years)									
< 65	20	12 (60.0)	2.6 [1.3; -]	35	20 (57.1)	3.9 [2.1; 7.8]	1.05 [0.51; 2.15]	0.902	0.400
≥ 65	21	13 (61.9)	3.2 [1.2; -]	14	8 (57.1)	1.6 [0.6; -]	0.68 [0.28; 1.65]	0.394	
Severity of disease									
ECOG 0	22	15 (68.2)	2.1 [1.2; 5.3]	23	14 (60.9)	3.7 [1.4; -]	1.27 [0.61; 2.64]	0.521	0.261
ECOG ≥ 1	19	10 (52.6)	4.9 [1.4; -]	26	14 (53.8)	3.0 [1.2; -]	0.66 [0.29; 1.50]	0.318	
Region									
EU	16	11 (68.8)	2.1 [1.1; -]	7	5 (71.4)	2.3 [0.7; -]	1.22 [0.42; 3.56]	0.715	0.465
Ex-EU	25	14 (56.0)	4.9 [1.4; -]	42	23 (54.8)	3.7 [1.6; 4.2]	0.78 [0.40; 1.52]	0.459	
Region									
Asia	8	5 (62.5)	4.8 [0.7; -]	8	4 (50.0)	Not reached [0.7; -]	1.05 [0.28; 3.92]	0.942	0.859
Rest of World	33	20 (60.6)	2.6 [1.4; 7.1]	41	24 (58.5)	3.7 [2.0; 4.2]	0.93 [0.52; 1.70]	0.825	
Disease Status									
Metastatic	39	24 (61.5)	n.c.	47	27 (57.4)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: full-analysis-set population with adenocarcinoma and PD-L1 CPS≥10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G11.4: Nebenwirkungen

Unerwünschte Ereignisse

Unerwünschte Ereignisse gesamt

Tabelle 4G-113: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	4	4 (100.0)	0.8 [0.4; -]	9	9 (100.0)	0.3 [0.1; 1.7]	0.77 [0.22; 2.65]	0.675	0.309
Male	38	38 (100.0)	0.3 [0.3; 0.4]	44	43 (97.7)	0.3 [0.3; 0.9]	1.43 [0.91; 2.24]	0.117	
Age category									
< 65	21	21 (100.0)	0.3 [0.1; 0.4]	39	39 (100.0)	0.3 [0.3; 0.7]	1.49 [0.87; 2.58]	0.150	0.644
≥ 65	21	21 (100.0)	0.4 [0.3; 0.7]	14	13 (92.9)	0.6 [0.1; 1.0]	1.25 [0.62; 2.52]	0.528	
Severity of disease									
ECOG 0	23	23 (100.0)	0.3 [0.1; 0.4]	26	26 (100.0)	0.4 [0.3; 0.9]	1.90 [1.06; 3.43]	0.032	0.196
ECOG ≥ 1	19	19 (100.0)	0.4 [0.3; 0.7]	27	26 (96.3)	0.3 [0.1; 1.0]	0.99 [0.54; 1.81]	0.965	
Region									
EU	16	16 (100.0)	0.3 [0.1; 0.4]	7	7 (100.0)	0.4 [0.1; 1.1]	2.57 [0.90; 7.38]	0.078	0.425
Ex-EU	26	26 (100.0)	0.4 [0.3; 0.6]	46	45 (97.8)	0.3 [0.3; 0.7]	1.15 [0.70; 1.87]	0.586	
Region									
Asia	8	8 (100.0)	0.2 [0.1; 0.4]	8	8 (100.0)	0.4 [0.1; 1.7]	1.82 [0.65; 5.12]	0.254	0.311
Rest of World	34	34 (100.0)	0.4 [0.3; 0.6]	45	44 (97.8)	0.3 [0.3; 0.7]	1.25 [0.79; 1.97]	0.342	
Disease Status									
Metastatic	40	40 (100.0)	n.c.	51	50 (98.0)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	2 (100.0)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: all-participants-as-treated population with adenocarcinoma and PD-L1 CPS≥10

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

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

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

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

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-114: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Serious Adverse Events	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	4	3 (75.0)	8.6 [1.7; -]	9	8 (88.9)	17.1 [2.1; 37.7]	1.50 [0.37; 6.06]	0.567	0.675
Male	38	25 (65.8)	16.3 [8.0; 27.9]	44	22 (50.0)	38.3 [17.3; -]	1.50 [0.84; 2.68]	0.169	
Age category									
< 65	21	14 (66.7)	15.6 [2.3; -]	39	21 (53.8)	37.7 [18.3; 60.3]	1.69 [0.84; 3.39]	0.143	0.138
≥ 65	21	14 (66.7)	17.7 [2.6; -]	14	9 (64.3)	16.3 [1.1; -]	0.85 [0.37; 1.98]	0.708	
Severity of disease									
ECOG 0	23	16 (69.6)	16.3 [2.0; 106.7]	26	16 (61.5)	31.1 [16.3; 60.3]	1.47 [0.72; 2.99]	0.285	0.658
ECOG ≥ 1	19	12 (63.2)	15.6 [6.7; -]	27	14 (51.9)	24.3 [8.4; -]	1.21 [0.56; 2.61]	0.634	
Region									
EU	16	12 (75.0)	12.0 [1.7; 106.7]	7	6 (85.7)	31.1 [1.1; -]	1.09 [0.40; 2.99]	0.866	0.737
Ex-EU	26	16 (61.5)	16.9 [3.3; -]	46	24 (52.2)	30.6 [16.3; -]	1.35 [0.72; 2.54]	0.356	
Region									
Asia	8	5 (62.5)	14.9 [0.1; -]	8	3 (37.5)	Not reached [3.0; -]	2.55 [0.60; 10.79]	0.204	0.429
Rest of World	34	23 (67.6)	15.6 [6.7; 27.9]	45	27 (60.0)	30.6 [14.6; 49.7]	1.24 [0.71; 2.19]	0.447	
Disease Status									
Metastatic	40	26 (65.0)	n.c.	51	29 (56.9)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	2 (100.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: all-participants-as-treated population with adenocarcinoma and PD-L1 CPS≥10

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

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

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

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

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5)

Tabelle 4G-115: 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 – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	4	4 (100.0)	2.5 [1.7; -]	9	9 (100.0)	5.6 [2.1; 17.1]	5.22 [1.09; 24.97]	0.038	0.306
Male	38	33 (86.8)	6.4 [2.3; 9.3]	44	35 (79.5)	7.1 [3.9; 13.9]	1.12 [0.69; 1.81]	0.641	
Age category									
< 65	21	19 (90.5)	6.1 [1.7; 15.0]	39	32 (82.1)	9.0 [6.0; 14.7]	1.32 [0.74; 2.36]	0.346	0.053
≥ 65	21	18 (85.7)	3.3 [1.4; 8.0]	14	12 (85.7)	2.2 [1.1; 11.6]	0.65 [0.30; 1.40]	0.272	
Severity of disease									
ECOG 0	23	21 (91.3)	6.1 [0.7; 9.3]	26	21 (80.8)	12.4 [3.9; 17.1]	1.43 [0.77; 2.66]	0.254	0.272
ECOG ≥ 1	19	16 (84.2)	3.0 [2.4; 15.0]	27	23 (85.2)	6.1 [2.9; 8.1]	0.91 [0.47; 1.73]	0.765	
Region									
EU	16	14 (87.5)	6.8 [1.7; 15.0]	7	7 (100.0)	5.6 [1.1; 9.1]	0.72 [0.28; 1.82]	0.485	0.218
Ex-EU	26	23 (88.5)	3.1 [1.4; 8.0]	46	37 (80.4)	7.1 [3.6; 13.9]	1.37 [0.81; 2.31]	0.239	
Region									
Asia	8	7 (87.5)	2.6 [0.1; 17.6]	8	4 (50.0)	Not reached [0.9; -]	2.49 [0.72; 8.55]	0.147	0.122
Rest of World	34	30 (88.2)	6.1 [2.4; 8.0]	45	40 (88.9)	6.1 [3.9; 9.3]	0.97 [0.60; 1.58]	0.917	
Disease Status									
Metastatic	40	35 (87.5)	n.c.	51	42 (82.4)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	2 (100.0)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: all-participants-as-treated population with adenocarcinoma and PD-L1 CPS≥10

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

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

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

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

CI: Confidence Interval; CPS: Combined Proportion Score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-116: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Adverse Events Leading to Treatment Discontinuation	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	4	0 (0.0)	Not reached [-; -]	9	1 (11.1)	Not reached [2.3; -]	n.a. [n.a.; n.a.]	0.505	0.130
Male	38	10 (26.3)	Not reached [-; -]	44	2 (4.5)	Not reached [-; -]	5.97 [1.31; 27.27]	0.021	
Age category									
< 65	21	3 (14.3)	n.c.	39	3 (7.7)	n.c.	n.c.	n.c.	n.c.
≥ 65	21	7 (33.3)	n.c.	14	0 (0.0)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	23	6 (26.1)	n.c.	26	2 (7.7)	n.c.	n.c.	n.c.	n.c.
ECOG ≥ 1	19	4 (21.1)	n.c.	27	1 (3.7)	n.c.	n.c.	n.c.	
Region									
EU	16	4 (25.0)	n.c.	7	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Ex-EU	26	6 (23.1)	n.c.	46	3 (6.5)	n.c.	n.c.	n.c.	
Region									
Asia	8	2 (25.0)	Not reached [0.1; -]	8	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.143	0.322
Rest of World	34	8 (23.5)	Not reached [-; -]	45	3 (6.7)	Not reached [-; -]	3.61 [0.96; 13.61]	0.058	
Disease Status									
Metastatic	40	9 (22.5)	n.c.	51	3 (5.9)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	0 (0.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: all-participants-as-treated population with adenocarcinoma and PD-L1 CPS≥10

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

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

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

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

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-117: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
SOC[h]: Endocrine disorders									
Gender									
Female	4	0 (0.0)	n.c.	9	1 (11.1)	n.c.	n.c.	n.c.	n.c.
Male	38	8 (21.1)	n.c.	44	1 (2.3)	n.c.	n.c.	n.c.	
Age category									
< 65	21	4 (19.0)	n.c.	39	1 (2.6)	n.c.	n.c.	n.c.	n.c.
≥ 65	21	4 (19.0)	n.c.	14	1 (7.1)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	23	4 (17.4)	n.c.	26	0 (0.0)	n.c.	n.c.	n.c.	n.c.
ECOG ≥ 1	19	4 (21.1)	n.c.	27	2 (7.4)	n.c.	n.c.	n.c.	
Region									
EU	16	3 (18.8)	n.c.	7	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Ex-EU	26	5 (19.2)	n.c.	46	2 (4.3)	n.c.	n.c.	n.c.	
Region									
Asia	8	1 (12.5)	n.c.	8	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Rest of World	34	7 (20.6)	n.c.	45	2 (4.4)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	40	8 (20.0)	n.c.	51	2 (3.9)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	0 (0.0)	n.c.	2	0 (0.0)	n.c.	n.c.	n.c.	
SOC[h]: Nervous system disorders									
Gender									
Female	4	2 (50.0)	Not reached [0.4; -]	9	6 (66.7)	2.1 [0.1; -]	0.63 [0.13; 3.11]	0.566	0.876
Male	38	16 (42.1)	32.7 [22.3; -]	44	26 (59.1)	20.0 [9.3; 29.0]	0.51 [0.27; 0.96]	0.038	
Age category									
< 65	21	10 (47.6)	25.3 [13.1; -]	39	25 (64.1)	18.1 [4.4; 29.0]	0.56 [0.27; 1.17]	0.123	0.796
≥ 65	21	8 (38.1)	Not reached [9.7; -]	14	7 (50.0)	24.9 [0.4; -]	0.53 [0.19; 1.48]	0.223	

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Severity of disease									
ECOG 0	23	10 (43.5)	28.0 [16.0; -]	26	20 (76.9)	9.8 [3.1; 22.9]	0.37 [0.17; 0.81]	0.012	0.273
ECOG ≥ 1	19	8 (42.1)	Not reached [3.1; -]	27	12 (44.4)	30.0 [4.4; -]	0.80 [0.32; 1.97]	0.629	
Region									
EU	16	7 (43.8)	28.0 [9.7; -]	7	5 (71.4)	22.9 [0.4; -]	0.61 [0.19; 1.93]	0.398	0.828
Ex-EU	26	11 (42.3)	32.7 [16.0; -]	46	27 (58.7)	17.1 [4.4; 30.0]	0.50 [0.25; 1.02]	0.058	
Region									
Asia	8	2 (25.0)	Not reached [6.6; -]	8	4 (50.0)	29.0 [1.7; -]	0.36 [0.06; 2.15]	0.262	0.629
Rest of World	34	16 (47.1)	28.0 [13.1; -]	45	28 (62.2)	17.1 [4.3; 28.6]	0.57 [0.31; 1.06]	0.078	
Disease Status									
Metastatic	40	17 (42.5)	n.c.	51	31 (60.8)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	1 (50.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: all-participants-as-treated population with adenocarcinoma and PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
h: A system organ class appears on this report only if its incidence ≥10% or (incidence ≥1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05 or rule of 10 is not met
CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; SOC: System Organ Class

Tabelle 4G-118: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (PT) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC: Endocrine disorders, PT[h]: Hyperthyroidism									
Gender									
Female	4	0 (0.0)	n.c.	9	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Male	38	6 (15.8)	n.c.	44	0 (0.0)	n.c.	n.c.	n.c.	

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Age category									
< 65	21	4 (19.0)	n.c.	39	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	21	2 (9.5)	n.c.	14	0 (0.0)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	23	2 (8.7)	n.c.	26	0 (0.0)	n.c.	n.c.	n.c.	n.c.
ECOG ≥ 1	19	4 (21.1)	n.c.	27	0 (0.0)	n.c.	n.c.	n.c.	
Region									
EU	16	2 (12.5)	n.c.	7	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Ex-EU	26	4 (15.4)	n.c.	46	0 (0.0)	n.c.	n.c.	n.c.	
Region									
Asia	8	1 (12.5)	n.c.	8	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Rest of World	34	5 (14.7)	n.c.	45	0 (0.0)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	40	6 (15.0)	n.c.	51	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	0 (0.0)	n.c.	2	0 (0.0)	n.c.	n.c.	n.c.	
SOC: General disorders and administration site conditions, PT[h]: Asthenia									
Gender									
Female	4	0 (0.0)	Not reached [-; -]	9	1 (11.1)	Not reached [0.4; -]	n.a. [n.a.; n.a.]	0.505	0.184
Male	38	14 (36.8)	Not reached [16.1; -]	44	6 (13.6)	Not reached [-; -]	3.05 [1.17; 7.94]	0.022	
Age category									
< 65	21	7 (33.3)	Not reached [16.1; -]	39	5 (12.8)	Not reached [-; -]	2.85 [0.90; 8.97]	0.074	0.842
≥ 65	21	7 (33.3)	Not reached [7.0; -]	14	2 (14.3)	Not reached [15.7; -]	2.33 [0.48; 11.22]	0.292	
Severity of disease									
ECOG 0	23	8 (34.8)	Not reached [16.1; -]	26	5 (19.2)	Not reached [-; -]	2.08 [0.68; 6.37]	0.200	0.403
ECOG ≥ 1	19	6 (31.6)	Not reached [6.9; -]	27	2 (7.4)	Not reached [-; -]	4.47 [0.90; 22.14]	0.067	
Region									
EU	16	8 (50.0)	17.4 [3.3; -]	7	3 (42.9)	Not reached [0.3; -]	1.22 [0.32; 4.62]	0.771	0.413
Ex-EU	26	6 (23.1)	Not reached [-; -]	46	4 (8.7)	Not reached [-; -]	2.67 [0.75; 9.48]	0.128	
Region									
Asia	8	0 (0.0)	Not reached [-; -]	8	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	0.997

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Rest of World	34	14 (41.2)	Not reached [12.1; -]	45	7 (15.6)	Not reached [-; -]	2.91 [1.17; 7.22]	0.021	
Disease Status									
Metastatic	40	14 (35.0)	n.c.	51	7 (13.7)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	0 (0.0)	n.c.	2	0 (0.0)	n.c.	n.c.	n.c.	
SOC: Infections and infestations, PT[h]: Urinary tract infection									
Gender									
Female	4	0 (0.0)	n.c.	9	3 (33.3)	n.c.	n.c.	n.c.	n.c.
Male	38	0 (0.0)	n.c.	44	3 (6.8)	n.c.	n.c.	n.c.	
Age category									
< 65	21	0 (0.0)	n.c.	39	4 (10.3)	n.c.	n.c.	n.c.	n.c.
≥ 65	21	0 (0.0)	n.c.	14	2 (14.3)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	23	0 (0.0)	n.c.	26	2 (7.7)	n.c.	n.c.	n.c.	n.c.
ECOG ≥ 1	19	0 (0.0)	n.c.	27	4 (14.8)	n.c.	n.c.	n.c.	
Region									
EU	16	0 (0.0)	n.c.	7	1 (14.3)	n.c.	n.c.	n.c.	n.c.
Ex-EU	26	0 (0.0)	n.c.	46	5 (10.9)	n.c.	n.c.	n.c.	
Region									
Asia	8	0 (0.0)	n.c.	8	1 (12.5)	n.c.	n.c.	n.c.	n.c.
Rest of World	34	0 (0.0)	n.c.	45	5 (11.1)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	40	0 (0.0)	n.c.	51	6 (11.8)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	0 (0.0)	n.c.	2	0 (0.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: all-participants-as-treated population with adenocarcinoma and PD-L1 CPS≥10

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

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

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

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

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

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term; SOC: System Organ Class

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

Tabelle 4G-119: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5) (SOC) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
SOC[h]: Cardiac disorders									
Gender									
Female	4	0 (0.0)	n.c.	9	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Male	38	3 (7.9)	n.c.	44	0 (0.0)	n.c.	n.c.	n.c.	
Age category									
< 65	21	0 (0.0)	n.c.	39	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	21	3 (14.3)	n.c.	14	0 (0.0)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	23	2 (8.7)	n.c.	26	0 (0.0)	n.c.	n.c.	n.c.	n.c.
ECOG ≥ 1	19	1 (5.3)	n.c.	27	0 (0.0)	n.c.	n.c.	n.c.	
Region									
EU	16	1 (6.3)	n.c.	7	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Ex-EU	26	2 (7.7)	n.c.	46	0 (0.0)	n.c.	n.c.	n.c.	
Region									
Asia	8	1 (12.5)	n.c.	8	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Rest of World	34	2 (5.9)	n.c.	45	0 (0.0)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	40	3 (7.5)	n.c.	51	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	0 (0.0)	n.c.	2	0 (0.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: all-participants-as-treated population with adenocarcinoma and PD-L1 CPS≥10

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

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

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

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

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

CI: Confidence Interval; CPS: Combined Proportion Score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; SOC: System Organ Class

Tabelle 4G-120: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5) (PT) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
SOC: General disorders and administration site conditions, PT[h]: Asthenia									
Gender									
Female	4	0 (0.0)	n.c.	9	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Male	38	5 (13.2)	n.c.	44	0 (0.0)	n.c.	n.c.	n.c.	
Age category									
< 65	21	2 (9.5)	n.c.	39	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	21	3 (14.3)	n.c.	14	0 (0.0)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	23	3 (13.0)	n.c.	26	0 (0.0)	n.c.	n.c.	n.c.	n.c.
ECOG ≥ 1	19	2 (10.5)	n.c.	27	0 (0.0)	n.c.	n.c.	n.c.	
Region									
EU	16	2 (12.5)	n.c.	7	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Ex-EU	26	3 (11.5)	n.c.	46	0 (0.0)	n.c.	n.c.	n.c.	
Region									
Asia	8	0 (0.0)	n.c.	8	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Rest of World	34	5 (14.7)	n.c.	45	0 (0.0)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	40	5 (12.5)	n.c.	51	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	0 (0.0)	n.c.	2	0 (0.0)	n.c.	n.c.	n.c.	
SOC: Metabolism and nutrition disorders, PT[h]: Hypophosphataemia									
Gender									
Female	4	0 (0.0)	n.c.	9	1 (11.1)	n.c.	n.c.	n.c.	n.c.
Male	38	0 (0.0)	n.c.	44	4 (9.1)	n.c.	n.c.	n.c.	
Age category									
< 65	21	0 (0.0)	n.c.	39	3 (7.7)	n.c.	n.c.	n.c.	n.c.
≥ 65	21	0 (0.0)	n.c.	14	2 (14.3)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	23	0 (0.0)	n.c.	26	1 (3.8)	n.c.	n.c.	n.c.	n.c.

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		p-Value for Interaction Test[g]
Severe Adverse Events (CTCAE-Grade 3-5)	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	
ECOG ≥ 1	19	0 (0.0)	n.c.	27	4 (14.8)	n.c.	n.c.	n.c.	
Region									
EU	16	0 (0.0)	n.c.	7	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Ex-EU	26	0 (0.0)	n.c.	46	5 (10.9)	n.c.	n.c.	n.c.	
Region									
Asia	8	0 (0.0)	n.c.	8	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Rest of World	34	0 (0.0)	n.c.	45	5 (11.1)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	40	0 (0.0)	n.c.	51	4 (7.8)	n.c.	n.c.	n.c.	n.c.
Unresectable - Locally Advanced	2	0 (0.0)	n.c.	2	1 (50.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: Number of participants: all-participants-as-treated population with adenocarcinoma and PD-L1 CPS≥10

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

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

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

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

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

CI: Confidence Interval; CPS: Combined Proportion Score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term; SOC: System Organ Class

Anhang 4-G12: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest (p ≥ 0,05) – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

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 finalen Datenschnitt (26. März 2019).

