Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD Sharp & Dohme GmbH

Modul 4 B

Anhang 4-G: Weitere Ergebnisse

Erstlinienbehandlung des metastasierenden Kolorektalkarzinoms mit MSI-H oder dMMR bei Erwachsenen

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Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.1.1., bzw. Abschnitt 4.3.1.3.1.2.1 die Rücklaufquoten des EORTC QLQ-C30, EORTC QLQ-CR29 und die Rücklaufquoten des EQ-5D VAS dargestellt.

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 19. Februar 2020 der KEYNOTE 177.

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

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

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 152 n (%)	N[c] = 141 n (%)
Week 0	Missing by Design[d]	0 (0.0)	0 (0.0)
	Discontinued due to adverse event	0 (0.0)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	0 (0.0)
	Discontinued due to complete response	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	0 (0.0)	0 (0.0)
	No visit scheduled	0 (0.0)	0 (0.0)
	Expected to Complete Questionnaires	152 (100.0)	141 (100.0)
	Not completed	11 (7.2)	10 (7.1)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	2 (1.3)	5 (3.5)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	2 (1.3)	0 (0.0)
	Other	4 (2.6)	3 (2.1)
	With visit, no record	3 (2.0)	2 (1.4)
	Completed	141 (92.8)	131 (92.9)
	Compliance (completed per protocol)[e]	141 (92.8)	131 (92.9)
Week 2/3	Missing by Design[d]	8 (5.3)	5 (3.5)
	Discontinued due to adverse event	0 (0.0)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	0 (0.0)
	Discontinued due to complete response	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	4 (2.6)	0 (0.0)
	No visit scheduled	4 (2.6)	5 (3.5)
	Expected to Complete Questionnaires	144 (94.7)	136 (96.5)
	Not completed	12 (7.9)	11 (7.8)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	7 (4.6)	4 (2.8)
	Subject in hospital or hospice	2 (1.3)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 152 n (%)	N[c] = 141 n (%)
	Subject refused for other reasons	1 (0.7)	2 (1.4)
	Other	1 (0.7)	4 (2.8)
	With visit, no record	1 (0.7)	1 (0.7)
	Completed	132 (86.8)	125 (88.7)
	Compliance (completed per protocol)[e]	132 (91.7)	125 (91.9)
Week 6	Missing by Design[d]	16 (10.5)	14 (9.9)
	Discontinued due to adverse event	2 (1.3)	0 (0.0)
	Discontinued due to clinical progression	4 (2.6)	0 (0.0)
	Discontinued due to complete response	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to progressive disease	5 (3.3)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	1 (0.7)
	Subject died	1 (0.7)	1 (0.7)
	No visit scheduled	4 (2.6)	12 (8.5)
	Expected to Complete Questionnaires	136 (89.5)	127 (90.1)
	Not completed	10 (6.6)	25 (17.7)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.7)
	Not completed due to site staff error	5 (3.3)	3 (2.1)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.7)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	3 (2.1)
	Other	4 (2.6)	5 (3.5)
	With visit, no record	1 (0.7)	12 (8.5)
	Completed	126 (82.9)	102 (72.3)
	Compliance (completed per protocol)[e]	126 (92.6)	102 (80.3)
Week 9	Missing by Design[d]	24 (15.8)	23 (16.3)
	Discontinued due to adverse event	4 (2.6)	4 (2.8)
	Discontinued due to clinical progression	5 (3.3)	1 (0.7)
	Discontinued due to complete response	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.7)
	Discontinued due to progressive disease	6 (3.9)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (0.7)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	1 (0.7)
	Subject died	1 (0.7)	1 (0.7)
	No visit scheduled	8 (5.3)	14 (9.9)
	Expected to Complete Questionnaires	128 (84.2)	118 (83.7)
	Not completed	9 (5.9)	60 (42.6)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	5 (3.3)	14 (9.9)
	Subject in hospital or hospice	0 (0.0)	2 (1.4)
	Subject was physically unable to complete	2 (1.3)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	5 (3.5)
	Other	1 (0.7)	11 (7.8)
	With visit, no record	1 (0.7)	28 (19.9)
	Completed	119 (78.3)	58 (41.1)
	Compliance (completed per protocol)[e]	119 (93.0)	58 (49.2)
Week 12	Missing by Design[d]	28 (18.4)	22 (15.6)
	Discontinued due to adverse event	3 (2.0)	3 (2.1)
	Discontinued due to clinical progression	5 (3.3)	2 (1.4)
	Discontinued due to complete response	1 (0.7)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.7)

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 152 n (%)	N[c] = 141 n (%)
	Discontinued due to progressive disease	14 (9.2)	4 (2.8)
	Discontinued due to withdrawal by subject	0 (0.0)	2 (1.4)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	3 (2.0)	0 (0.0)
	No visit scheduled	2 (1.3)	10 (7.1)
	Expected to Complete Questionnaires	124 (81.6)	119 (84.4)
	Not completed	10 (6.6)	31 (22.0)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	7 (4.6)	12 (8.5)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.7)
	Subject refused for other reasons	2 (1.3)	3 (2.1)
	Other	0 (0.0)	9 (6.4)
	With visit, no record	1 (0.7)	6 (4.3)
	Completed	114 (75.0)	88 (62.4)
	Compliance (completed per protocol)[e]	114 (91.9)	88 (73.9)
Week 18	Missing by Design[d]	36 (23.7)	34 (24.1)
	Discontinued due to adverse event	5 (3.3)	5 (3.5)
	Discontinued due to clinical progression	5 (3.3)	2 (1.4)
	Discontinued due to complete response	0 (0.0)	1 (0.7)
	Discontinued due to physician decision	0 (0.0)	4 (2.8)
	Discontinued due to progressive disease	20 (13.2)	15 (10.6)
	Discontinued due to withdrawal by subject	0 (0.0)	3 (2.1)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	1 (0.7)	2 (1.4)
	No visit scheduled	5 (3.3)	2 (1.4)
	Expected to Complete Questionnaires	116 (76.3)	107 (75.9)
	Not completed	14 (9.2)	25 (17.7)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	7 (4.6)	13 (9.2)
	Subject in hospital or hospice	1 (0.7)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	2 (1.3)	2 (1.4)
	Other	1 (0.7)	2 (1.4)
	With visit, no record	3 (2.0)	8 (5.7)
	Completed	102 (67.1)	82 (58.2)
	Compliance (completed per protocol)[e]	102 (87.9)	82 (76.6)
Week 27	Missing by Design[d]	46 (30.3)	60 (42.6)
	Discontinued due to adverse event	7 (4.6)	7 (5.0)
	Discontinued due to clinical progression	7 (4.6)	3 (2.1)
	Discontinued due to complete response	0 (0.0)	1 (0.7)
	Discontinued due to physician decision	0 (0.0)	5 (3.5)
	Discontinued due to progressive disease	28 (18.4)	33 (23.4)
	Discontinued due to withdrawal by subject	0 (0.0)	6 (4.3)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	0 (0.0)	1 (0.7)
	No visit scheduled	4 (2.6)	4 (2.8)
	Expected to Complete Questionnaires	106 (69.7)	81 (57.4)
	Not completed	27 (17.8)	43 (30.5)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	12 (7.9)	10 (7.1)

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 152 n (%)	N[c] = 141 n (%)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	1 (0.7)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.7)
	Subject refused for other reasons	1 (0.7)	5 (3.5)
	Other	2 (1.3)	8 (5.7)
	With visit, no record	11 (7.2)	19 (13.5)
	Completed	79 (52.0)	38 (27.0)
	Compliance (completed per protocol)[e]	79 (74.5)	38 (46.9)
Week 36	Missing by Design[d]	52 (34.2)	75 (53.2)
	Discontinued due to adverse event	8 (5.3)	10 (7.1)
	Discontinued due to clinical progression	7 (4.6)	3 (2.1)
	Discontinued due to complete response	2 (1.3)	1 (0.7)
	Discontinued due to physician decision	0 (0.0)	6 (4.3)
	Discontinued due to progressive disease	34 (22.4)	47 (33.3)
	Discontinued due to withdrawal by subject	0 (0.0)	8 (5.7)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	0 (0.0)	0 (0.0)
	No visit scheduled	1 (0.7)	0 (0.0)
	Expected to Complete Questionnaires	100 (65.8)	66 (46.8)
	Not completed	20 (13.2)	31 (22.0)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.7)
	Not completed due to site staff error	9 (5.9)	10 (7.1)
	Subject in hospital or hospice	1 (0.7)	1 (0.7)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	6 (4.3)
	Other	3 (2.0)	6 (4.3)
	With visit, no record	7 (4.6)	7 (5.0)
	Completed	80 (52.6)	35 (24.8)
	Compliance (completed per protocol)[e]	80 (80.0)	35 (53.0)
Week 45	Missing by Design[d]	66 (43.4)	91 (64.5)
	Discontinued due to adverse event	12 (7.9)	11 (7.8)
	Discontinued due to clinical progression	7 (4.6)	4 (2.8)
	Discontinued due to complete response	3 (2.0)	2 (1.4)
	Discontinued due to physician decision	2 (1.3)	7 (5.0)
	Discontinued due to progressive disease	39 (25.7)	58 (41.1)
	Discontinued due to withdrawal by subject	0 (0.0)	7 (5.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	0 (0.0)	0 (0.0)
	No visit scheduled	3 (2.0)	2 (1.4)
	Expected to Complete Questionnaires	86 (56.6)	50 (35.5)
	Not completed	14 (9.2)	22 (15.6)
	Subject did not complete due to disease under study	1 (0.7)	1 (0.7)
	Not completed due to site staff error	4 (2.6)	10 (7.1)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	1 (0.7)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.7)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	2 (1.3)	4 (2.8)
	Other	3 (2.0)	3 (2.1)
	With visit, no record	3 (2.0)	3 (2.1)
	Completed	72 (47.4)	28 (19.9)
	Compliance (completed per protocol)[e]	72 (83.7)	28 (56.0)
a: Database Cutoff Date: 19FEB2020			

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EORTC QLQ-C30	N[c] = 152 n (%)	N[c] = 141 n (%)

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab
c: Number of patients: full-analysis-set population
d: Missing by design includes: death, discontinuation, translations not available, and no visit scheduled
e: Compliance is the proportion of subjects who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Anhang 4-G1.2: Rücklaufquoten des EORTC QLQ-CR29

Tabelle 4G-2: Gründe für das Fehlen von Werten im EORTC QLQ-CR29

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EORTC QLQ-CR29	N[c] = 152 n (%)	N[c] = 141 n (%)
Week 0	Missing by Design[d]	0 (0.0)	0 (0.0)
	Discontinued due to adverse event	0 (0.0)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	0 (0.0)
	Discontinued due to complete response	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	0 (0.0)	0 (0.0)
	No visit scheduled	0 (0.0)	0 (0.0)
	Expected to Complete Questionnaires	152 (100.0)	141 (100.0)
	Not completed	13 (8.6)	9 (6.4)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	3 (2.0)	5 (3.5)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	3 (2.0)	0 (0.0)
	Other	4 (2.6)	2 (1.4)
	With visit, no record	3 (2.0)	2 (1.4)
	Completed	139 (91.4)	132 (93.6)
	Compliance (completed per protocol)[e]	139 (91.4)	132 (93.6)
Week 2/3	Missing by Design[d]	8 (5.3)	5 (3.5)
	Discontinued due to adverse event	0 (0.0)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	0 (0.0)
	Discontinued due to complete response	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	4 (2.6)	0 (0.0)
	No visit scheduled	4 (2.6)	5 (3.5)
	Expected to Complete Questionnaires	144 (94.7)	136 (96.5)
	Not completed	13 (8.6)	11 (7.8)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	8 (5.3)	4 (2.8)
	Subject in hospital or hospice	2 (1.3)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EORTC QLQ-CR29	N[c] = 152 n (%)	N[c] = 141 n (%)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	1 (0.7)	2 (1.4)
	Other	1 (0.7)	4 (2.8)
	With visit, no record	1 (0.7)	1 (0.7)
	Completed	131 (86.2)	125 (88.7)
	Compliance (completed per protocol)[e]	131 (91.0)	125 (91.9)
Week 6	Missing by Design[d]	16 (10.5)	14 (9.9)
	Discontinued due to adverse event	2 (1.3)	0 (0.0)
	Discontinued due to clinical progression	4 (2.6)	0 (0.0)
	Discontinued due to complete response	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to progressive disease	5 (3.3)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	1 (0.7)
	Subject died	1 (0.7)	1 (0.7)
	No visit scheduled	4 (2.6)	12 (8.5)
	Expected to Complete Questionnaires	136 (89.5)	127 (90.1)
	Not completed	11 (7.2)	27 (19.1)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.7)
	Not completed due to site staff error	5 (3.3)	3 (2.1)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.7)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	4 (2.8)
	Other	5 (3.3)	6 (4.3)
	With visit, no record	1 (0.7)	12 (8.5)
	Completed	125 (82.2)	100 (70.9)
	Compliance (completed per protocol)[e]	125 (91.9)	100 (78.7)
Week 9	Missing by Design[d]	24 (15.8)	23 (16.3)
	Discontinued due to adverse event	4 (2.6)	4 (2.8)
	Discontinued due to clinical progression	5 (3.3)	1 (0.7)
	Discontinued due to complete response	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.7)
	Discontinued due to progressive disease	6 (3.9)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (0.7)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	1 (0.7)
	Subject died	1 (0.7)	1 (0.7)
	No visit scheduled	8 (5.3)	14 (9.9)
	Expected to Complete Questionnaires	128 (84.2)	118 (83.7)
	Not completed	9 (5.9)	60 (42.6)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	5 (3.3)	15 (10.6)
	Subject in hospital or hospice	0 (0.0)	2 (1.4)
	Subject was physically unable to complete	2 (1.3)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	5 (3.5)
	Other	1 (0.7)	10 (7.1)
	With visit, no record	1 (0.7)	28 (19.9)

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EORTC QLQ-CR29	N[c] = 152 n (%)	N[c] = 141 n (%)
	Completed	119 (78.3)	58 (41.1)
	Compliance (completed per protocol)[e]	119 (93.0)	58 (49.2)
Week 12	Missing by Design[d]	28 (18.4)	22 (15.6)
	Discontinued due to adverse event	3 (2.0)	3 (2.1)
	Discontinued due to clinical progression	5 (3.3)	2 (1.4)
	Discontinued due to complete response	1 (0.7)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.7)
	Discontinued due to progressive disease	14 (9.2)	4 (2.8)
	Discontinued due to withdrawal by subject	0 (0.0)	2 (1.4)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	3 (2.0)	0 (0.0)
	No visit scheduled	2 (1.3)	10 (7.1)
	Expected to Complete Questionnaires	124 (81.6)	119 (84.4)
	Not completed	11 (7.2)	31 (22.0)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	7 (4.6)	12 (8.5)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.7)
	Subject refused for other reasons	3 (2.0)	3 (2.1)
	Other	0 (0.0)	9 (6.4)
	With visit, no record	1 (0.7)	6 (4.3)
	Completed	113 (74.3)	88 (62.4)
	Compliance (completed per protocol)[e]	113 (91.1)	88 (73.9)
Week 18	Missing by Design[d]	36 (23.7)	34 (24.1)
	Discontinued due to adverse event	5 (3.3)	5 (3.5)
	Discontinued due to clinical progression	5 (3.3)	2 (1.4)
	Discontinued due to complete response	0 (0.0)	1 (0.7)
	Discontinued due to physician decision	0 (0.0)	4 (2.8)
	Discontinued due to progressive disease	20 (13.2)	15 (10.6)
	Discontinued due to withdrawal by subject	0 (0.0)	3 (2.1)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	1 (0.7)	2 (1.4)
	No visit scheduled	5 (3.3)	2 (1.4)
	Expected to Complete Questionnaires	116 (76.3)	107 (75.9)
	Not completed	14 (9.2)	25 (17.7)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	7 (4.6)	14 (9.9)
	Subject in hospital or hospice	1 (0.7)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	2 (1.3)	2 (1.4)
	Other	1 (0.7)	1 (0.7)
	With visit, no record	3 (2.0)	8 (5.7)
	Completed	102 (67.1)	82 (58.2)
	Compliance (completed per protocol)[e]	102 (87.9)	82 (76.6)
Week 27	Missing by Design[d]	46 (30.3)	60 (42.6)
	Discontinued due to adverse event	7 (4.6)	7 (5.0)
	Discontinued due to clinical progression	7 (4.6)	3 (2.1)

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EORTC QLQ-CR29	N[c] = 152 n (%)	N[c] = 141 n (%)
	Discontinued due to complete response	0 (0.0)	1 (0.7)
	Discontinued due to physician decision	0 (0.0)	5 (3.5)
	Discontinued due to progressive disease	28 (18.4)	33 (23.4)
	Discontinued due to withdrawal by subject	0 (0.0)	6 (4.3)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	0 (0.0)	1 (0.7)
	No visit scheduled	4 (2.6)	4 (2.8)
	Expected to Complete Questionnaires	106 (69.7)	81 (57.4)
	Not completed	27 (17.8)	43 (30.5)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	13 (8.6)	10 (7.1)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	1 (0.7)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.7)
	Subject refused for other reasons	1 (0.7)	5 (3.5)
	Other	1 (0.7)	8 (5.7)
	With visit, no record	11 (7.2)	19 (13.5)
	Completed	79 (52.0)	38 (27.0)
	Compliance (completed per protocol)[e]	79 (74.5)	38 (46.9)
Week 36	Missing by Design[d]	52 (34.2)	75 (53.2)
	Discontinued due to adverse event	8 (5.3)	10 (7.1)
	Discontinued due to clinical progression	7 (4.6)	3 (2.1)
	Discontinued due to complete response	2 (1.3)	1 (0.7)
	Discontinued due to physician decision	0 (0.0)	6 (4.3)
	Discontinued due to progressive disease	34 (22.4)	47 (33.3)
	Discontinued due to withdrawal by subject	0 (0.0)	8 (5.7)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	0 (0.0)	0 (0.0)
	No visit scheduled	1 (0.7)	0 (0.0)
	Expected to Complete Questionnaires	100 (65.8)	66 (46.8)
	Not completed	20 (13.2)	31 (22.0)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.7)
	Not completed due to site staff error	9 (5.9)	10 (7.1)
	Subject in hospital or hospice	1 (0.7)	1 (0.7)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	6 (4.3)
	Other	3 (2.0)	6 (4.3)
	With visit, no record	7 (4.6)	7 (5.0)
	Completed	80 (52.6)	35 (24.8)
	Compliance (completed per protocol)[e]	80 (80.0)	35 (53.0)
Week 45	Missing by Design[d]	66 (43.4)	91 (64.5)
	Discontinued due to adverse event	12 (7.9)	11 (7.8)
	Discontinued due to clinical progression	7 (4.6)	4 (2.8)
	Discontinued due to complete response	3 (2.0)	2 (1.4)
	Discontinued due to physician decision	2 (1.3)	7 (5.0)
	Discontinued due to progressive disease	39 (25.7)	58 (41.1)
	Discontinued due to withdrawal by subject	0 (0.0)	7 (5.0)
	Discontinued due to other	0 (0.0)	0 (0.0)

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EORTC QLQ-CR29	N[c] = 152 n (%)	N[c] = 141 n (%)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	0 (0.0)	0 (0.0)
	No visit scheduled	3 (2.0)	2 (1.4)
	Expected to Complete Questionnaires	86 (56.6)	50 (35.5)
	Not completed	14 (9.2)	23 (16.3)
	Subject did not complete due to disease under study	1 (0.7)	1 (0.7)
	Not completed due to site staff error	4 (2.6)	10 (7.1)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	1 (0.7)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.7)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	2 (1.3)	4 (2.8)
	Other	3 (2.0)	4 (2.8)
	With visit, no record	3 (2.0)	3 (2.1)
	Completed	72 (47.4)	27 (19.1)
	Compliance (completed per protocol)[e]	72 (83.7)	27 (54.0)