Anhang 4-G12.1: Mortalität

Gesamtüberleben

Tabelle 4G-121: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Overall Survival	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	7	6 (85.7)	12.3 [0.9; 16.5]	5	5 (100.0)	7.0 [1.3; -]	0.29 [0.07; 1.28]	0.102	0.078
Male	23	18 (78.3)	11.3 [8.1; 18.1]	15	11 (73.3)	12.3 [6.1; 24.4]	1.18 [0.56; 2.49]	0.671	
Age (Years)									
<65	17	13 (76.5)	11.3 [7.2; 19.0]	15	13 (86.7)	10.2 [4.0; 17.1]	0.81 [0.38; 1.75]	0.594	0.367
≥65	13	11 (84.6)	13.3 [4.1; 18.1]	5	3 (60.0)	10.6 [6.1; -]	1.64 [0.45; 5.94]	0.452	
Severity of disease									
ECOG 0	17	13 (76.5)	14.8 [9.1; 26.9]	6	4 (66.7)	15.4 [7.0; -]	1.16 [0.37; 3.62]	0.794	0.854
ECOG 1	13	11 (84.6)	9.4 [5.4; 18.1]	14	12 (85.7)	10.0 [4.0; 17.1]	1.04 [0.45; 2.36]	0.934	
Region									
EU	11	9 (81.8)	13.3 [3.0; -]	10	9 (90.0)	10.1 [6.1; 18.5]	0.65 [0.25; 1.69]	0.373	0.467
Ex-EU	19	15 (78.9)	11.3 [6.4; 17.2]	10	7 (70.0)	11.4 [1.3; -]	1.12 [0.46; 2.76]	0.798	
Region									
US/EU/Australia	20	16 (80.0)	n.c.	16	13 (81.3)	n.c.	n.c.	n.c.	n.c.
Asia	3	2 (66.7)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	6 (85.7)	n.c.	3	3 (100.0)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	28	22 (78.6)	n.c.	19	15 (78.9)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	2 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Overall Survival	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Backbone therapy									
5-FU	14	11 (78.6)	11.0 [4.1; -]	9	7 (77.8)	10.6 [4.0; -]	1.21 [0.47; 3.12]	0.697	0.537
Capecitabine	16	13 (81.3)	12.3 [8.1; 17.2]	11	9 (81.8)	10.0 [2.5; 17.1]	0.81 [0.35; 1.90]	0.630	
Number of Metastasis									
≤2	15	11 (73.3)	13.3 [6.4; -]	11	8 (72.7)	12.0 [6.1; -]	0.87 [0.34; 2.21]	0.775	0.867
≥3	13	11 (84.6)	9.7 [5.4; 18.1]	9	8 (88.9)	10.2 [1.3; 18.5]	0.84 [0.34; 2.12]	0.719	
Tumor Burden									
Above median	10	8 (80.0)	14.3 [3.0; -]	11	9 (81.8)	10.6 [4.0; 18.5]	0.77 [0.30; 2.02]	0.599	0.566
Below median	19	16 (84.2)	9.7 [5.6; 16.5]	7	6 (85.7)	10.0 [6.5; -]	1.22 [0.47; 3.13]	0.680	
Prior Gastrectomy									
Yes	11	9 (81.8)	8.1 [2.0; -]	5	3 (60.0)	17.1 [6.1; -]	1.49 [0.39; 5.64]	0.556	0.299
No	19	15 (78.9)	12.3 [9.4; 17.2]	15	13 (86.7)	10.2 [4.0; 12.3]	0.75 [0.35; 1.58]	0.445	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: intention-to-treat population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10

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

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

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

g: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G12.2: Morbidität

Zeit bis zur ersten Folgetherapie (oder Tod)

Zeit bis zur ersten Folgetherapie oder Tod

Tabelle 4G-122: 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 – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Time to Subsequent Oncologic Therapy or Death	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	7	7 (100.0)	9.7 [0.9; 14.0]	5	5 (100.0)	6.5 [1.3; -]	0.43 [0.11; 1.63]	0.214	0.616

Study: KEYNOTE 062[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Time to Subsequent Oncologic Therapy or Death	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Male	23	20 (87.0)	8.1 [5.6; 10.0]	15	14 (93.3)	8.3 [3.4; 9.2]	0.79 [0.40; 1.58]	0.508	
Age (Years)									
<65	17	15 (88.2)	9.0 [6.0; 10.1]	15	14 (93.3)	8.3 [3.1; 9.0]	0.64 [0.30; 1.33]	0.229	0.530
≥65	13	12 (92.3)	7.4 [3.8; 13.3]	5	5 (100.0)	6.5 [3.4; -]	0.85 [0.29; 2.45]	0.757	
Severity of disease									
ECOG 0	17	14 (82.4)	9.1 [5.8; 17.4]	6	5 (83.3)	8.4 [3.4; -]	0.84 [0.30; 2.35]	0.745	0.924
ECOG 1	13	13 (100.0)	6.1 [4.2; 9.7]	14	14 (100.0)	6.4 [3.1; 9.2]	0.76 [0.34; 1.68]	0.492	
Region									
EU	11	10 (90.9)	10.1 [3.0; 17.4]	10	9 (90.0)	8.4 [3.1; 9.0]	0.56 [0.22; 1.43]	0.221	0.615
Ex-EU	19	17 (89.5)	7.2 [5.6; 9.1]	10	10 (100.0)	6.2 [1.3; 10.3]	0.82 [0.37; 1.80]	0.621	
Region									
US/EU/Australia	20	19 (95.0)	n.c.	16	15 (93.8)	n.c.	n.c.	n.c.	n.c.
Asia	3	2 (66.7)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	6 (85.7)	n.c.	3	3 (100.0)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	28	25 (89.3)	n.c.	19	18 (94.7)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	2 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	14	13 (92.9)	6.9 [4.1; 12.3]	9	9 (100.0)	6.2 [3.1; 9.2]	0.57 [0.23; 1.42]	0.226	0.588
Capecitabine	16	14 (87.5)	9.0 [5.6; 13.3]	11	10 (90.9)	8.5 [2.5; 10.3]	0.79 [0.35; 1.78]	0.570	
Number of Metastasis									
≤2	15	13 (86.7)	9.0 [5.1; 14.0]	11	10 (90.9)	8.5 [3.4; 10.3]	0.76 [0.33; 1.75]	0.518	0.705
≥3	13	12 (92.3)	7.4 [4.1; 10.1]	9	9 (100.0)	6.2 [1.3; 9.9]	0.60 [0.24; 1.49]	0.274	
Tumor Burden									
Above median	10	9 (90.0)	8.4 [3.0; 15.0]	11	11 (100.0)	6.2 [3.1; 8.5]	0.38 [0.14; 1.03]	0.058	0.058
Below median	19	18 (94.7)	7.4 [4.2; 10.0]	7	6 (85.7)	9.2 [3.4; 10.3]	1.30 [0.52; 3.29]	0.577	
Prior Gastrectomy									
Yes	11	10 (90.9)	6.1 [2.0; 17.4]	5	4 (80.0)	6.5 [3.4; -]	1.30 [0.41; 4.18]	0.654	0.282
No	19	17 (89.5)	9.0 [6.0; 12.3]	15	15 (100.0)	8.3 [3.1; 9.0]	0.57 [0.28; 1.15]	0.114	
a: Database Cutoff Date: 26MAR2019									

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Time to Subsequent Oncologic Therapy or Death	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine									
c: Number of participants: intention-to-treat population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10									
d: From product-limit (Kaplan-Meier) method for censored data									
e: Based on Cox regression model with treatment as a covariate									
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)									
g: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1									

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30

EORTC QLQ-C30: Symptomskala Erschöpfung

Tabelle 4G-123: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Erschöpfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Fatigue	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	7	6 (85.7)	1.7 [0.7; -]	5	3 (60.0)	2.6 [0.7; -]	1.15 [0.27; 4.84]	0.854	0.541
Male	21	18 (85.7)	1.4 [1.0; 5.1]	15	12 (80.0)	0.8 [0.7; 1.6]	0.76 [0.36; 1.60]	0.469	
Age (Years)									
<65	16	12 (75.0)	2.0 [0.7; 8.3]	15	11 (73.3)	1.2 [0.7; 4.4]	0.84 [0.37; 1.90]	0.669	0.874
≥65	12	12 (100.0)	1.2 [0.7; 5.1]	5	4 (80.0)	0.8 [0.7; -]	0.54 [0.16; 1.79]	0.311	
Severity of disease									
ECOG 0	17	15 (88.2)	1.1 [0.7; 2.1]	6	5 (83.3)	0.7 [0.7; -]	0.60 [0.21; 1.70]	0.339	0.804
ECOG 1	11	9 (81.8)	2.0 [1.2; 7.9]	14	10 (71.4)	1.6 [0.7; 4.4]	0.67 [0.26; 1.73]	0.408	
Region									
EU	10	10 (100.0)	1.0 [0.7; 1.4]	10	8 (80.0)	1.2 [0.7; 4.4]	1.24 [0.47; 3.26]	0.660	0.246
Ex-EU	18	14 (77.8)	2.0 [1.0; 7.9]	10	7 (70.0)	0.8 [0.7; -]	0.65 [0.26; 1.62]	0.355	
Region									
US/EU/Australia	18	17 (94.4)	n.c.	16	13 (81.3)	n.c.	n.c.	n.c.	n.c.
Asia	3	2 (66.7)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Fatigue	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Rest of World	7	5 (71.4)	n.c.	3	1 (33.3)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	26	22 (84.6)	n.c.	19	14 (73.7)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	2 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	11 (84.6)	1.4 [0.7; 2.3]	9	6 (66.7)	0.9 [0.7; -]	1.38 [0.50; 3.79]	0.534	0.194
Capecitabine	15	13 (86.7)	1.4 [0.7; 8.3]	11	9 (81.8)	0.8 [0.7; 1.6]	0.58 [0.24; 1.40]	0.228	
Number of Metastasis									
≤2	15	14 (93.3)	1.4 [0.7; 2.1]	11	9 (81.8)	0.7 [0.7; 4.4]	0.84 [0.36; 1.98]	0.692	0.744
≥3	11	8 (72.7)	2.3 [1.0; 8.3]	9	6 (66.7)	1.2 [0.7; -]	0.73 [0.25; 2.12]	0.563	
Tumor Burden									
Above median	10	9 (90.0)	1.3 [0.7; 2.3]	11	9 (81.8)	1.6 [0.7; 4.4]	1.21 [0.48; 3.05]	0.693	0.604
Below median	17	15 (88.2)	1.4 [1.0; 5.1]	7	5 (71.4)	0.7 [0.7; -]	0.77 [0.27; 2.16]	0.618	
Prior Gastrectomy									
Yes	10	7 (70.0)	1.4 [0.7; -]	5	3 (60.0)	0.8 [0.7; -]	0.99 [0.25; 3.85]	0.984	0.392
No	18	17 (94.4)	1.7 [0.7; 5.1]	15	12 (80.0)	0.8 [0.7; 3.0]	0.69 [0.32; 1.48]	0.338	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-124: 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 – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Nausea and Vomiting	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	7	5 (71.4)	2.9 [0.7; -]	5	4 (80.0)	1.6 [1.4; -]	0.55 [0.13; 2.28]	0.411	0.582
Male	21	14 (66.7)	1.9 [0.8; -]	15	13 (86.7)	0.8 [0.7; 1.6]	0.54 [0.25; 1.15]	0.111	
Age (Years)									
<65	16	10 (62.5)	2.7 [0.7; -]	15	12 (80.0)	1.1 [0.7; 3.3]	0.56 [0.24; 1.31]	0.181	0.840
≥65	12	9 (75.0)	1.5 [0.7; 5.3]	5	5 (100.0)	1.5 [0.7; -]	0.46 [0.14; 1.53]	0.206	
Severity of disease									
ECOG 0	17	11 (64.7)	2.4 [0.7; -]	6	5 (83.3)	1.1 [0.7; -]	0.59 [0.20; 1.73]	0.338	0.884
ECOG 1	11	8 (72.7)	1.9 [0.7; -]	14	12 (85.7)	1.5 [0.7; 1.9]	0.59 [0.24; 1.47]	0.254	
Region									
EU	10	7 (70.0)	1.0 [0.7; -]	10	9 (90.0)	1.1 [0.7; 1.6]	0.76 [0.28; 2.06]	0.594	0.628
Ex-EU	18	12 (66.7)	2.7 [0.8; 5.3]	10	8 (80.0)	1.5 [0.7; 1.9]	0.42 [0.16; 1.08]	0.073	
Region									
US/EU/Australia	18	14 (77.8)	n.c.	16	14 (87.5)	n.c.	n.c.	n.c.	n.c.
Asia	3	0 (0.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	5 (71.4)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	26	17 (65.4)	n.c.	19	16 (84.2)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	2 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	11 (84.6)	1.5 [0.7; 4.4]	9	8 (88.9)	0.8 [0.7; 1.5]	0.68 [0.27; 1.71]	0.409	0.498
Capecitabine	15	8 (53.3)	3.3 [0.7; -]	11	9 (81.8)	1.6 [0.7; 3.3]	0.44 [0.17; 1.18]	0.102	
Number of Metastasis									
≤2	15	9 (60.0)	3.1 [0.8; -]	11	11 (100.0)	0.8 [0.7; 1.6]	0.32 [0.13; 0.81]	0.016	0.204
≥3	11	8 (72.7)	1.9 [0.7; -]	9	6 (66.7)	1.5 [0.7; -]	0.83 [0.28; 2.42]	0.731	
Tumor Burden									
Above median	10	8	2.1	11	9	0.8	0.76	0.585	0.556

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Nausea and Vomiting	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(80.0)	[0.7; 4.4]		(81.8)	[0.7; 8.3]	[0.29; 2.00]		
Below median	17	11 (64.7)	1.9 [0.7; -]	7	7 (100.0)	1.4 [0.7; 1.9]	0.49 [0.18; 1.31]	0.153	
Prior Gastrectomy									
Yes	10	9 (90.0)	1.4 [0.7; 3.3]	5	5 (100.0)	0.8 [0.7; -]	0.57 [0.18; 1.82]	0.346	0.597
No	18	10 (55.6)	3.7 [0.7; -]	15	12 (80.0)	1.5 [0.7; 3.3]	0.49 [0.21; 1.16]	0.105	

a: Database Cutoff Date: 26MAR2019
b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine
c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Schmerzen

Tabelle 4G-125: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schmerzen des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Pain	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	7	4 (57.1)	2.7 [1.4; -]	5	3 (60.0)	3.0 [1.0; -]	0.87 [0.19; 3.93]	0.858	0.744
Male	21	12 (57.1)	6.5 [2.4; 8.8]	15	9 (60.0)	7.4 [1.4; -]	0.84 [0.35; 2.01]	0.700	
Age (Years)									
<65	16	10 (62.5)	8.3 [1.4; 8.8]	15	8 (53.3)	7.4 [1.0; -]	0.99 [0.39; 2.52]	0.990	0.212
≥65	12	6 (50.0)	6.5 [1.4; -]	5	4 (80.0)	1.6 [1.4; -]	0.43 [0.10; 1.73]	0.232	
Severity of disease									
ECOG 0	17	9 (52.9)	8.5 [2.4; -]	6	4 (66.7)	5.1 [1.6; -]	0.66 [0.20; 2.17]	0.495	0.597
ECOG 1	11	7 (63.6)	3.4 [1.4; -]	14	8 (57.1)	3.3 [1.0; -]	1.01 [0.36; 2.83]	0.980	
Region									

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Pain	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
EU	10	4 (40.0)	Not reached [1.4; -]	10	6 (60.0)	7.4 [1.0; -]	0.56 [0.16; 2.04]	0.382	0.624
Ex-EU	18	12 (66.7)	4.2 [1.4; 8.3]	10	6 (60.0)	1.6 [0.7; -]	0.80 [0.30; 2.14]	0.657	
Region									
US/EU/Australia	18	10 (55.6)	n.c.	16	10 (62.5)	n.c.	n.c.	n.c.	n.c.
Asia	3	3 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	3 (42.9)	n.c.	3	1 (33.3)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	26	15 (57.7)	n.c.	19	12 (63.2)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	8 (61.5)	3.0 [1.4; -]	9	5 (55.6)	7.4 [0.7; -]	1.35 [0.44; 4.16]	0.597	0.327
Capecitabine	15	8 (53.3)	8.5 [2.4; -]	11	7 (63.6)	2.9 [0.7; -]	0.59 [0.21; 1.64]	0.314	
Number of Metastasis									
≤2	15	9 (60.0)	5.1 [1.4; -]	11	7 (63.6)	2.8 [1.0; -]	0.85 [0.31; 2.28]	0.742	0.757
≥3	11	6 (54.5)	6.5 [1.4; -]	9	5 (55.6)	3.3 [0.7; -]	0.61 [0.17; 2.11]	0.430	
Tumor Burden									
Above median	10	6 (60.0)	5.8 [1.3; -]	11	8 (72.7)	2.6 [0.7; -]	0.51 [0.16; 1.58]	0.242	0.164
Below median	17	9 (52.9)	6.5 [1.4; -]	7	3 (42.9)	Not reached [2.1; -]	1.47 [0.40; 5.47]	0.565	
Prior Gastrectomy									
Yes	10	3 (30.0)	Not reached [1.4; -]	5	2 (40.0)	Not reached [0.7; -]	0.92 [0.15; 5.52]	0.925	0.656
No	18	13 (72.2)	5.1 [2.4; 8.8]	15	10 (66.7)	3.0 [1.4; 8.3]	0.63 [0.27; 1.48]	0.287	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Dyspnoe

Tabelle 4G-126: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Dyspnoe des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Dyspnea	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	7	2 (28.6)	Not reached [0.7; -]	5	3 (60.0)	4.0 [1.0; -]	0.30 [0.05; 1.92]	0.205	0.564
Male	21	10 (47.6)	6.5 [3.2; -]	15	10 (66.7)	2.6 [0.7; -]	0.49 [0.20; 1.17]	0.108	
Age (Years)									
<65	16	9 (56.3)	5.9 [1.4; -]	15	10 (66.7)	2.3 [0.7; 6.0]	0.56 [0.22; 1.38]	0.205	0.463
≥65	12	3 (25.0)	Not reached [5.3; -]	5	3 (60.0)	3.4 [0.7; -]	0.26 [0.05; 1.34]	0.108	
Severity of disease									
ECOG 0	17	7 (41.2)	8.6 [2.1; -]	6	4 (66.7)	1.8 [0.7; -]	0.45 [0.13; 1.54]	0.204	0.880
ECOG 1	11	5 (45.5)	4.4 [1.4; -]	14	9 (64.3)	3.4 [0.8; 6.0]	0.49 [0.16; 1.46]	0.197	
Region									
EU	10	3 (30.0)	Not reached [1.2; -]	10	6 (60.0)	3.0 [0.7; -]	0.40 [0.10; 1.66]	0.208	0.932
Ex-EU	18	9 (50.0)	6.5 [3.2; -]	10	7 (70.0)	0.9 [0.7; 6.0]	0.41 [0.15; 1.12]	0.082	
Region									
US/EU/Australia	18	7 (38.9)	n.c.	16	10 (62.5)	n.c.	n.c.	n.c.	n.c.
Asia	3	3 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	2 (28.6)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	26	10 (38.5)	n.c.	19	12 (63.2)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	2 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	7 (53.8)	5.3 [1.2; -]	9	4 (44.4)	Not reached [0.7; -]	0.95 [0.28; 3.30]	0.941	0.067
Capecitabine	15	5 (33.3)	Not reached [2.1; -]	11	9 (81.8)	2.0 [0.7; 4.7]	0.23 [0.07; 0.68]	0.008	
Number of Metastasis									
≤2	15	6 (40.0)	8.6 [2.1; -]	11	9 (81.8)	2.1 [0.7; 4.7]	0.31 [0.11; 0.89]	0.030	0.543
≥3	11	4 (36.4)	Not reached [3.2; -]	9	4 (44.4)	6.0 [0.7; -]	0.53 [0.13; 2.13]	0.370	
Tumor Burden									
Above median	10	4	Not reached	11	7	2.6	0.52	0.294	0.961

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Dyspnea	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(40.0)	[0.7; -]		(63.6)	[0.7; -]	[0.15; 1.77]		
Below median	17	7 (41.2)	8.6 [3.4; -]	7	5 (71.4)	4.7 [0.7; -]	0.41 [0.13; 1.31]	0.132	
Prior Gastrectomy									
Yes	10	4 (40.0)	5.3 [1.2; -]	5	2 (40.0)	4.7 [3.4; -]	1.41 [0.25; 7.95]	0.694	0.072
No	18	8 (44.4)	8.6 [4.4; -]	15	11 (73.3)	1.2 [0.7; 6.0]	0.29 [0.11; 0.73]	0.009	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

Tabelle 4G-127: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schlaflosigkeit des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Insomnia	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age (Years)									
<65	16	8 (50.0)	3.0 [0.7; -]	15	7 (46.7)	6.0 [0.7; -]	1.04 [0.38; 2.89]	0.938	0.118
≥65	12	3 (25.0)	Not reached [3.0; -]	5	3 (60.0)	0.8 [0.7; -]	0.20 [0.03; 1.22]	0.081	
Severity of disease									
ECOG 0	17	6 (35.3)	Not reached [2.1; -]	6	4 (66.7)	4.1 [0.7; -]	0.41 [0.11; 1.46]	0.168	0.257
ECOG 1	11	5 (45.5)	Not reached [0.7; -]	14	6 (42.9)	6.0 [0.7; -]	1.09 [0.33; 3.59]	0.887	
Region									
EU	10	3 (30.0)	Not reached [0.7; -]	10	5 (50.0)	8.3 [0.7; -]	0.59 [0.14; 2.52]	0.481	0.870
Ex-EU	18	8 (44.4)	Not reached [2.6; -]	10	5 (50.0)	5.8 [0.7; -]	0.65 [0.21; 2.00]	0.449	
Region									

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Insomnia	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
US/EU/Australia	18	9 (50.0)	n.c.	16	8 (50.0)	n.c.	n.c.	n.c.	n.c.
Asia	3	1 (33.3)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	1 (14.3)	n.c.	3	1 (33.3)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	26	10 (38.5)	n.c.	19	9 (47.4)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Number of Metastasis									
≤2	15	7 (46.7)	3.0 [0.7; -]	11	6 (54.5)	8.3 [0.7; -]	0.81 [0.27; 2.41]	0.703	0.579
≥3	11	3 (27.3)	Not reached [2.6; -]	9	4 (44.4)	5.9 [0.7; -]	0.37 [0.08; 1.71]	0.203	
Tumor Burden									
Above median	10	3 (30.0)	Not reached [0.7; -]	11	5 (45.5)	5.8 [0.7; -]	0.52 [0.12; 2.22]	0.377	0.653
Below median	17	8 (47.1)	6.5 [1.6; -]	7	4 (57.1)	6.0 [0.7; -]	0.82 [0.25; 2.75]	0.754	
Prior Gastrectomy									
Yes	10	3 (30.0)	Not reached [0.7; -]	5	2 (40.0)	Not reached [0.7; -]	0.94 [0.16; 5.63]	0.943	0.712
No	18	8 (44.4)	Not reached [2.7; -]	15	8 (53.3)	5.8 [0.7; 8.3]	0.57 [0.21; 1.55]	0.272	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Appetitverlust

Tabelle 4G-128: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Appetitverlust des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Appetite Loss	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	7	4 (57.1)	7.3 [1.4; -]	5	3 (60.0)	3.8 [0.7; -]	0.49 [0.10; 2.44]	0.382	0.594
Male	21	14 (66.7)	5.8 [1.4; 9.7]	15	10 (66.7)	3.4 [1.4; 8.3]	0.75 [0.32; 1.72]	0.492	
Age (Years)									
<65	16	11 (68.8)	4.4 [1.4; 9.7]	15	9 (60.0)	2.1 [1.4; -]	0.70 [0.28; 1.79]	0.461	0.753
≥65	12	7 (58.3)	7.2 [0.8; -]	5	4 (80.0)	3.4 [0.7; -]	0.56 [0.16; 2.00]	0.370	
Severity of disease									
ECOG 0	17	11 (64.7)	5.3 [1.4; -]	6	6 (100.0)	1.4 [0.7; -]	0.36 [0.13; 1.02]	0.054	0.168
ECOG 1	11	7 (63.6)	5.8 [1.4; -]	14	7 (50.0)	5.0 [1.6; -]	0.88 [0.29; 2.65]	0.818	
Region									
EU	10	5 (50.0)	Not reached [0.7; -]	10	8 (80.0)	1.9 [0.7; -]	0.61 [0.20; 1.90]	0.394	0.274
Ex-EU	18	13 (72.2)	5.8 [1.9; 9.7]	10	5 (50.0)	5.0 [0.7; -]	0.84 [0.29; 2.44]	0.745	
Region									
US/EU/Australia	18	11 (61.1)	n.c.	16	10 (62.5)	n.c.	n.c.	n.c.	n.c.
Asia	3	2 (66.7)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	5 (71.4)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	26	17 (65.4)	n.c.	19	12 (63.2)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	10 (76.9)	2.0 [1.2; 10.2]	9	5 (55.6)	5.0 [0.7; -]	1.35 [0.45; 4.06]	0.588	0.062
Capecitabine	15	8 (53.3)	8.0 [1.4; -]	11	8 (72.7)	1.9 [0.7; -]	0.29 [0.10; 0.88]	0.029	
Number of Metastasis									
≤2	15	9 (60.0)	3.2 [1.2; -]	11	8 (72.7)	1.9 [0.7; -]	0.64 [0.24; 1.74]	0.383	0.332
≥3	11	8 (72.7)	6.2 [1.9; 10.2]	9	5 (55.6)	6.0 [1.5; -]	0.86 [0.27; 2.74]	0.802	
Tumor Burden									
Above median	10	6	8.0	11	5	5.0	0.78	0.708	0.257

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Appetite Loss	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(60.0)	[0.7; -]		(45.5)	[1.6; -]	[0.22; 2.79]		
Below median	17	11 (64.7)	4.4 [1.4; 9.7]	7	7 (100.0)	1.5 [0.7; 2.1]	0.36 [0.13; 1.02]	0.054	

a: Database Cutoff Date: 26MAR2019
b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine
c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Verstopfung

Tabelle 4G-129: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Verstopfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Constipation	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	7	6 (85.7)	1.6 [0.7; -]	5	4 (80.0)	2.7 [0.7; -]	2.02 [0.50; 8.22]	0.327	0.248
Male	21	9 (42.9)	9.7 [2.0; -]	15	10 (66.7)	3.4 [0.8; -]	0.59 [0.24; 1.46]	0.252	
Age (Years)									
<65	16	10 (62.5)	3.0 [0.7; -]	15	10 (66.7)	4.4 [0.7; 8.3]	0.93 [0.38; 2.24]	0.867	0.440
≥65	12	5 (41.7)	Not reached [1.0; -]	5	4 (80.0)	3.2 [0.8; -]	0.60 [0.16; 2.25]	0.449	
Severity of disease									
ECOG 0	17	10 (58.8)	2.3 [1.0; -]	6	5 (83.3)	2.2 [0.7; -]	0.65 [0.22; 1.93]	0.434	0.916
ECOG 1	11	5 (45.5)	4.1 [1.0; -]	14	9 (64.3)	3.4 [1.4; -]	0.74 [0.25; 2.25]	0.601	
Region									
EU	10	4 (40.0)	Not reached [0.7; -]	10	8 (80.0)	3.3 [0.7; 8.3]	0.57 [0.17; 1.91]	0.367	0.511
Ex-EU	18	11 (61.1)	3.0 [1.0; -]	10	6 (60.0)	2.8 [0.8; -]	0.94 [0.35; 2.55]	0.903	
Region									

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Constipation	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
US/EU/Australia	18	11 (61.1)	n.c.	16	12 (75.0)	n.c.	n.c.	n.c.	n.c.
Asia	3	1 (33.3)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	3 (42.9)	n.c.	3	1 (33.3)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	26	14 (53.8)	n.c.	19	14 (73.7)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	8 (61.5)	2.7 [1.0; -]	9	5 (55.6)	3.2 [0.7; -]	1.25 [0.41; 3.85]	0.693	0.284
Capecitabine	15	7 (46.7)	9.7 [0.7; -]	11	9 (81.8)	3.1 [0.7; 6.1]	0.52 [0.19; 1.41]	0.198	
Number of Metastasis									
≤2	15	8 (53.3)	4.1 [1.4; -]	11	8 (72.7)	3.4 [0.7; -]	0.68 [0.25; 1.83]	0.446	0.826
≥3	11	6 (54.5)	2.3 [1.0; -]	9	6 (66.7)	3.0 [0.7; -]	0.87 [0.28; 2.73]	0.811	
Tumor Burden									
Above median	10	6 (60.0)	3.0 [1.0; -]	11	8 (72.7)	2.8 [0.8; 8.3]	0.75 [0.26; 2.16]	0.589	0.685
Below median	17	9 (52.9)	2.7 [0.7; -]	7	5 (71.4)	6.0 [0.7; -]	0.95 [0.31; 2.86]	0.925	
Prior Gastrectomy									
Yes	10	3 (30.0)	Not reached [0.7; -]	5	4 (80.0)	3.4 [1.4; -]	0.60 [0.13; 2.72]	0.510	0.680
No	18	12 (66.7)	2.9 [1.0; -]	15	10 (66.7)	2.6 [0.7; 8.3]	0.79 [0.34; 1.87]	0.595	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Symptomskala Diarrhoe

Tabelle 4G-130: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Diarrhoe des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Diarrhea	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	7	4 (57.1)	4.4 [0.7; -]	5	1 (20.0)	Not reached [0.7; -]	2.00 [0.22; 18.13]	0.537	0.416
Male	21	11 (52.4)	5.3 [1.4; -]	15	8 (53.3)	2.2 [0.7; -]	0.92 [0.37; 2.29]	0.858	
Age (Years)									
<65	16	9 (56.3)	4.4 [1.4; -]	15	8 (53.3)	1.6 [0.7; -]	0.73 [0.28; 1.92]	0.524	0.126
≥65	12	6 (50.0)	5.3 [0.7; -]	5	1 (20.0)	Not reached [2.2; -]	3.59 [0.43; 30.02]	0.238	
Severity of disease									
ECOG 0	17	10 (58.8)	4.4 [1.0; -]	6	2 (33.3)	Not reached [0.7; -]	1.95 [0.43; 8.91]	0.389	0.228
ECOG 1	11	5 (45.5)	4.4 [1.4; -]	14	7 (50.0)	2.2 [0.7; -]	0.64 [0.20; 2.05]	0.454	
Region									
EU	10	4 (40.0)	Not reached [0.7; -]	10	4 (40.0)	Not reached [0.7; -]	0.87 [0.21; 3.56]	0.851	0.951
Ex-EU	18	11 (61.1)	3.0 [1.0; -]	10	5 (50.0)	2.2 [0.7; -]	0.95 [0.33; 2.74]	0.921	
Region									
US/EU/Australia	18	10 (55.6)	n.c.	16	7 (43.8)	n.c.	n.c.	n.c.	n.c.
Asia	3	2 (66.7)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	3 (42.9)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	26	14 (53.8)	n.c.	19	8 (42.1)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	8 (61.5)	4.4 [1.0; -]	9	4 (44.4)	Not reached [0.7; -]	1.31 [0.39; 4.37]	0.660	0.515
Capecitabine	15	7 (46.7)	8.3 [0.7; -]	11	5 (45.5)	1.9 [0.7; -]	0.84 [0.27; 2.66]	0.767	
Number of Metastasis									
≤2	15	7 (46.7)	5.3 [0.7; -]	11	5 (45.5)	Not reached [0.7; -]	1.07 [0.34; 3.40]	0.910	0.940
≥3	11	7 (63.6)	3.0 [1.0; -]	9	4 (44.4)	2.2 [0.7; -]	1.09 [0.32; 3.75]	0.893	
Tumor Burden									
Above median	10	4	Not reached	11	5	Not reached	0.63	0.499	0.652

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Diarrhea	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(40.0)	[0.7; -]		(45.5)	[0.7; -]	[0.17; 2.40]		
Below median	17	10 (58.8)	2.6 [1.0; -]	7	4 (57.1)	1.9 [0.7; -]	1.03 [0.32; 3.30]	0.964	
Prior Gastrectomy									
Yes	10	5 (50.0)	2.6 [0.7; -]	5	2 (40.0)	Not reached [0.7; -]	1.50 [0.29; 7.86]	0.633	0.598
No	18	10 (55.6)	4.4 [1.4; -]	15	7 (46.7)	2.2 [0.7; -]	0.91 [0.34; 2.41]	0.850	

a: Database Cutoff Date: 26MAR2019
b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine
c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-STO22

EORTC QLQ-STO22: Symptomskala Dysphagie

Tabelle 4G-131: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Dysphagie des EORTC QLQ-STO22 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-STO22 Dysphagia	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	6	2 (33.3)	Not reached [4.4; -]	5	3 (60.0)	1.4 [0.8; -]	n.a. [n.a.; n.a.]	> 0.999	0.357
Male	21	10 (47.6)	8.6 [1.4; -]	15	10 (66.7)	4.4 [0.7; 10.4]	0.54 [0.22; 1.29]	0.165	
Age (Years)									
<65	16	9 (56.3)	4.8 [1.4; -]	15	9 (60.0)	4.4 [0.7; -]	0.63 [0.25; 1.60]	0.330	0.147
≥65	11	3 (27.3)	Not reached [1.0; -]	5	4 (80.0)	0.9 [0.7; -]	0.20 [0.04; 0.89]	0.035	
Severity of disease									
ECOG 0	16	7 (43.8)	8.6 [2.8; -]	6	3 (50.0)	10.4 [0.7; -]	0.82 [0.21; 3.19]	0.779	0.282
ECOG 1	11	5 (45.5)	Not reached [1.4; -]	14	10 (71.4)	1.0 [0.7; 7.1]	0.36 [0.12; 1.08]	0.068	

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-STO22 Dysphagia	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Region									
EU	9	3 (33.3)	Not reached [1.4; -]	10	8 (80.0)	1.0 [0.7; -]	0.26 [0.07; 0.99]	0.048	0.211
Ex-EU	18	9 (50.0)	4.9 [1.4; -]	10	5 (50.0)	4.4 [0.7; -]	0.68 [0.23; 2.05]	0.494	
Region									
US/EU/Australia	17	7 (41.2)	n.c.	16	12 (75.0)	n.c.	n.c.	n.c.	n.c.
Asia	3	2 (66.7)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	3 (42.9)	n.c.	3	1 (33.3)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	25	11 (44.0)	n.c.	19	12 (63.2)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	5 (38.5)	Not reached [1.4; -]	9	6 (66.7)	1.4 [0.7; -]	0.38 [0.11; 1.26]	0.114	0.550
Capecitabine	14	7 (50.0)	8.6 [1.4; -]	11	7 (63.6)	1.9 [0.7; -]	0.54 [0.19; 1.57]	0.259	
Number of Metastasis									
≤2	14	5 (35.7)	8.6 [2.3; -]	11	7 (63.6)	7.1 [0.7; -]	0.46 [0.14; 1.44]	0.182	0.968
≥3	11	6 (54.5)	4.9 [1.0; -]	9	6 (66.7)	1.7 [0.7; -]	0.45 [0.14; 1.44]	0.181	
Tumor Burden									
Above median	10	4 (40.0)	Not reached [1.4; -]	11	8 (72.7)	1.0 [0.7; -]	0.29 [0.09; 0.98]	0.047	0.185
Below median	16	8 (50.0)	4.9 [1.4; -]	7	5 (71.4)	7.1 [0.7; -]	0.70 [0.23; 2.15]	0.532	
Prior Gastrectomy									
Yes	10	4 (40.0)	Not reached [1.0; -]	5	4 (80.0)	0.8 [0.7; -]	0.36 [0.09; 1.46]	0.153	0.981
No	17	8 (47.1)	8.6 [4.4; -]	15	9 (60.0)	1.9 [0.9; -]	0.39 [0.15; 1.02]	0.054	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-STO22: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Gastric Cancer 22 items; n.a.: not applicable; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-STO22: Symptomskala Schmerzen

Tabelle 4G-132: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schmerzen des EORTC QLQ-STO22 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-STO22 Pain	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	6	1 (16.7)	Not reached [3.0; -]	5	4 (80.0)	2.2 [1.5; -]	0.09 [0.01; 0.85]	0.036	0.053
Male	21	10 (47.6)	8.3 [5.8; -]	15	8 (53.3)	8.3 [0.9; -]	0.82 [0.32; 2.08]	0.670	
Age (Years)									
<65	16	7 (43.8)	9.7 [2.7; -]	15	8 (53.3)	5.8 [1.6; -]	0.60 [0.21; 1.68]	0.331	0.977
≥65	11	4 (36.4)	14.1 [3.0; -]	5	4 (80.0)	3.4 [0.9; -]	0.56 [0.13; 2.36]	0.430	
Severity of disease									
ECOG 0	16	6 (37.5)	14.1 [6.7; -]	6	3 (50.0)	Not reached [0.7; -]	0.72 [0.18; 2.87]	0.636	0.863
ECOG 1	11	5 (45.5)	5.8 [0.7; -]	14	9 (64.3)	3.4 [1.6; -]	0.78 [0.25; 2.47]	0.671	
Region									
EU	9	4 (44.4)	8.3 [0.7; -]	10	6 (60.0)	3.4 [0.7; -]	0.90 [0.25; 3.25]	0.867	0.484
Ex-EU	18	7 (38.9)	9.7 [5.8; -]	10	6 (60.0)	3.3 [0.7; -]	0.44 [0.15; 1.32]	0.141	
Region									
US/EU/Australia	17	7 (41.2)	n.c.	16	10 (62.5)	n.c.	n.c.	n.c.	n.c.
Asia	3	1 (33.3)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	3 (42.9)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	25	10 (40.0)	n.c.	19	12 (63.2)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	5 (38.5)	14.1 [2.7; -]	9	4 (44.4)	8.8 [0.9; -]	0.68 [0.17; 2.73]	0.586	0.376
Capecitabine	14	6 (42.9)	9.7 [5.8; -]	11	8 (72.7)	2.8 [0.7; 8.3]	0.41 [0.14; 1.20]	0.103	
Number of Metastasis									
≤2	14	5 (35.7)	9.7 [2.7; -]	11	6 (54.5)	8.3 [1.9; -]	0.61 [0.18; 2.01]	0.416	0.629
≥3	11	5 (45.5)	8.3 [0.7; -]	9	6 (66.7)	2.4 [0.7; -]	0.49 [0.15; 1.62]	0.242	
Tumor Burden									
Above median	10	5	8.3	11	7	8.3	0.60	0.386	0.804

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-STO22 Pain	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(50.0)	[0.7; -]		(63.6)	[0.9; -]	[0.19; 1.91]		
Below median	16	6 (37.5)	9.7 [2.7; -]	7	5 (71.4)	2.1 [0.7; -]	0.41 [0.12; 1.41]	0.157	
Prior Gastrectomy									
Yes	10	6 (60.0)	6.2 [0.7; -]	5	3 (60.0)	3.4 [1.5; -]	1.01 [0.24; 4.30]	0.993	0.116
No	17	5 (29.4)	9.7 [8.3; -]	15	9 (60.0)	5.8 [0.9; -]	0.32 [0.11; 0.97]	0.044	

a: Database Cutoff Date: 26MAR2019
b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine
c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-STO22: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Gastric Cancer 22 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-STO22: Symptomskala Reflux

Tabelle 4G-133: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Reflux des EORTC QLQ-STO22 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-STO22 Reflux Symptoms	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	6	1 (16.7)	Not reached [4.4; -]	5	3 (60.0)	2.4 [1.5; -]	n.a. [n.a.; n.a.]	> 0.999	0.183
Male	21	13 (61.9)	4.2 [1.4; -]	15	12 (80.0)	1.9 [0.7; 7.1]	0.62 [0.28; 1.37]	0.235	
Age (Years)									
<65	16	7 (43.8)	9.7 [1.4; -]	15	10 (66.7)	2.0 [0.7; -]	0.43 [0.16; 1.16]	0.095	0.571
≥65	11	7 (63.6)	4.1 [1.2; -]	5	5 (100.0)	1.9 [1.5; -]	0.64 [0.20; 2.04]	0.451	
Severity of disease									
ECOG 0	16	7 (43.8)	9.7 [1.6; -]	6	2 (33.3)	Not reached [2.1; -]	1.48 [0.30; 7.22]	0.626	0.100
ECOG 1	11	7 (63.6)	4.2 [0.7; -]	14	13 (92.9)	1.6 [0.7; 1.9]	0.35 [0.13; 0.93]	0.036	
Region									

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-STO22 Reflux Symptoms	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
EU	9	4 (44.4)	Not reached [0.7; -]	10	6 (60.0)	2.4 [0.7; -]	0.59 [0.17; 2.13]	0.423	0.637
Ex-EU	18	10 (55.6)	8.3 [1.4; -]	10	9 (90.0)	1.9 [0.7; 7.1]	0.34 [0.13; 0.89]	0.028	
Region									
US/EU/Australia	17	7 (41.2)	n.c.	16	12 (75.0)	n.c.	n.c.	n.c.	n.c.
Asia	3	1 (33.3)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	6 (85.7)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	25	13 (52.0)	n.c.	19	14 (73.7)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	6 (46.2)	4.4 [1.2; -]	9	7 (77.8)	1.5 [0.7; 7.9]	0.51 [0.17; 1.52]	0.226	0.848
Capecitabine	14	8 (57.1)	8.3 [1.4; -]	11	8 (72.7)	2.3 [1.0; 7.1]	0.48 [0.18; 1.32]	0.155	
Number of Metastasis									
≤2	14	6 (42.9)	9.7 [1.2; -]	11	8 (72.7)	2.6 [0.7; -]	0.50 [0.17; 1.45]	0.202	0.995
≥3	11	7 (63.6)	4.2 [0.7; -]	9	7 (77.8)	1.7 [0.7; 7.9]	0.54 [0.18; 1.56]	0.251	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-STO22: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Gastric Cancer 22 items; n.a.: not applicable; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-STO22: Symptomskala Einschränkungen beim Essen

Tabelle 4G-134: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Einschränkungen beim Essen des EORTC QLQ-STO22 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-STO22 Eating Restrictions	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	6	3 (50.0)	10.2 [2.3; -]	5	3 (60.0)	2.1 [1.4; -]	0.31 [0.05; 1.93]	0.210	0.577
Male	21	11 (52.4)	8.3 [3.5; -]	15	10 (66.7)	2.8 [1.6; -]	0.54 [0.22; 1.31]	0.173	
Age (Years)									
<65	16	8 (50.0)	8.3 [3.0; -]	15	8 (53.3)	2.8 [1.6; -]	0.51 [0.18; 1.39]	0.186	0.679
≥65	11	6 (54.5)	10.2 [1.0; -]	5	5 (100.0)	2.2 [1.4; -]	0.43 [0.12; 1.52]	0.188	
Severity of disease									
ECOG 0	16	9 (56.3)	6.2 [2.1; -]	6	4 (66.7)	3.7 [1.4; -]	0.84 [0.26; 2.74]	0.771	0.228
ECOG 1	11	5 (45.5)	10.2 [1.0; -]	14	9 (64.3)	2.2 [1.5; -]	0.29 [0.08; 1.09]	0.068	
Region									
EU	9	4 (44.4)	8.3 [0.7; -]	10	6 (60.0)	2.8 [1.4; -]	0.78 [0.22; 2.78]	0.700	0.479
Ex-EU	18	10 (55.6)	6.2 [3.0; -]	10	7 (70.0)	2.6 [1.4; -]	0.22 [0.07; 0.71]	0.011	
Region									
US/EU/Australia	17	9 (52.9)	n.c.	16	10 (62.5)	n.c.	n.c.	n.c.	n.c.
Asia	3	2 (66.7)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	3 (42.9)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	25	13 (52.0)	n.c.	19	12 (63.2)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	8 (61.5)	3.0 [1.0; 10.2]	9	6 (66.7)	2.1 [1.4; -]	0.79 [0.26; 2.39]	0.672	0.460
Capecitabine	14	6 (42.9)	8.8 [4.2; -]	11	7 (63.6)	2.8 [1.6; -]	0.30 [0.10; 0.93]	0.038	
Number of Metastasis									
≤2	14	7 (50.0)	8.3 [2.1; -]	11	8 (72.7)	2.6 [1.4; -]	0.48 [0.17; 1.36]	0.168	0.930
≥3	11	6 (54.5)	10.2 [1.0; -]	9	5 (55.6)	2.6 [1.4; -]	0.53 [0.14; 1.94]	0.335	
Tumor Burden									
Above median	10	4	10.2	11	6	2.8	0.45	0.261	0.610

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-STO22 Eating Restrictions	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(40.0)	[0.7; -]		(54.5)	[1.6; -]	[0.11; 1.82]		
Below median	16	10 (62.5)	5.5 [2.1; -]	7	6 (85.7)	1.9 [1.4; 3.1]	0.56 [0.19; 1.59]	0.274	
Prior Gastrectomy									
Yes	10	6 (60.0)	3.5 [0.7; -]	5	4 (80.0)	2.1 [1.5; -]	0.94 [0.26; 3.42]	0.930	0.184
No	17	8 (47.1)	8.8 [4.2; -]	15	9 (60.0)	2.8 [1.4; -]	0.28 [0.09; 0.82]	0.020	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-STO22: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Gastric Cancer 22 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-STO22: Symptomskala Angst

Tabelle 4G-135: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Angst des EORTC QLQ-STO22 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-STO22 Anxiety	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	6	4 (66.7)	1.4 [0.7; -]	5	2 (40.0)	3.3 [2.8; -]	3.35 [0.58; 19.29]	0.176	0.215
Male	21	12 (57.1)	6.5 [1.4; -]	15	9 (60.0)	3.1 [0.8; -]	0.80 [0.33; 1.90]	0.612	
Age (Years)									
<65	16	9 (56.3)	2.0 [0.7; -]	15	7 (46.7)	3.3 [0.8; -]	1.23 [0.45; 3.33]	0.688	0.450
≥65	11	7 (63.6)	3.1 [1.0; -]	5	4 (80.0)	2.6 [0.8; -]	0.57 [0.16; 2.05]	0.390	
Severity of disease									
ECOG 0	16	9 (56.3)	6.5 [0.7; -]	6	4 (66.7)	3.7 [1.4; -]	1.03 [0.31; 3.49]	0.957	0.847
ECOG 1	11	7 (63.6)	2.1 [1.4; -]	14	7 (50.0)	3.3 [0.8; -]	0.95 [0.33; 2.72]	0.924	
Region									

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-STO22 Anxiety	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
EU	9	5 (55.6)	3.1 [1.2; -]	10	5 (50.0)	Not reached [0.7; -]	1.37 [0.39; 4.79]	0.619	0.677
Ex-EU	18	11 (61.1)	2.0 [0.9; -]	10	6 (60.0)	3.3 [0.7; -]	0.80 [0.29; 2.17]	0.656	
Region									
US/EU/Australia	17	11 (64.7)	n.c.	16	9 (56.3)	n.c.	n.c.	n.c.	n.c.
Asia	3	1 (33.3)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	4 (57.1)	n.c.	3	1 (33.3)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	25	15 (60.0)	n.c.	19	10 (52.6)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	9 (69.2)	1.4 [0.9; 6.5]	9	6 (66.7)	0.9 [0.7; -]	0.93 [0.33; 2.66]	0.895	0.905
Capecitabine	14	7 (50.0)	9.7 [1.0; -]	11	5 (45.5)	4.4 [1.4; -]	0.99 [0.31; 3.17]	0.992	
Number of Metastasis									
≤2	14	9 (64.3)	2.1 [1.2; 9.7]	11	8 (72.7)	2.8 [0.7; -]	0.99 [0.38; 2.58]	0.976	0.657
≥3	11	6 (54.5)	6.5 [0.9; -]	9	3 (33.3)	Not reached [0.8; -]	1.31 [0.32; 5.29]	0.709	
Tumor Burden									
Above median	10	5 (50.0)	Not reached [0.7; -]	11	5 (45.5)	Not reached [0.8; -]	0.99 [0.29; 3.42]	0.985	0.770
Below median	16	11 (68.8)	2.1 [1.0; 9.7]	7	5 (71.4)	3.1 [0.7; -]	1.12 [0.38; 3.27]	0.835	
Prior Gastrectomy									
Yes	10	6 (60.0)	1.4 [0.7; -]	5	3 (60.0)	2.6 [0.7; -]	1.67 [0.41; 6.82]	0.477	0.525
No	17	10 (58.8)	6.5 [1.4; -]	15	8 (53.3)	3.3 [0.8; -]	0.80 [0.31; 2.09]	0.648	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-STO22: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Gastric Cancer 22 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-STO22: Symptomskala Mundtrockenheit

Tabelle 4G-136: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Mundtrockenheit des EORTC QLQ-STO22 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-STO22 Dry Mouth	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	6	3 (50.0)	2.0 [1.4; -]	5	1 (20.0)	Not reached [3.3; -]	3.07 [0.32; 29.76]	0.332	0.391
Male	21	14 (66.7)	3.1 [1.4; 8.8]	15	10 (66.7)	1.9 [0.7; -]	0.89 [0.40; 2.02]	0.789	
Age (Years)									
<65	16	8 (50.0)	8.8 [1.4; -]	15	7 (46.7)	3.3 [1.4; -]	0.92 [0.32; 2.62]	0.872	0.736
≥65	11	9 (81.8)	1.6 [1.0; 3.5]	5	4 (80.0)	0.9 [0.7; -]	1.18 [0.31; 4.44]	0.809	
Severity of disease									
ECOG 0	16	9 (56.3)	4.4 [1.4; -]	6	3 (50.0)	11.2 [0.7; -]	1.23 [0.33; 4.56]	0.754	0.982
ECOG 1	11	8 (72.7)	1.6 [1.3; -]	14	8 (57.1)	2.1 [0.8; -]	1.26 [0.47; 3.39]	0.642	
Region									
EU	9	6 (66.7)	2.1 [0.7; -]	10	4 (40.0)	Not reached [0.7; -]	2.08 [0.59; 7.42]	0.257	0.199
Ex-EU	18	11 (61.1)	3.1 [1.4; -]	10	7 (70.0)	1.9 [0.7; -]	0.67 [0.26; 1.75]	0.418	
Region									
US/EU/Australia	17	11 (64.7)	n.c.	16	8 (50.0)	n.c.	n.c.	n.c.	n.c.
Asia	3	3 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	3 (42.9)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	25	16 (64.0)	n.c.	19	10 (52.6)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	8 (61.5)	1.6 [1.3; -]	9	4 (44.4)	Not reached [0.8; -]	1.68 [0.50; 5.65]	0.398	0.392
Capecitabine	14	9 (64.3)	3.3 [1.4; -]	11	7 (63.6)	2.6 [0.7; -]	0.82 [0.30; 2.20]	0.691	
Number of Metastasis									
≤2	14	10 (71.4)	2.0 [1.3; 5.3]	11	5 (45.5)	11.2 [1.4; -]	2.05 [0.70; 6.04]	0.191	0.050
≥3	11	6 (54.5)	3.5 [1.3; -]	9	6 (66.7)	1.5 [0.7; -]	0.45 [0.14; 1.42]	0.175	
Tumor Burden									
Above median	10	5	5.3	11	6	2.1	0.64	0.467	0.207

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-STO22 Dry Mouth	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(50.0)	[1.3; -]		(54.5)	[0.7; -]	[0.19; 2.12]		
Below median	16	11 (68.8)	1.4 [1.3; -]	7	4 (57.1)	3.3 [1.4; -]	1.56 [0.49; 5.03]	0.453	
Prior Gastrectomy									
Yes	10	6 (60.0)	2.4 [1.4; -]	5	3 (60.0)	1.9 [0.7; -]	0.95 [0.22; 4.00]	0.943	> 0.999
No	17	11 (64.7)	2.1 [1.3; -]	15	8 (53.3)	3.3 [0.8; -]	1.03 [0.41; 2.57]	0.951	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-STO22: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Gastric Cancer 22 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-STO22: Symptomskala Geschmacksstörungen

Tabelle 4G-137: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Geschmacksstörungen des EORTC QLQ-STO22 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-STO22 Taste	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	6	5 (83.3)	2.3 [0.7; -]	5	3 (60.0)	1.7 [0.7; -]	0.73 [0.16; 3.36]	0.681	0.626
Male	21	19 (90.5)	1.4 [1.0; 2.3]	15	9 (60.0)	1.4 [0.7; -]	1.49 [0.67; 3.32]	0.328	
Age (Years)									
<65	16	14 (87.5)	2.3 [0.8; 4.4]	15	7 (46.7)	Not reached [0.7; -]	1.83 [0.73; 4.56]	0.195	0.145
≥65	11	10 (90.9)	1.2 [0.8; 1.4]	5	5 (100.0)	0.9 [0.7; -]	0.74 [0.24; 2.26]	0.601	
Severity of disease									
ECOG 0	16	14 (87.5)	2.3 [1.0; 4.4]	6	4 (66.7)	1.1 [0.7; -]	1.15 [0.37; 3.56]	0.813	0.450
ECOG 1	11	10 (90.9)	1.4 [0.7; 2.8]	14	8 (57.1)	1.9 [0.8; -]	1.82 [0.72; 4.62]	0.209	
Region									