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

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

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

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

EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

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

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

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EQ-5D VAS	N[c] = 152 n (%)	N[c] = 142 n (%)
Week 0	Missing by Design[d]	0 (0.0)	0 (0.0)
	Discontinued due to adverse event	0 (0.0)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	0 (0.0)
	Discontinued due to complete response	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	0 (0.0)	0 (0.0)
	No visit scheduled	0 (0.0)	0 (0.0)
	Expected to Complete Questionnaires	152 (100.0)	142 (100.0)
	Not completed	10 (6.6)	9 (6.3)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	2 (1.3)	5 (3.5)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	2 (1.3)	0 (0.0)
	Other	3 (2.0)	2 (1.4)

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EQ-5D VAS	N[c] = 152 n (%)	N[c] = 142 n (%)
	With visit, no record	3 (2.0)	2 (1.4)
	Completed	142 (93.4)	133 (93.7)
	Compliance (completed per protocol)[e]	142 (93.4)	133 (93.7)
Week 2/3	Missing by Design[d]	8 (5.3)	5 (3.5)
	Discontinued due to adverse event	0 (0.0)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	0 (0.0)
	Discontinued due to complete response	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	4 (2.6)	0 (0.0)
	No visit scheduled	4 (2.6)	5 (3.5)
	Expected to Complete Questionnaires	144 (94.7)	137 (96.5)
	Not completed	12 (7.9)	9 (6.3)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	7 (4.6)	5 (3.5)
	Subject in hospital or hospice	2 (1.3)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	1 (0.7)	2 (1.4)
	Other	1 (0.7)	2 (1.4)
	With visit, no record	1 (0.7)	0 (0.0)
	Completed	132 (86.8)	128 (90.1)
	Compliance (completed per protocol)[e]	132 (91.7)	128 (93.4)
Week 6	Missing by Design[d]	16 (10.5)	14 (9.9)
	Discontinued due to adverse event	2 (1.3)	0 (0.0)
	Discontinued due to clinical progression	4 (2.6)	0 (0.0)
	Discontinued due to complete response	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to progressive disease	5 (3.3)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	1 (0.7)
	Subject died	1 (0.7)	1 (0.7)
	No visit scheduled	4 (2.6)	12 (8.5)
	Expected to Complete Questionnaires	136 (89.5)	128 (90.1)
	Not completed	10 (6.6)	26 (18.3)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.7)
	Not completed due to site staff error	5 (3.3)	4 (2.8)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.7)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	3 (2.1)
	Other	4 (2.6)	5 (3.5)
	With visit, no record	1 (0.7)	12 (8.5)
	Completed	126 (82.9)	102 (71.8)
	Compliance (completed per protocol)[e]	126 (92.6)	102 (79.7)
Week 9	Missing by Design[d]	24 (15.8)	23 (16.2)
	Discontinued due to adverse event	4 (2.6)	4 (2.8)
	Discontinued due to clinical progression	5 (3.3)	1 (0.7)

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EQ-5D VAS	N[c] = 152 n (%)	N[c] = 142 n (%)
	Discontinued due to complete response	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.7)
	Discontinued due to progressive disease	6 (3.9)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	1 (0.7)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	1 (0.7)
	Subject died	1 (0.7)	1 (0.7)
	No visit scheduled	8 (5.3)	14 (9.9)
	Expected to Complete Questionnaires	128 (84.2)	119 (83.8)
	Not completed	9 (5.9)	61 (43.0)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	5 (3.3)	15 (10.6)
	Subject in hospital or hospice	0 (0.0)	2 (1.4)
	Subject was physically unable to complete	2 (1.3)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	5 (3.5)
	Other	1 (0.7)	11 (7.7)
	With visit, no record	1 (0.7)	28 (19.7)
	Completed	119 (78.3)	58 (40.8)
	Compliance (completed per protocol)[e]	119 (93.0)	58 (48.7)
Week 12	Missing by Design[d]	28 (18.4)	22 (15.5)
	Discontinued due to adverse event	3 (2.0)	3 (2.1)
	Discontinued due to clinical progression	5 (3.3)	2 (1.4)
	Discontinued due to complete response	1 (0.7)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	1 (0.7)
	Discontinued due to progressive disease	14 (9.2)	4 (2.8)
	Discontinued due to withdrawal by subject	0 (0.0)	2 (1.4)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	3 (2.0)	0 (0.0)
	No visit scheduled	2 (1.3)	10 (7.0)
	Expected to Complete Questionnaires	124 (81.6)	120 (84.5)
	Not completed	10 (6.6)	31 (21.8)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	7 (4.6)	11 (7.7)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.7)
	Subject refused for other reasons	2 (1.3)	3 (2.1)
	Other	0 (0.0)	10 (7.0)
	With visit, no record	1 (0.7)	6 (4.2)
	Completed	114 (75.0)	89 (62.7)
	Compliance (completed per protocol)[e]	114 (91.9)	89 (74.2)
Week 18	Missing by Design[d]	36 (23.7)	34 (23.9)
	Discontinued due to adverse event	5 (3.3)	5 (3.5)
	Discontinued due to clinical progression	5 (3.3)	2 (1.4)
	Discontinued due to complete response	0 (0.0)	1 (0.7)
	Discontinued due to physician decision	0 (0.0)	4 (2.8)
	Discontinued due to progressive disease	20 (13.2)	15 (10.6)
	Discontinued due to withdrawal by subject	0 (0.0)	3 (2.1)
	Discontinued due to other	0 (0.0)	0 (0.0)

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EQ-5D VAS	N[c] = 152 n (%)	N[c] = 142 n (%)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	1 (0.7)	2 (1.4)
	No visit scheduled	5 (3.3)	2 (1.4)
	Expected to Complete Questionnaires	116 (76.3)	108 (76.1)
	Not completed	14 (9.2)	26 (18.3)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	7 (4.6)	13 (9.2)
	Subject in hospital or hospice	1 (0.7)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	2 (1.3)	2 (1.4)
	Other	1 (0.7)	3 (2.1)
	With visit, no record	3 (2.0)	8 (5.6)
	Completed	102 (67.1)	82 (57.7)
	Compliance (completed per protocol)[e]	102 (87.9)	82 (75.9)
Week 27	Missing by Design[d]	46 (30.3)	60 (42.3)
	Discontinued due to adverse event	7 (4.6)	7 (4.9)
	Discontinued due to clinical progression	7 (4.6)	3 (2.1)
	Discontinued due to complete response	0 (0.0)	1 (0.7)
	Discontinued due to physician decision	0 (0.0)	5 (3.5)
	Discontinued due to progressive disease	28 (18.4)	33 (23.2)
	Discontinued due to withdrawal by subject	0 (0.0)	6 (4.2)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	0 (0.0)	1 (0.7)
	No visit scheduled	4 (2.6)	4 (2.8)
	Expected to Complete Questionnaires	106 (69.7)	82 (57.7)
	Not completed	27 (17.8)	43 (30.3)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	12 (7.9)	10 (7.0)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	1 (0.7)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	1 (0.7)
	Subject refused for other reasons	1 (0.7)	4 (2.8)
	Other	2 (1.3)	9 (6.3)
	With visit, no record	11 (7.2)	19 (13.4)
	Completed	79 (52.0)	39 (27.5)
	Compliance (completed per protocol)[e]	79 (74.5)	39 (47.6)
Week 36	Missing by Design[d]	52 (34.2)	75 (52.8)
	Discontinued due to adverse event	8 (5.3)	10 (7.0)
	Discontinued due to clinical progression	7 (4.6)	3 (2.1)
	Discontinued due to complete response	2 (1.3)	1 (0.7)
	Discontinued due to physician decision	0 (0.0)	6 (4.2)
	Discontinued due to progressive disease	34 (22.4)	47 (33.1)
	Discontinued due to withdrawal by subject	0 (0.0)	8 (5.6)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	0 (0.0)	0 (0.0)
	No visit scheduled	1 (0.7)	0 (0.0)
	Expected to Complete Questionnaires	100 (65.8)	67 (47.2)
	Not completed	20 (13.2)	31 (21.8)

Study: KEYNOTE-177[a]		Pembrolizumab	Chemotherapy[b]
Visit	EQ-5D VAS	N[c] = 152 n (%)	N[c] = 142 n (%)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.7)
	Not completed due to site staff error	9 (5.9)	10 (7.0)
	Subject in hospital or hospice	1 (0.7)	1 (0.7)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	0 (0.0)	6 (4.2)
	Other	3 (2.0)	6 (4.2)
	With visit, no record	7 (4.6)	7 (4.9)
	Completed	80 (52.6)	36 (25.4)
	Compliance (completed per protocol)[e]	80 (80.0)	36 (53.7)
Week 45	Missing by Design[d]	66 (43.4)	91 (64.1)
	Discontinued due to adverse event	12 (7.9)	11 (7.7)
	Discontinued due to clinical progression	7 (4.6)	4 (2.8)
	Discontinued due to complete response	3 (2.0)	2 (1.4)
	Discontinued due to physician decision	2 (1.3)	7 (4.9)
	Discontinued due to progressive disease	39 (25.7)	58 (40.8)
	Discontinued due to withdrawal by subject	0 (0.0)	7 (4.9)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	0 (0.0)	0 (0.0)
	No visit scheduled	3 (2.0)	2 (1.4)
	Expected to Complete Questionnaires	86 (56.6)	51 (35.9)
	Not completed	14 (9.2)	23 (16.2)
	Subject did not complete due to disease under study	1 (0.7)	1 (0.7)
	Not completed due to site staff error	4 (2.6)	11 (7.7)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	1 (0.7)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.7)
	Subject did not complete due to side effects of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	2 (1.3)	4 (2.8)
	Other	3 (2.0)	3 (2.1)
	With visit, no record	3 (2.0)	3 (2.1)
	Completed	72 (47.4)	28 (19.7)
	Compliance (completed per protocol)[e]	72 (83.7)	28 (54.9)

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

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

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

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

EQ-5D: European Quality of Life 5 Dimensions; VAS: Visual Analog Scale

Anhang 4-G3: Kaplan-Meier-Kurven der Subgruppen mit signifikantem Interaktionstest (p < 0,05) der Studie KEYNOTE 177

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 Datenschnitt vom 19. Februar 2020 der KEYNOTE 177.

Anhang 4-G3.1: Morbidität

Krankheitssymptomatik und Gesundheitszustand

Im Folgenden werden die Kaplan-Meier-Kurven der Subgruppenanalysen für die Hauptanalyse der Endpunkte Krankheitssymptomatik und Gesundheitszustand (Zeit bis zur ersten Verschlechterung) dargestellt, für die ein signifikanter Interaktionstest (p < 0,05) vorliegt.

EORTC QLQ-CR29: Symptomskala Blähungen

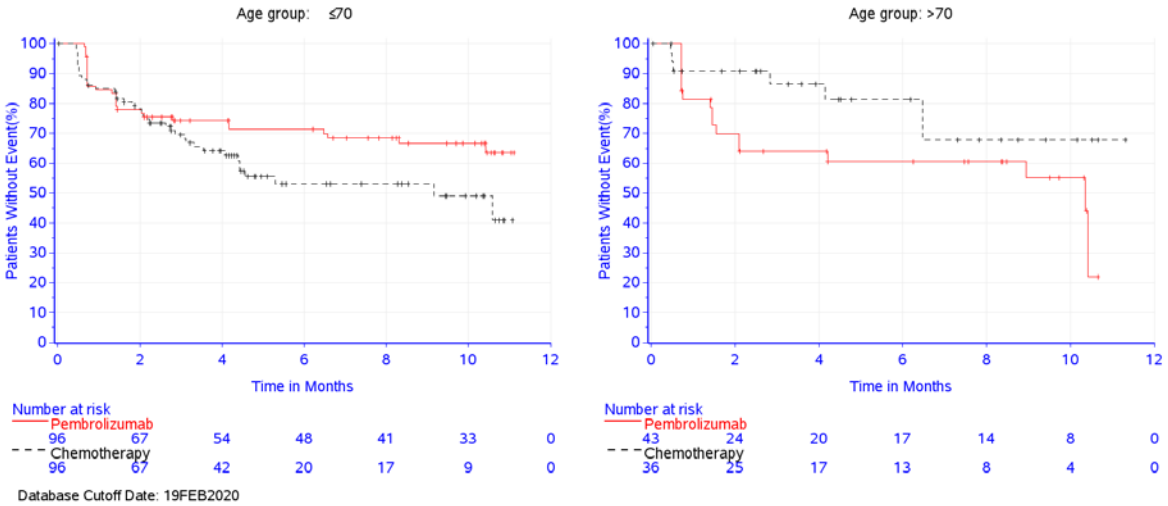

Abbildung 4G-1: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Alter für die Symptomskala Blähungen des EORTC QLQ-CR29 der Studie KEYNOTE 177

EORTC QLQ-CR29: Symptomskala Trockener Mund

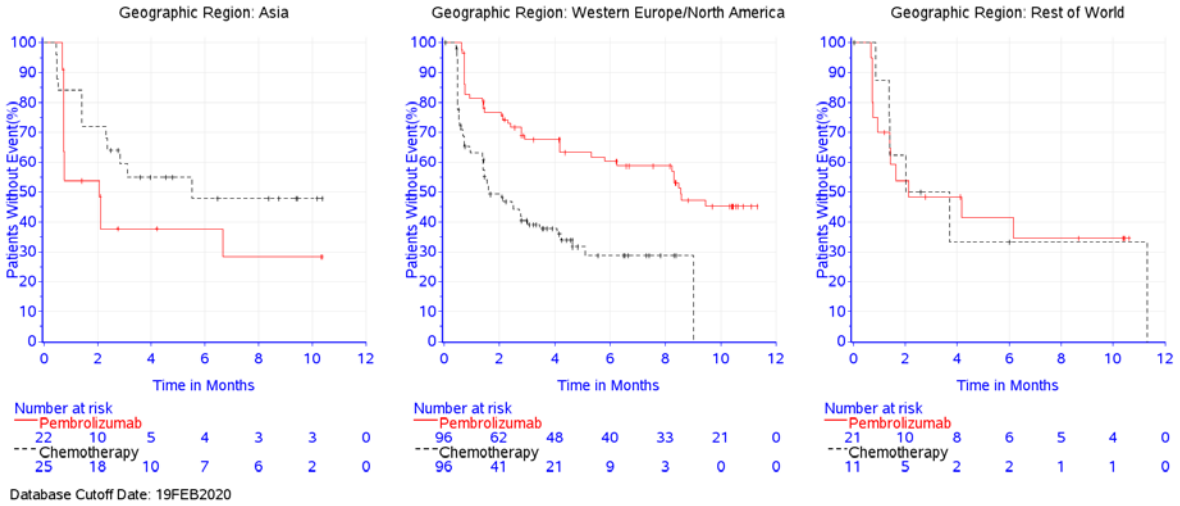

Abbildung 4G-2: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Trockener Mund des EORTC QLQ-CR29 der Studie KEYNOTE 177

EORTC QLQ-R29: Symptomskala Haarausfall

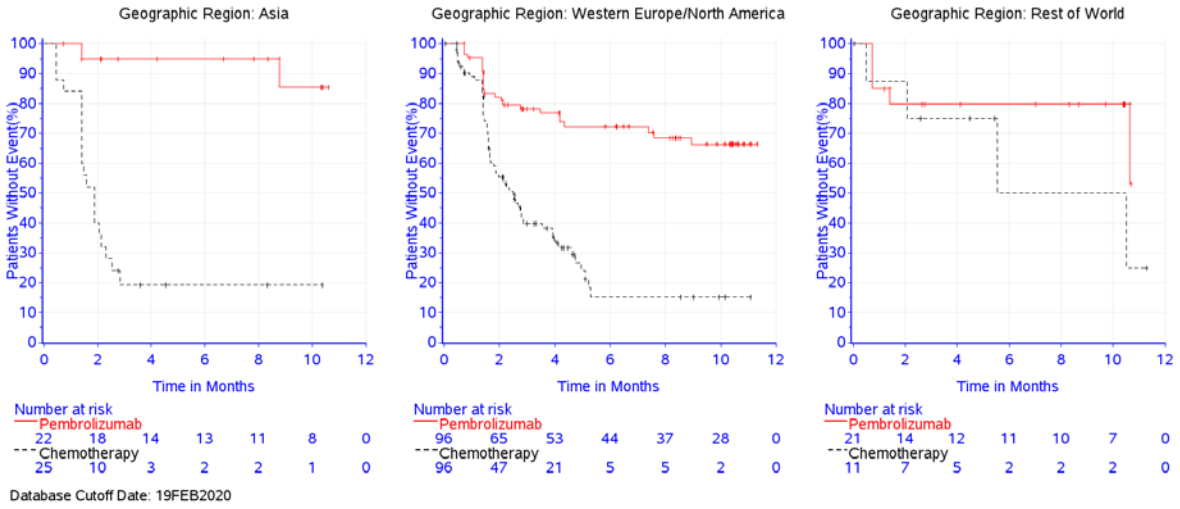

Abbildung 4G-3: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Haarausfall des EORTC QLQ-CR29 der Studie KEYNOTE 177

EORTC QLQ-R29: Symptomskala Darmgasentweichungen

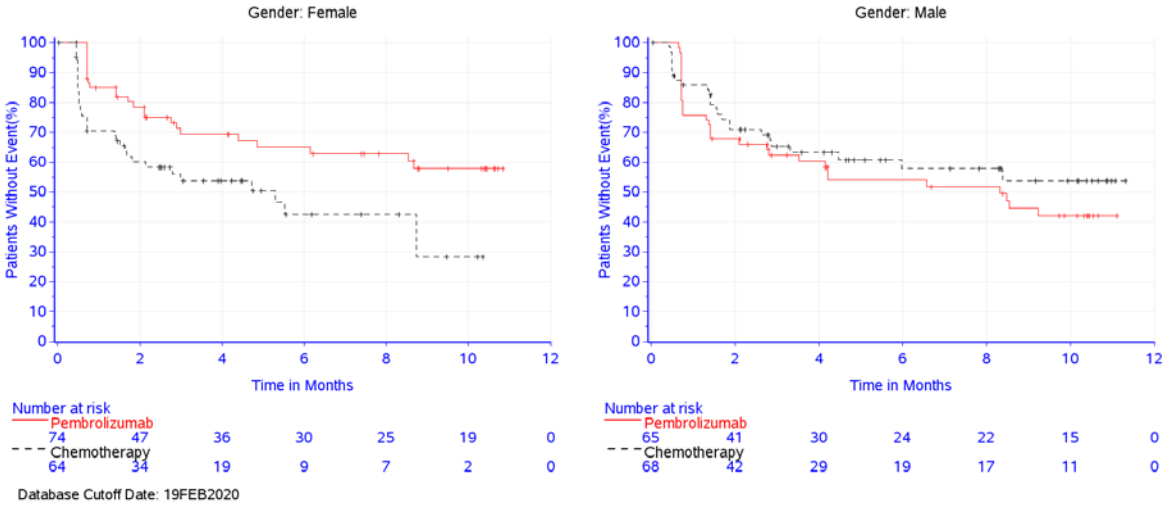

Abbildung 4G-4: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Geschlecht für die Symptomskala Darmgasentweichungen des EORTC QLQ-CR29 der Studie KEYNOTE 177

Anhang 4-G3.2: Gesundheitsbezogene Lebensqualität

Im Folgenden werden die Kaplan-Meier-Kurven der Subgruppenanalysen für die Hauptanalyse des Endpunkts Gesundheitsbezogene Lebensqualität (Zeit bis zur ersten Verschlechterung) dargestellt, für die ein signifikanter Interaktionstest ($p < 0,05$) vorliegt.