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-STO22 Taste	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
EU	9	7 (77.8)	1.4 [0.7; -]	10	5 (50.0)	Not reached [0.7; -]	1.83 [0.58; 5.80]	0.302	0.134
Ex-EU	18	17 (94.4)	2.0 [1.0; 4.4]	10	7 (70.0)	0.9 [0.7; -]	0.60 [0.23; 1.53]	0.284	
Region									
US/EU/Australia	17	15 (88.2)	n.c.	16	9 (56.3)	n.c.	n.c.	n.c.	n.c.
Asia	3	3 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	6 (85.7)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	25	23 (92.0)	n.c.	19	12 (63.2)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	12 (92.3)	1.1 [0.7; 2.3]	9	5 (55.6)	1.5 [0.7; -]	2.26 [0.79; 6.47]	0.128	0.115
Capecitabine	14	12 (85.7)	2.3 [1.4; 8.3]	11	7 (63.6)	1.6 [0.7; -]	0.89 [0.35; 2.26]	0.800	
Number of Metastasis									
≤2	14	12 (85.7)	2.1 [1.2; 4.4]	11	5 (45.5)	Not reached [0.7; -]	2.15 [0.75; 6.16]	0.152	0.137
≥3	11	11 (100.0)	1.4 [0.7; 2.8]	9	7 (77.8)	0.8 [0.7; 1.9]	0.82 [0.31; 2.14]	0.680	
Tumor Burden									
Above median	10	9 (90.0)	2.3 [0.7; 4.4]	11	6 (54.5)	1.9 [0.7; -]	1.40 [0.50; 3.94]	0.527	0.813
Below median	16	14 (87.5)	1.4 [0.8; 2.3]	7	5 (71.4)	1.5 [0.7; -]	1.66 [0.59; 4.69]	0.338	
Prior Gastrectomy									
Yes	10	9 (90.0)	1.4 [0.7; 2.8]	5	3 (60.0)	1.9 [1.1; -]	2.51 [0.67; 9.34]	0.170	0.261
No	17	15 (88.2)	2.1 [1.0; 7.9]	15	9 (60.0)	1.1 [0.7; -]	1.12 [0.49; 2.58]	0.783	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-STO22: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Gastric Cancer 22 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-STO22: Symptomskala Körperbild

Tabelle 4G-138: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Körperbild des EORTC QLQ-STO22 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-STO22 Body Image	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	6	3 (50.0)	2.0 [0.7; -]	5	2 (40.0)	3.0 [2.6; -]	1.76 [0.29; 10.77]	0.541	0.735
Male	21	12 (57.1)	2.0 [1.4; -]	15	7 (46.7)	Not reached [0.7; -]	1.13 [0.44; 2.89]	0.794	
Age (Years)									
<65	16	7 (43.8)	Not reached [0.7; -]	15	5 (33.3)	Not reached [0.8; -]	1.36 [0.43; 4.27]	0.604	0.578
≥65	11	8 (72.7)	1.4 [1.0; 2.0]	5	4 (80.0)	0.9 [0.7; -]	0.77 [0.22; 2.61]	0.670	
Severity of disease									
ECOG 0	16	6 (37.5)	Not reached [1.0; -]	6	2 (33.3)	Not reached [0.7; -]	1.04 [0.21; 5.16]	0.961	0.583
ECOG 1	11	9 (81.8)	1.4 [0.7; 2.0]	14	7 (50.0)	4.9 [0.8; -]	2.14 [0.78; 5.92]	0.141	
Region									
EU	9	4 (44.4)	Not reached [0.7; -]	10	3 (30.0)	Not reached [0.7; -]	1.75 [0.39; 7.87]	0.465	0.396
Ex-EU	18	11 (61.1)	2.0 [1.0; -]	10	6 (60.0)	2.6 [0.7; -]	0.82 [0.30; 2.23]	0.704	
Region									
US/EU/Australia	17	10 (58.8)	n.c.	16	7 (43.8)	n.c.	n.c.	n.c.	n.c.
Asia	3	1 (33.3)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	4 (57.1)	n.c.	3	1 (33.3)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	25	14 (56.0)	n.c.	19	9 (47.4)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	9 (69.2)	1.4 [0.7; 2.0]	9	4 (44.4)	4.9 [0.7; -]	2.20 [0.67; 7.26]	0.195	0.178
Capecitabine	14	6 (42.9)	Not reached [1.4; -]	11	5 (45.5)	3.0 [0.7; -]	0.74 [0.23; 2.44]	0.626	
Number of Metastasis									
≤2	14	7 (50.0)	2.8 [1.2; -]	11	6 (54.5)	3.0 [0.7; -]	0.83 [0.28; 2.49]	0.745	0.241
≥3	11	7 (63.6)	1.4 [1.0; -]	9	3 (33.3)	4.9 [0.9; -]	2.23 [0.57; 8.71]	0.247	
Tumor Burden									
Above median	10	6	2.0	11	6	4.9	0.97	0.955	0.248

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-STO22 Body Image	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(60.0)	[1.0; -]		(54.5)	[0.7; -]	[0.31; 3.02]		
Below median	16	9 (56.3)	1.4 [0.7; -]	7	2 (28.6)	Not reached [0.7; -]	2.85 [0.61; 13.29]	0.182	
Prior Gastrectomy									
Yes	10	7 (70.0)	1.4 [0.7; 1.4]	5	2 (40.0)	Not reached [0.7; -]	2.31 [0.47; 11.41]	0.305	0.166
No	17	8 (47.1)	Not reached [1.4; -]	15	7 (46.7)	4.9 [0.8; -]	0.85 [0.31; 2.35]	0.757	

a: Database Cutoff Date: 26MAR2019
b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine
c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 10 points or more increase from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-STO22: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Gastric Cancer 22 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-STO22: Symptomskala Haarausfall

Tabelle 4G-139: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Haarausfall des EORTC QLQ-STO22 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-STO22 Hair Loss (Imputed)[i]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	6	5 (83.3)	n.c.	5	1 (20.0)	n.c.	n.c.	n.c.	n.c.
Male	21	6 (28.6)	n.c.	15	2 (13.3)	n.c.	n.c.	n.c.	
Age (Years)									
<65	16	7 (43.8)	Not reached [1.4; -]	15	3 (20.0)	Not reached [2.1; -]	2.45 [0.63; 9.53]	0.195	0.185
≥65	11	4 (36.4)	Not reached [1.0; -]	5	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.114	
Severity of disease									
ECOG 0	16	6 (37.5)	n.c.	6	0 (0.0)	n.c.	n.c.	n.c.	n.c.
ECOG 1	11	5 (45.5)	n.c.	14	3 (21.4)	n.c.	n.c.	n.c.	
Region									

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-STO22 Hair Loss (Imputed)[i]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
EU	9	1 (11.1)	Not reached [1.4; -]	10	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.264	0.344
Ex-EU	18	10 (55.6)	4.6 [1.4; -]	10	3 (30.0)	Not reached [1.9; -]	2.26 [0.62; 8.23]	0.216	
Region									
US/EU/Australia	17	8 (47.1)	n.c.	16	2 (12.5)	n.c.	n.c.	n.c.	n.c.
Asia	3	1 (33.3)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	2 (28.6)	n.c.	3	1 (33.3)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	25	10 (40.0)	n.c.	19	3 (15.8)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	9 (69.2)	1.4 [1.0; 6.4]	9	2 (22.2)	Not reached [1.9; -]	5.88 [1.25; 27.56]	0.025	0.320
Capecitabine	14	2 (14.3)	Not reached [-; -]	11	1 (9.1)	Not reached [1.9; -]	1.51 [0.14; 16.60]	0.738	
Number of Metastasis									
≤2	14	5 (35.7)	n.c.	11	2 (18.2)	n.c.	n.c.	n.c.	n.c.
≥3	11	5 (45.5)	n.c.	9	1 (11.1)	n.c.	n.c.	n.c.	
Tumor Burden									
Above median	10	4 (40.0)	n.c.	11	2 (18.2)	n.c.	n.c.	n.c.	n.c.
Below median	16	7 (43.8)	n.c.	7	1 (14.3)	n.c.	n.c.	n.c.	
Prior Gastrectomy									
Yes	10	3 (30.0)	Not reached [1.0; -]	5	1 (20.0)	Not reached [2.1; -]	2.64 [0.27; 25.80]	0.404	0.767
No	17	8 (47.1)	Not reached [1.4; -]	15	2 (13.3)	Not reached [-; -]	3.86 [0.82; 18.24]	0.088	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

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

i: For participants who did not lose any hair, the response was imputed as not upset at all by the loss of hair

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-STO22: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Gastric Cancer 22 items; n.a.: not applicable; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EQ-5D VAS

EQ-5D VAS (7 Punkte)

Tabelle 4G-140: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS (7 Punkte) aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EQ-5D VAS (7 Points)	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	7	5 (71.4)	2.7 [1.0; -]	5	4 (80.0)	2.7 [0.8; -]	0.54 [0.13; 2.23]	0.394	0.409
Male	22	16 (72.7)	2.3 [0.8; 8.8]	15	10 (66.7)	5.0 [0.7; 8.3]	1.15 [0.52; 2.54]	0.731	
Age (Years)									
<65	16	12 (75.0)	2.4 [0.7; 8.8]	15	10 (66.7)	2.8 [0.7; 8.3]	0.91 [0.38; 2.21]	0.842	0.870
≥65	13	9 (69.2)	1.9 [1.0; -]	5	4 (80.0)	1.9 [0.8; -]	0.94 [0.29; 3.08]	0.916	
Region									
EU	10	7 (70.0)	2.3 [0.7; -]	10	7 (70.0)	4.6 [0.7; -]	1.17 [0.39; 3.51]	0.783	0.725
Ex-EU	19	14 (73.7)	2.7 [0.8; 8.8]	10	7 (70.0)	2.6 [0.7; 5.0]	0.86 [0.34; 2.16]	0.752	
Region									
US/EU/Australia	19	14 (73.7)	n.c.	16	12 (75.0)	n.c.	n.c.	n.c.	n.c.
Asia	3	3 (100.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	4 (57.1)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	27	19 (70.4)	n.c.	19	13 (68.4)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	2 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	14	10 (71.4)	2.3 [0.8; -]	9	7 (77.8)	1.9 [0.7; 5.0]	0.80 [0.30; 2.15]	0.654	0.670
Capecitabine	15	11 (73.3)	2.4 [0.7; 11.3]	11	7 (63.6)	3.0 [0.7; 8.3]	1.10 [0.42; 2.87]	0.840	
Number of Metastasis									
≤2	15	10 (66.7)	3.0 [0.8; 11.3]	11	9 (81.8)	2.8 [0.7; 8.3]	0.88 [0.35; 2.18]	0.778	0.863
≥3	12	9 (75.0)	2.0 [0.7; -]	9	5 (55.6)	2.6 [0.7; -]	1.00 [0.33; 3.08]	0.994	
Tumor Burden									
Above median	10	7 (70.0)	2.7 [0.7; -]	11	8 (72.7)	3.0 [0.7; 8.3]	0.81 [0.28; 2.34]	0.697	0.990
Below median	18	13 (72.2)	2.3 [0.8; 8.8]	7	6 (85.7)	2.6 [0.7; 6.1]	0.81 [0.30; 2.25]	0.692	
Prior Gastrectomy									

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EQ-5D VAS (7 Points)	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Yes	10	6 (60.0)	1.2 [0.7; -]	5	5 (100.0)	1.9 [0.7; -]	0.75 [0.23; 2.50]	0.644	0.273
No	19	15 (78.9)	2.4 [1.0; 8.8]	15	9 (60.0)	3.0 [0.8; -]	1.24 [0.54; 2.85]	0.611	

a: Database Cutoff Date: 26MAR2019
b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine
c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline
d: Time to first deterioration is defined as the time from first dose of treatment to first onset of 7 points or more decrease from baseline
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox regression 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 Proportion Score; EQ-5D: European Quality of Life 5 Dimensions; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; VAS: Visual Analog Scale

EQ-5D VAS (10 Punkte)

Tabelle 4G-141: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS (10 Punkte) aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EQ-5D VAS (10 Points)	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	7	5 (71.4)	3.7 [1.9; -]	5	4 (80.0)	2.7 [0.8; -]	0.32 [0.07; 1.51]	0.150	0.130
Male	22	16 (72.7)	2.3 [1.0; 8.8]	15	7 (46.7)	8.3 [0.8; -]	1.86 [0.76; 4.54]	0.171	
Age (Years)									
<65	16	12 (75.0)	2.4 [0.7; 8.8]	15	8 (53.3)	3.0 [1.9; -]	1.33 [0.53; 3.35]	0.538	> 0.999
≥65	13	9 (69.2)	4.4 [1.0; -]	5	3 (60.0)	1.9 [0.8; -]	1.20 [0.32; 4.50]	0.787	
Region									
EU	10	7 (70.0)	2.3 [0.7; -]	10	6 (60.0)	5.7 [0.7; -]	1.49 [0.49; 4.51]	0.480	0.936
Ex-EU	19	14 (73.7)	3.7 [1.3; 8.3]	10	5 (50.0)	2.6 [0.7; -]	1.33 [0.48; 3.71]	0.587	
Region									
US/EU/Australia	19	14 (73.7)	n.c.	16	9 (56.3)	n.c.	n.c.	n.c.	n.c.
Asia	3	3 (100.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	4 (57.1)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EQ-5D VAS (10 Points)	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Disease Status									
Metastatic	27	19 (70.4)	n.c.	19	10 (52.6)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	2 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	14	10 (71.4)	3.0 [1.2; 5.3]	9	6 (66.7)	1.9 [0.7; -]	0.82 [0.29; 2.30]	0.702	0.312
Capecitabine	15	11 (73.3)	2.4 [0.7; 11.3]	11	5 (45.5)	8.3 [1.9; -]	1.86 [0.64; 5.36]	0.252	
Number of Metastasis									
≤2	15	10 (66.7)	3.0 [1.2; 11.3]	11	8 (72.7)	2.8 [0.7; -]	1.06 [0.42; 2.69]	0.902	0.497
≥3	12	9 (75.0)	3.4 [0.8; -]	9	3 (33.3)	Not reached [0.8; -]	1.75 [0.46; 6.63]	0.407	
Tumor Burden									
Above median	10	7 (70.0)	3.7 [0.7; -]	11	6 (54.5)	8.3 [0.8; -]	1.11 [0.35; 3.45]	0.863	0.972
Below median	18	13 (72.2)	2.3 [1.0; 8.8]	7	5 (71.4)	2.6 [0.7; -]	1.18 [0.42; 3.32]	0.758	
Prior Gastrectomy									
Yes	10	6 (60.0)	1.3 [0.7; -]	5	4 (80.0)	1.9 [0.7; -]	0.87 [0.24; 3.13]	0.835	0.403
No	19	15 (78.9)	3.0 [1.6; 8.8]	15	7 (46.7)	8.3 [1.9; -]	1.63 [0.66; 4.02]	0.286	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; EQ-5D: European Quality of Life 5 Dimensions; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; VAS: Visual Analog Scale

Anhang 4-G12.3: Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-142: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den globalen Gesundheitsstatus des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
EORTC QLQ-C30 Global Health Status	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**N[c]**	**Participants with Event[d] n (%)**	**Median Time[e] in Months [95 %-CI]**	**Hazard Ratio[f] [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Gender									
Female	7	4 (57.1)	4.4 [0.7; -]	5	3 (60.0)	4.4 [1.0; -]	0.59 [0.12; 2.95]	0.517	0.944
Male	21	12 (57.1)	8.3 [2.4; -]	15	10 (66.7)	2.1 [0.8; -]	0.59 [0.25; 1.39]	0.230	
Age (Years)									
<65	16	9 (56.3)	8.3 [1.4; -]	15	11 (73.3)	2.1 [1.0; 6.0]	0.36 [0.14; 0.94]	0.038	0.181
≥65	12	7 (58.3)	6.5 [0.7; -]	5	2 (40.0)	Not reached [0.7; -]	1.38 [0.28; 6.74]	0.687	
Severity of disease									
ECOG 0	17	11 (64.7)	6.5 [2.4; 9.7]	6	5 (83.3)	2.6 [0.7; -]	0.60 [0.21; 1.74]	0.345	0.782
ECOG 1	11	5 (45.5)	10.2 [0.7; -]	14	8 (57.1)	1.9 [1.0; -]	0.57 [0.17; 1.88]	0.352	
Region									
EU	10	4 (40.0)	Not reached [0.7; -]	10	7 (70.0)	2.6 [0.7; -]	0.56 [0.16; 1.93]	0.359	0.423
Ex-EU	18	12 (66.7)	6.5 [1.4; 9.7]	10	6 (60.0)	1.9 [0.7; -]	0.73 [0.27; 1.99]	0.543	
Region									
US/EU/Australia	18	9 (50.0)	n.c.	16	11 (68.8)	n.c.	n.c.	n.c.	n.c.
Asia	3	3 (100.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	4 (57.1)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	26	14 (53.8)	n.c.	19	13 (68.4)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	2 (100.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	7 (53.8)	5.3 [1.4; -]	9	5 (55.6)	7.4 [0.8; -]	0.80 [0.24; 2.65]	0.718	0.414
Capecitabine	15	9 (60.0)	8.6 [0.7; -]	11	8 (72.7)	1.9 [0.7; 6.0]	0.45 [0.17; 1.21]	0.112	
Number of Metastasis									
≤2	15	7 (46.7)	8.8 [1.4; -]	11	9 (81.8)	1.9 [0.8; 2.8]	0.37 [0.13; 1.04]	0.058	0.222

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Global Health Status	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
≥3	11	7 (63.6)	6.5 [0.7; 10.2]	9	4 (44.4)	6.0 [0.7; -]	0.74 [0.19; 2.84]	0.665	
Tumor Burden									
Above median	10	5 (50.0)	10.2 [0.7; -]	11	8 (72.7)	1.4 [0.7; -]	0.35 [0.10; 1.21]	0.096	0.181
Below median	17	10 (58.8)	6.5 [1.4; 9.7]	7	5 (71.4)	2.8 [1.9; -]	0.68 [0.22; 2.13]	0.509	
Prior Gastrectomy									
Yes	10	4 (40.0)	5.3 [0.7; -]	5	4 (80.0)	1.9 [0.7; -]	0.44 [0.10; 1.96]	0.278	0.324
No	18	12 (66.7)	8.3 [2.4; 10.2]	15	9 (60.0)	2.8 [1.0; -]	0.69 [0.28; 1.66]	0.406	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-143: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Physical Functioning	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	7	5 (71.4)	1.7 [1.0; -]	5	4 (80.0)	1.2 [0.7; -]	0.37 [0.08; 1.65]	0.191	0.573
Male	21	16 (76.2)	4.2 [1.4; 8.3]	15	11 (73.3)	1.4 [0.7; 2.6]	0.65 [0.30; 1.41]	0.272	
Age (Years)									
<65	16	12 (75.0)	4.2 [1.4; 8.3]	15	11 (73.3)	1.4 [0.7; 2.6]	0.50 [0.21; 1.17]	0.110	0.542
≥65	12	9 (75.0)	1.9 [1.0; 6.5]	5	4 (80.0)	1.5 [0.7; -]	0.76 [0.23; 2.49]	0.654	
Severity of disease									
ECOG 0	17	12	4.4	6	3	Not reached	1.36	0.631	0.103

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Physical Functioning	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(70.6)	[1.4; 8.3]		(50.0)	[0.7; -]	[0.38; 4.84]		
ECOG 1	11	9 (81.8)	1.4 [1.0; 5.1]	14	12 (85.7)	1.1 [0.7; 1.9]	0.38 [0.14; 1.03]	0.056	
Region									
EU	10	6 (60.0)	4.2 [1.2; -]	10	8 (80.0)	1.4 [0.7; 2.6]	0.47 [0.16; 1.39]	0.170	0.405
Ex-EU	18	15 (83.3)	3.4 [1.0; 6.5]	10	7 (70.0)	1.4 [0.7; -]	0.74 [0.30; 1.84]	0.521	
Region									
US/EU/Australia	18	12 (66.7)	n.c.	16	13 (81.3)	n.c.	n.c.	n.c.	n.c.
Asia	3	3 (100.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	6 (85.7)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	26	19 (73.1)	n.c.	19	14 (73.7)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	2 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	9 (69.2)	1.4 [1.0; 6.5]	9	7 (77.8)	0.8 [0.7; -]	0.61 [0.22; 1.67]	0.340	0.969
Capecitabine	15	12 (80.0)	4.2 [1.4; 8.3]	11	8 (72.7)	1.4 [0.7; 2.6]	0.55 [0.22; 1.38]	0.207	
Number of Metastasis									
≤2	15	10 (66.7)	3.4 [1.4; 8.6]	11	10 (90.9)	1.0 [0.7; 1.4]	0.34 [0.14; 0.84]	0.020	0.087
≥3	11	9 (81.8)	4.2 [1.0; 8.3]	9	5 (55.6)	2.1 [0.8; -]	1.11 [0.36; 3.38]	0.857	
Tumor Burden									
Above median	10	7 (70.0)	2.8 [1.0; -]	11	8 (72.7)	1.4 [0.7; -]	0.65 [0.23; 1.80]	0.406	0.411
Below median	17	13 (76.5)	3.4 [1.4; 6.5]	7	7 (100.0)	1.4 [0.7; 1.5]	0.22 [0.07; 0.71]	0.011	
Prior Gastrectomy									
Yes	10	7 (70.0)	1.4 [0.7; 1.4]	5	5 (100.0)	1.1 [0.7; -]	0.76 [0.24; 2.41]	0.638	0.747
No	18	14 (77.8)	4.7 [2.8; 8.3]	15	10 (66.7)	1.6 [0.8; -]	0.58 [0.25; 1.31]	0.189	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated.

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Physical Functioning	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1									

EORTC QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-144: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Rollenfunktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Role Functioning	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	7	5 (71.4)	2.1 [0.7; -]	5	4 (80.0)	0.8 [0.7; -]	0.62 [0.16; 2.40]	0.493	0.252
Male	21	18 (85.7)	2.1 [1.4; 5.6]	15	9 (60.0)	3.0 [0.7; -]	1.31 [0.59; 2.93]	0.504	
Age (Years)									
<65	16	13 (81.3)	3.0 [1.4; 8.3]	15	8 (53.3)	4.0 [0.7; -]	1.42 [0.59; 3.43]	0.437	0.137
≥65	12	10 (83.3)	1.8 [1.0; 5.1]	5	5 (100.0)	0.8 [0.7; -]	0.45 [0.14; 1.39]	0.164	
Severity of disease									
ECOG 0	17	15 (88.2)	2.7 [1.4; 5.6]	6	4 (66.7)	1.1 [0.7; -]	1.04 [0.34; 3.16]	0.947	0.889
ECOG 1	11	8 (72.7)	2.1 [0.7; -]	14	9 (64.3)	3.0 [0.7; -]	1.13 [0.43; 2.93]	0.807	
Region									
EU	10	8 (80.0)	2.0 [0.7; 8.5]	10	7 (70.0)	3.1 [0.7; -]	1.19 [0.43; 3.29]	0.742	0.740
Ex-EU	18	15 (83.3)	2.3 [1.4; 5.6]	10	6 (60.0)	0.8 [0.7; -]	0.96 [0.37; 2.50]	0.935	
Region									
US/EU/Australia	18	14 (77.8)	n.c.	16	11 (68.8)	n.c.	n.c.	n.c.	n.c.
Asia	3	3 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	6 (85.7)	n.c.	3	1 (33.3)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	26	21 (80.8)	n.c.	19	13 (68.4)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	2 (100.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	10 (76.9)	1.5 [0.7; 3.7]	9	5 (55.6)	3.2 [0.7; -]	2.04 [0.69; 6.03]	0.196	0.077

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Role Functioning	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Capecitabine	15	13 (86.7)	3.1 [1.4; 8.3]	11	8 (72.7)	0.8 [0.7; 5.1]	0.64 [0.26; 1.55]	0.323	
Number of Metastasis									
≤2	15	11 (73.3)	4.4 [1.4; 8.5]	11	6 (54.5)	5.1 [0.7; -]	1.18 [0.44; 3.20]	0.743	0.643
≥3	11	10 (90.9)	2.1 [1.0; 3.1]	9	7 (77.8)	1.5 [0.7; 3.2]	0.97 [0.36; 2.56]	0.945	
Tumor Burden									
Above median	10	8 (80.0)	2.2 [1.0; -]	11	8 (72.7)	2.2 [0.7; -]	0.80 [0.29; 2.20]	0.660	0.349
Below median	17	14 (82.4)	2.0 [1.0; 5.6]	7	4 (57.1)	3.2 [0.7; -]	1.65 [0.54; 5.03]	0.379	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-145: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Emotional Functioning	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	7	2 (28.6)	Not reached [0.7; -]	5	1 (20.0)	Not reached [3.3; -]	1.30 [0.12; 14.43]	0.833	0.904
Male	21	13 (61.9)	5.9 [1.4; -]	15	7 (46.7)	6.1 [0.8; -]	1.24 [0.50; 3.12]	0.641	
Age (Years)									
<65	16	8 (50.0)	7.1 [1.4; -]	15	6 (40.0)	6.1 [1.4; -]	1.06 [0.36; 3.06]	0.920	0.818
≥65	12	7 (58.3)	4.4 [0.7; -]	5	2 (40.0)	Not reached [0.7; -]	1.28 [0.27; 6.21]	0.755	
Severity of disease									
ECOG 0	17	9	5.9	6	2	Not reached	2.02	0.369	0.465

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Emotional Functioning	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(52.9)	[1.4; -]		(33.3)	[4.7; -]	[0.44; 9.39]		
ECOG 1	11	6 (54.5)	5.8 [0.7; -]	14	6 (42.9)	Not reached [0.8; -]	0.98 [0.31; 3.06]	0.972	
Region									
EU	10	6 (60.0)	4.3 [0.7; -]	10	4 (40.0)	6.1 [0.7; -]	1.50 [0.41; 5.46]	0.535	0.600
Ex-EU	18	9 (50.0)	5.9 [1.6; -]	10	4 (40.0)	Not reached [0.7; -]	0.97 [0.30; 3.15]	0.958	
Region									
US/EU/Australia	18	9 (50.0)	n.c.	16	7 (43.8)	n.c.	n.c.	n.c.	n.c.
Asia	3	2 (66.7)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	4 (57.1)	n.c.	3	1 (33.3)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	26	14 (53.8)	n.c.	19	7 (36.8)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	7 (53.8)	2.2 [0.8; -]	9	4 (44.4)	Not reached [0.7; -]	1.21 [0.35; 4.13]	0.764	0.861
Capecitabine	15	8 (53.3)	7.2 [1.4; -]	11	4 (36.4)	6.1 [0.7; -]	1.23 [0.37; 4.10]	0.735	
Number of Metastasis									
≤2	15	9 (60.0)	2.8 [0.8; -]	11	6 (54.5)	6.1 [0.7; -]	1.17 [0.42; 3.30]	0.762	0.828
≥3	11	5 (45.5)	8.3 [1.6; -]	9	2 (22.2)	Not reached [0.8; -]	1.23 [0.23; 6.54]	0.810	
Tumor Burden									
Above median	10	4 (40.0)	Not reached [0.7; -]	11	4 (36.4)	Not reached [0.7; -]	0.94 [0.23; 3.80]	0.932	0.674
Below median	17	10 (58.8)	5.0 [1.4; -]	7	4 (57.1)	4.7 [1.4; -]	1.21 [0.38; 3.89]	0.747	
Prior Gastrectomy									
Yes	10	6 (60.0)	1.4 [0.7; -]	5	3 (60.0)	6.1 [0.7; -]	1.23 [0.29; 5.16]	0.775	0.932
No	18	9 (50.0)	8.3 [2.7; -]	15	5 (33.3)	Not reached [1.4; -]	1.18 [0.39; 3.55]	0.774	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated.