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

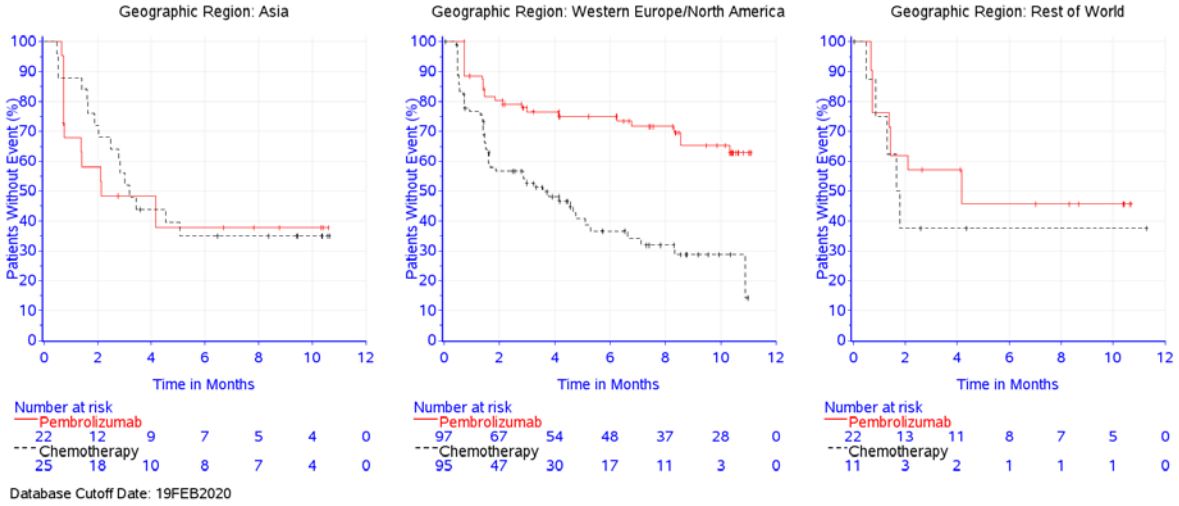

Abbildung 4G-5: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Symptomskala Körperliche Funktion des EORTC QLQ-C30 der Studie KEYNOTE 177

EORTC QLQ-C30: Funktionsskala Rollenfunktion

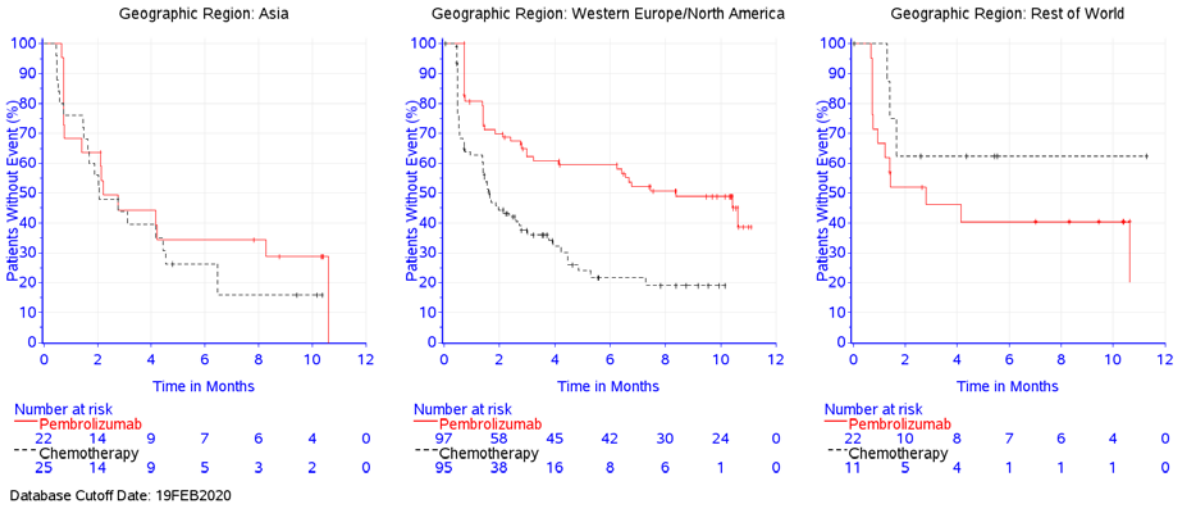

Abbildung 4G-6: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach Region für die Rollenfunktion des EORTC QLQ-C30 der Studie KEYNOTE 177

EORTC QLQ-CR29: Funktionsskala Körperbild

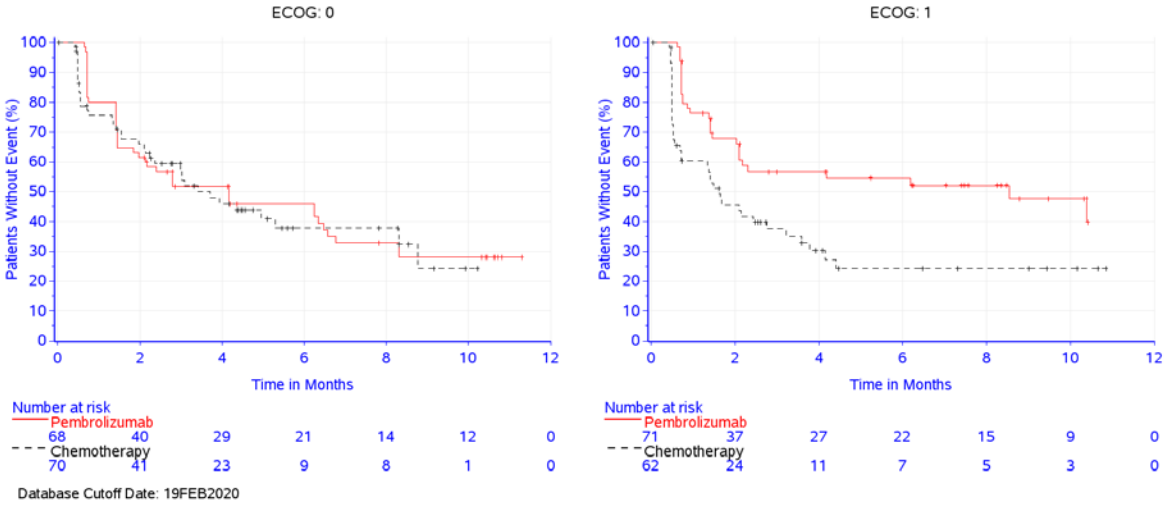

Abbildung 4G-7: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Zeit bis zur ersten Verschlechterung nach ECOG-Leistungsstatus für die Funktionsskala Körperbild des EORTC QLQ-CR29 der Studie KEYNOTE 177

Anhang 4-G3.3: Nebenwirkungen

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Im Folgenden werden die Ergebnisse der Subgruppenanalysen des Endpunkts Unerwünschte Ereignisse (SOC und PT) dargestellt, für die ein signifikanter Interaktionstest ($p < 0,05$) vorliegt.

Unerwünschte Ereignisse gesamt (SOC und PT)

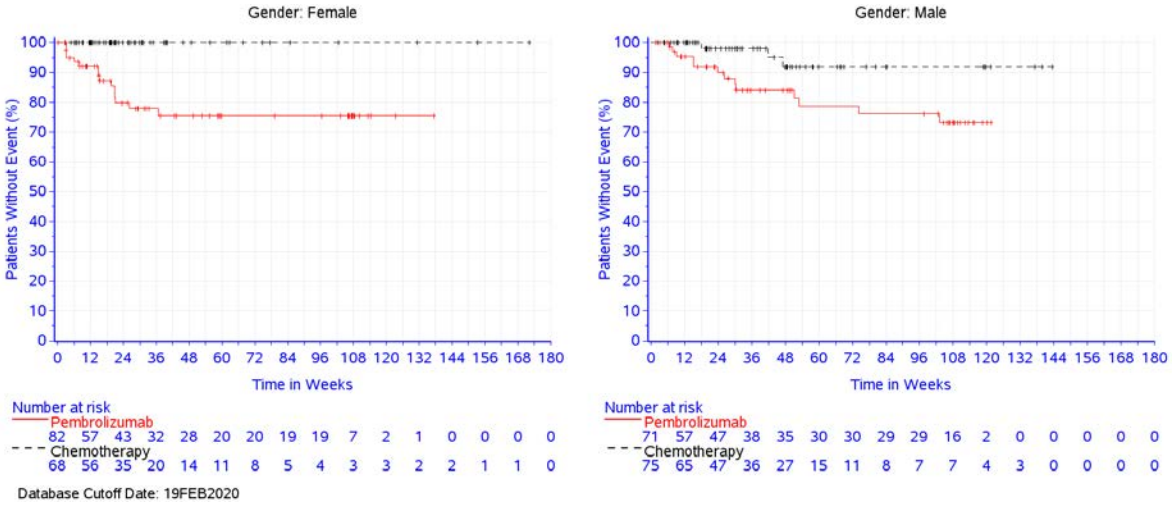

Abbildung 4G-8: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC „Endokrine Erkrankungen“ der Studie KEYNOTE 177

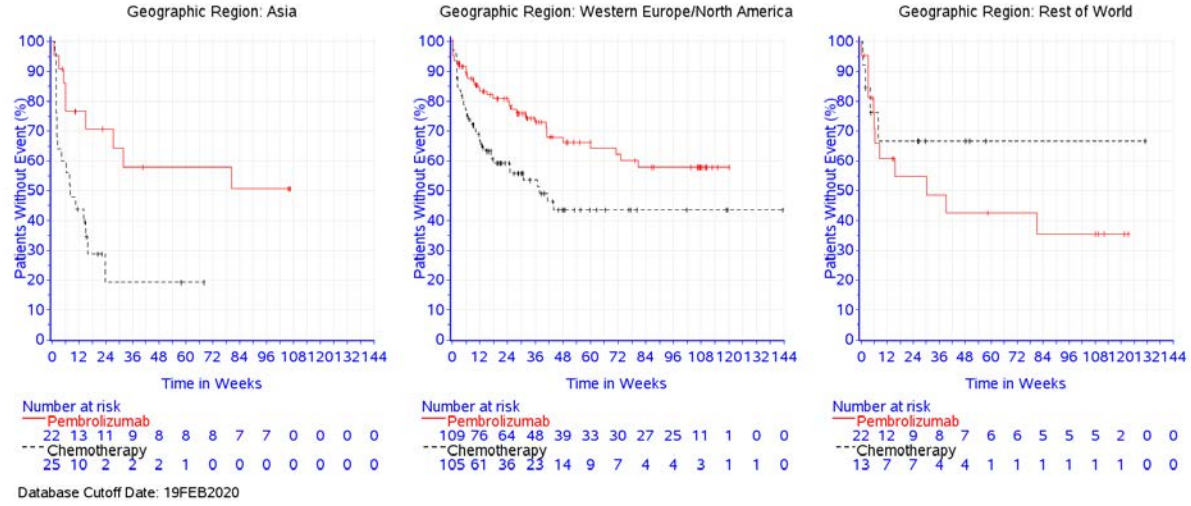

Abbildung 4G-9: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC „Untersuchungen“ der Studie KEYNOTE 177

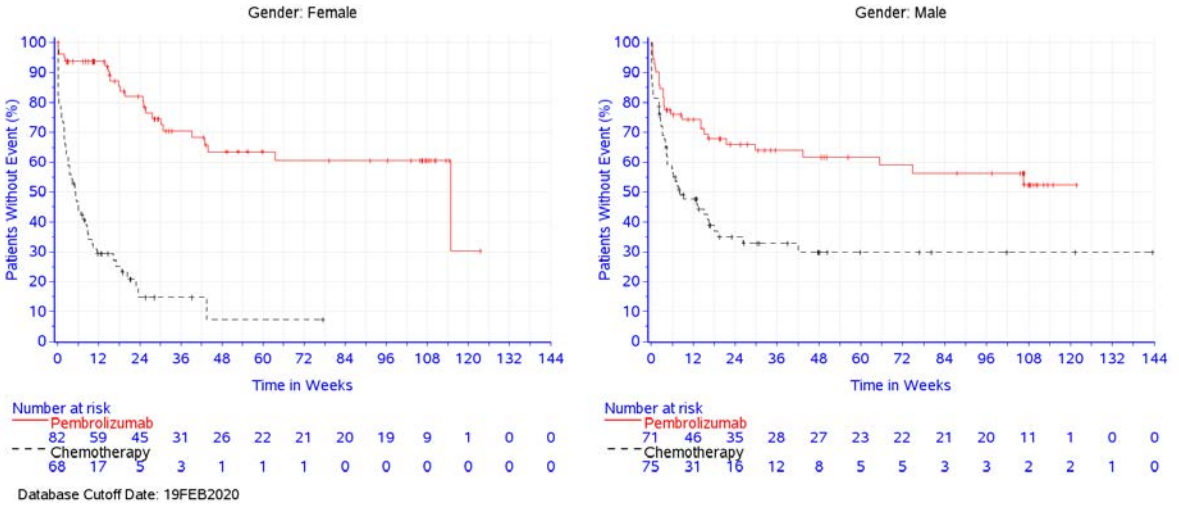

Abbildung 4G-10: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC „Erkrankungen des Nervensystems“ der Studie KEYNOTE 177

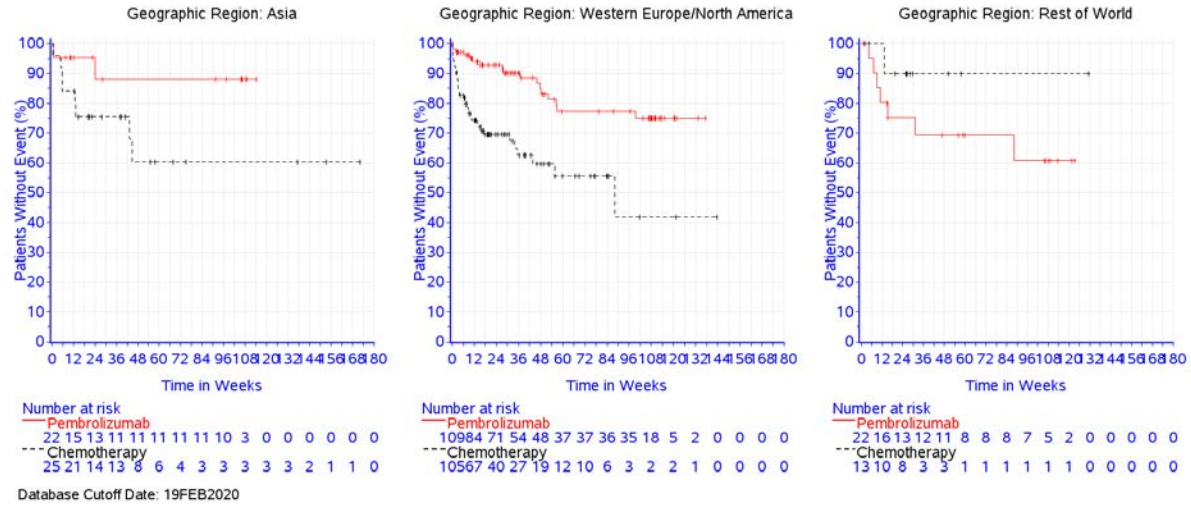

Abbildung 4G-11: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Verstopfung“ (SOC „Erkrankungen des Gastrointestinaltrakts“) der Studie KEYNOTE 177

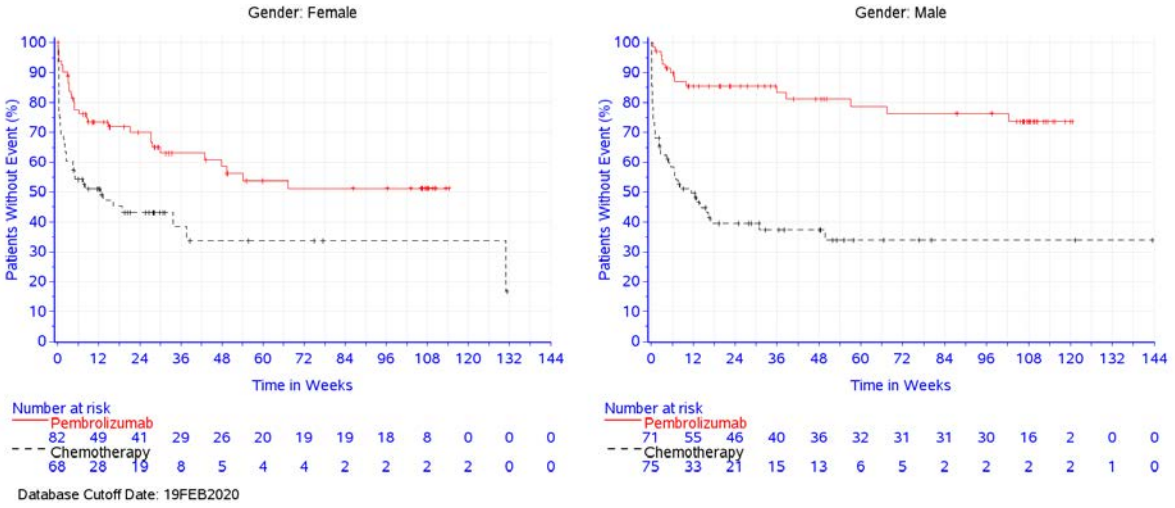

Abbildung 4G-12: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Übelkeit“ (SOC „Erkrankungen des Gastrointestinaltrakts“) der Studie KEYNOTE 177

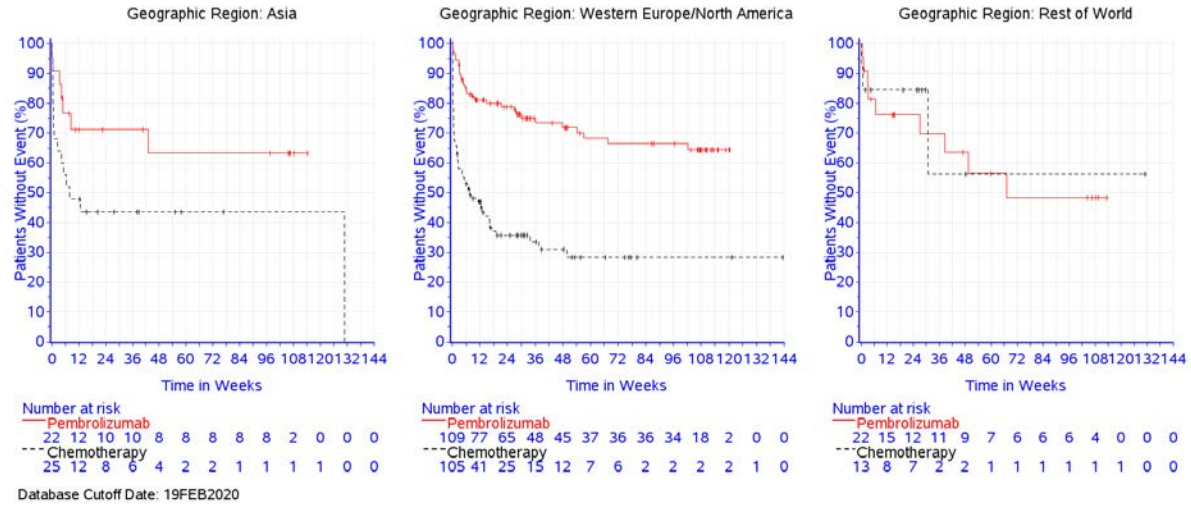

Abbildung 4G-13: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Übelkeit“ (SOC „Erkrankungen des Gastrointestinaltrakts“) der Studie KEYNOTE 177