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Emotional Functioning	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1									

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-146: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Kognitive Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Cognitive Functioning	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	7	5 (71.4)	2.0 [0.7; -]	5	2 (40.0)	Not reached [0.7; -]	1.48 [0.27; 8.12]	0.652	0.374
Male	21	12 (57.1)	4.6 [1.4; -]	15	10 (66.7)	1.4 [0.7; -]	0.62 [0.26; 1.44]	0.264	
Age (Years)									
<65	16	10 (62.5)	4.6 [1.4; -]	15	7 (46.7)	3.1 [0.7; -]	0.96 [0.36; 2.55]	0.936	0.164
≥65	12	7 (58.3)	3.0 [0.7; -]	5	5 (100.0)	0.9 [0.7; -]	0.26 [0.07; 0.97]	0.046	
Severity of disease									
ECOG 0	17	9 (52.9)	8.3 [2.1; -]	6	3 (50.0)	3.1 [0.7; -]	0.83 [0.22; 3.16]	0.788	0.853
ECOG 1	11	8 (72.7)	1.4 [0.7; -]	14	9 (64.3)	0.9 [0.7; -]	0.97 [0.37; 2.52]	0.944	
Region									
EU	10	5 (50.0)	2.6 [0.7; -]	10	5 (50.0)	3.1 [0.7; -]	1.18 [0.34; 4.11]	0.791	0.431
Ex-EU	18	12 (66.7)	4.6 [1.4; 9.7]	10	7 (70.0)	0.9 [0.7; -]	0.50 [0.20; 1.29]	0.154	
Region									
US/EU/Australia	18	12 (66.7)	n.c.	16	10 (62.5)	n.c.	n.c.	n.c.	n.c.
Asia	3	2 (66.7)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	3 (42.9)	n.c.	3	1 (33.3)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	26	15 (57.7)	n.c.	19	11 (57.9)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	2 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	9 (69.2)	1.4 [0.7; 7.9]	9	6 (66.7)	0.9 [0.7; -]	0.87 [0.30; 2.46]	0.786	0.728

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Cognitive Functioning	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Capecitabine	15	8 (53.3)	8.3 [2.1; -]	11	6 (54.5)	2.3 [0.7; -]	0.64 [0.22; 1.87]	0.417	
Number of Metastasis									
≤2	15	10 (66.7)	3.0 [1.4; 9.7]	11	7 (63.6)	1.6 [0.7; -]	0.81 [0.31; 2.14]	0.667	0.598
≥3	11	5 (45.5)	8.3 [1.0; -]	9	5 (55.6)	1.5 [0.7; -]	0.54 [0.15; 1.90]	0.336	
Tumor Burden									
Above median	10	5 (50.0)	7.9 [0.7; -]	11	6 (54.5)	1.4 [0.7; -]	0.68 [0.21; 2.26]	0.531	0.768
Below median	17	12 (70.6)	3.0 [1.0; 8.3]	7	5 (71.4)	1.5 [0.7; -]	0.81 [0.28; 2.32]	0.700	
Prior Gastrectomy									
Yes	10	3 (30.0)	Not reached [1.0; -]	5	4 (80.0)	1.5 [0.7; -]	0.30 [0.07; 1.34]	0.114	0.158
No	18	14 (77.8)	2.4 [1.4; 8.3]	15	8 (53.3)	1.5 [0.7; -]	1.01 [0.42; 2.45]	0.985	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

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

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

h: Based on Cox regression 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 Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

EORTC QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-147: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Soziale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Social Functioning	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Gender									
Female	7	4 (57.1)	3.7 [0.7; -]	5	4 (80.0)	1.8 [1.5; -]	0.21 [0.04; 1.19]	0.077	0.584
Male	21	12 (57.1)	3.6 [1.4; -]	15	11 (73.3)	2.3 [0.7; 4.9]	0.67 [0.29; 1.52]	0.333	
Age (Years)									
<65	16	7	Not reached	15	10	1.9	0.49	0.149	0.483

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Social Functioning	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	N[c]	Participants with Event[d] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(43.8)	[1.4; -]		(66.7)	[0.7; -]	[0.18; 1.29]		
≥65	12	9 (75.0)	1.9 [1.3; 5.1]	5	5 (100.0)	2.3 [0.9; -]	0.74 [0.24; 2.29]	0.605	
Severity of disease									
ECOG 0	17	9 (52.9)	3.0 [1.4; -]	6	4 (66.7)	3.7 [0.7; -]	0.92 [0.28; 3.02]	0.890	0.544
ECOG 1	11	7 (63.6)	4.4 [1.3; -]	14	11 (78.6)	1.9 [0.9; 2.6]	0.58 [0.22; 1.51]	0.264	
Region									
EU	10	6 (60.0)	1.9 [0.7; -]	10	6 (60.0)	3.7 [1.0; -]	1.29 [0.41; 4.04]	0.659	0.050
Ex-EU	18	10 (55.6)	4.4 [1.6; -]	10	9 (90.0)	1.9 [0.7; 2.3]	0.28 [0.11; 0.71]	0.008	
Region									
US/EU/Australia	18	11 (61.1)	n.c.	16	12 (75.0)	n.c.	n.c.	n.c.	n.c.
Asia	3	0 (0.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Rest of World	7	5 (71.4)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	26	14 (53.8)	n.c.	19	15 (78.9)	n.c.	n.c.	n.c.[i]	n.c.
Locally Advanced	2	2 (100.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	13	8 (61.5)	2.1 [1.2; -]	9	6 (66.7)	2.8 [0.7; -]	1.28 [0.44; 3.75]	0.655	0.071
Capecitabine	15	8 (53.3)	8.3 [1.4; -]	11	9 (81.8)	1.9 [0.7; 2.6]	0.34 [0.12; 0.92]	0.034	
Number of Metastasis									
≤2	15	7 (46.7)	5.1 [1.4; -]	11	9 (81.8)	2.3 [1.0; 4.7]	0.51 [0.19; 1.37]	0.182	0.844
≥3	11	7 (63.6)	4.4 [1.4; -]	9	6 (66.7)	1.7 [0.7; -]	0.60 [0.20; 1.78]	0.354	
Tumor Burden									
Above median	10	7 (70.0)	2.6 [1.2; -]	11	9 (81.8)	1.6 [0.7; 4.9]	0.62 [0.23; 1.66]	0.340	0.669
Below median	17	9 (52.9)	5.1 [1.6; -]	7	5 (71.4)	2.8 [1.5; -]	0.84 [0.28; 2.53]	0.759	
Prior Gastrectomy									
Yes	10	6 (60.0)	2.0 [1.2; -]	5	5 (100.0)	1.9 [0.7; -]	0.81 [0.24; 2.67]	0.727	0.798
No	18	10 (55.6)	5.1 [1.6; -]	15	10 (66.7)	2.1 [0.9; -]	0.58 [0.24; 1.41]	0.233	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: full-analysis-set population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS ≥ 10, participants with baseline

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

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

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]		Chemotherapy[b]		Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
EORTC QLQ-C30 Social Functioning	Participants with Event[d] N[c] n (%)	Median Time[e] in Months [95 %-CI]	Participants with Event[d] N[c] n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio[f] [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]

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

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

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

i: Unrounded p-value: 0.04982403

CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G12.4: Nebenwirkungen

Unerwünschte Ereignisse

Unerwünschte Ereignisse gesamt

Tabelle 4G-148: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	Participants with Event N[c]	n (%)	Median Time[d] in Weeks [95 %-CI]	Participants with Event N[c]	n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	7	7 (100.0)	0.4 [0.1; 2.6]	5	4 (80.0)	0.7 [0.1; -]	1.25 [0.37; 4.31]	0.719	0.702
Male	23	23 (100.0)	0.3 [0.1; 0.4]	15	15 (100.0)	0.4 [0.1; 1.0]	1.75 [0.85; 3.59]	0.128	
Age (Years)									
<65	17	17 (100.0)	0.3 [0.1; 1.1]	15	14 (93.3)	0.4 [0.1; 3.1]	1.63 [0.75; 3.55]	0.222	0.849
≥65	13	13 (100.0)	0.3 [0.1; 0.4]	5	5 (100.0)	0.7 [0.1; -]	1.61 [0.55; 4.70]	0.386	
Severity of disease									
ECOG 0	17	17 (100.0)	0.3 [0.1; 1.1]	6	6 (100.0)	1.7 [0.1; -]	2.66 [0.82; 8.59]	0.102	0.930
ECOG 1	13	13 (100.0)	0.3 [0.1; 0.6]	14	13 (92.9)	0.6 [0.1; 1.0]	1.54 [0.70; 3.39]	0.286	
Region									
EU	11	11 (100.0)	0.3 [0.1; 0.9]	10	10 (100.0)	0.7 [0.1; 3.6]	2.18 [0.83; 5.71]	0.114	0.213
Ex-EU	19	19 (100.0)	0.3 [0.3; 0.9]	10	9 (90.0)	0.3 [0.1; 1.0]	1.17 [0.53; 2.63]	0.696	
Region									
US/EU/Australia	20	20 (100.0)	n.c.	16	16 (100.0)	n.c.	n.c.	n.c.	n.c.
Asia	3	3 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Rest of World	7	7 (100.0)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	28	28 (100.0)	n.c.	19	18 (94.7)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	2 (100.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	14	14 (100.0)	0.3 [0.3; 1.0]	9	9 (100.0)	0.3 [0.1; 9.1]	1.31 [0.52; 3.30]	0.563	0.784
Capecitabine	16	16 (100.0)	0.3 [0.1; 0.9]	11	10 (90.9)	0.7 [0.1; 3.1]	1.83 [0.79; 4.22]	0.159	
Number of Metastasis									
≤2	15	15 (100.0)	0.3 [0.1; 1.1]	11	11 (100.0)	0.3 [0.1; 0.7]	1.22 [0.53; 2.81]	0.640	0.300
≥3	13	13 (100.0)	0.3 [0.1; 0.4]	9	8 (88.9)	1.0 [0.1; -]	2.62 [0.99; 6.90]	0.052	
Tumor Burden									
Above median	10	10 (100.0)	0.4 [0.1; 0.6]	11	11 (100.0)	0.7 [0.1; 1.0]	1.55 [0.63; 3.77]	0.339	0.582
Below median	19	19 (100.0)	0.3 [0.1; 0.9]	7	7 (100.0)	0.3 [0.1; 3.6]	1.74 [0.64; 4.77]	0.280	
Prior Gastrectomy									
Yes	11	11 (100.0)	0.3 [0.1; 0.3]	5	5 (100.0)	0.7 [0.1; -]	1.77 [0.55; 5.66]	0.336	0.760
No	19	19 (100.0)	0.4 [0.3; 0.9]	15	14 (93.3)	0.4 [0.1; 1.0]	1.46 [0.70; 3.05]	0.317	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: all-participants-as-treated population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS≥10

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

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

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

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

5-FU: 5-Fluorouracil; CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-149: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Serious Adverse Events	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	7	3 (42.9)	Not reached [1.0; -]	5	2 (40.0)	Not reached [0.7; -]	1.11 [0.18; 6.69]	0.910	0.456
Male	23	16 (69.6)	8.1 [2.1; 42.4]	15	7 (46.7)	36.7 [5.6; -]	1.93 [0.79; 4.70]	0.149	
Severity of disease									
ECOG 0	17	9 (52.9)	30.4 [2.6; -]	6	1 (16.7)	Not reached [15.9; -]	4.33 [0.55; 34.30]	0.165	0.437
ECOG 1	13	10 (76.9)	2.1 [0.6; -]	14	8 (57.1)	29.4 [1.3; -]	1.76 [0.69; 4.49]	0.233	
Region									
EU	11	8 (72.7)	8.1 [0.7; -]	10	3 (30.0)	Not reached [0.7; -]	3.28 [0.86; 12.49]	0.082	0.176
Ex-EU	19	11 (57.9)	15.1 [1.0; -]	10	6 (60.0)	6.6 [0.4; -]	1.08 [0.40; 2.94]	0.876	
Region									
US/EU/Australia	20	14 (70.0)	n.c.	16	7 (43.8)	n.c.	n.c.	n.c.	n.c.
Asia	3	0 (0.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	5 (71.4)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	28	19 (67.9)	n.c.	19	8 (42.1)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	0 (0.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	14	10 (71.4)	5.4 [1.0; -]	9	4 (44.4)	36.7 [1.3; -]	2.47 [0.76; 7.94]	0.131	0.436
Capecitabine	16	9 (56.3)	30.4 [1.4; -]	11	5 (45.5)	Not reached [0.7; -]	1.25 [0.42; 3.73]	0.693	
Number of Metastasis									
≤2	15	9 (60.0)	15.1 [1.4; -]	11	5 (45.5)	29.4 [5.6; -]	1.64 [0.55; 4.90]	0.378	0.674
≥3	13	10 (76.9)	2.1 [0.7; 42.4]	9	4 (44.4)	36.7 [0.4; -]	2.10 [0.65; 6.77]	0.213	
Tumor Burden									
Above median	10	6 (60.0)	10.3 [0.3; -]	11	5 (45.5)	36.7 [0.7; -]	1.62 [0.49; 5.34]	0.426	0.870
Below median	19	13 (68.4)	8.1 [2.1; -]	7	4 (57.1)	29.4 [4.7; -]	1.47 [0.47; 4.54]	0.508	
Prior Gastrectomy									
Yes	11	9	2.6	5	1	Not reached	6.24	0.084	0.076

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		p-Value for Interaction Test[g]
Serious Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	
		(81.8)	[0.7; 42.4]		(20.0)	[6.6; -]	[0.78; 49.58]		
No	19	10 (52.6)	30.4 [1.4; -]	15	8 (53.3)	29.4 [1.3; -]	1.03 [0.41; 2.62]	0.943	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: all-participants-as-treated population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS≥10

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

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

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

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

5-FU: 5-Fluorouracil; CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5)

Tabelle 4G-150: 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 – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		p-Value for Interaction Test[g]
Severe Adverse Events (CTCAE-Grade 3-5)	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	
Gender									
Female	7	7 (100.0)	5.3 [1.0; 22.3]	5	3 (60.0)	6.0 [0.7; -]	0.91 [0.22; 3.83]	0.895	0.921
Male	23	19 (82.6)	5.6 [2.6; 9.0]	15	12 (80.0)	5.6 [1.1; 29.4]	1.31 [0.63; 2.73]	0.467	
Age (Years)									
<65	17	14 (82.4)	9.0 [3.1; 22.3]	15	11 (73.3)	6.0 [1.1; 19.1]	0.95 [0.43; 2.11]	0.908	0.125
≥65	13	12 (92.3)	2.6 [1.0; 5.3]	5	4 (80.0)	1.3 [0.7; -]	1.62 [0.45; 5.85]	0.458	
Severity of disease									
ECOG 0	17	15 (88.2)	5.3 [2.6; 9.0]	6	3 (50.0)	19.1 [3.6; -]	3.80 [1.07; 13.50]	0.039	0.068
ECOG 1	13	11 (84.6)	5.9 [0.6; 22.3]	14	12 (85.7)	3.6 [0.7; 29.4]	1.05 [0.44; 2.50]	0.907	
Region									
EU	11	9 (81.8)	9.0 [3.0; 22.3]	10	7 (70.0)	9.7 [0.7; -]	1.19 [0.44; 3.23]	0.739	0.601
Ex-EU	19	17 (89.5)	3.1 [1.7; 7.4]	10	8 (80.0)	5.6 [0.4; 36.7]	1.42 [0.61; 3.33]	0.415	
Region									
US/EU/Australia	20	18 (90.0)	n.c.	16	13 (81.3)	n.c.	n.c.	n.c.	n.c.

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Severe Adverse Events (CTCAE-Grade 3-5)	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Asia	3	2 (66.7)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	6 (85.7)	n.c.	3	2 (66.7)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	28	25 (89.3)	n.c.	19	14 (73.7)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	1 (100.0)	n.c.	n.c.	n.c.	
Number of Metastasis									
≤2	15	14 (93.3)	5.6 [2.6; 7.4]	11	9 (81.8)	3.9 [0.7; 29.4]	1.21 [0.52; 2.83]	0.659	0.458
≥3	13	11 (84.6)	3.0 [1.0; 9.0]	9	6 (66.7)	19.1 [0.4; -]	2.05 [0.70; 6.03]	0.193	
Tumor Burden									
Above median	10	7 (70.0)	8.8 [0.6; -]	11	9 (81.8)	3.9 [0.7; -]	0.70 [0.26; 1.88]	0.477	0.284
Below median	19	18 (94.7)	5.3 [2.1; 8.0]	7	6 (85.7)	6.0 [1.0; -]	1.57 [0.62; 3.98]	0.346	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: all-participants-as-treated population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS≥10

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

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

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

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

CI: Confidence Interval; CPS: Combined Proportion Score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-151: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events Leading to Treatment Discontinuation	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	7	2 (28.6)	Not reached [2.6; -]	5	1 (20.0)	Not reached [24.0; -]	1.00 [0.09; 11.31]	> 0.999	0.591
Male	23	9 (39.1)	Not reached [18.0; -]	15	3 (20.0)	Not reached [19.9; -]	2.21 [0.60; 8.18]	0.235	
Age (Years)									
<65	17	6	n.c.	15	2	n.c.	n.c.	n.c.	n.c.

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events Leading to Treatment Discontinuation	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
		(35.3)			(13.3)				
≥65	13	5 (38.5)	n.c.	5	2 (40.0)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	17	9 (52.9)	30.4 [8.1; -]	6	1 (16.7)	Not reached [15.9; -]	3.77 [0.48; 29.82]	0.208	0.161
ECOG 1	13	2 (15.4)	Not reached [-; -]	14	3 (21.4)	Not reached [19.9; -]	0.57 [0.09; 3.46]	0.544	
Region									
EU	11	4 (36.4)	Not reached [3.0; -]	10	1 (10.0)	Not reached [15.9; -]	4.34 [0.48; 38.90]	0.190	0.344
Ex-EU	19	7 (36.8)	Not reached [20.0; -]	10	3 (30.0)	Not reached [19.9; -]	1.11 [0.29; 4.29]	0.883	
Region									
US/EU/Australia	20	6 (30.0)	n.c.	16	3 (18.8)	n.c.	n.c.	n.c.	n.c.
Asia	3	1 (33.3)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	4 (57.1)	n.c.	3	1 (33.3)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	28	10 (35.7)	n.c.	19	4 (21.1)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	1 (50.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	14	6 (42.9)	n.c.	9	2 (22.2)	n.c.	n.c.	n.c.	n.c.
Capecitabine	16	5 (31.3)	n.c.	11	2 (18.2)	n.c.	n.c.	n.c.	
Number of Metastasis									
≤2	15	5 (33.3)	n.c.	11	1 (9.1)	n.c.	n.c.	n.c.	n.c.
≥3	13	5 (38.5)	n.c.	9	3 (33.3)	n.c.	n.c.	n.c.	
Tumor Burden									
Above median	10	4 (40.0)	n.c.	11	2 (18.2)	n.c.	n.c.	n.c.	n.c.
Below median	19	6 (31.6)	n.c.	7	2 (28.6)	n.c.	n.c.	n.c.	
Prior Gastrectomy									
Yes	11	5 (45.5)	18.0 [3.0; -]	5	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.090	0.052
No	19	6 (31.6)	Not reached [22.6; -]	15	4 (26.7)	Not reached [19.9; -]	0.96 [0.27; 3.40]	0.943	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: all-participants-as-treated population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS≥10

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

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

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events Leading to Treatment Discontinuation	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)									
g: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
5-FU: 5-Fluorouracil; CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1									

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-152: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (PT) – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC: Gastrointestinal disorders, PT[h]: Upper gastrointestinal haemorrhage									
Gender									
Female	7	0 (0.0)	n.c.	5	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Male	23	0 (0.0)	n.c.	15	2 (13.3)	n.c.	n.c.	n.c.	
Age (Years)									
<65	17	0 (0.0)	n.c.	15	1 (6.7)	n.c.	n.c.	n.c.	n.c.
≥65	13	0 (0.0)	n.c.	5	1 (20.0)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	17	0 (0.0)	n.c.	6	1 (16.7)	n.c.	n.c.	n.c.	n.c.
ECOG 1	13	0 (0.0)	n.c.	14	1 (7.1)	n.c.	n.c.	n.c.	
Region									
EU	11	0 (0.0)	n.c.	10	1 (10.0)	n.c.	n.c.	n.c.	n.c.
Ex-EU	19	0 (0.0)	n.c.	10	1 (10.0)	n.c.	n.c.	n.c.	
Region									
US/EU/Australia	20	0 (0.0)	n.c.	16	2 (12.5)	n.c.	n.c.	n.c.	n.c.
Asia	3	0 (0.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	0 (0.0)	n.c.	3	0 (0.0)	n.c.	n.c.	n.c.	
Disease Status									

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Metastatic	28	0 (0.0)	n.c.	19	2 (10.5)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	0 (0.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	14	0 (0.0)	n.c.	9	1 (11.1)	n.c.	n.c.	n.c.	n.c.
Capecitabine	16	0 (0.0)	n.c.	11	1 (9.1)	n.c.	n.c.	n.c.	
Number of Metastasis									
≤2	15	0 (0.0)	n.c.	11	1 (9.1)	n.c.	n.c.	n.c.	n.c.
≥3	13	0 (0.0)	n.c.	9	1 (11.1)	n.c.	n.c.	n.c.	
Tumor Burden									
Above median	10	0 (0.0)	n.c.	11	1 (9.1)	n.c.	n.c.	n.c.	n.c.
Below median	19	0 (0.0)	n.c.	7	1 (14.3)	n.c.	n.c.	n.c.	
Prior Gastrectomy									
Yes	11	0 (0.0)	n.c.	5	0 (0.0)	n.c.	n.c.	n.c.	n.c.
No	19	0 (0.0)	n.c.	15	2 (13.3)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: all-participants-as-treated population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS≥10

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

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

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

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

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

5-FU: 5-Fluorouracil; CI: Confidence Interval; CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term; SOC: System Organ Class

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

Tabelle 4G-153: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5) (SOC) – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Pembrolizumab + Chemotherapy[b]**			**Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
SOC[h]: Investigations									
Gender									
Female	7	2 (28.6)	n.c.	5	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Male	23	7 (30.4)	n.c.	15	0 (0.0)	n.c.	n.c.	n.c.	
Age (Years)									
<65	17	6 (35.3)	n.c.	15	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥65	13	3 (23.1)	n.c.	5	0 (0.0)	n.c.	n.c.	n.c.	
Severity of disease									
ECOG 0	17	6 (35.3)	n.c.	6	0 (0.0)	n.c.	n.c.	n.c.	n.c.
ECOG 1	13	3 (23.1)	n.c.	14	0 (0.0)	n.c.	n.c.	n.c.	
Region									
EU	11	3 (27.3)	n.c.	10	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Ex-EU	19	6 (31.6)	n.c.	10	0 (0.0)	n.c.	n.c.	n.c.	
Region									
US/EU/Australia	20	7 (35.0)	n.c.	16	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Asia	3	0 (0.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Rest of World	7	2 (28.6)	n.c.	3	0 (0.0)	n.c.	n.c.	n.c.	
Disease Status									
Metastatic	28	9 (32.1)	n.c.	19	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Locally Advanced	2	0 (0.0)	n.c.	1	0 (0.0)	n.c.	n.c.	n.c.	
Backbone therapy									
5-FU	14	6 (42.9)	n.c.	9	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Capecitabine	16	3 (18.8)	n.c.	11	0 (0.0)	n.c.	n.c.	n.c.	
Number of Metastasis									
≤2	15	6 (40.0)	n.c.	11	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥3	13	3 (23.1)	n.c.	9	0 (0.0)	n.c.	n.c.	n.c.	
Tumor Burden									