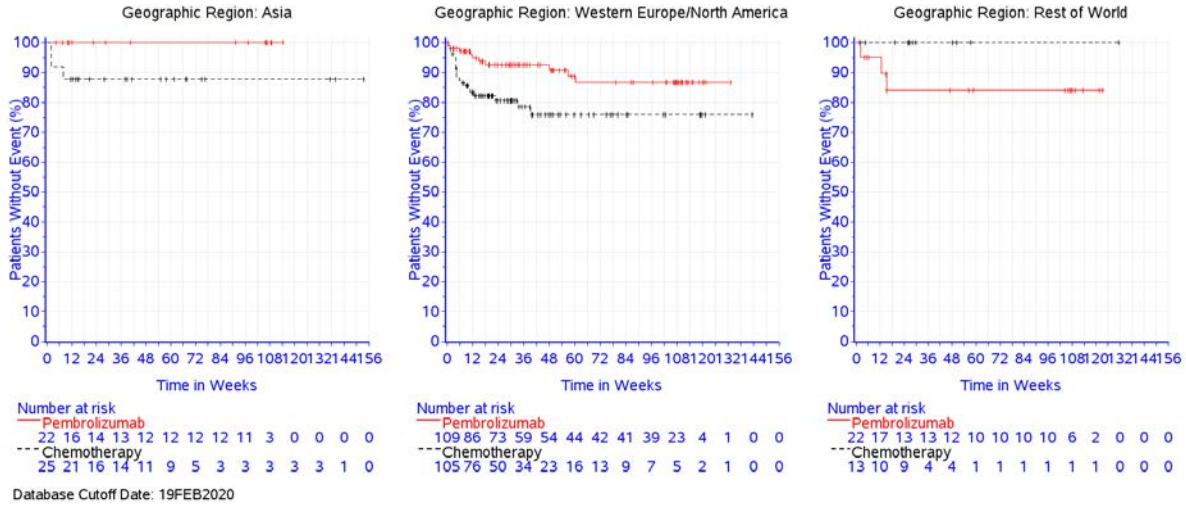

Abbildung 4G-14: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Hypokaliaemie“ (SOC „Stoffwechsel- und Ernährungsstörungen“) der Studie KEYNOTE 177

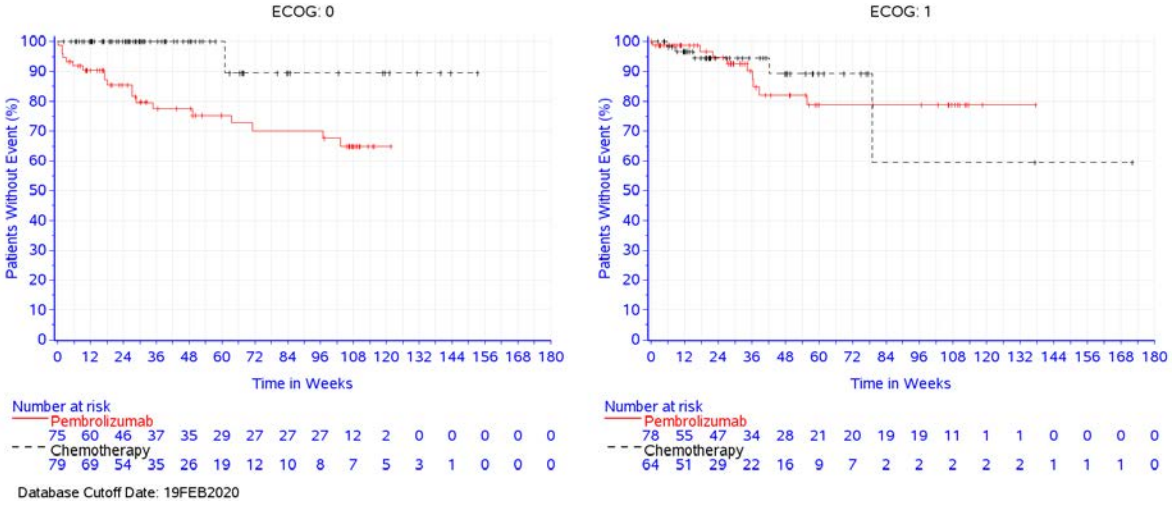

Abbildung 4G-15: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Arthralgie“ (SOC „Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen“) der Studie KEYNOTE 177

Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT)

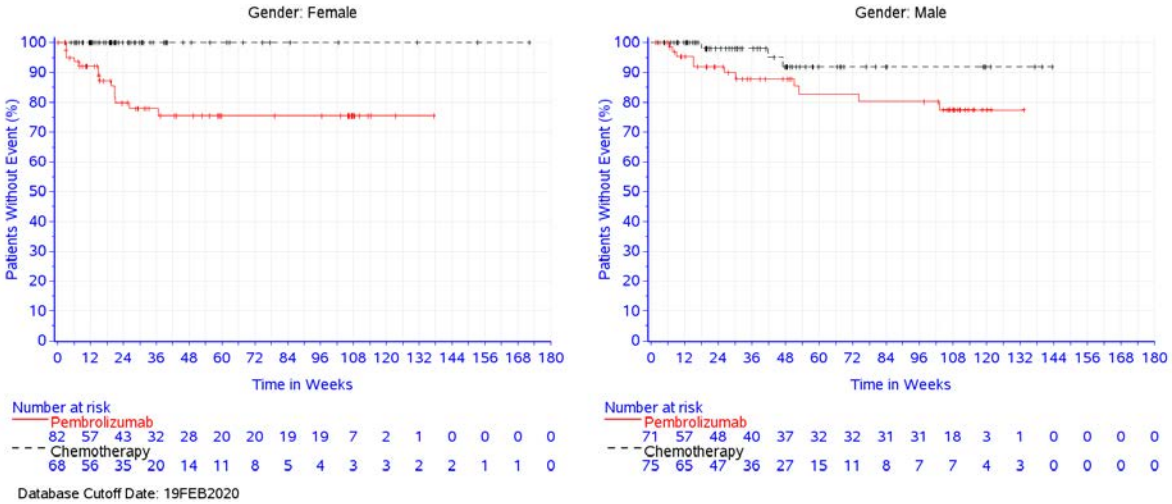

Abbildung 4G-16: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für die SOC „Endokrine Erkrankungen“ der Studie KEYNOTE 177

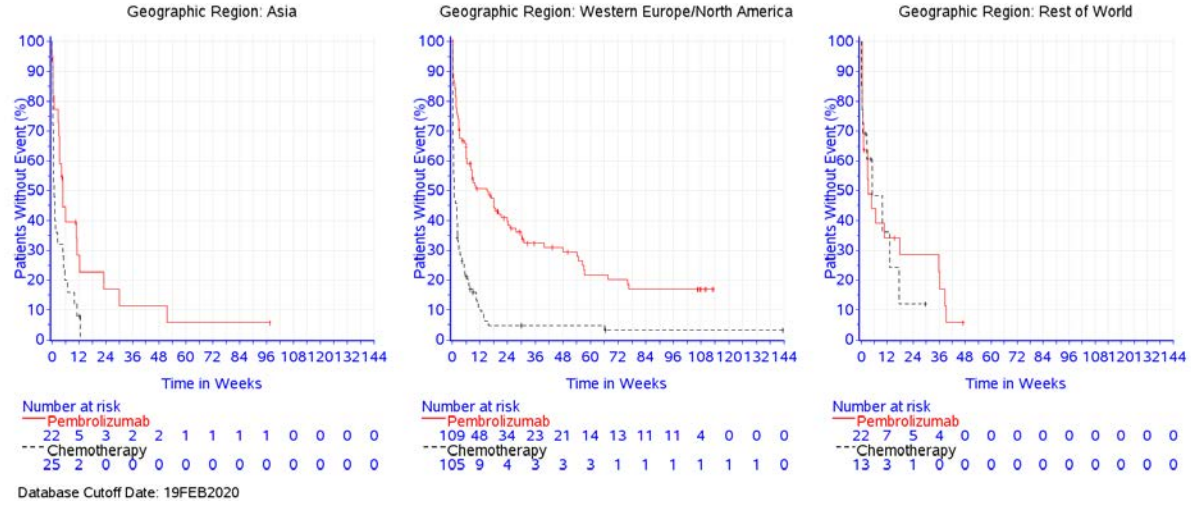

Abbildung 4G-17: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für die SOC „Erkrankungen des Gastrointestinaltrakts“ der Studie KEYNOTE 177

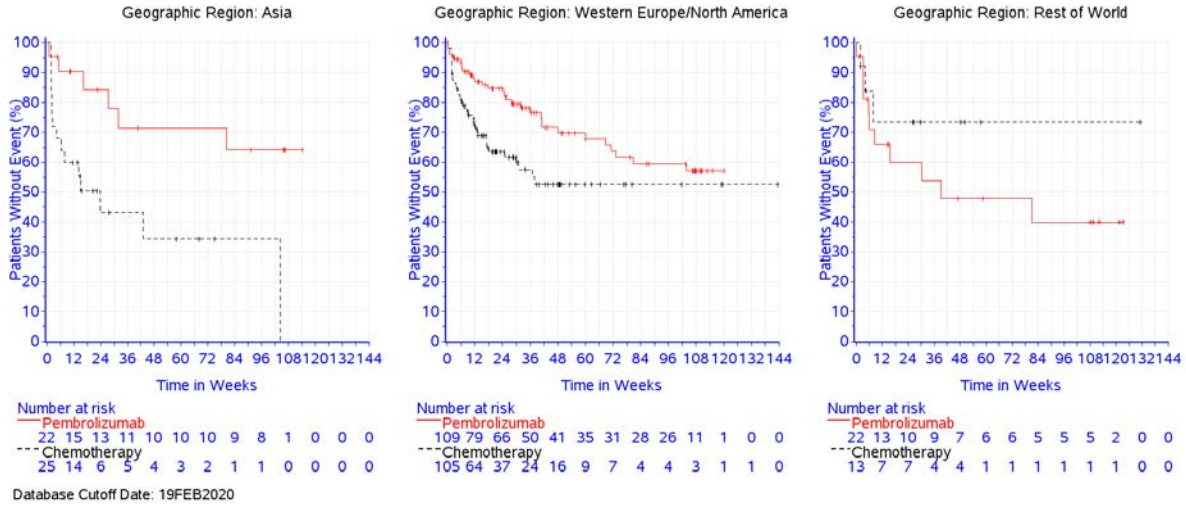

Abbildung 4G-18: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für die SOC „Untersuchungen“ der Studie KEYNOTE 177

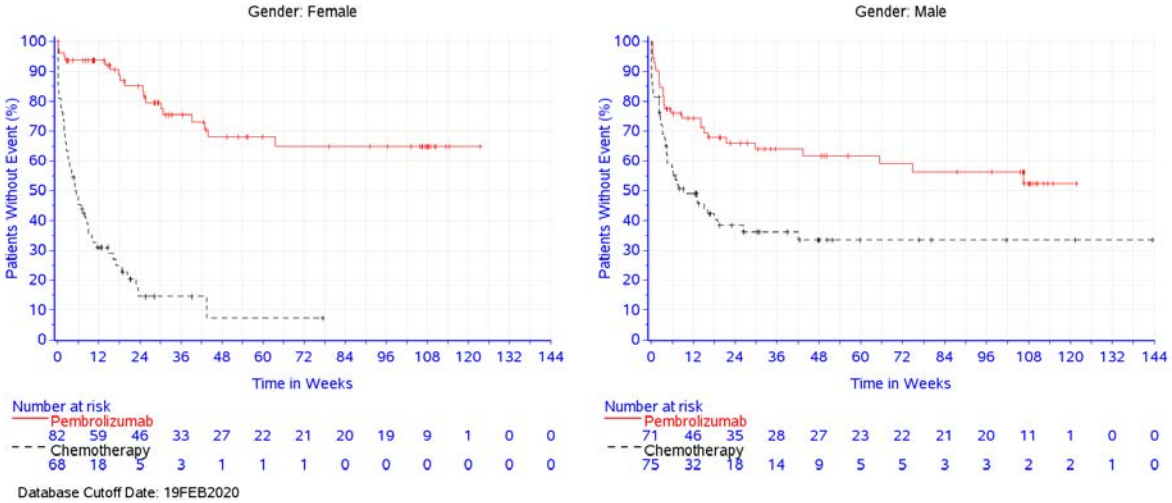

Abbildung 4G-19: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für die SOC „Erkrankungen des Nervensystems“ der Studie KEYNOTE 177

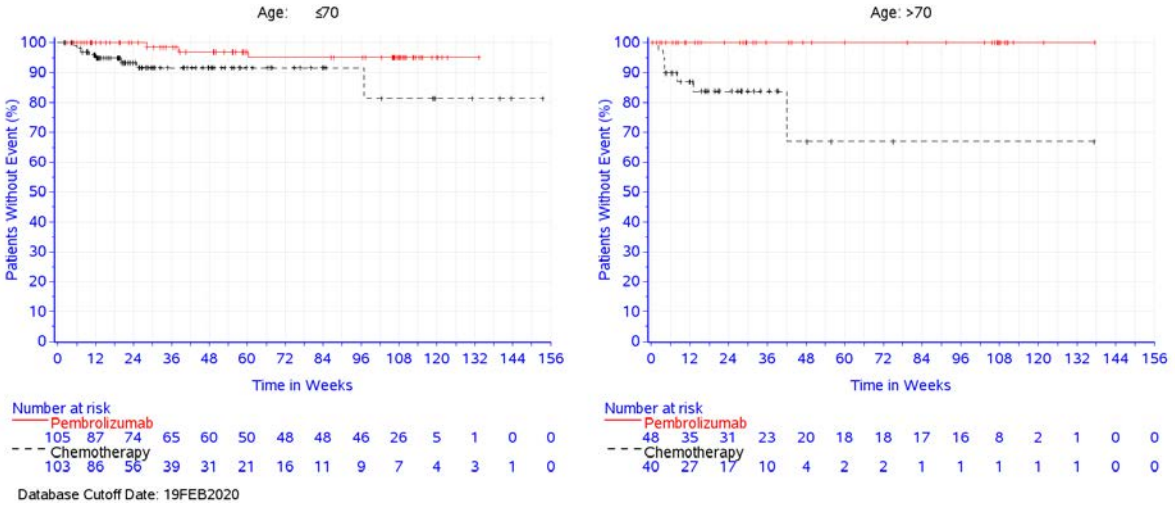

Abbildung 4G-20: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Neutropenie“ (SOC „Erkrankungen des Blutes und des Lymphsystems“) der Studie KEYNOTE 177

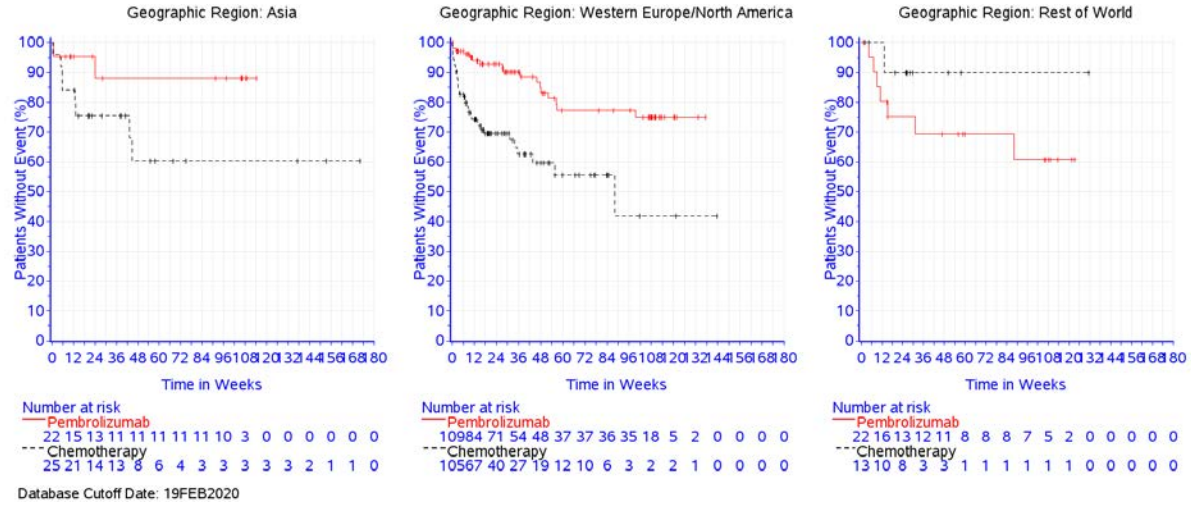

Abbildung 4G-21: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Verstopfung“ (SOC „Erkrankungen des Gastrointestinaltrakts“) der Studie KEYNOTE 177

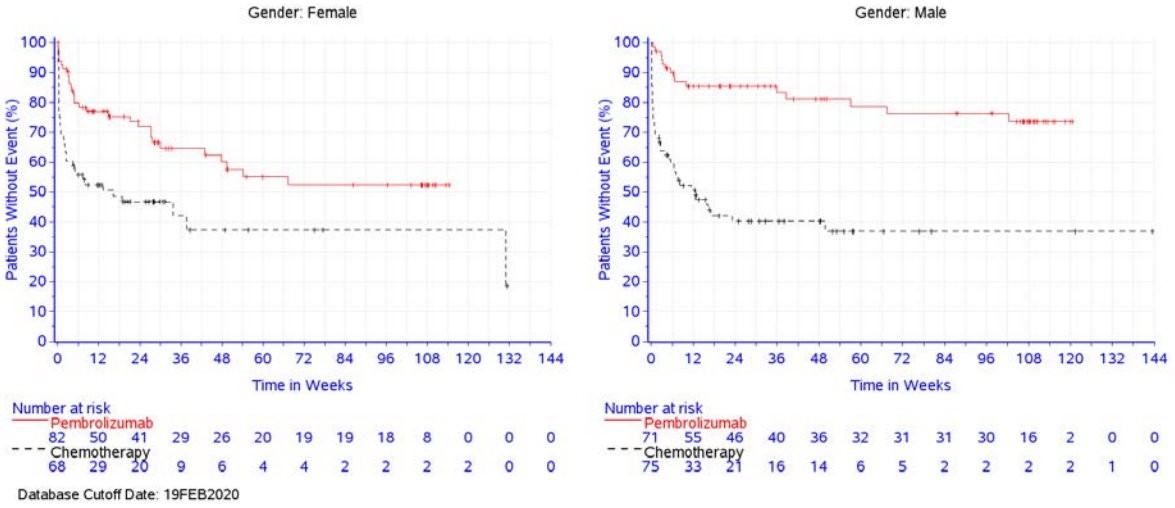

Abbildung 4G-22: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Übelkeit“ (SOC „Erkrankungen des Gastrointestinaltrakts“) der Studie KEYNOTE 177

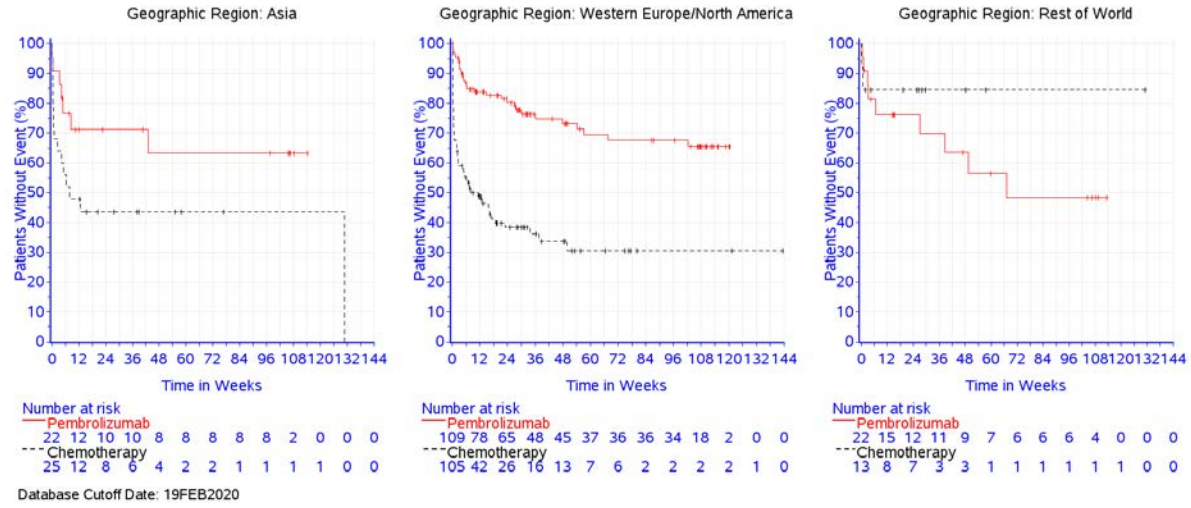

Abbildung 4G-23: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Übelkeit“ (SOC „Erkrankungen des Gastrointestinaltrakts“) der Studie KEYNOTE 177

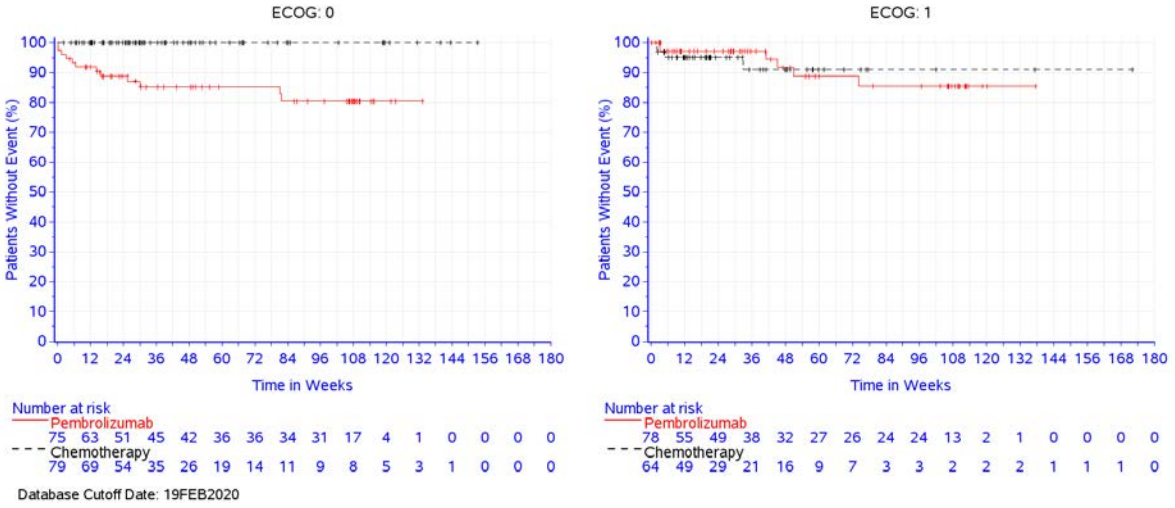

Abbildung 4G-24: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Alkalischen Phosphatase im Blut erhöht“ (SOC „Untersuchungen“) der Studie KEYNOTE 177

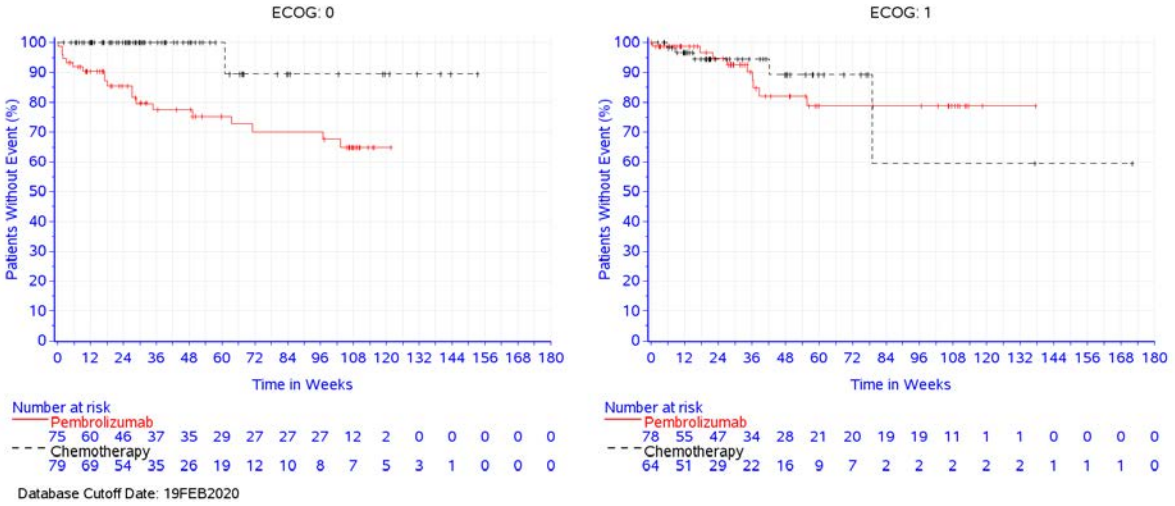

Abbildung 4G-25: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Arthralgie“ (SOC „Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen“) der Studie KEYNOTE 177

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

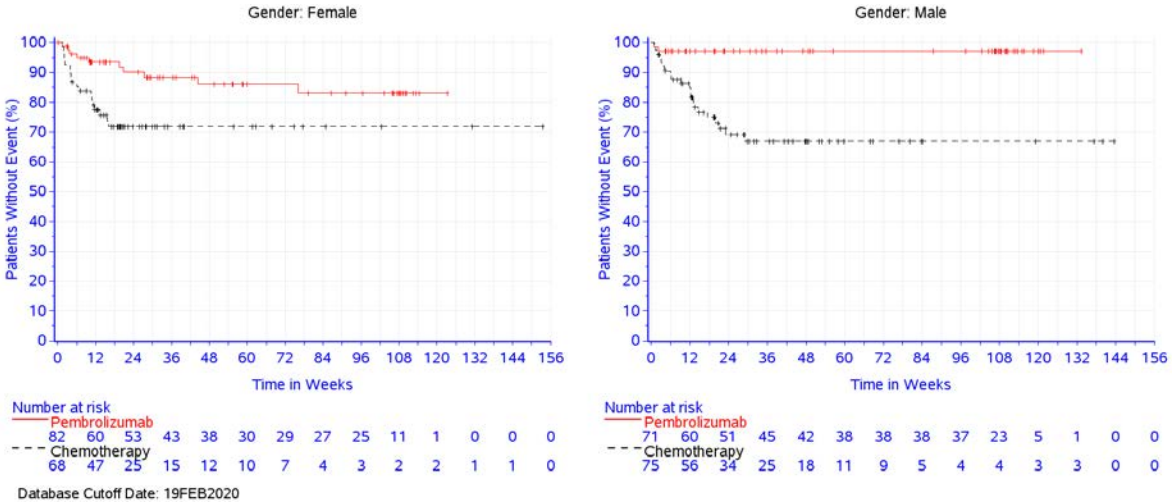

Abbildung 4G-26: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für die SOC „Erkrankungen des Blutes und des Lymphsystems“ der Studie KEYNOTE 177

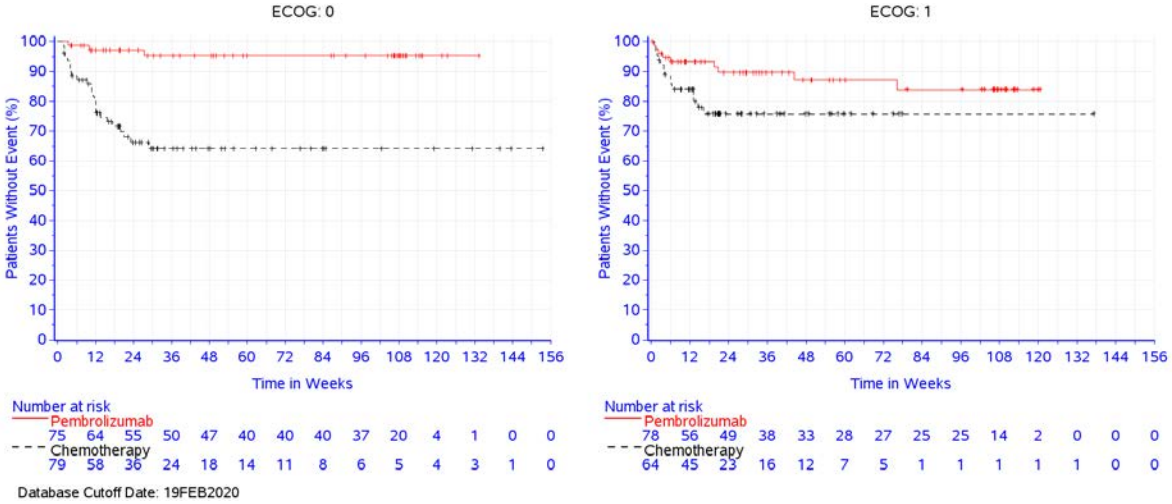

Abbildung 4G-27: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für die SOC „Erkrankungen des Blutes und des Lymphsystems“ der Studie KEYNOTE 177

Anhang 4-G4: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest (p ≥ 0,05) der Studie KEYNOTE 177

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 Datenschnitt vom 19. Februar 2020 der KEYNOTE 177.

Anhang 4-G4.1: Mortalität

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

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab 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	82	32 (39.0)	Not reached [31.6; -]	72	30 (41.7)	Not reached [21.0; -]	0.90 [0.54; 1.47]	0.665	0.407
Male	71	24 (33.8)	Not reached [32.4; -]	82	39 (47.6)	30.6 [23.5; -]	0.64 [0.39; 1.07]	0.090	
Age									
≤70	105	33 (31.4)	Not reached [-; -]	112	47 (42.0)	Not reached [29.3; -]	0.69 [0.44; 1.07]	0.100	0.545
>70	48	23 (47.9)	Not reached [12.5; -]	42	22 (52.4)	22.0 [9.1; -]	0.89 [0.50; 1.60]	0.705	
ECOG									
0	75	21 (28.0)	Not reached [-; -]	84	32 (38.1)	Not reached [29.3; -]	0.65 [0.37; 1.13]	0.125	0.558
1	78	35 (44.9)	Not reached [17.8; -]	70	37 (52.9)	29.9 [14.7; -]	0.83 [0.52; 1.32]	0.439	
Geographic Region									
Asia	22	8 (36.4)	Not reached [13.8; -]	26	13 (50.0)	Not reached [14.7; -]	0.69 [0.29; 1.68]	0.418	0.648
Western Europe/North America	109	40 (36.7)	Not reached [-; -]	113	47 (41.6)	Not reached [29.9; -]	0.83 [0.55; 1.27]	0.398	
Rest of World	22	8 (36.4)	31.6 [9.1; -]	15	9 (60.0)	16.1 [6.6; -]	0.53 [0.20; 1.38]	0.192	
Metastases									
Hepatic or pulmonary	86	44 (51.2)	31.6 [13.8; -]	73	44 (60.3)	22.0 [13.7; 29.9]	0.82 [0.54; 1.25]	0.354	0.255
Other Metastases	67	12 (17.9)	Not reached [-; -]	81	25 (30.9)	Not reached [34.8; -]	0.52 [0.26; 1.04]	0.066	
Diagnosis									
Recurrent	80	25 (31.3)	Not reached [-; -]	74	29 (39.2)	Not reached [27.6; -]	0.73 [0.43; 1.25]	0.250	0.802
Newly diagnosed stage IV CRC	73	31 (42.5)	Not reached [22.1; -]	80	40 (50.0)	30.6 [16.6; -]	0.82 [0.51; 1.31]	0.396	
BRAF Mutation Status									
BRAF/KRAS/NRAS all Wild type	34	9 (26.5)	Not reached [32.4; -]	35	16 (45.7)	34.2 [16.6; -]	0.44 [0.19; 1.00]	0.049	0.370
BRAF V600E	34	11	Not reached	43	16	Not reached	0.80	0.566	

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab 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]
		(32.4)	[22.1; -]		(37.2)	[21.0; -]	[0.37; 1.72]		
KRAS/NRAS Status									
BRAF/KRAS/NRAS all Wild type	34	9 (26.5)	Not reached [32.4; -]	35	16 (45.7)	34.2 [16.6; -]	0.44 [0.19; 1.00]	0.049	0.209
KRAS or NRAS Mutant	33	14 (42.4)	Not reached [13.5; -]	41	20 (48.8)	31.2 [20.3; -]	0.89 [0.45; 1.76]	0.740	
Site of Primary Tumor									
Right	102	37 (36.3)	Not reached [-; -]	107	47 (43.9)	34.8 [26.3; -]	0.78 [0.51; 1.20]	0.264	0.965
Left	46	17 (37.0)	Not reached [31.6; -]	42	18 (42.9)	Not reached [20.3; -]	0.80 [0.41; 1.55]	0.510	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

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

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

e: Based on Cox regression model with treatment as 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; CRC: Colorectal Carcinoma; ECOG: Eastern Cooperative Oncology Group

Anhang 4-G4.2: Morbidität

Zeit bis zur ersten Folgetherapie (oder Tod)

Zeit bis zur ersten Folgetherapie oder Tod

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

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
Time to Subsequent 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	82	44 (53.7)	26.7 [12.4; -]	72	63 (87.5)	6.8 [5.6; 7.9]	0.42 [0.28; 0.62]	< 0.001	0.895
Male	71	33 (46.5)	35.7 [12.3; -]	82	69 (84.1)	12.3 [9.0; 13.4]	0.39 [0.26; 0.60]	< 0.001	
Age									
≤70	105	47 (44.8)	35.7 [15.3; -]	112	97 (86.6)	9.9 [7.0; 12.9]	0.36 [0.25; 0.51]	< 0.001	0.298
>70	48	30 (62.5)	14.9 [6.7; 31.6]	42	35 (83.3)	7.4 [4.8; 9.1]	0.53 [0.32; 0.87]	0.013	
ECOG									
0	75	30 (40.0)	Not reached [28.8; -]	84	71 (84.5)	10.8 [7.4; 13.4]	0.31 [0.20; 0.47]	< 0.001	0.212
1	78	47 (60.3)	13.5 [7.2; 34.1]	70	61 (87.1)	6.8 [4.7; 9.1]	0.52 [0.35; 0.76]	< 0.001	
Geographic Region									
Asia	22	10 (45.5)	Not reached [2.8; -]	26	20 (76.9)	11.3 [5.7; 15.6]	0.53 [0.25; 1.14]	0.104	0.773
Western Europe/North America	109	57 (52.3)	29.3 [12.4; -]	113	100 (88.5)	8.5 [6.6; 10.8]	0.40 [0.29; 0.56]	< 0.001	
Rest of World	22	10 (45.5)	31.6 [7.2; -]	15	12 (80.0)	9.0 [4.6; 11.7]	0.31 [0.13; 0.76]	0.010	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

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

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

e: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group

Krankheitssymptomatik und Gesundheitszustand

Im Folgenden werden die Ergebnisse der Subgruppenanalysen für die Hauptanalyse der Endpunkte Krankheitssymptomatik und Gesundheitszustand (Zeit bis zur ersten Verschlechterung) dargestellt, für die ein nicht signifikanter Interaktionstest ($p \geq 0,05$) vorliegt.

EORTC QLQ-C30

EORTC QLQ-C30: Symptomskala Erschöpfung

Tabelle 4G-6: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Erschöpfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab 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	75	47 (62.7)	2.1 [1.4; 2.8]	63	45 (71.4)	1.6 [0.6; 2.0]	0.67 [0.44; 1.01]	0.057	0.443
Male	66	38 (57.6)	2.1 [1.4; 8.3]	68	52 (76.5)	1.4 [0.6; 1.6]	0.57 [0.37; 0.86]	0.008	
Age									
≤70	98	58 (59.2)	2.1 [1.4; 6.8]	95	75 (78.9)	1.4 [0.7; 1.6]	0.54 [0.38; 0.76]	< 0.001	0.076
>70	43	27 (62.8)	1.4 [0.7; 3.5]	36	22 (61.1)	2.1 [0.7; 4.1]	0.94 [0.53; 1.65]	0.823	
ECOG									
0	70	44 (62.9)	1.4 [1.4; 6.2]	70	59 (84.3)	0.9 [0.6; 1.5]	0.45 [0.31; 0.68]	< 0.001	0.054
1	71	41 (57.7)	2.1 [1.4; 4.1]	61	38 (62.3)	1.8 [1.4; 3.3]	0.84 [0.54; 1.31]	0.449	
Geographic Region									
Asia	22	16 (72.7)	1.4 [0.7; 2.8]	25	19 (76.0)	2.1 [1.4; 4.8]	1.17 [0.59; 2.31]	0.647	0.054
Western Europe/North America	97	55 (56.7)	2.1 [1.4; 6.8]	95	71 (74.7)	1.4 [0.6; 1.6]	0.56 [0.39; 0.80]	0.001	
Rest of World	22	14 (63.6)	2.8 [1.0; 8.3]	11	7 (63.6)	0.5 [0.4; 2.1]	0.27 [0.10; 0.71]	0.008	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-7: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Übelkeit und Erbrechen des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab 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	75	30 (40.0)	10.4 [3.3; -]	63	42 (66.7)	2.1 [1.4; 3.5]	0.39 [0.24; 0.63]	< 0.001	0.598
Male	66	20 (30.3)	Not reached [10.6; -]	68	40 (58.8)	2.3 [1.4; 6.0]	0.34 [0.20; 0.58]	< 0.001	
Age									
≤70	98	38 (38.8)	Not reached [6.8; -]	95	63 (66.3)	1.5 [1.0; 3.2]	0.38 [0.25; 0.57]	< 0.001	0.838
>70	43	12 (27.9)	Not reached [7.7; -]	36	19 (52.8)	3.9 [1.9; 10.2]	0.37 [0.18; 0.77]	0.008	
ECOG									
0	70	25 (35.7)	Not reached [6.8; -]	70	41 (58.6)	2.5 [1.4; 4.8]	0.42 [0.25; 0.69]	< 0.001	0.767
1	71	25 (35.2)	10.6 [7.5; -]	61	41 (67.2)	1.6 [1.4; 3.1]	0.34 [0.20; 0.56]	< 0.001	
Geographic Region									
Asia	22	7 (31.8)	Not reached [2.1; -]	25	20 (80.0)	2.1 [1.4; 4.2]	0.29 [0.12; 0.70]	0.006	0.051
Western Europe/North America	97	34 (35.1)	Not reached [7.5; -]	95	60 (63.2)	1.5 [1.4; 3.2]	0.35 [0.23; 0.55]	< 0.001	
Rest of World	22	9 (40.9)	10.6 [1.4; -]	11	2 (18.2)	6.0 [3.9; -]	1.67 [0.35; 7.87]	0.517	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

EORTC QLQ-C30: Symptomskala Schmerzen

Tabelle 4G-8: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik die Symptomskala Schmerzen des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab 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	75	32 (42.7)	8.3 [3.0; -]	63	31 (49.2)	4.5 [1.9; -]	0.68 [0.41; 1.12]	0.133	0.842
Male	66	28 (42.4)	10.3 [3.0; -]	68	35 (51.5)	2.8 [1.5; -]	0.67 [0.41; 1.10]	0.112	
Age									
≤70	98	43 (43.9)	Not reached [3.0; -]	95	48 (50.5)	3.3 [1.9; -]	0.71 [0.47; 1.08]	0.106	0.890
>70	43	17 (39.5)	10.3 [4.2; -]	36	18 (50.0)	3.1 [1.4; -]	0.61 [0.31; 1.20]	0.152	
ECOG									
0	70	37 (52.9)	6.2 [2.1; -]	70	38 (54.3)	2.8 [1.5; 8.1]	0.74 [0.47; 1.16]	0.192	0.596
1	71	23 (32.4)	Not reached [10.3; -]	61	28 (45.9)	4.5 [1.9; -]	0.60 [0.35; 1.05]	0.073	
Geographic Region									
Asia	22	12 (54.5)	4.2 [0.7; -]	25	14 (56.0)	2.1 [1.4; -]	0.94 [0.43; 2.04]	0.876	0.604
Western Europe/North America	97	38 (39.2)	10.4 [6.2; -]	95	48 (50.5)	3.3 [2.4; 8.1]	0.58 [0.38; 0.90]	0.015	
Rest of World	22	10 (45.5)	Not reached [1.4; -]	11	4 (36.4)	Not reached [0.5; -]	0.90 [0.28; 2.88]	0.859	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