Study: KEYNOTE 062[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]		
Severe Adverse Events (CTCAE-Grade 3-5)	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Above median	10	4 (40.0)	n.c.	11	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Below median	19	5 (26.3)	n.c.	7	0 (0.0)	n.c.	n.c.	n.c.	
Prior Gastrectomy									
Yes	11	4 (36.4)	n.c.	5	0 (0.0)	n.c.	n.c.	n.c.	n.c.
No	19	5 (26.3)	n.c.	15	0 (0.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 26MAR2019

b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine

c: Number of participants: all-participants-as-treated population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS≥10

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

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

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

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

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

5-FU: 5-Fluorouracil; CI: Confidence Interval; CPS: Combined Proportion Score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PD-L1: Programmed Cell Death - Ligand 1; SOC: System Organ Class

Anhang 4-G13: Definition und Inzidenzen der Immunvermittelten unerwünschten Ereignisse (AEOSI)

Anhang 4-G13.1: Ergebnisse für den Endpunkt Immunvermittelte unerwünschte Ereignisse (AEOSI) nach Kategorie und PT aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Schwerwiegende AEOSI

Tabelle 4G-154: Ergebnisse für den Endpunkt Schwerwiegende immunvermittelte unerwünschte Ereignisse (AEOSI) nach Kategorie und PT aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Patients with Event n(%)**	
Serious AEOSI by Category and PT[c]	**Pembrolizumab + Chemotherapy[b] N[d]=185**	**Chemotherapy[b] N[d]=193**
Patients with one or more adverse events	15 (8.1)	3 (1.6)
Adrenal Insufficiency	1 (0.5)	0 (0.0)
Adrenal insufficiency	1 (0.5)	0 (0.0)
Colitis	2 (1.1)	2 (1.0)
Autoimmune colitis	1 (0.5)	0 (0.0)
Colitis	0 (0.0)	1 (0.5)
Enterocolitis	1 (0.5)	1 (0.5)
Hepatitis	1 (0.5)	0 (0.0)
Autoimmune hepatitis	1 (0.5)	0 (0.0)
Hyperthyroidism	1 (0.5)	0 (0.0)
Hyperthyroidism	1 (0.5)	0 (0.0)
Hypophysitis	1 (0.5)	0 (0.0)
Hypophysitis	1 (0.5)	0 (0.0)
Infusion Reactions	1 (0.5)	0 (0.0)
Infusion related reaction	1 (0.5)	0 (0.0)
Pneumonitis	7 (3.8)	1 (0.5)
Interstitial lung disease	1 (0.5)	1 (0.5)
Pneumonitis	6 (3.2)	0 (0.0)
Severe Skin Reactions	2 (1.1)	0 (0.0)
Rash maculo-papular	2 (1.1)	0 (0.0)

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: A category or specific adverse event appears on this report only if its incidence is > 0% in one or more treatment groups
d: Number of participants: all-participants-as-treated population with PD-L1 CPS≥10
AEOSI: Adverse Events of Special Interest; CPS: Combined Proportion Score; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term

Schwere AEOSI (CTCAE-Grad 3-5)

Tabelle 4G-155: Ergebnisse für den Endpunkt Schwere immunvermittelte unerwünschte Ereignisse (AEOSI) nach Kategorie und PT aus RCT mit dem zu bewertenden Arzneimittel – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Patients with Event n(%)**	
Severe AEOSI (CTCAE-Grade 3-5) **by Category and PT[c]**	**Pembrolizumab + Chemotherapy[b]** **N[d]=185**	**Chemotherapy[b]** **N[d]=193**
Patients with one or more adverse events	15 (8.1)	4 (2.1)
Adrenal Insufficiency	2 (1.1)	0 (0.0)
Adrenal insufficiency	2 (1.1)	0 (0.0)
Colitis	1 (0.5)	3 (1.6)
Autoimmune colitis	1 (0.5)	0 (0.0)
Colitis	0 (0.0)	2 (1.0)
Enterocolitis	0 (0.0)	1 (0.5)
Hepatitis	2 (1.1)	0 (0.0)
Autoimmune hepatitis	1 (0.5)	0 (0.0)
Hepatitis	1 (0.5)	0 (0.0)
Hypophysitis	1 (0.5)	0 (0.0)
Hypophysitis	1 (0.5)	0 (0.0)
Infusion Reactions	1 (0.5)	0 (0.0)
Infusion related reaction	1 (0.5)	0 (0.0)
Myositis	1 (0.5)	0 (0.0)
Myopathy	1 (0.5)	0 (0.0)
Pneumonitis	5 (2.7)	1 (0.5)
Interstitial lung disease	1 (0.5)	1 (0.5)
Pneumonitis	4 (2.2)	0 (0.0)
Severe Skin Reactions	4 (2.2)	0 (0.0)
Pruritus	1 (0.5)	0 (0.0)
Rash maculo-papular	4 (2.2)	0 (0.0)
Type 1 Diabetes Mellitus	1 (0.5)	0 (0.0)
Type 1 diabetes mellitus	1 (0.5)	0 (0.0)

a: Database Cutoff Date: 02JUL2020

b: Chemotherapy: Cisplatin and 5-Fluorouracil

c: A category or specific adverse event appears on this report only if its incidence is > 0% in one or more treatment groups

d: Number of participants: all-participants-as-treated population with PD-L1 CPS≥10

AEOSI: Adverse Events of Special Interest; CPS: Combined Proportion Score; CTCAE: Common Terminology Criteria for Adverse Events; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term

Anhang 4-G13.2: Ergebnisse für den Endpunkt Immunvermittelte unerwünschte Ereignisse (AEOSI) nach Kategorie und PT aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Schwerwiegende AEOSI

Tabelle 4G-156: Ergebnisse für den Endpunkt Schwerwiegende immunvermittelte unerwünschte Ereignisse (AEOSI) nach Kategorie und PT aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Patients with Event n(%)**	
Serious AEOSI by Category and PT[c]	**Pembrolizumab + Chemotherapy[b] N[d]=143**	**Chemotherapy[b] N[d]=140**
Patients with one or more adverse events	12 (8.4)	2 (1.4)
Adrenal Insufficiency	1 (0.7)	0 (0.0)
Adrenal insufficiency	1 (0.7)	0 (0.0)
Colitis	2 (1.4)	1 (0.7)
Autoimmune colitis	1 (0.7)	0 (0.0)
Enterocolitis	1 (0.7)	1 (0.7)
Hepatitis	1 (0.7)	0 (0.0)
Autoimmune hepatitis	1 (0.7)	0 (0.0)
Hyperthyroidism	1 (0.7)	0 (0.0)
Hyperthyroidism	1 (0.7)	0 (0.0)
Infusion Reactions	1 (0.7)	0 (0.0)
Infusion related reaction	1 (0.7)	0 (0.0)
Pneumonitis	5 (3.5)	1 (0.7)
Interstitial lung disease	1 (0.7)	1 (0.7)
Pneumonitis	4 (2.8)	0 (0.0)
Severe Skin Reactions	2 (1.4)	0 (0.0)
Rash maculo-papular	2 (1.4)	0 (0.0)

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: A category or specific adverse event appears on this report only if its incidence is > 0% in one or more treatment groups
d: Number of participants: all-participants-as-treated population with squamous cell carcinoma and PD-L1 CPS≥10
AEOSI: Adverse Events of Special Interest; CPS: Combined Proportion Score; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term

Schwere AEOSI (CTCAE-Grad 3-5)

Tabelle 4G-157: Ergebnisse für den Endpunkt Schwere immunvermittelte unerwünschte Ereignisse (AEOSI) nach Kategorie und PT aus RCT mit dem zu bewertenden Arzneimittel – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Patients with Event n(%)**	
Severe AEOSI (CTCAE-Grade 3-5) **by Category and PT[c]**	**Pembrolizumab + Chemotherapy[b]** **N[d]=143**	**Chemotherapy[b]** **N[d]=140**
Patients with one or more adverse events	12 (8.4)	3 (2.1)
Adrenal Insufficiency	2 (1.4)	0 (0.0)
Adrenal insufficiency	2 (1.4)	0 (0.0)
Colitis	1 (0.7)	2 (1.4)
Autoimmune colitis	1 (0.7)	0 (0.0)
Colitis	0 (0.0)	1 (0.7)
Enterocolitis	0 (0.0)	1 (0.7)
Hepatitis	1 (0.7)	0 (0.0)
Autoimmune hepatitis	1 (0.7)	0 (0.0)
Infusion Reactions	1 (0.7)	0 (0.0)
Infusion related reaction	1 (0.7)	0 (0.0)
Myositis	1 (0.7)	0 (0.0)
Myopathy	1 (0.7)	0 (0.0)
Pneumonitis	3 (2.1)	1 (0.7)
Interstitial lung disease	1 (0.7)	1 (0.7)
Pneumonitis	2 (1.4)	0 (0.0)
Severe Skin Reactions	4 (2.8)	0 (0.0)
Pruritus	1 (0.7)	0 (0.0)
Rash maculo-papular	4 (2.8)	0 (0.0)
Type 1 Diabetes Mellitus	1 (0.7)	0 (0.0)
Type 1 diabetes mellitus	1 (0.7)	0 (0.0)

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: A category or specific adverse event appears on this report only if its incidence is > 0% in one or more treatment groups
d: Number of participants: all-participants-as-treated population with squamous cell carcinoma and PD-L1 CPS≥10
AEOSI: Adverse Events of Special Interest; CPS: Combined Proportion Score; CTCAE: Common Terminology Criteria for Adverse Events; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term

Anhang 4-G13.3: Ergebnisse für den Endpunkt Immunvermittelte unerwünschte Ereignisse (AEOSI) nach Kategorie und PT aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Schwerwiegende AEOSI

Tabelle 4G-158: Ergebnisse für den Endpunkt Schwerwiegende immunvermittelte unerwünschte Ereignisse (AEOSI) nach Kategorie und PT aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Patients with Event n(%)**	
Serious AEOSI by Category and PT[c]	**Pembrolizumab + Chemotherapy[b] N[d]=42**	**Chemotherapy[b] N[d]=53**
Patients with one or more adverse events	3 (7.1)	1 (1.9)
Colitis	0 (0.0)	1 (1.9)
Colitis	0 (0.0)	1 (1.9)
Hypophysitis	1 (2.4)	0 (0.0)
Hypophysitis	1 (2.4)	0 (0.0)
Pneumonitis	2 (4.8)	0 (0.0)
Pneumonitis	2 (4.8)	0 (0.0)

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: A category or specific adverse event appears on this report only if its incidence is > 0% in one or more treatment groups
d: Number of participants: all-participants-as-treated population with adenocarcinoma and PD-L1 CPS≥10
AEOSI: Adverse Events of Special Interest; CPS: Combined Proportion Score; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term

Schwere AEOSI (CTCAE-Grad 3-5)

Tabelle 4G-159: Ergebnisse für den Endpunkt Schwere immunvermittelte unerwünschte Ereignisse (AEOSI) nach Kategorie und PT aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	**Patients with Event n(%)**	
Severe AEOSI (CTCAE-Grade 3-5) by Category and PT[c]	**Pembrolizumab + Chemotherapy[b] N[d]=42**	**Chemotherapy[b] N[d]=53**
Patients with one or more adverse events	3 (7.1)	1 (1.9)
Colitis	0 (0.0)	1 (1.9)
Colitis	0 (0.0)	1 (1.9)
Hepatitis	1 (2.4)	0 (0.0)
Hepatitis	1 (2.4)	0 (0.0)
Hypophysitis	1 (2.4)	0 (0.0)
Hypophysitis	1 (2.4)	0 (0.0)
Pneumonitis	2 (4.8)	0 (0.0)
Pneumonitis	2 (4.8)	0 (0.0)

a: Database Cutoff Date: 02JUL2020
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: A category or specific adverse event appears on this report only if its incidence is > 0% in one or more treatment groups
d: Number of participants: all-participants-as-treated population with adenocarcinoma and PD-L1 CPS≥10
AEOSI: Adverse Events of Special Interest; CPS: Combined Proportion Score; CTCAE: Common Terminology Criteria for Adverse Events; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term

Anhang 4-G13.4: Ergebnisse für den Endpunkt Immunvermittelte unerwünschte Ereignisse (AEOSI) nach Kategorie und PT aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Schwerwiegende AEOSI

Tabelle 4G-160: Ergebnisse für den Endpunkt Schwerwiegende immunvermittelte unerwünschte Ereignisse (AEOSI) nach Kategorie und PT aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Patients with Event n(%)**	
Serious AEOSI by Category and PT[c]	**Pembrolizumab + Chemotherapy[b] N[d]=30**	**Chemotherapy[b] N[d]=20**
Patients with one or more adverse events	2 (6.7)	1 (5.0)
Colitis	1 (3.3)	0 (0.0)
Colitis	1 (3.3)	0 (0.0)
Nephritis	1 (3.3)	0 (0.0)
Autoimmune nephritis	1 (3.3)	0 (0.0)
Pancreatitis	0 (0.0)	1 (5.0)
Pancreatitis	0 (0.0)	1 (5.0)

a: Database Cutoff Date: 26MAR2019
b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine
c: A category or specific adverse event appears on this report only if its incidence is > 0% in one or more treatment groups
d: Number of participants: all-participants-as-treated population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS≥10
AEOSI: Adverse Events of Special Interest; CPS: Combined Proportion Score; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term

Schwere AEOSI (CTCAE-Grad 3-5)

Tabelle 4G-161: Ergebnisse für den Endpunkt Schwere immunvermittelte unerwünschte Ereignisse (AEOSI) nach Kategorie und PT aus RCT mit dem zu bewertenden Arzneimittel – Adenokarzinom GEJ CPS ≥ 10 (KEYNOTE 062)

Study: KEYNOTE 062[a]	**Patients with Event n(%)**	
Severe AEOSI (CTCAE-Grade 3-5) by Category and PT[c]	**Pembrolizumab + Chemotherapy[b] N[d]=30**	**Chemotherapy[b] N[d]=20**
Patients with one or more adverse events	2 (6.7)	1 (5.0)
Nephritis	1 (3.3)	0 (0.0)
Autoimmune nephritis	1 (3.3)	0 (0.0)
Pancreatitis	0 (0.0)	1 (5.0)
Pancreatitis	0 (0.0)	1 (5.0)
Severe Skin Reactions	1 (3.3)	0 (0.0)
Rash	1 (3.3)	0 (0.0)

a: Database Cutoff Date: 26MAR2019
b: Chemotherapy: Cisplatin and 5-Fluorouracil or Cisplatin and Capecitabine
c: A category or specific adverse event appears on this report only if its incidence is > 0% in one or more treatment groups
d: Number of participants: all-participants-as-treated population with adenocarcinoma of the gastroesophageal junction and PD-L1 CPS≥10
AEOSI: Adverse Events of Special Interest; CPS: Combined Proportion Score; CTCAE: Common Terminology Criteria for Adverse Events; PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term

Anhang 4-G13.5: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI)

Tabelle 4G-162: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) Version 18.0 basierend auf MedDRA Version 23.0 anhand der zugeordneten PT in der Studie KEYNOTE 590

AEOSI	MedDRA Preferred Terms	Immune-Mediated
Pneumonitis	Acute interstitial pneumonitis, Autoimmune lung disease, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organising pneumonia, Immune-mediated pneumonitis	Yes
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive, Autoimmune colitis, Immune-mediated enterocolitis	Yes
Hepatitis	Hepatitis, Immune-mediated hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitis fulminant, Drug-induced liver injury	Yes
Nephritis	Nephritis, Autoimmune nephritis, Chronic autoimmune glomerulonephritis, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Mesangioproliferative glomerulonephritis, Nephritis haemorrhagic, Tubulointerstitial nephritis, Nephrotic syndrome, Immune-mediated nephritis	Yes
Adrenal Insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency, Primary adrenal insufficiency, Addison's disease	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis	Yes

Hyperthyroidism	Hyperthyroidism, Basedow's disease, Thyrotoxic crisis, Immune-mediated hyperthyroidism	Yes
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism, 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	Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis, Vogt-Koyanagi-Harada disease, Chorioretinitis, Choroiditis, Immune-mediated uveitis	Yes
Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Immune-mediated pancreatitis	Yes
Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated myositis, Rhabdomyolysis, Myopathy, Dermatomyositis, Autoimmune myositis	Yes

Guillain-Barre Syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome, Subacute inflammatory demyelinating polyneuropathy	Yes
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis	Yes
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis, Immune-mediated encephalitis	Yes
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis	Yes
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction, Infusion related hypersensitivity reaction	No
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia	Yes
Myelitis	Myelitis, Myelitis transverse	Yes

Tabelle 4G-163: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) Version 15.0 basierend auf MedDRA Version 21.1 anhand der zugeordneten PT in der Studie KEYNOTE 062

AEOSI	**MedDRA Preferred Terms**	**Immune-Mediated**
Pneumonitis	Acute interstitial pneumonitis, Autoimmune lung disease, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organising pneumonia	Yes
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive, Autoimmune colitis	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	Yes
Adrenal Insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis	Yes
Hyperthyroidism	Hyperthyroidism, Basedow’s disease, Thyrotoxic crisis	Yes
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism	Yes

Thyroiditis	Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute, Silent thyroiditis, Autoimmune thyroid disorder	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	Yes
Severe Skin (continued): If grade 3 or higher	Rash, Rash erythematous, Rash generalised, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus generalised, Pruritus genital	Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis, Vogt-Koyanagi-Harada syndrome	Yes
Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising	Yes
Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated necrotising myopathy, Rhabdomyolysis, Myopathy, Dermatomyositis	Yes
Guillain-Barre Syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome, Subacute inflammatory demyelinating polyneuropathy	Yes
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis	Yes
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective 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	No
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia	Yes

Anhang 4-G14: Ergebnisse für den (post-hoc) Datenschnitt 09. Juli 2021 – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3 die Ergebnisse des (post-hoc) Datenschnitts (09. Juli 2021) dargestellt. Der Datenschnitt wurde lediglich für eine Präsentation im Rahmen eines wissenschaftliches Kongresses durchgeführt. Für diesen Datenschnitt liegt kein Studienbericht vor. Es werden die Ergebnisse zu Mortalität und Nebenwirkungen dargestellt.

Anhang 4-G14.1: Mortalität (09. Juli 2021)

Gesamtüberleben (09. Juli 2021) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Tabelle 4G-164: Ergebnisse für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel (09. Juli 2021) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]	
	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]
Overall Survival	186	148 (79.6)	13.6 [11.1; 15.2]	197	178 (90.4)	9.4 [8.0; 10.7]	0.64 [0.51; 0.80]	< 0.001

a: Database Cutoff Date: 09JUL2021
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: intention-to-treat population with PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma)
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
CI: Confidence Interval; CPS: Combined Positive Score; PD-L1: Programmed Cell Death - Ligand 1

Die Überlebensrate zu Monat 30 beträgt 25,5 % im Interventionsarm und 12,2 % im Kontrollarm. Die Überlebensrate zu Monat 36 beträgt 20,8 % im Interventionsarm und 9,4 % im Kontrollarm.

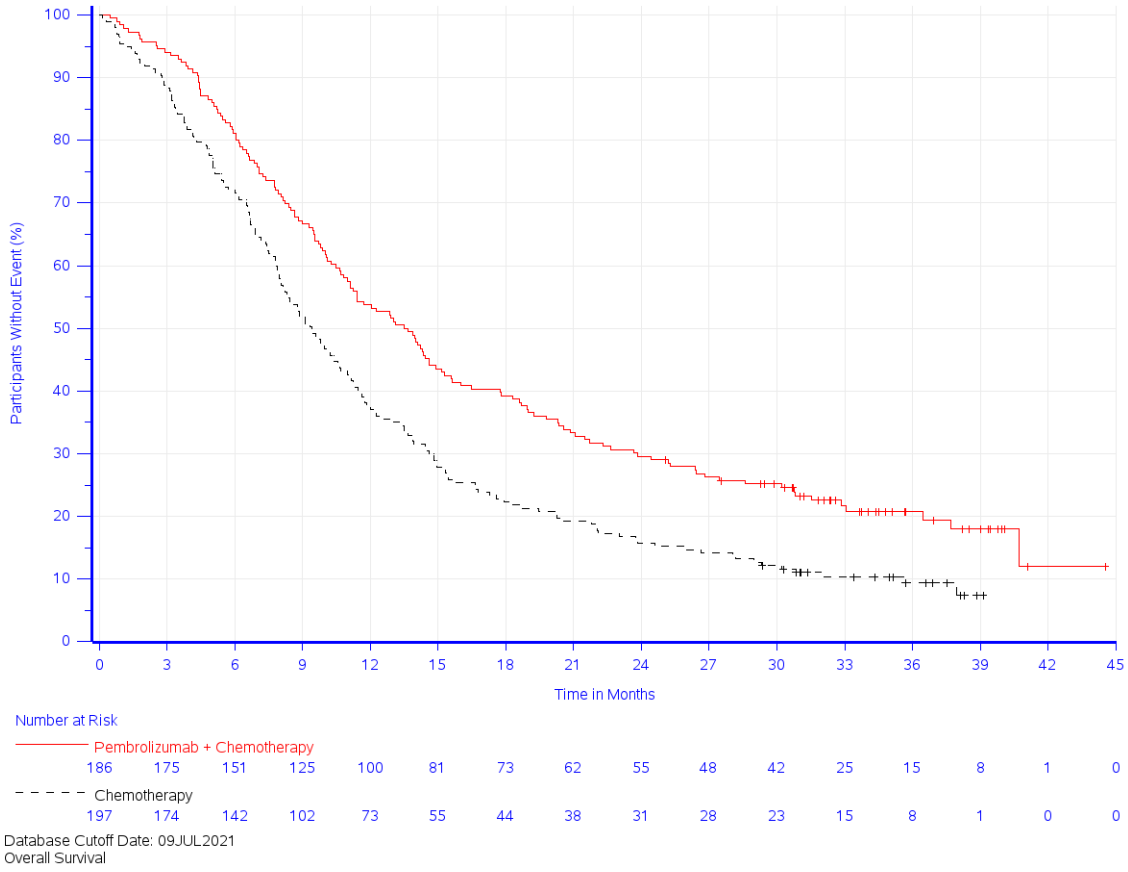

Abbildung 4G-42: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Gesamtüberleben (09. Juli 2021) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G14.2: Nebenwirkungen (09. Juli 2021)

Unerwünschte Ereignisse gesamt (09. Juli 2021) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Tabelle 4G-165: Ergebnisse für den Endpunkt Unerwünschte Ereignisse Gesamtraten aus RCT mit dem zu bewertenden Arzneimittel (09. Juli 2021) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]	
	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]
Adverse Events	185	185 (100.0)	0.4 [0.3; 0.4]	193	192 (99.5)	0.4 [0.4; 0.6]	1.27 [1.03; 1.55]	0.024
Serious Adverse Events	185	107 (57.8)	27.1 [16.3; 45.9]	193	109 (56.5)	28.0 [19.1; 46.4]	0.97 [0.74; 1.27]	0.818
Severe Adverse Events (CTCAE-Grade 3-5)	185	163 (88.1)	4.4 [3.1; 6.3]	193	163 (84.5)	6.1 [3.9; 8.7]	1.05 [0.84; 1.31]	0.658
Adverse Events Leading to Treatment Discontinuation	185	48 (25.9)	Not reached [-; -]	193	40 (20.7)	Not reached [71.3; -]	1.20 [0.79; 1.83]	0.393

a: Database Cutoff Date: 09JUL2021
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: all-participants-as-treated population with PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
CI: Confidence Interval; CPS: Combined Positive Score; CTCAE: Common Terminology Criteria for Adverse Events; PD-L1: Programmed Cell Death - Ligand 1