EORTC QLQ-C30: Symptomskala Atemnot

Tabelle 4G-9: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Atemnot des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-C30 Dyspnoea	**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	75	25 (33.3)	Not reached [7.5; -]	63	29 (46.0)	4.8 [2.6; -]	0.56 [0.33; 0.97]	0.039	0.527
Male	66	28 (42.4)	11.0 [5.8; -]	68	30 (44.1)	7.1 [3.0; -]	0.74 [0.44; 1.25]	0.261	
Age									
≤70	98	38 (38.8)	Not reached [6.6; -]	95	41 (43.2)	7.1 [3.8; 11.0]	0.74 [0.48; 1.16]	0.188	0.323
>70	43	15 (34.9)	11.0 [8.3; 11.0]	36	18 (50.0)	4.1 [1.9; 6.5]	0.47 [0.23; 0.94]	0.034	
ECOG									
0	70	25 (35.7)	Not reached [6.6; -]	70	27 (38.6)	8.3 [4.8; -]	0.75 [0.43; 1.30]	0.306	0.475
1	71	28 (39.4)	10.4 [7.5; 11.0]	61	32 (52.5)	3.8 [1.9; 6.5]	0.55 [0.33; 0.93]	0.025	
Geographic Region									
Asia	22	7 (31.8)	Not reached [4.2; -]	25	17 (68.0)	2.1 [1.5; 8.3]	0.37 [0.15; 0.89]	0.026	0.243
Western Europe/North America	97	38 (39.2)	10.4 [6.6; -]	95	37 (38.9)	9.5 [4.1; 11.0]	0.79 [0.50; 1.26]	0.321	
Rest of World	22	8 (36.4)	Not reached [2.1; -]	11	5 (45.5)	4.5 [0.9; -]	0.51 [0.16; 1.58]	0.245	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

Tabelle 4G-10: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Schlaflosigkeit des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab 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	75	28 (37.3)	10.4 [4.2; -]	63	25 (39.7)	7.4 [2.8; -]	0.84 [0.49; 1.45]	0.528	0.352
Male	66	28 (42.4)	Not reached [2.8; -]	68	22 (32.4)	10.3 [5.4; -]	1.22 [0.70; 2.14]	0.487	
Age									
≤70	98	41 (41.8)	8.3 [4.2; -]	95	36 (37.9)	10.3 [5.6; -]	1.04 [0.66; 1.63]	0.872	0.802
>70	43	15 (34.9)	Not reached [2.8; -]	36	11 (30.6)	Not reached [2.8; -]	0.96 [0.44; 2.10]	0.913	
ECOG									
0	70	30 (42.9)	8.3 [2.8; -]	70	23 (32.9)	10.3 [5.4; -]	1.30 [0.75; 2.25]	0.347	0.240
1	71	26 (36.6)	10.4 [6.2; -]	61	24 (39.3)	7.4 [2.8; -]	0.79 [0.45; 1.38]	0.399	
Geographic Region									
Asia	22	13 (59.1)	2.8 [0.8; -]	25	16 (64.0)	2.8 [1.4; -]	1.02 [0.49; 2.14]	0.948	0.686
Western Europe/North America	97	36 (37.1)	Not reached [6.2; -]	95	27 (28.4)	10.9 [9.2; -]	1.17 [0.71; 1.95]	0.537	
Rest of World	22	7 (31.8)	Not reached [2.1; -]	11	4 (36.4)	5.6 [1.3; -]	0.60 [0.17; 2.09]	0.422	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

EORTC QLQ-C30: Symptomskala Appetitverlust

Tabelle 4G-11: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Appetitverlust des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab 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	75	27 (36.0)	Not reached [6.8; -]	63	26 (41.3)	6.6 [2.8; -]	0.67 [0.39; 1.17]	0.162	0.112
Male	66	23 (34.8)	10.8 [8.2; -]	68	40 (58.8)	2.1 [1.4; 6.5]	0.38 [0.22; 0.63]	< 0.001	
Age									
≤70	98	35 (35.7)	10.8 [8.5; -]	95	52 (54.7)	2.8 [1.5; 7.1]	0.43 [0.28; 0.66]	< 0.001	0.228
>70	43	15 (34.9)	10.4 [8.2; -]	36	14 (38.9)	6.5 [2.1; -]	0.70 [0.34; 1.47]	0.345	
ECOG									
0	70	29 (41.4)	10.8 [6.7; -]	70	35 (50.0)	4.1 [2.1; 7.1]	0.52 [0.31; 0.87]	0.012	0.425
1	71	21 (29.6)	10.6 [10.4; -]	61	31 (50.8)	2.8 [1.4; -]	0.43 [0.25; 0.76]	0.003	
Geographic Region									
Asia	22	9 (40.9)	8.5 [2.8; -]	25	14 (56.0)	3.1 [1.4; -]	0.63 [0.27; 1.47]	0.287	0.713
Western Europe/North America	97	35 (36.1)	10.8 [8.2; -]	95	47 (49.5)	4.1 [1.9; 9.5]	0.48 [0.31; 0.76]	0.002	
Rest of World	22	6 (27.3)	Not reached [10.6; -]	11	5 (45.5)	4.2 [0.7; -]	0.38 [0.12; 1.26]	0.115	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

EORTC QLQ-C30: Symptomskala Verstopfung

Tabelle 4G-12: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Verstopfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab 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	75	16 (21.3)	Not reached [-; -]	63	27 (42.9)	5.1 [3.8; 10.6]	0.37 [0.19; 0.69]	0.002	0.402
Male	66	15 (22.7)	11.1 [-; -]	68	22 (32.4)	Not reached [8.5; -]	0.56 [0.29; 1.08]	0.081	
Age									
≤70	98	24 (24.5)	11.1 [-; -]	95	41 (43.2)	8.5 [3.8; -]	0.43 [0.26; 0.72]	0.001	0.471
>70	43	7 (16.3)	Not reached [-; -]	36	8 (22.2)	Not reached [7.3; -]	0.56 [0.20; 1.56]	0.268	
ECOG									
0	70	15 (21.4)	11.1 [-; -]	70	24 (34.3)	Not reached [4.8; -]	0.48 [0.25; 0.92]	0.026	0.909
1	71	16 (22.5)	Not reached [-; -]	61	25 (41.0)	10.2 [3.8; -]	0.46 [0.25; 0.87]	0.017	
Geographic Region									
Asia	22	5 (22.7)	Not reached [6.2; -]	25	12 (48.0)	10.6 [2.5; -]	0.50 [0.17; 1.42]	0.191	0.056
Western Europe/North America	97	17 (17.5)	11.1 [-; -]	95	35 (36.8)	7.3 [4.8; -]	0.33 [0.18; 0.60]	< 0.001	
Rest of World	22	9 (40.9)	Not reached [2.1; -]	11	2 (18.2)	Not reached [0.5; -]	1.52 [0.33; 7.12]	0.593	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

EORTC QLQ-C30: Symptomskala Diarrhoe

Tabelle 4G-13: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Diarrhoe des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-C30 Diarrhoea	**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	75	34 (45.3)	8.3 [2.8; -]	63	37 (58.7)	2.7 [1.4; 5.6]	0.60 [0.37; 0.96]	0.034	0.268
Male	66	22 (33.3)	Not reached [8.3; -]	68	35 (51.5)	2.7 [1.4; -]	0.43 [0.25; 0.74]	0.002	
Age									
≤70	98	41 (41.8)	10.4 [6.5; -]	95	54 (56.8)	2.1 [1.4; 5.3]	0.48 [0.32; 0.73]	< 0.001	0.457
>70	43	15 (34.9)	Not reached [2.1; -]	36	18 (50.0)	5.2 [2.0; 8.7]	0.66 [0.33; 1.33]	0.245	
ECOG									
0	70	33 (47.1)	8.3 [4.1; -]	70	41 (58.6)	2.0 [1.4; 5.3]	0.51 [0.32; 0.82]	0.005	0.914
1	71	23 (32.4)	10.6 [8.3; -]	61	31 (50.8)	5.2 [2.0; 8.7]	0.53 [0.31; 0.91]	0.022	
Geographic Region									
Asia	22	12 (54.5)	2.8 [1.4; -]	25	13 (52.0)	8.7 [2.0; -]	1.04 [0.47; 2.28]	0.925	0.159
Western Europe/North America	97	38 (39.2)	10.6 [6.8; -]	95	55 (57.9)	2.5 [1.4; 3.4]	0.44 [0.29; 0.68]	< 0.001	
Rest of World	22	6 (27.3)	Not reached [2.1; -]	11	4 (36.4)	5.9 [0.5; -]	0.47 [0.13; 1.69]	0.246	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

EORTC QLQ-CR29

EORTC QLQ-CR29: Symptomskala Häufiger Harndrang

Tabelle 4G-14: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Häufiger Harndrang des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Urinary Frequency	**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	74	33 (44.6)	8.3 [1.4; -]	64	33 (51.6)	3.2 [1.9; 10.6]	0.73 [0.45; 1.20]	0.219	0.873
Male	65	30 (46.2)	6.2 [2.8; -]	68	32 (47.1)	4.6 [2.0; -]	0.79 [0.48; 1.31]	0.362	
Age									
≤70	96	45 (46.9)	8.3 [4.1; -]	96	47 (49.0)	4.6 [2.1; -]	0.78 [0.51; 1.17]	0.228	0.873
>70	43	18 (41.9)	6.5 [1.4; -]	36	18 (50.0)	2.7 [1.6; -]	0.76 [0.40; 1.47]	0.423	
ECOG									
0	68	33 (48.5)	6.2 [2.0; -]	70	33 (47.1)	4.6 [2.1; -]	0.87 [0.53; 1.41]	0.560	0.675
1	71	30 (42.3)	8.3 [4.2; -]	62	32 (51.6)	2.8 [1.6; -]	0.72 [0.44; 1.19]	0.196	
Geographic Region									
Asia	22	9 (40.9)	Not reached [1.4; -]	25	13 (52.0)	10.6 [1.9; -]	0.77 [0.33; 1.81]	0.548	0.995
Western Europe/North America	96	43 (44.8)	8.3 [4.1; -]	96	47 (49.0)	3.7 [2.1; -]	0.75 [0.49; 1.14]	0.179	
Rest of World	21	11 (52.4)	4.1 [1.4; -]	11	5 (45.5)	3.3 [0.5; -]	0.74 [0.26; 2.14]	0.576	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Blut und Schleim im Stuhl

Tabelle 4G-15: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Blut und Schleim im Stuhl des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Blood and Mucus in Stool	**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	74	9 (12.2)	Not reached [-; -]	64	17 (26.6)	Not reached [6.1; -]	0.40 [0.18; 0.90]	0.026	0.222
Male	65	17 (26.2)	Not reached [10.4; -]	68	19 (27.9)	Not reached [-; -]	0.72 [0.37; 1.40]	0.335	
Age									
≤70	96	21 (21.9)	Not reached [-; -]	96	31 (32.3)	Not reached [6.1; -]	0.54 [0.31; 0.95]	0.033	0.659
>70	43	5 (11.6)	Not reached [-; -]	36	5 (13.9)	Not reached [-; -]	0.68 [0.20; 2.38]	0.552	
ECOG									
0	68	11 (16.2)	Not reached [-; -]	70	18 (25.7)	Not reached [6.1; -]	0.44 [0.21; 0.95]	0.038	0.522
1	71	15 (21.1)	Not reached [-; -]	62	18 (29.0)	Not reached [4.9; -]	0.65 [0.33; 1.30]	0.224	
Geographic Region									
Asia	22	5 (22.7)	Not reached [2.8; -]	25	9 (36.0)	Not reached [2.7; -]	0.59 [0.20; 1.78]	0.352	0.881
Western Europe/North America	96	16 (16.7)	Not reached [-; -]	96	23 (24.0)	Not reached [9.0; -]	0.53 [0.27; 1.01]	0.054	
Rest of World	21	5 (23.8)	Not reached [7.7; -]	11	4 (36.4)	Not reached [0.7; -]	0.41 [0.11; 1.56]	0.191	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Häufiger Stuhlgang

Tabelle 4G-16: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Häufiger Stuhlgang des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Stool Frequency	**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	74	31 (41.9)	8.8 [4.5; -]	64	41 (64.1)	3.1 [1.6; 5.6]	0.46 [0.28; 0.74]	0.002	0.247
Male	65	31 (47.7)	8.3 [5.3; -]	68	35 (51.5)	3.3 [2.1; 11.3]	0.73 [0.45; 1.18]	0.200	
Age									
≤70	96	44 (45.8)	8.5 [6.2; -]	96	56 (58.3)	2.8 [1.9; 5.6]	0.57 [0.38; 0.85]	0.006	0.659
>70	43	18 (41.9)	8.5 [2.1; -]	36	20 (55.6)	4.8 [2.4; 8.6]	0.63 [0.32; 1.21]	0.163	
ECOG									
0	68	30 (44.1)	10.4 [7.7; -]	70	40 (57.1)	3.2 [2.1; 5.3]	0.53 [0.32; 0.86]	0.010	0.505
1	71	32 (45.1)	7.5 [2.8; -]	62	36 (58.1)	3.1 [1.6; 7.3]	0.66 [0.41; 1.06]	0.085	
Geographic Region									
Asia	22	11 (50.0)	8.8 [2.8; -]	25	14 (56.0)	7.3 [1.5; -]	0.82 [0.37; 1.81]	0.623	0.067
Western Europe/North America	96	39 (40.6)	8.5 [7.4; -]	96	58 (60.4)	2.7 [1.7; 3.7]	0.46 [0.30; 0.70]	< 0.001	
Rest of World	21	12 (57.1)	6.2 [0.7; -]	11	4 (36.4)	5.6 [0.9; 11.3]	1.52 [0.42; 5.49]	0.523	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Unkontrollierbarer Harndrang

Tabelle 4G-17: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Unkontrollierbarer Harndrang des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Urinary Incontinence	**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	74	13 (17.6)	10.8 [10.8; -]	64	14 (21.9)	Not reached [7.3; -]	0.67 [0.31; 1.45]	0.305	0.334
Male	65	11 (16.9)	Not reached [-; -]	68	8 (11.8)	Not reached [10.3; -]	1.10 [0.44; 2.76]	0.842	
Age									
≤70	96	14 (14.6)	Not reached [10.8; -]	96	13 (13.5)	Not reached [-; -]	0.87 [0.40; 1.88]	0.728	0.982
>70	43	10 (23.3)	Not reached [8.1; -]	36	9 (25.0)	Not reached [6.4; -]	0.79 [0.32; 1.97]	0.619	
ECOG									
0	68	9 (13.2)	Not reached [10.8; -]	70	10 (14.3)	Not reached [10.3; -]	0.73 [0.29; 1.82]	0.497	0.533
1	71	15 (21.1)	Not reached [-; -]	62	12 (19.4)	Not reached [-; -]	0.97 [0.45; 2.08]	0.935	
Geographic Region									
Asia	22	6 (27.3)	10.8 [6.3; 10.8]	25	8 (32.0)	10.3 [7.1; -]	0.76 [0.25; 2.35]	0.639	0.912
Western Europe/North America	96	12 (12.5)	Not reached [-; -]	96	12 (12.5)	Not reached [-; -]	0.85 [0.38; 1.92]	0.703	
Rest of World	21	6 (28.6)	Not reached [6.5; -]	11	2 (18.2)	Not reached [2.1; -]	0.96 [0.19; 4.85]	0.961	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Schmerzen beim Wasserlassen

Tabelle 4G-18: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Schmerzen beim Wasserlassen des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Dysuria	**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	74	10 (13.5)	Not reached [-; -]	64	11 (17.2)	Not reached [-; -]	0.69 [0.28; 1.66]	0.406	0.668
Male	65	9 (13.8)	Not reached [-; -]	68	9 (13.2)	Not reached [-; -]	0.89 [0.35; 2.26]	0.811	
Age									
≤70	96	12 (12.5)	Not reached [-; -]	96	15 (15.6)	Not reached [-; -]	0.70 [0.33; 1.52]	0.370	0.582
>70	43	7 (16.3)	Not reached [-; -]	36	5 (13.9)	Not reached [-; -]	1.01 [0.32; 3.20]	0.992	
ECOG									
0	68	7 (10.3)	Not reached [-; -]	70	10 (14.3)	Not reached [-; -]	0.59 [0.22; 1.56]	0.287	0.460
1	71	12 (16.9)	Not reached [-; -]	62	10 (16.1)	Not reached [-; -]	0.97 [0.41; 2.25]	0.936	
Geographic Region									
Asia	22	3 (13.6)	Not reached [-; -]	25	6 (24.0)	Not reached [6.0; -]	0.60 [0.15; 2.41]	0.474	0.637
Western Europe/North America	96	11 (11.5)	Not reached [-; -]	96	13 (13.5)	Not reached [-; -]	0.77 [0.34; 1.74]	0.537	
Rest of World	21	5 (23.8)	Not reached [7.7; -]	11	1 (9.1)	Not reached [2.1; -]	1.61 [0.18; 14.54]	0.670	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Bauchschmerzen

Tabelle 4G-19: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Bauchschmerzen des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Abdominal 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	74	24 (32.4)	Not reached [8.3; -]	64	27 (42.2)	6.5 [4.8; 10.6]	0.63 [0.36; 1.09]	0.099	0.984
Male	65	21 (32.3)	Not reached [4.5; -]	68	28 (41.2)	10.5 [3.7; -]	0.70 [0.40; 1.23]	0.210	
Age									
≤70	96	31 (32.3)	Not reached [8.3; -]	96	46 (47.9)	5.6 [4.1; 10.6]	0.54 [0.34; 0.85]	0.008	0.054
>70	43	14 (32.6)	Not reached [4.2; -]	36	9 (25.0)	10.5 [6.5; -]	1.33 [0.58; 3.08]	0.503	
ECOG									
0	68	19 (27.9)	Not reached [-; -]	70	29 (41.4)	6.0 [4.2; -]	0.53 [0.30; 0.95]	0.032	0.208
1	71	26 (36.6)	Not reached [2.8; -]	62	26 (41.9)	6.5 [4.4; -]	0.85 [0.49; 1.46]	0.551	
Geographic Region									
Asia	22	10 (45.5)	8.3 [1.4; -]	25	15 (60.0)	6.5 [3.6; 10.6]	0.83 [0.37; 1.87]	0.661	0.692
Western Europe/North America	96	25 (26.0)	Not reached [-; -]	96	35 (36.5)	9.0 [4.8; -]	0.60 [0.36; 1.00]	0.050	
Rest of World	21	10 (47.6)	4.2 [2.1; -]	11	5 (45.5)	5.6 [0.5; -]	0.75 [0.26; 2.21]	0.604	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Schmerzen im Analbereich

Tabelle 4G-20: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Schmerzen im Analbereich des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Buttock 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	74	14 (18.9)	Not reached [-; -]	64	30 (46.9)	5.1 [3.5; -]	0.31 [0.16; 0.59]	< 0.001	0.394
Male	65	19 (29.2)	Not reached [-; -]	68	31 (45.6)	9.9 [2.1; -]	0.52 [0.29; 0.92]	0.024	
Age									
≤70	96	23 (24.0)	Not reached [-; -]	96	46 (47.9)	5.1 [2.7; -]	0.40 [0.24; 0.67]	< 0.001	0.588
>70	43	10 (23.3)	Not reached [8.7; -]	36	15 (41.7)	6.5 [2.8; -]	0.44 [0.20; 1.00]	0.051	
ECOG									
0	68	15 (22.1)	Not reached [-; -]	70	31 (44.3)	4.8 [3.0; -]	0.39 [0.21; 0.72]	0.003	0.603
1	71	18 (25.4)	Not reached [10.3; -]	62	30 (48.4)	5.1 [2.7; 8.3]	0.43 [0.24; 0.78]	0.005	
Geographic Region									
Asia	22	8 (36.4)	Not reached [2.2; -]	25	12 (48.0)	6.5 [2.1; -]	0.67 [0.27; 1.68]	0.394	0.328
Western Europe/North America	96	19 (19.8)	Not reached [-; -]	96	43 (44.8)	5.1 [3.0; -]	0.35 [0.20; 0.61]	< 0.001	
Rest of World	21	6 (28.6)	Not reached [2.1; -]	11	6 (54.5)	1.5 [0.5; -]	0.27 [0.09; 0.83]	0.023	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Blähungen

Tabelle 4G-21: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Blähungen des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Bloating	**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	74	24 (32.4)	Not reached [8.3; -]	64	24 (37.5)	6.5 [4.4; 10.6]	0.72 [0.40; 1.29]	0.274	0.643
Male	65	22 (33.8)	Not reached [8.9; -]	68	22 (32.4)	Not reached [4.4; -]	0.96 [0.53; 1.73]	0.882	
ECOG									
0	68	17 (25.0)	Not reached [-; -]	70	24 (34.3)	Not reached [4.4; -]	0.56 [0.30; 1.06]	0.074	0.067
1	71	29 (40.8)	10.4 [2.1; -]	62	22 (35.5)	10.6 [4.4; -]	1.22 [0.70; 2.13]	0.481	
Geographic Region									
Asia	22	7 (31.8)	Not reached [1.4; -]	25	10 (40.0)	10.6 [4.4; -]	0.90 [0.34; 2.37]	0.828	0.963
Western Europe/North America	96	31 (32.3)	Not reached [10.4; -]	96	33 (34.4)	9.2 [4.6; -]	0.81 [0.49; 1.33]	0.411	
Rest of World	21	8 (38.1)	Not reached [2.1; -]	11	3 (27.3)	Not reached [0.5; -]	0.98 [0.26; 3.72]	0.980	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Trockener Mund

Tabelle 4G-22: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Trockener Mund des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 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	74	33 (44.6)	8.3 [2.1; -]	64	34 (53.1)	3.1 [1.6; -]	0.75 [0.46; 1.23]	0.255	0.184
Male	65	33 (50.8)	6.2 [2.4; -]	68	44 (64.7)	1.5 [0.9; 3.0]	0.49 [0.31; 0.78]	0.002	
Age									
≤70	96	46 (47.9)	6.2 [2.8; -]	96	60 (62.5)	2.1 [1.4; 3.7]	0.57 [0.39; 0.84]	0.005	0.338
>70	43	20 (46.5)	8.3 [2.1; -]	36	18 (50.0)	2.8 [1.6; 11.3]	0.80 [0.41; 1.54]	0.499	
ECOG									
0	68	32 (47.1)	6.7 [2.9; -]	70	44 (62.9)	1.6 [1.4; 3.4]	0.50 [0.32; 0.80]	0.004	0.218
1	71	34 (47.9)	8.2 [2.1; -]	62	34 (54.8)	2.8 [1.5; 9.0]	0.74 [0.45; 1.20]	0.217	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Haarausfall

Tabelle 4G-23: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Haarausfall des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Hair 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	74	24 (32.4)	10.6 [7.4; -]	64	48 (75.0)	1.9 [1.6; 2.6]	0.26 [0.15; 0.44]	< 0.001	0.071
Male	65	8 (12.3)	Not reached [-; -]	68	38 (55.9)	2.7 [1.9; 5.1]	0.14 [0.07; 0.31]	< 0.001	
Age									
≤70	96	21 (21.9)	Not reached [-; -]	96	63 (65.6)	2.1 [1.6; 2.8]	0.21 [0.13; 0.35]	< 0.001	0.380
>70	43	11 (25.6)	10.6 [8.9; -]	36	23 (63.9)	2.5 [1.9; 3.9]	0.28 [0.13; 0.59]	< 0.001	
ECOG									
0	68	12 (17.6)	Not reached [10.6; -]	70	45 (64.3)	2.5 [2.0; 4.0]	0.16 [0.08; 0.30]	< 0.001	0.161
1	71	20 (28.2)	Not reached [7.6; -]	62	41 (66.1)	1.9 [1.6; 2.8]	0.31 [0.18; 0.53]	< 0.001	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Geschmacksstörungen

Tabelle 4G-24: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Geschmacksstörungen des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 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	74	24 (32.4)	Not reached [8.3; -]	64	44 (68.8)	1.8 [1.4; 3.0]	0.31 [0.19; 0.53]	< 0.001	0.240
Male	65	16 (24.6)	Not reached [-; -]	68	44 (64.7)	1.9 [1.4; 3.3]	0.23 [0.13; 0.42]	< 0.001	
Age									
≤70	96	26 (27.1)	Not reached [10.6; -]	96	67 (69.8)	1.6 [1.4; 2.4]	0.21 [0.13; 0.34]	< 0.001	0.065
>70	43	14 (32.6)	Not reached [1.4; -]	36	21 (58.3)	3.0 [1.4; 6.5]	0.50 [0.25; 0.98]	0.044	
ECOG									
0	68	20 (29.4)	Not reached [8.8; -]	70	51 (72.9)	1.6 [1.4; 2.5]	0.22 [0.13; 0.38]	< 0.001	0.330
1	71	20 (28.2)	Not reached [10.6; -]	62	37 (59.7)	2.1 [1.4; 4.9]	0.35 [0.20; 0.62]	< 0.001	
Geographic Region									
Asia	22	8 (36.4)	Not reached [1.4; -]	25	19 (76.0)	2.8 [1.4; 5.2]	0.35 [0.14; 0.87]	0.024	0.403
Western Europe/North America	96	25 (26.0)	Not reached [10.6; -]	96	64 (66.7)	1.6 [1.4; 2.5]	0.24 [0.15; 0.39]	< 0.001	
Rest of World	21	7 (33.3)	Not reached [1.4; -]	11	5 (45.5)	1.9 [0.5; -]	0.45 [0.14; 1.43]	0.173	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Darmgasentweichungen

Tabelle 4G-25: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Darmgasentweichungen des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Flatulence	**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									
≤70	96	40 (41.7)	9.2 [4.4; -]	96	45 (46.9)	5.5 [2.8; -]	0.76 [0.49; 1.16]	0.206	0.614
>70	43	16 (37.2)	Not reached [2.8; -]	36	12 (33.3)	8.7 [2.8; -]	0.92 [0.43; 1.94]	0.820	
ECOG									
0	68	23 (33.8)	Not reached [8.5; -]	70	29 (41.4)	6.0 [2.9; -]	0.66 [0.38; 1.14]	0.134	0.298
1	71	33 (46.5)	4.9 [2.9; -]	62	28 (45.2)	8.4 [1.9; -]	0.93 [0.56; 1.54]	0.776	
Geographic Region									
Asia	22	9 (40.9)	Not reached [1.4; -]	25	13 (52.0)	6.0 [0.7; -]	0.70 [0.30; 1.64]	0.413	0.974
Western Europe/North America	96	39 (40.6)	8.7 [4.4; -]	96	41 (42.7)	8.4 [2.9; -]	0.81 [0.52; 1.26]	0.349	
Rest of World	21	8 (38.1)	Not reached [1.7; -]	11	3 (27.3)	Not reached [0.4; -]	0.94 [0.25; 3.55]	0.926	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Unkontrollierbarer Stuhldrang

Tabelle 4G-26: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Unkontrollierbarer Stuhldrang des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Faecal Incontinence	**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	74	13 (17.6)	10.8 [10.7; 10.8]	64	17 (26.6)	Not reached [7.1; -]	0.43 [0.19; 0.96]	0.040	0.238
Male	65	15 (23.1)	Not reached [-; -]	68	14 (20.6)	Not reached [9.9; -]	1.01 [0.49; 2.10]	0.975	
Age									
≤70	96	19 (19.8)	10.8 [10.7; -]	96	22 (22.9)	Not reached [9.9; -]	0.77 [0.42; 1.43]	0.415	0.914
>70	43	9 (20.9)	10.8 [10.3; -]	36	9 (25.0)	Not reached [4.8; -]	0.67 [0.26; 1.71]	0.399	
ECOG									
0	68	16 (23.5)	10.8 [10.7; -]	70	15 (21.4)	Not reached [9.9; -]	0.93 [0.46; 1.90]	0.846	0.424
1	71	12 (16.9)	10.8 [10.8; -]	62	16 (25.8)	Not reached [7.1; -]	0.55 [0.25; 1.19]	0.128	
Geographic Region									
Asia	22	6 (27.3)	10.8 [10.3; 10.8]	25	10 (40.0)	Not reached [3.1; -]	0.60 [0.20; 1.75]	0.347	0.892
Western Europe/North America	96	17 (17.7)	Not reached [10.8; -]	96	18 (18.8)	Not reached [9.9; -]	0.80 [0.41; 1.56]	0.507	
Rest of World	21	5 (23.8)	10.7 [-; -]	11	3 (27.3)	Not reached [0.4; -]	0.68 [0.16; 2.93]	0.610	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Wunde Hautstellen

Tabelle 4G-27: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Wunde Hautstellen des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Sore Skin	**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	74	19 (25.7)	Not reached [8.8; -]	64	31 (48.4)	3.5 [2.7; 6.5]	0.32 [0.18; 0.58]	< 0.001	0.418
Male	65	23 (35.4)	Not reached [8.2; -]	68	34 (50.0)	3.7 [2.0; -]	0.51 [0.30; 0.88]	0.015	
Age									
≤70	96	29 (30.2)	Not reached [9.9; -]	96	50 (52.1)	3.3 [2.1; 7.1]	0.39 [0.24; 0.62]	< 0.001	0.291
>70	43	13 (30.2)	10.3 [8.2; -]	36	15 (41.7)	5.2 [2.5; 10.2]	0.50 [0.23; 1.08]	0.079	
ECOG									
0	68	22 (32.4)	Not reached [8.8; -]	70	37 (52.9)	3.4 [2.4; 7.1]	0.38 [0.22; 0.66]	< 0.001	0.545
1	71	20 (28.2)	Not reached [8.7; -]	62	28 (45.2)	4.8 [2.5; -]	0.45 [0.25; 0.81]	0.008	
Geographic Region									
Asia	22	10 (45.5)	10.3 [2.8; -]	25	14 (56.0)	2.8 [1.4; -]	0.62 [0.27; 1.41]	0.252	0.509
Western Europe/North America	96	25 (26.0)	Not reached [-; -]	96	45 (46.9)	4.1 [3.2; 10.2]	0.39 [0.23; 0.64]	< 0.001	
Rest of World	21	7 (33.3)	10.4 [2.8; -]	11	6 (54.5)	1.7 [0.5; -]	0.30 [0.10; 0.91]	0.033	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Peinlichkeitsempfinden

Tabelle 4G-28: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Peinlichkeitsempfinden des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Embarrassment	**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	74	15 (20.3)	10.8 [10.4; -]	64	21 (32.8)	8.7 [7.4; -]	0.40 [0.20; 0.80]	0.009	0.089
Male	65	18 (27.7)	Not reached [-; -]	68	16 (23.5)	Not reached [-; -]	1.18 [0.60; 2.31]	0.632	
Age									
≤70	96	25 (26.0)	10.8 [10.8; -]	96	31 (32.3)	Not reached [7.4; -]	0.74 [0.43; 1.25]	0.255	0.539
>70	43	8 (18.6)	Not reached [10.4; -]	36	6 (16.7)	Not reached [8.3; -]	0.88 [0.30; 2.56]	0.816	
ECOG									
0	68	16 (23.5)	10.8 [10.8; -]	70	16 (22.9)	Not reached [10.2; -]	0.93 [0.46; 1.88]	0.850	0.526
1	71	17 (23.9)	Not reached [10.4; -]	62	21 (33.9)	Not reached [4.8; -]	0.64 [0.34; 1.22]	0.174	
Geographic Region									
Asia	22	6 (27.3)	10.8 [6.2; 10.8]	25	6 (24.0)	Not reached [10.2; -]	0.96 [0.29; 3.15]	0.943	0.132
Western Europe/North America	96	20 (20.8)	Not reached [-; -]	96	30 (31.3)	Not reached [4.8; -]	0.55 [0.31; 0.98]	0.044	
Rest of World	21	7 (33.3)	Not reached [4.2; -]	11	1 (9.1)	Not reached [1.8; -]	2.94 [0.36; 24.04]	0.314	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-CR29: Symptomskala Probleme bei der Stomapflege

Tabelle 4G-29: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Probleme bei der Stomapflege des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Stoma Care Problems	**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	6	2 (33.3)	n.c.	7	3 (42.9)	n.c.	n.c.	n.c.	n.c.
Male	18	5 (27.8)	n.c.	14	1 (7.1)	n.c.	n.c.	n.c.	
Age									
≤70	22	7 (31.8)	n.c.	16	3 (18.8)	n.c.	n.c.	n.c.	n.c.
>70	2	0 (0.0)	n.c.	5	1 (20.0)	n.c.	n.c.	n.c.	
ECOG									
0	9	4 (44.4)	n.c.	8	2 (25.0)	n.c.	n.c.	n.c.	n.c.
1	15	3 (20.0)	n.c.	13	2 (15.4)	n.c.	n.c.	n.c.	
Geographic Region									
Asia	4	2 (50.0)	n.c.	9	1 (11.1)	n.c.	n.c.	n.c.	n.c.
Western Europe/North America	17	4 (23.5)	n.c.	9	2 (22.2)	n.c.	n.c.	n.c.	
Rest of World	3	1 (33.3)	n.c.	3	1 (33.3)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items; n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary

EORTC QLQ-CR29: Symptomskala Sexuelle Beschwerden Mann

Tabelle 4G-30: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Sexuelle Beschwerden Mann des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Impotence	**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									
Male	64	24 (37.5)	Not reached [6.2; -]	68	22 (32.4)	Not reached [8.5; -]	1.00 [0.56; 1.78]	0.995	n.a.
Age									
≤70	49	19 (38.8)	Not reached [4.2; -]	55	17 (30.9)	Not reached [7.1; -]	1.09 [0.57; 2.11]	0.787	0.551
>70	15	5 (33.3)	Not reached [1.4; -]	13	5 (38.5)	10.2 [0.5; -]	0.77 [0.22; 2.70]	0.686	
ECOG									
0	36	13 (36.1)	Not reached [4.1; -]	40	13 (32.5)	Not reached [7.1; -]	1.00 [0.46; 2.16]	0.996	0.820
1	28	11 (39.3)	8.4 [2.8; -]	28	9 (32.1)	10.2 [1.4; -]	1.05 [0.43; 2.53]	0.916	
Geographic Region									
Asia	9	4 (44.4)	6.2 [0.7; -]	13	7 (53.8)	8.5 [1.3; -]	0.81 [0.24; 2.77]	0.737	0.819
Western Europe/North America	45	15 (33.3)	Not reached [6.2; -]	50	13 (26.0)	Not reached [10.2; -]	1.06 [0.50; 2.24]	0.877	
Rest of World	10	5 (50.0)	2.8 [1.4; -]	5	2 (40.0)	2.1 [0.4; -]	0.69 [0.12; 3.80]	0.668	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items; n.a.: not applicable (when estimation not possible)

EORTC QLQ-CR29: Symptomskala Sexuelle Beschwerden Frau

Tabelle 4G-31: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Krankheitssymptomatik für die Symptomskala Sexuelle Beschwerden Frau des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Dyspareunia	**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	67	9 (13.4)	Not reached [10.6; -]	59	8 (13.6)	Not reached [10.3; -]	0.71 [0.26; 1.92]	0.502	n.a.
Age									
≤70	42	8 (19.0)	Not reached [10.6; -]	38	7 (18.4)	Not reached [10.3; -]	0.76 [0.26; 2.19]	0.605	0.921
>70	25	1 (4.0)	Not reached [-; -]	21	1 (4.8)	Not reached [-; -]	0.61 [0.04; 9.93]	0.730	
ECOG									
0	29	5 (17.2)	n.c.	27	4 (14.8)	n.c.	n.c.	n.c.	n.c.
1	38	4 (10.5)	n.c.	32	4 (12.5)	n.c.	n.c.	n.c.	
Geographic Region									
Asia	13	0 (0.0)	Not reached [-; -]	10	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	0.247
Western Europe/North America	46	9 (19.6)	10.6 [10.6; -]	43	7 (16.3)	10.3 [6.5; -]	0.90 [0.32; 2.50]	0.835	
Rest of World	8	0 (0.0)	Not reached [-; -]	6	1 (16.7)	Not reached [0.5; -]	n.a. [n.a.; n.a.]	0.206	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items; 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

EQ-5D VAS

EQ-5D VAS (7 Punkte)

Tabelle 4G-32: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Gesundheitszustand für die EQ-5D VAS (7 Punkte) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab 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	76	31 (40.8)	8.3 [3.1; -]	64	37 (57.8)	2.5 [1.6; 6.6]	0.57 [0.35; 0.92]	0.021	0.614
Male	66	30 (45.5)	6.7 [2.2; -]	69	38 (55.1)	3.1 [2.1; 8.4]	0.70 [0.43; 1.13]	0.148	
Age									
≤70	98	42 (42.9)	Not reached [3.1; -]	96	55 (57.3)	2.9 [1.9; 6.6]	0.61 [0.41; 0.92]	0.018	0.875
>70	44	19 (43.2)	8.0 [1.5; -]	37	20 (54.1)	3.3 [1.3; 6.2]	0.65 [0.34; 1.23]	0.186	
ECOG									
0	70	30 (42.9)	Not reached [3.0; -]	71	39 (54.9)	2.9 [2.1; 6.6]	0.63 [0.39; 1.01]	0.055	0.937
1	72	31 (43.1)	8.3 [1.5; -]	62	36 (58.1)	2.5 [1.6; 4.5]	0.65 [0.40; 1.05]	0.079	
Geographic Region									
Asia	22	10 (45.5)	Not reached [1.4; -]	25	17 (68.0)	2.1 [1.4; 10.6]	0.59 [0.27; 1.30]	0.191	0.916
Western Europe/North America	98	39 (39.8)	Not reached [4.1; -]	97	53 (54.6)	2.9 [2.3; 6.2]	0.59 [0.39; 0.90]	0.014	
Rest of World	22	12 (54.5)	2.1 [0.8; -]	11	5 (45.5)	1.9 [0.5; -]	0.92 [0.32; 2.62]	0.876	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 7 points or more decrease from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EQ-5D: European Quality of Life 5 Dimensions; VAS: Visual Analog Scale

EQ-5D VAS (10 Punkte)

Tabelle 4G-33: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Gesundheitszustand für die EQ-5D VAS (10 Punkte) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab 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									
Female	76	27 (35.5)	Not reached [4.2; -]	64	34 (53.1)	3.7 [1.7; 10.6]	0.53 [0.32; 0.89]	0.016	0.601
Male	66	27 (40.9)	Not reached [3.0; -]	69	37 (53.6)	3.6 [2.6; 11.3]	0.67 [0.40; 1.10]	0.113	
Age									
≤70	98	36 (36.7)	Not reached [6.6; -]	96	52 (54.2)	3.6 [2.5; 8.4]	0.55 [0.36; 0.85]	0.007	0.525
>70	44	18 (40.9)	8.3 [2.1; -]	37	19 (51.4)	4.4 [1.4; 11.3]	0.70 [0.36; 1.36]	0.293	
ECOG									
0	70	25 (35.7)	Not reached [6.6; -]	71	36 (50.7)	4.2 [2.6; 11.3]	0.60 [0.35; 1.00]	0.050	0.991
1	72	29 (40.3)	Not reached [3.0; -]	62	35 (56.5)	3.6 [1.7; 4.5]	0.60 [0.36; 0.98]	0.041	
Geographic Region									
Asia	22	10 (45.5)	Not reached [1.4; -]	25	17 (68.0)	2.8 [1.6; 10.6]	0.62 [0.28; 1.36]	0.232	0.969
Western Europe/North America	98	36 (36.7)	Not reached [6.6; -]	97	49 (50.5)	3.8 [2.6; 8.4]	0.58 [0.38; 0.90]	0.015	
Rest of World	22	8 (36.4)	Not reached [1.4; -]	11	5 (45.5)	3.7 [1.3; 11.3]	0.84 [0.25; 2.81]	0.782	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EQ-5D: European Quality of Life 5 Dimensions; VAS: Visual Analog Scale

Anhang 4-G4.3: Gesundheitsbezogene Lebensqualität

Gesundheitsbezogene Lebensqualität

Im Folgenden werden die Ergebnisse der Subgruppenanalysen für die Hauptanalyse des Endpunkts Gesundheitsbezogene Lebensqualität (Zeit bis zur ersten Verschlechterung) dargestellt, für die ein nicht signifikanter Interaktionstest ($p \geq 0,05$) vorliegt.