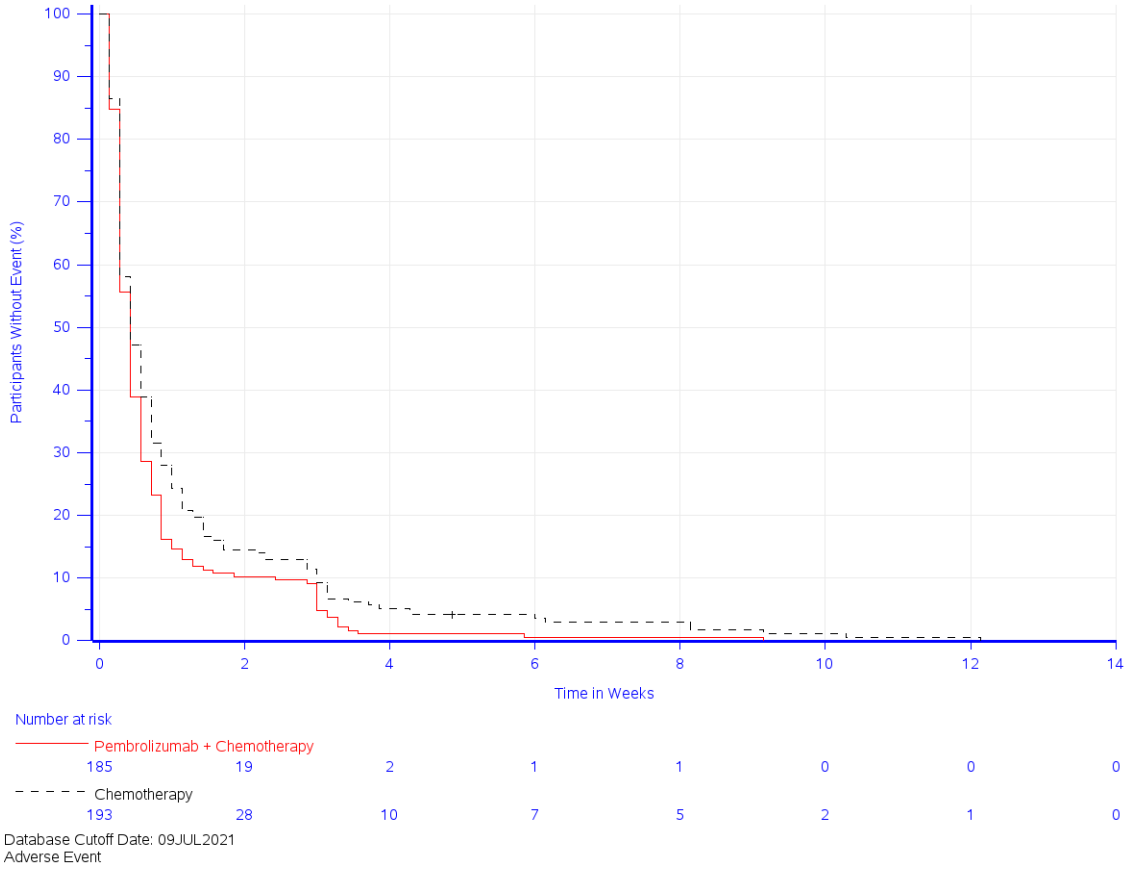

Abbildung 4G-43: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Unerwünschte Ereignisse gesamt (09. Juli 2021) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

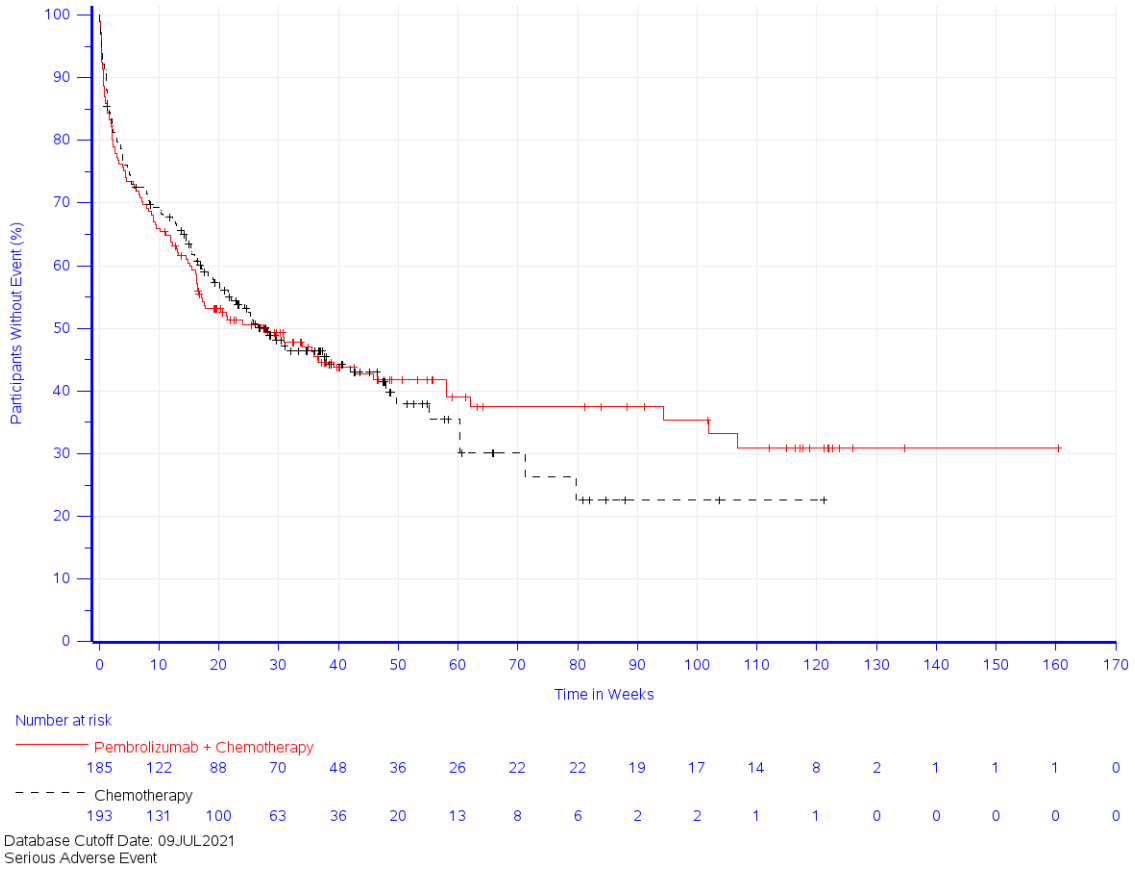

Abbildung 4G-44: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwerwiegende unerwünschte Ereignisse (09. Juli 2021) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

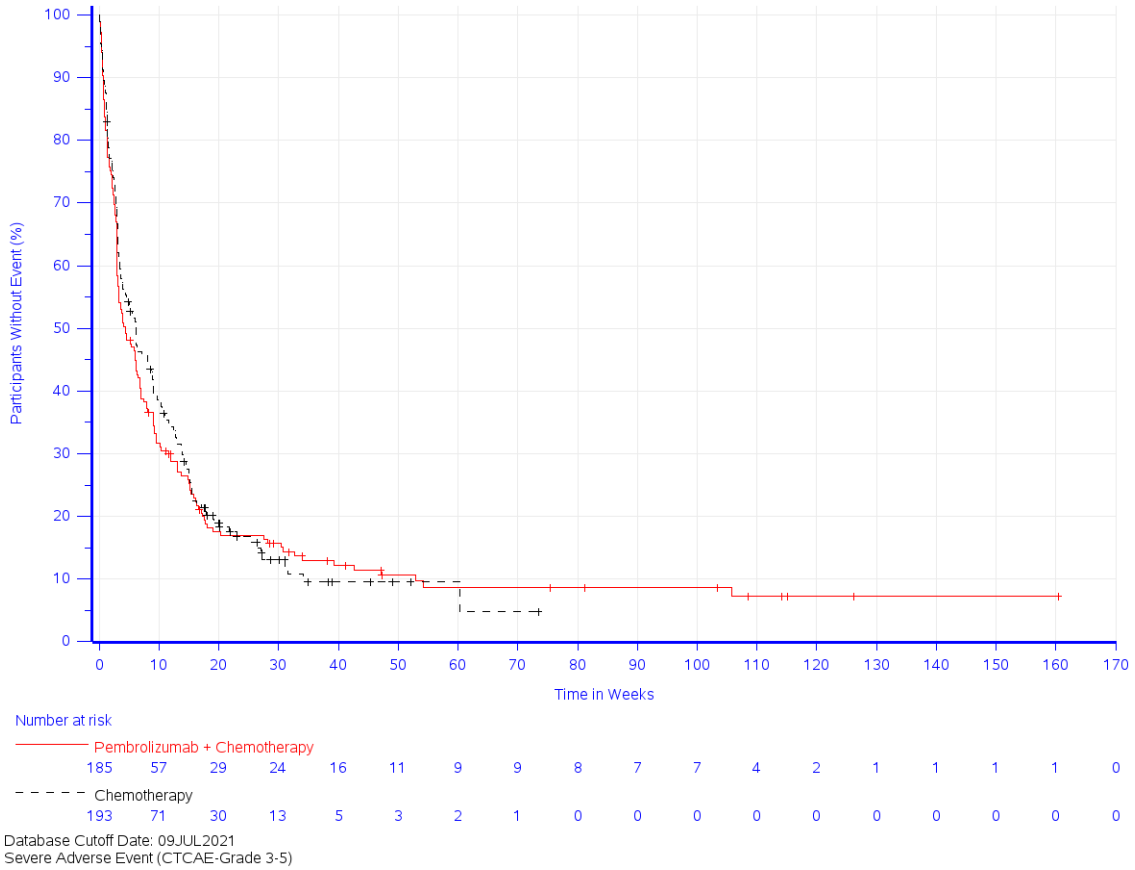

Abbildung 4G-45: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (09. Juli 2021) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

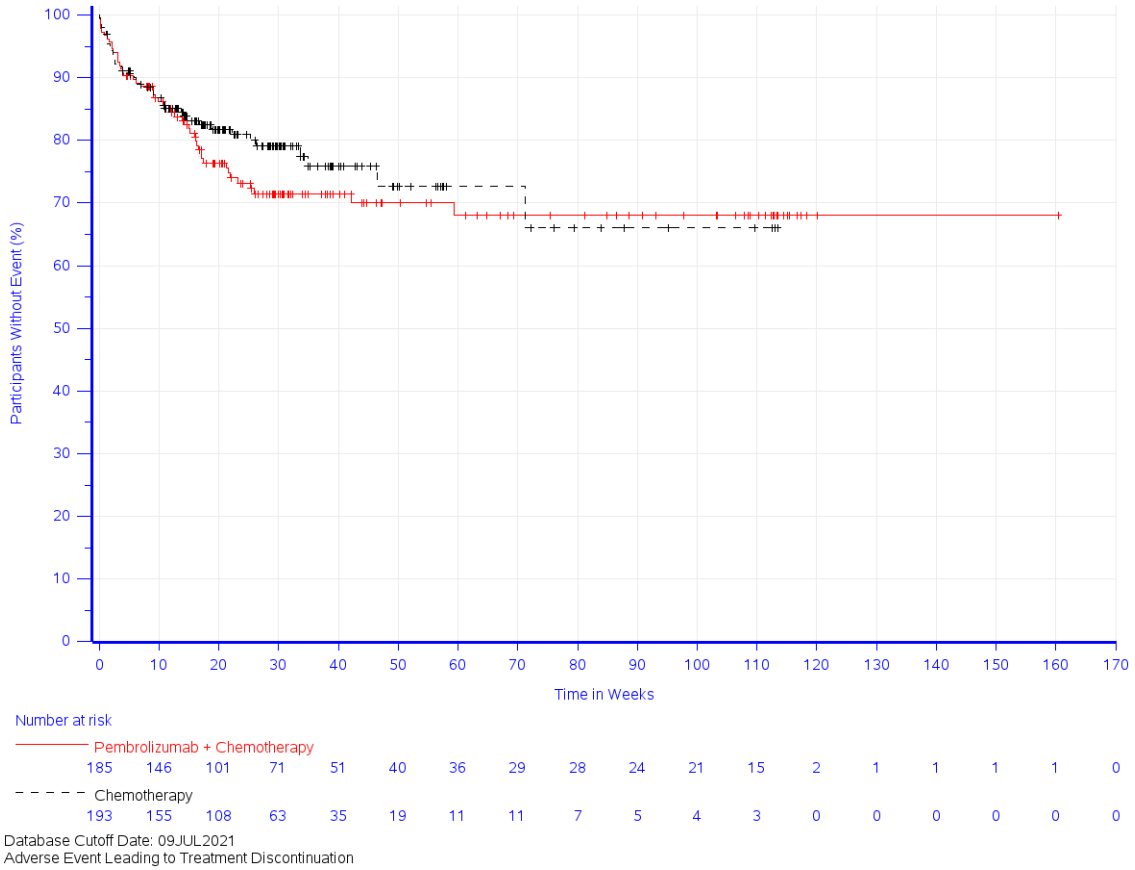

Abbildung 4G-46: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse (09. Juli 2021) – Gesamtpopulation CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G15: Ergebnisse für den (post-hoc) Datenschnitt 09. Juli 2021 – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3 die Ergebnisse des (post-hoc) Datenschnitts (09. Juli 2021) dargestellt. Der Datenschnitt wurde lediglich für eine Präsentation im Rahmen eines wissenschaftliches Kongresses durchgeführt. Für diesen Datenschnitt liegt kein Studienbericht vor. Es werden aussschließlich die Ergebnisse zu Mortalität und Nebenwirkungen präsentiert.

Anhang 4-G15.1: Mortalität (09. Juli 2021)

Gesamtüberleben (09. Juli 2021) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Tabelle 4G-166: Ergebnisse für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel (09. Juli 2021) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]	
	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]
Overall Survival	143	111 (77.6)	13.9 [11.1; 16.0]	143	129 (90.2)	8.8 [7.8; 10.5]	0.59 [0.45; 0.76]	< 0.001

a: Database Cutoff Date: 09JUL2021
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: intention-to-treat population with squamous cell carcinoma and PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1)
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
CI: Confidence Interval; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Die Überlebensrate zu Monat 30 beträgt 25,8 % im Interventionsarm und 12,6 % im Kontrollarm. Die Überlebensrate zu Monat 36 beträgt 22,5 % im Interventionsarm und 9,8 % im Kontrollarm.

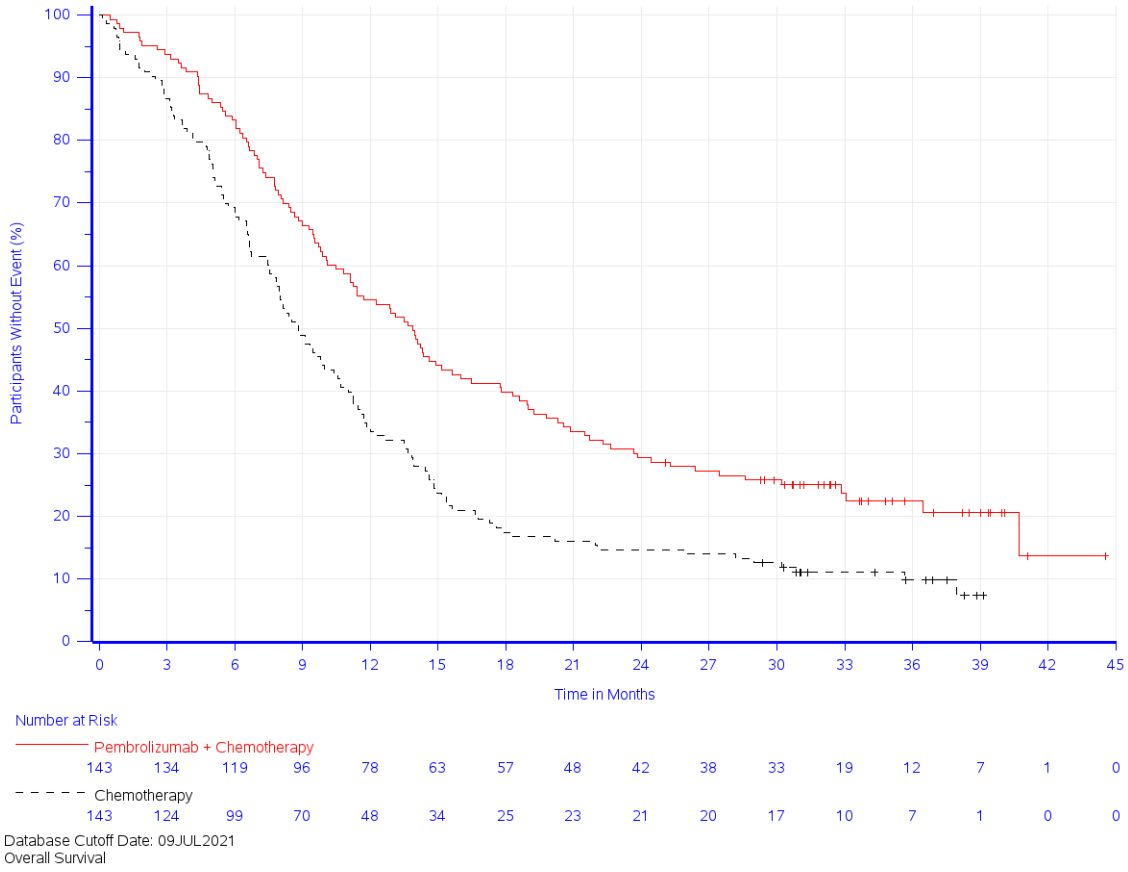

Abbildung 4G-47: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Gesamtüberleben (09. Juli 2021) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G15.1: Nebenwirkungen (09. Juli 2021)

Unerwünschte Ereignisse gesamt (09. Juli 2021) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Tabelle 4G-167: Ergebnisse für den Endpunkt Unerwünschte Ereignisse Gesamtraten aus RCT mit dem zu bewertenden Arzneimittel (09. Juli 2021) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]	
	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]
Adverse Events	143	143 (100.0)	0.4 [0.3; 0.4]	140	140 (100.0)	0.4 [0.4; 0.6]	1.25 [0.99; 1.59]	0.059
Serious Adverse Events	143	79 (55.2)	35.6 [16.4; 62.1]	140	79 (56.4)	25.7 [16.7; 48.0]	0.87 [0.64; 1.20]	0.396
Severe Adverse Events (CTCAE-Grade 3-5)	143	126 (88.1)	4.4 [3.1; 6.3]	140	119 (85.0)	5.0 [3.3; 8.9]	1.01 [0.78; 1.30]	0.952
Adverse Events Leading to Treatment Discontinuation	143	38 (26.6)	Not reached [-; -]	140	37 (26.4)	Not reached [46.4; -]	0.93 [0.59; 1.47]	0.759

a: Database Cutoff Date: 09JUL2021
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: all-participants-as-treated population with squamous cell carcinoma and PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
CI: Confidence Interval; CPS: Combined Positive Score; CTCAE: Common Terminology Criteria for Adverse Events; PD-L1: Programmed Cell Death - Ligand 1

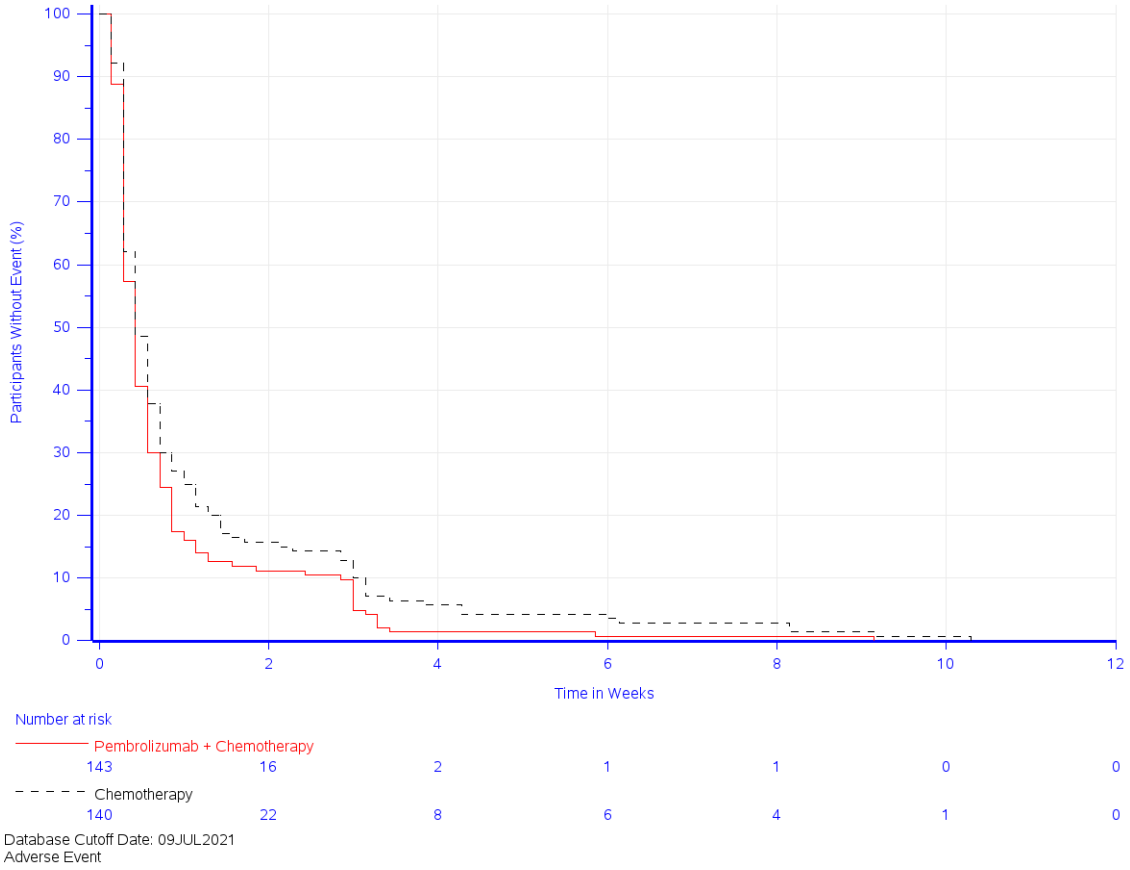

Abbildung 4G-48: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Unerwünschte Ereignisse gesamt (09. Juli 2021) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

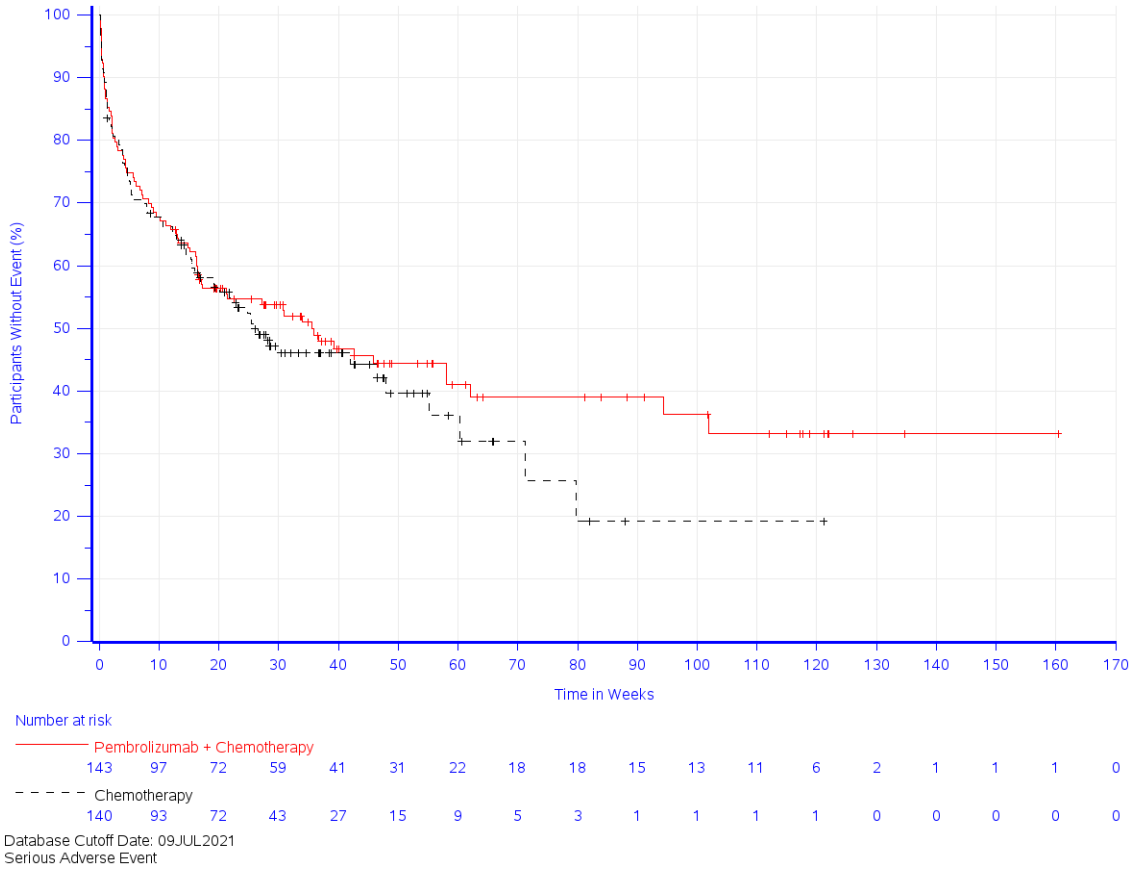

Abbildung 4G-49: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwerwiegende unerwünschte Ereignisse (09. Juli 2021) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

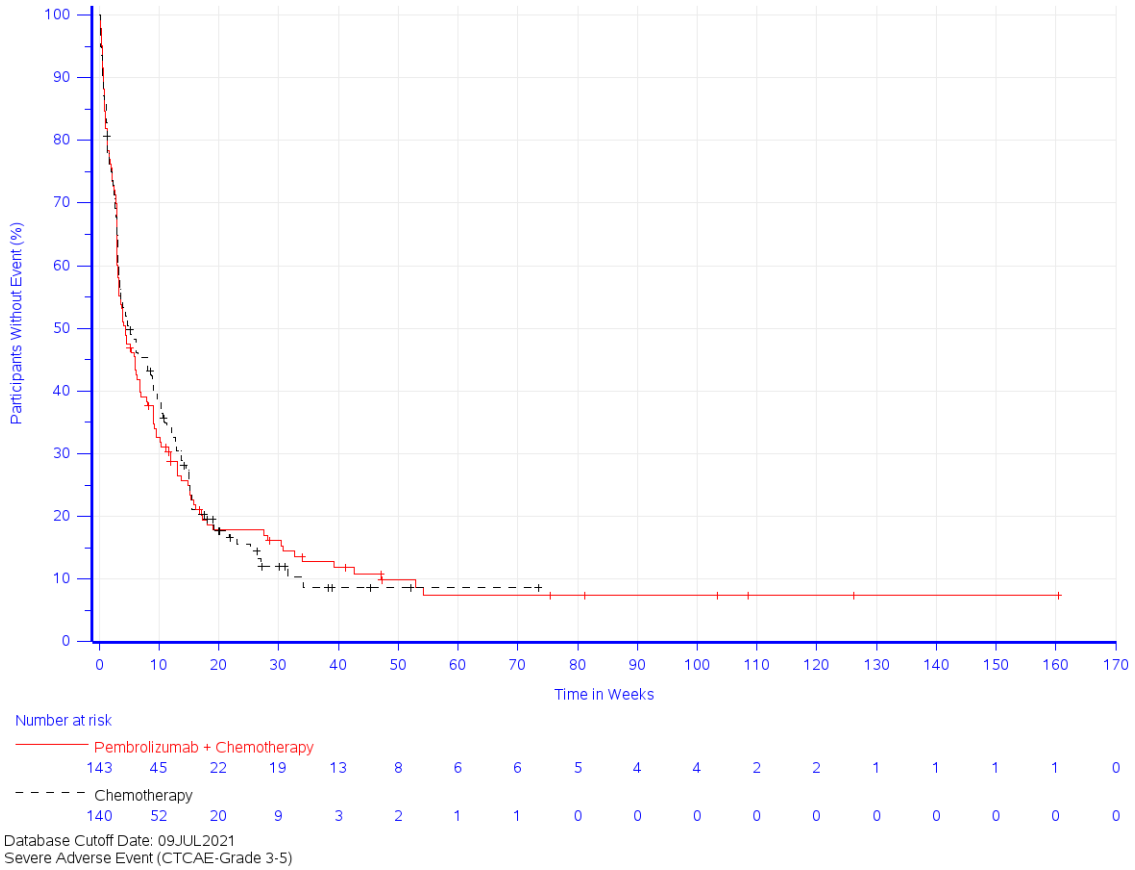

Abbildung 4G-50: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (09. Juli 2021) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

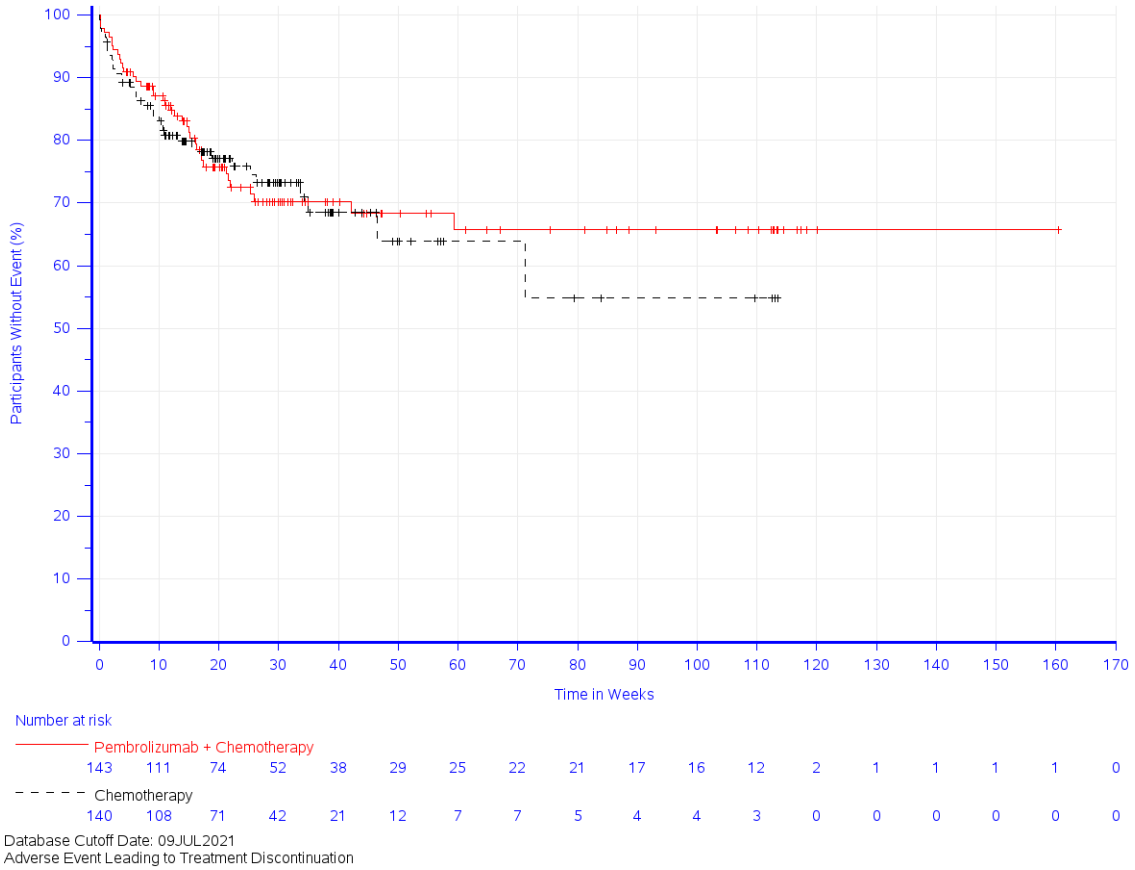

Abbildung 4G-51: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse (09. Juli 2021) – Plattenepithelkarzinom CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G16: Ergebnisse für den (post-hoc) Datenschnitt 09. Juli 2021 – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3 die Ergebnisse des (post-hoc) Datenschnitts (09. Juli 2021) dargestellt. Der Datenschnitt wurde lediglich für eine Präsentation im Rahmen eines wissenschaftliches Kongresses durchgeführt. Für diesen Datenschnitt liegt kein Studienbericht vor. Es werden aussschließlich die Ergebnisse zu Mortalität und Nebenwirkungen präsentiert.

Anhang 4-G16.1: Mortalität (09. Juli 2021)

Gesamtüberleben (09. Juli 2021) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Tabelle 4G-168: Ergebnisse für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel (09. Juli 2021) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]	
	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]
Overall Survival	43	37 (86.0)	12.1 [9.6; 18.7]	54	49 (90.7)	10.7 [8.2; 15.3]	0.82 [0.53; 1.28]	0.391

a: Database Cutoff Date: 09JUL2021
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: intention-to-treat population with adenocarcinoma and PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1)
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
CI: Confidence Interval; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Die Überlebensrate zu Monat 30 beträgt 23,3 % im Interventionsarm und 11,1 % im Kontrollarm. Die Überlebensrate zu Monat 36 beträgt 15,5 % im Interventionsarm und 9,3 % im Kontrollarm.

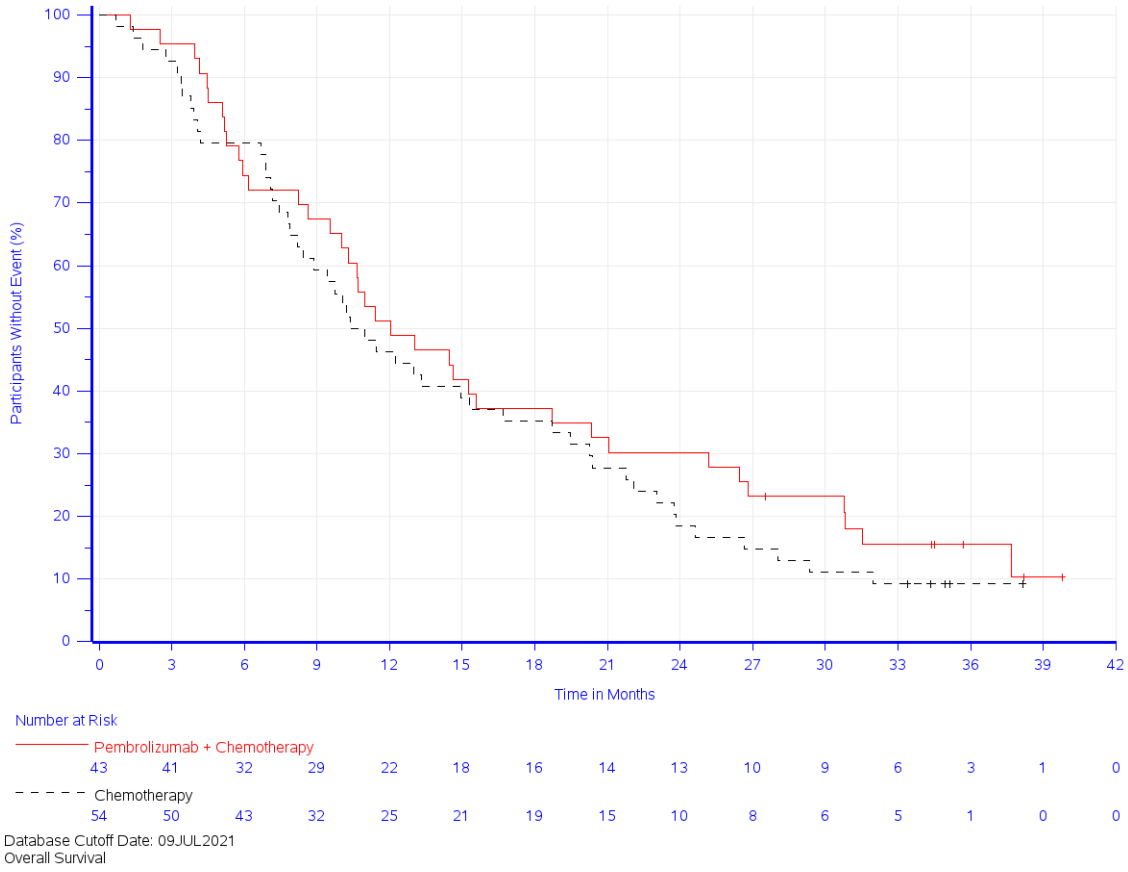

Abbildung 4G-52: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Gesamtüberleben (09. Juli 2021) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Anhang 4-G16.1: Nebenwirkungen (09. Juli 2021)

Unerwünschte Ereignisse gesamt (09. Juli 2021) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Tabelle 4G-169: Ergebnisse für den Endpunkt Unerwünschte Ereignisse Gesamtraten aus RCT mit dem zu bewertenden Arzneimittel (09. Juli 2021) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

Study: KEYNOTE 590[a]	Pembrolizumab + Chemotherapy[b]			Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Chemotherapy[b]	
	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]
Adverse Events	42	42 (100.0)	0.4 [0.3; 0.4]	53	52 (98.1)	0.3 [0.3; 0.7]	1.33 [0.88; 2.02]	0.174
Serious Adverse Events	42	28 (66.7)	15.6 [8.0; 27.9]	53	30 (56.6)	31.1 [17.1; 60.3]	1.34 [0.80; 2.26]	0.266
Severe Adverse Events (CTCAE-Grade 3-5)	42	37 (88.1)	4.7 [2.4; 7.4]	53	44 (83.0)	6.3 [3.9; 11.6]	1.14 [0.73; 1.77]	0.567
Adverse Events Leading to Treatment Discontinuation	42	10 (23.8)	Not reached [-; -]	53	3 (5.7)	Not reached [-; -]	4.35 [1.20; 15.82]	0.025

a: Database Cutoff Date: 09JUL2021
b: Chemotherapy: Cisplatin and 5-Fluorouracil
c: Number of participants: all-participants-as-treated population with adenocarcinoma and PD-L1 CPS≥10
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
CI: Confidence Interval; CPS: Combined Positive Score; CTCAE: Common Terminology Criteria for Adverse Events; PD-L1: Programmed Cell Death - Ligand 1

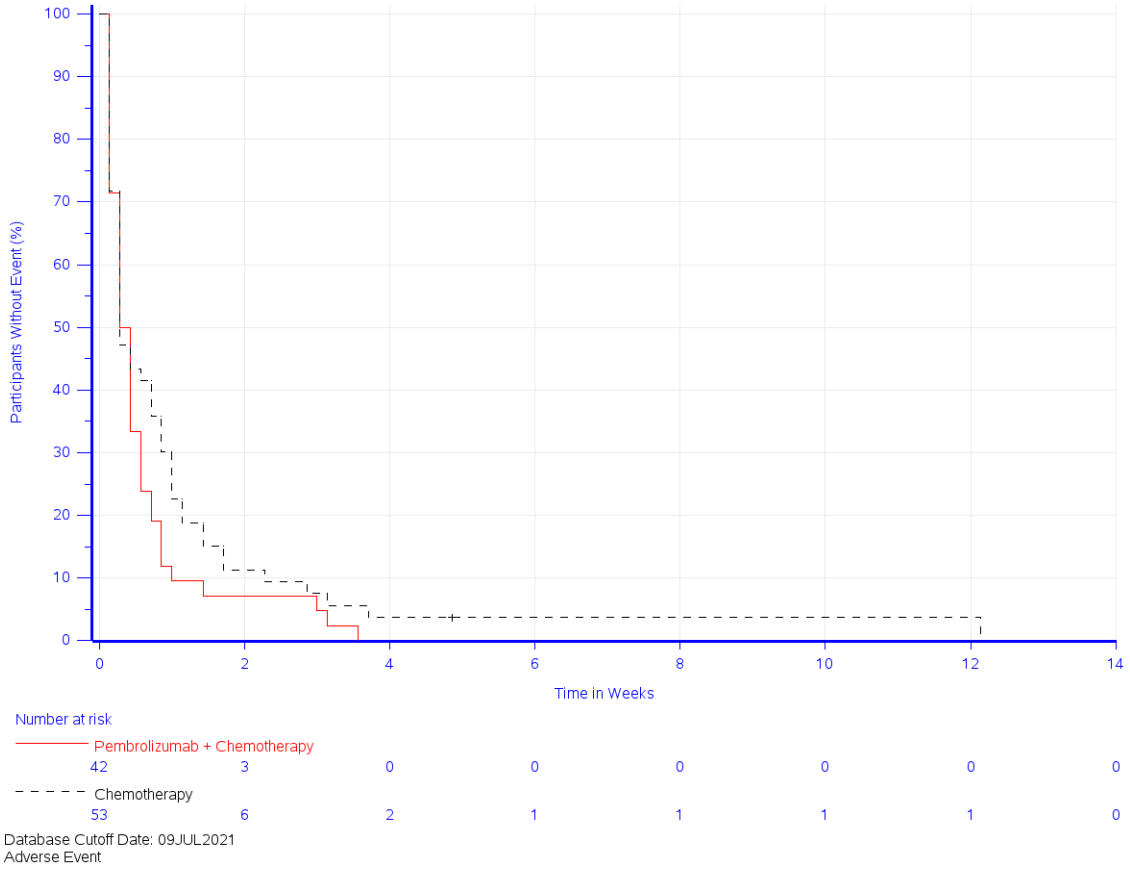

Abbildung 4G-53: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Unerwünschte Ereignisse gesamt (09. Juli 2021) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

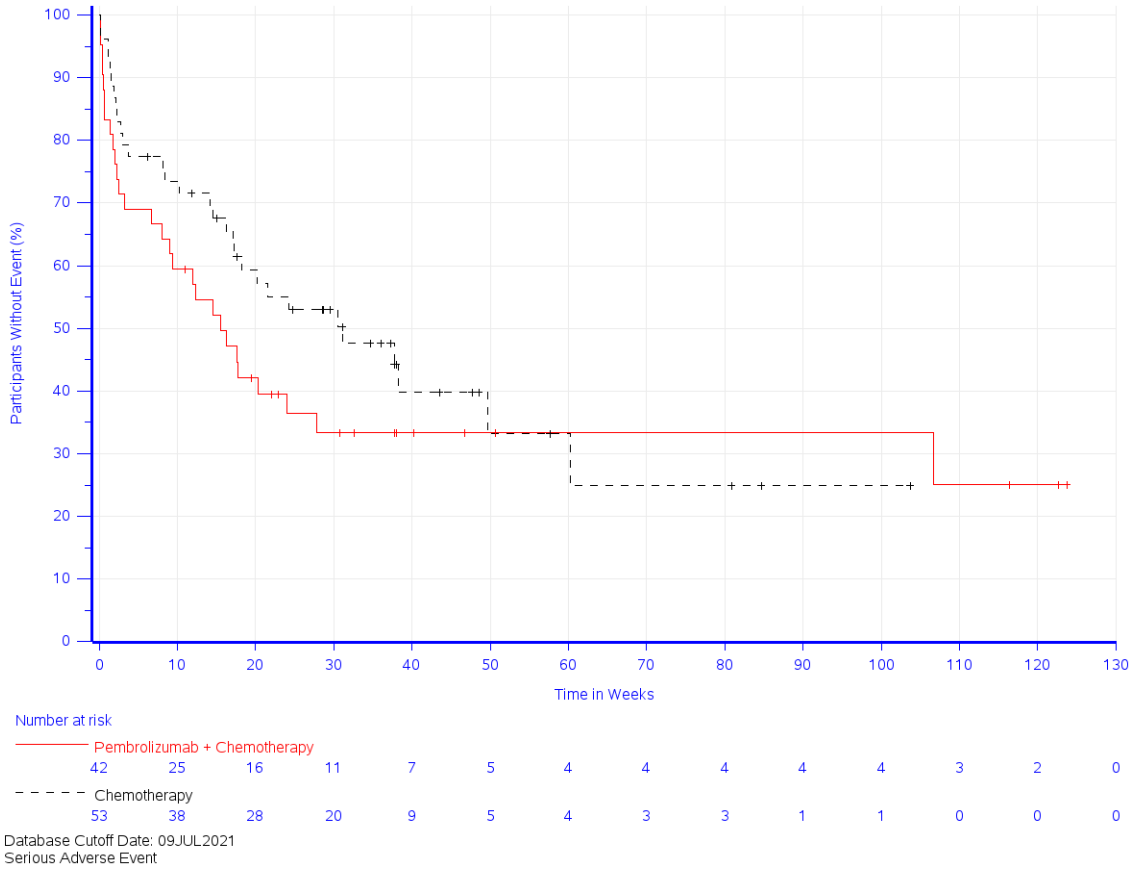

Abbildung 4G-54: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwerwiegende unerwünschte Ereignisse (09. Juli 2021) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

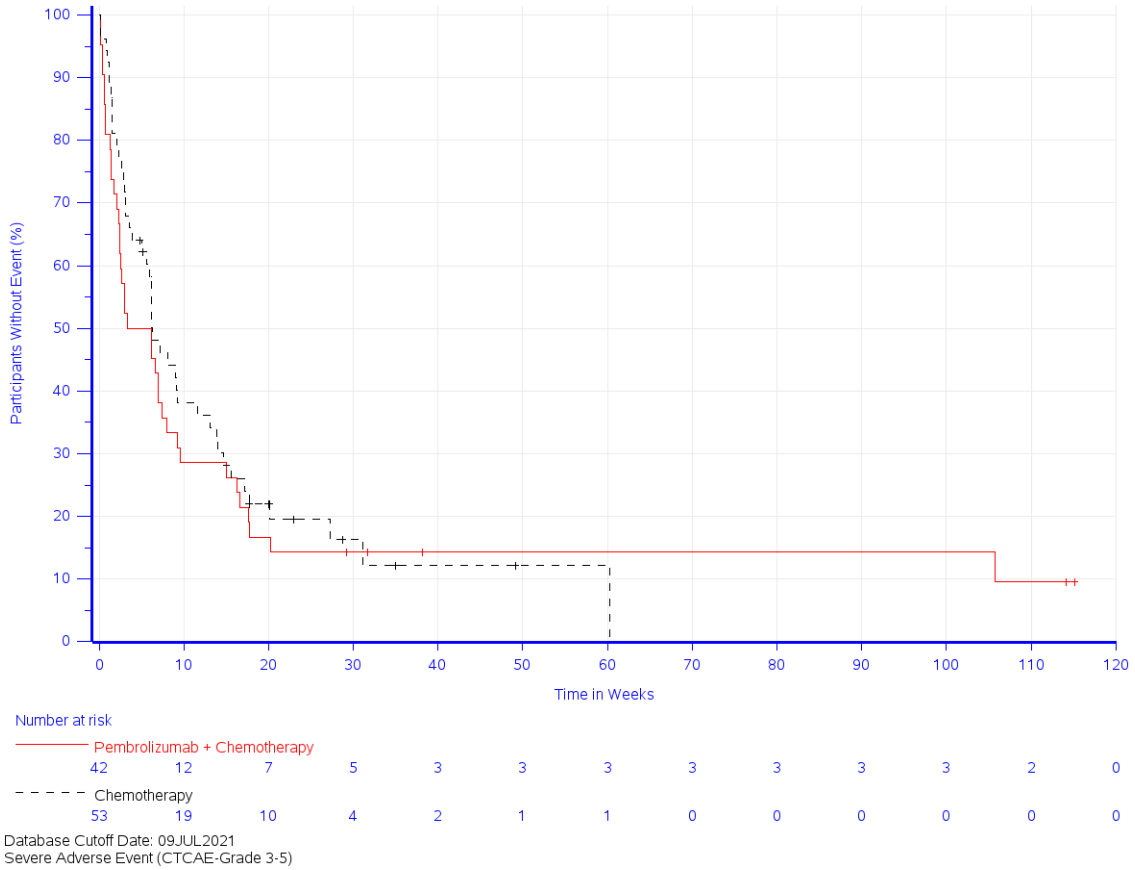

Abbildung 4G-55: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (09. Juli 2021) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)

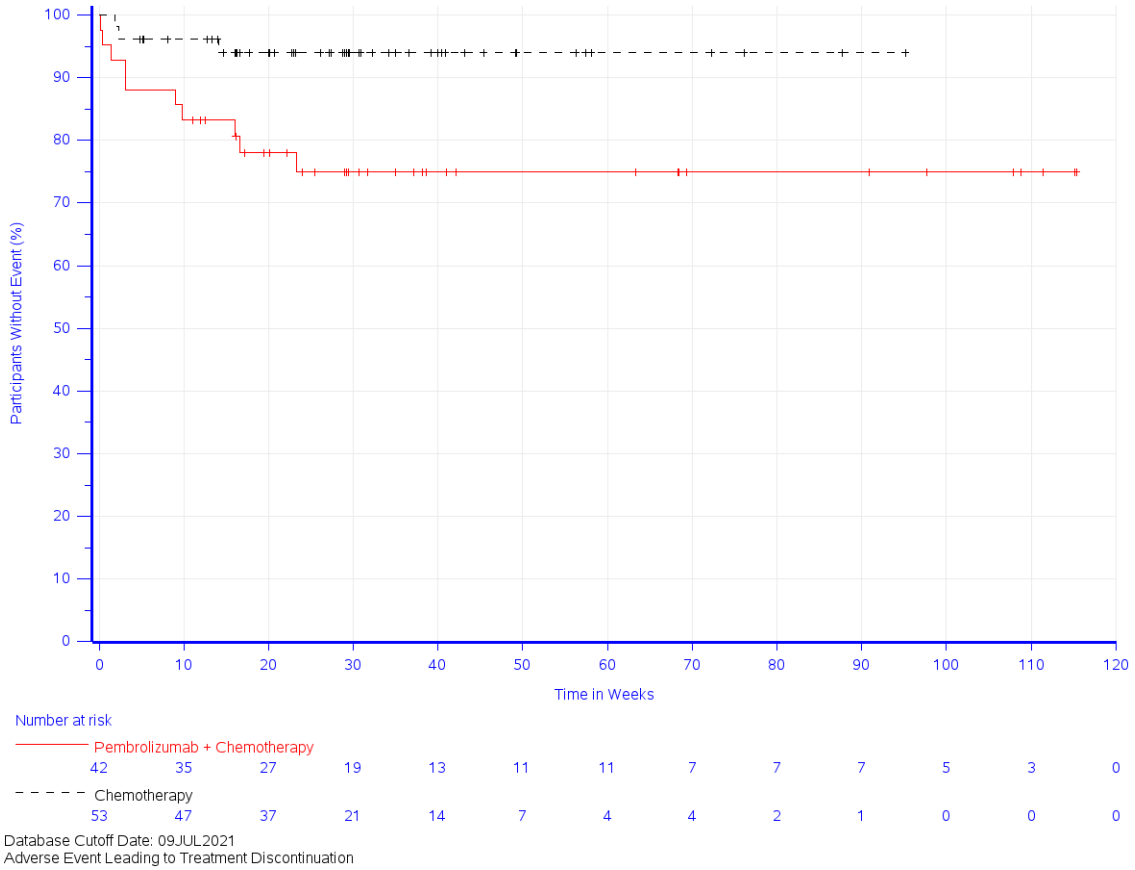

Abbildung 4G-56: Zeit bis zum ersten Eintreten eines Ereignisses: Kaplan-Meier-Kurve für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse (09. Juli 2021) – Adenokarzinom CPS ≥ 10 (KEYNOTE 590)