EORTC QLQ-C30

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-34: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Gesundheitsbezogene Lebensqualität für den globalen Gesundheitsstatus des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
EORTC QLQ-C30 Global Health Status/QoL	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	75	31 (41.3)	8.5 [4.2; -]	63	37 (58.7)	3.1 [1.7; 5.5]	0.52 [0.32; 0.84]	0.008	0.721
Male	66	33 (50.0)	6.6 [2.3; -]	68	42 (61.8)	2.4 [1.4; 4.1]	0.62 [0.39; 0.98]	0.040	
Age									
≤70	98	46 (46.9)	6.6 [2.8; -]	95	61 (64.2)	2.4 [1.5; 3.4]	0.56 [0.38; 0.83]	0.003	0.705
>70	43	18 (41.9)	8.6 [4.1; -]	36	18 (50.0)	4.1 [1.4; -]	0.59 [0.30; 1.14]	0.117	
ECOG									
0	70	35 (50.0)	6.3 [2.8; -]	70	44 (62.9)	2.4 [1.4; 3.9]	0.59 [0.37; 0.92]	0.020	0.839
1	71	29 (40.8)	10.6 [4.1; -]	61	35 (57.4)	3.4 [1.4; 6.5]	0.54 [0.33; 0.89]	0.016	
Geographic Region									
Asia	22	12 (54.5)	2.8 [0.7; -]	25	16 (64.0)	5.2 [1.3; -]	0.86 [0.41; 1.83]	0.701	0.514
Western Europe/North America	97	42 (43.3)	8.5 [3.0; -]	95	58 (61.1)	2.4 [1.4; 4.2]	0.52 [0.35; 0.77]	0.001	
Rest of World	22	10 (45.5)	10.6 [2.1; -]	11	5 (45.5)	2.9 [0.9; -]	0.59 [0.20; 1.76]	0.344	

a: Database Cutoff Date: 19FEB2020
b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab
c: Number of patients: full-analysis-set population, subjects with baseline
d: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation
e: From product-limit (Kaplan-Meier) method
f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and

Treatment of Cancer Quality of Life Questionnaire - Core 30 items; QoL: Quality of Life

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-35: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab 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	75	27 (36.0)	Not reached [4.2; -]	63	33 (52.4)	4.5 [1.7; 6.6]	0.59 [0.35; 0.99]	0.045	0.439
Male	66	24 (36.4)	Not reached [6.2; -]	68	42 (61.8)	3.0 [1.5; 4.6]	0.45 [0.27; 0.74]	0.002	
Age									
≤70	98	34 (34.7)	Not reached [8.5; -]	95	56 (58.9)	3.0 [1.7; 4.7]	0.47 [0.30; 0.72]	< 0.001	0.448
>70	43	17 (39.5)	10.3 [2.1; -]	36	19 (52.8)	3.6 [1.4; 8.3]	0.60 [0.31; 1.16]	0.126	
ECOG									
0	70	25 (35.7)	Not reached [6.2; -]	70	43 (61.4)	3.2 [1.6; 5.1]	0.44 [0.27; 0.73]	0.001	0.492
1	71	26 (36.6)	Not reached [8.3; -]	61	32 (52.5)	3.4 [1.7; -]	0.61 [0.36; 1.03]	0.065	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

EORTC QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-36: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Rollenfunktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab 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	75	34 (45.3)	8.3 [2.8; -]	63	44 (69.8)	1.9 [1.5; 3.1]	0.41 [0.26; 0.66]	< 0.001	0.233
Male	66	38 (57.6)	4.1 [2.2; 10.6]	68	43 (63.2)	1.7 [1.3; 4.2]	0.67 [0.43; 1.04]	0.072	
Age									
≤70	98	50 (51.0)	6.8 [3.0; 10.6]	95	64 (67.4)	1.9 [1.4; 2.8]	0.48 [0.33; 0.71]	< 0.001	0.391
>70	43	22 (51.2)	4.1 [1.4; 10.4]	36	23 (63.9)	1.7 [1.3; 4.9]	0.68 [0.38; 1.22]	0.198	
ECOG									
0	70	40 (57.1)	6.4 [2.8; 10.6]	70	46 (65.7)	1.7 [1.4; 3.0]	0.54 [0.35; 0.83]	0.005	0.731
1	71	32 (45.1)	7.5 [1.4; -]	61	41 (67.2)	1.9 [0.7; 3.8]	0.52 [0.32; 0.82]	0.006	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-37: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab 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	75	18 (24.0)	Not reached [-; -]	63	18 (28.6)	8.7 [6.5; 10.6]	0.64 [0.32; 1.26]	0.194	0.495
Male	66	21 (31.8)	10.8 [8.3; 10.8]	68	20 (29.4)	11.3 [9.2; 11.3]	0.99 [0.53; 1.85]	0.982	
Age									
≤70	98	29 (29.6)	10.8 [10.8; -]	95	29 (30.5)	10.6 [7.4; -]	0.79 [0.47; 1.33]	0.377	0.820
>70	43	10 (23.3)	Not reached [-; -]	36	9 (25.0)	11.3 [8.7; 11.3]	0.97 [0.38; 2.47]	0.951	
ECOG									
0	70	22 (31.4)	10.8 [8.5; 10.8]	70	19 (27.1)	11.3 [9.2; 11.3]	0.98 [0.52; 1.85]	0.954	0.500
1	71	17 (23.9)	Not reached [10.4; -]	61	19 (31.1)	10.6 [6.5; -]	0.72 [0.37; 1.39]	0.325	
Geographic Region									
Asia	22	9 (40.9)	Not reached [2.1; -]	25	11 (44.0)	10.6 [2.8; -]	1.04 [0.43; 2.52]	0.932	0.860
Western Europe/North America	97	22 (22.7)	10.8 [10.8; -]	95	23 (24.2)	Not reached [9.2; -]	0.79 [0.44; 1.42]	0.428	
Rest of World	22	8 (36.4)	Not reached [3.1; -]	11	4 (36.4)	11.3 [1.3; 11.3]	0.93 [0.24; 3.58]	0.915	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-38: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Kognitive Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab 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	75	34 (45.3)	4.9 [2.7; -]	63	26 (41.3)	8.8 [3.0; 10.6]	1.00 [0.60; 1.67]	0.996	0.144
Male	66	26 (39.4)	10.4 [6.2; -]	68	33 (48.5)	4.2 [1.9; -]	0.59 [0.35; 0.99]	0.047	
Age									
≤70	98	42 (42.9)	8.3 [4.4; -]	95	47 (49.5)	4.5 [2.8; 10.6]	0.68 [0.45; 1.04]	0.073	0.264
>70	43	18 (41.9)	8.3 [2.1; -]	36	12 (33.3)	Not reached [2.4; -]	1.18 [0.56; 2.47]	0.661	
ECOG									
0	70	29 (41.4)	10.4 [4.2; -]	70	32 (45.7)	4.5 [2.8; -]	0.68 [0.41; 1.13]	0.138	0.430
1	71	31 (43.7)	7.5 [2.8; -]	61	27 (44.3)	9.4 [2.3; -]	0.93 [0.55; 1.58]	0.801	
Geographic Region									
Asia	22	13 (59.1)	2.2 [0.7; -]	25	14 (56.0)	6.0 [2.5; -]	1.56 [0.72; 3.40]	0.261	0.131
Western Europe/North America	97	35 (36.1)	10.4 [7.5; -]	95	41 (43.2)	6.5 [2.3; -]	0.59 [0.37; 0.93]	0.023	
Rest of World	22	12 (54.5)	3.5 [0.8; -]	11	4 (36.4)	3.9 [0.5; -]	1.40 [0.45; 4.35]	0.565	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

EORTC QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-39: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Soziale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-C30 Social 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	75	33 (44.0)	10.4 [2.1; -]	63	32 (50.8)	4.6 [1.6; 8.3]	0.66 [0.40; 1.09]	0.102	0.163
Male	66	26 (39.4)	10.6 [6.3; -]	68	42 (61.8)	1.9 [1.4; 3.4]	0.41 [0.25; 0.68]	< 0.001	
Age									
≤70	98	44 (44.9)	10.6 [4.2; -]	95	56 (58.9)	2.8 [1.5; 5.5]	0.56 [0.37; 0.83]	0.004	0.610
>70	43	15 (34.9)	10.4 [7.4; -]	36	18 (50.0)	2.5 [0.6; -]	0.46 [0.23; 0.91]	0.027	
ECOG									
0	70	31 (44.3)	9.7 [6.2; -]	70	40 (57.1)	3.0 [1.5; 9.5]	0.49 [0.30; 0.79]	0.003	0.917
1	71	28 (39.4)	10.4 [2.3; -]	61	34 (55.7)	1.9 [1.4; 8.3]	0.58 [0.35; 0.96]	0.036	
Geographic Region									
Asia	22	9 (40.9)	10.6 [2.1; 10.6]	25	16 (64.0)	3.4 [1.4; 10.3]	0.53 [0.23; 1.21]	0.135	0.888
Western Europe/North America	97	37 (38.1)	Not reached [6.6; -]	95	53 (55.8)	2.5 [1.5; 7.1]	0.50 [0.33; 0.77]	0.002	
Rest of World	22	13 (59.1)	7.2 [1.4; 10.6]	11	5 (45.5)	1.1 [0.4; -]	0.61 [0.22; 1.75]	0.362	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

EORTC QLQ-CR29

EORTC QLQ-C29: Funktionsskala Körperbild

Tabelle 4G-40: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Körperbild des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Body Image	**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	74	34 (45.9)	8.3 [2.0; -]	64	40 (62.5)	2.2 [0.7; 3.2]	0.51 [0.32; 0.81]	0.005	0.089
Male	65	38 (58.5)	4.2 [2.1; 6.3]	68	38 (55.9)	3.4 [1.5; 8.3]	0.90 [0.57; 1.41]	0.639	
Age									
≤70	96	54 (56.3)	4.2 [2.1; 8.3]	96	60 (62.5)	2.4 [1.4; 3.4]	0.69 [0.48; 1.00]	0.048	0.967
>70	43	18 (41.9)	6.2 [1.4; -]	36	18 (50.0)	3.6 [1.6; -]	0.73 [0.38; 1.40]	0.341	
Geographic Region									
Asia	22	14 (63.6)	2.1 [0.7; -]	25	19 (76.0)	1.6 [1.3; 4.4]	0.75 [0.37; 1.51]	0.420	0.977
Western Europe/North America	96	46 (47.9)	6.2 [2.8; 8.5]	96	54 (56.3)	3.2 [2.0; 4.4]	0.65 [0.44; 0.97]	0.033	
Rest of World	21	12 (57.1)	2.1 [1.4; -]	11	5 (45.5)	2.1 [0.4; -]	0.76 [0.26; 2.21]	0.617	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-C29: Funktionsskala Sorge um die Gesundheit

Tabelle 4G-41: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Sorge um die Gesundheit des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Anxiety	**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	74	21 (28.4)	Not reached [8.8; -]	64	19 (29.7)	Not reached [5.0; -]	0.86 [0.46; 1.62]	0.641	0.625
Male	65	21 (32.3)	Not reached [8.5; -]	68	17 (25.0)	Not reached [-; -]	1.14 [0.60; 2.17]	0.686	
Age									
≤70	96	30 (31.3)	Not reached [-; -]	96	28 (29.2)	Not reached [-; -]	0.94 [0.56; 1.58]	0.822	0.668
>70	43	12 (27.9)	Not reached [6.2; -]	36	8 (22.2)	Not reached [3.1; -]	1.20 [0.49; 2.95]	0.692	
ECOG									
0	68	22 (32.4)	Not reached [8.5; -]	70	15 (21.4)	Not reached [-; -]	1.32 [0.68; 2.56]	0.415	0.210
1	71	20 (28.2)	Not reached [8.5; -]	62	21 (33.9)	Not reached [3.3; -]	0.76 [0.41; 1.42]	0.393	
Geographic Region									
Asia	22	9 (40.9)	Not reached [2.2; -]	25	9 (36.0)	Not reached [2.9; -]	1.18 [0.47; 2.97]	0.732	0.752
Western Europe/North America	96	25 (26.0)	Not reached [-; -]	96	23 (24.0)	Not reached [-; -]	0.91 [0.51; 1.62]	0.758	
Rest of World	21	8 (38.1)	Not reached [1.4; -]	11	4 (36.4)	Not reached [0.5; -]	0.69 [0.21; 2.29]	0.544	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-C29: Funktionsskala Sorge um das Gewicht

Tabelle 4G-42: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Sorge um das Gewicht des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Weight	**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	74	27 (36.5)	10.4 [7.4; -]	64	28 (43.8)	5.5 [2.5; -]	0.56 [0.32; 0.98]	0.043	0.237
Male	65	25 (38.5)	11.1 [8.2; 11.3]	68	22 (32.4)	Not reached [4.3; -]	0.98 [0.55; 1.74]	0.933	
Age									
≤70	96	37 (38.5)	10.6 [8.8; 11.3]	96	42 (43.8)	6.6 [4.1; -]	0.61 [0.39; 0.97]	0.037	0.061
>70	43	15 (34.9)	10.4 [6.3; -]	36	8 (22.2)	Not reached [4.1; -]	1.43 [0.60; 3.38]	0.422	
ECOG									
0	68	30 (44.1)	10.4 [6.3; 11.3]	70	26 (37.1)	8.5 [4.3; -]	0.87 [0.51; 1.50]	0.619	0.346
1	71	22 (31.0)	10.4 [8.2; -]	62	24 (38.7)	Not reached [2.1; -]	0.66 [0.37; 1.17]	0.155	
Geographic Region									
Asia	22	11 (50.0)	8.8 [2.1; 10.4]	25	12 (48.0)	5.5 [1.6; -]	1.07 [0.47; 2.43]	0.876	0.260
Western Europe/North America	96	31 (32.3)	11.1 [10.3; 11.3]	96	35 (36.5)	8.5 [4.3; -]	0.56 [0.34; 0.94]	0.028	
Rest of World	21	10 (47.6)	4.2 [1.4; -]	11	3 (27.3)	Not reached [0.5; -]	1.24 [0.34; 4.54]	0.740	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items

EORTC QLQ-C29: Funktionsskala Sexuelles Interesse Mann

Tabelle 4G-43: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Sexuelles Interesse Mann des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Sexual Interest (men)	**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									
Male	65	24 (36.9)	Not reached [6.2; -]	68	26 (38.2)	Not reached [3.0; -]	0.80 [0.46; 1.40]	0.443	n.a.
Age									
≤70	50	20 (40.0)	Not reached [4.2; -]	55	23 (41.8)	9.9 [2.9; -]	0.76 [0.41; 1.38]	0.361	0.621
>70	15	4 (26.7)	Not reached [0.8; -]	13	3 (23.1)	Not reached [2.4; -]	1.17 [0.26; 5.25]	0.842	
ECOG									
0	36	13 (36.1)	Not reached [3.2; -]	40	16 (40.0)	9.9 [2.9; -]	0.72 [0.35; 1.51]	0.390	0.662
1	29	11 (37.9)	Not reached [0.8; -]	28	10 (35.7)	Not reached [1.4; -]	0.91 [0.38; 2.14]	0.825	
Geographic Region									
Asia	9	1 (11.1)	Not reached [0.7; -]	13	1 (7.7)	Not reached [-; -]	1.39 [0.09; 22.20]	0.817	0.368
Western Europe/North America	46	17 (37.0)	Not reached [4.2; -]	50	24 (48.0)	3.3 [1.6; -]	0.56 [0.30; 1.05]	0.069	
Rest of World	10	6 (60.0)	2.8 [0.7; -]	5	1 (20.0)	Not reached [0.4; -]	1.97 [0.24; 16.53]	0.531	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items; n.a.: not applicable (when estimation not possible)

EORTC QLQ-C29: Funktionsskala Sexuelles Interesse Frau

Tabelle 4G-44: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Zeit bis zur ersten Verschlechterung für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Sexuelles Interesse Frau des EORTC QLQ-CR29 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
EORTC QLQ-CR29 Sexual Interest (women)	**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	72	6 (8.3)	Not reached [-; -]	63	13 (20.6)	Not reached [-; -]	0.38 [0.14; 1.00]	0.049	n.a.
Age									
≤70	45	5 (11.1)	Not reached [-; -]	41	9 (22.0)	Not reached [-; -]	0.47 [0.16; 1.40]	0.173	0.423
>70	27	1 (3.7)	Not reached [-; -]	22	4 (18.2)	Not reached [-; -]	0.19 [0.02; 1.74]	0.143	
ECOG									
0	31	5 (16.1)	Not reached [-; -]	30	10 (33.3)	Not reached [2.5; -]	0.40 [0.13; 1.17]	0.093	0.752
1	41	1 (2.4)	Not reached [-; -]	33	3 (9.1)	Not reached [-; -]	0.29 [0.03; 2.80]	0.285	
Geographic Region									
Asia	13	0 (0.0)	Not reached [-; -]	11	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	0.978
Western Europe/North America	50	5 (10.0)	Not reached [-; -]	46	12 (26.1)	Not reached [5.0; -]	0.36 [0.13; 1.03]	0.056	
Rest of World	9	1 (11.1)	Not reached [0.7; -]	6	1 (16.7)	Not reached [0.7; -]	0.50 [0.03; 7.98]	0.621	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: full-analysis-set population, subjects with baseline

d: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation

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

f: Based on Cox regression model with treatment as 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; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-CR29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal Cancer 29 items; n.a.: not applicable (when estimation not possible)

Anhang 4-G4.4: Nebenwirkungen

Unerwünschte Ereignisse Gesamtraten

Unerwünschte Ereignisse gesamt

Tabelle 4G-45: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
Adverse Events	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio[e] [95 %-CI]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	82	80 (97.6)	1.1 [0.3; 1.9]	68	68 (100.0)	0.3 [0.3; 0.4]	0.49 [0.35; 0.70]	< 0.001	0.882
Male	71	69 (97.2)	1.3 [0.4; 2.9]	75	74 (98.7)	0.3 [0.3; 0.6]	0.50 [0.35; 0.70]	< 0.001	
Age									
≤70	105	103 (98.1)	0.7 [0.3; 1.4]	103	102 (99.0)	0.3 [0.3; 0.4]	0.54 [0.40; 0.71]	< 0.001	0.676
>70	48	46 (95.8)	2.0 [0.6; 3.1]	40	40 (100.0)	0.6 [0.3; 1.0]	0.45 [0.28; 0.72]	< 0.001	
ECOG									
0	75	74 (98.7)	0.7 [0.3; 2.4]	79	78 (98.7)	0.3 [0.1; 0.6]	0.55 [0.39; 0.77]	< 0.001	0.484
1	78	75 (96.2)	1.2 [0.6; 2.0]	64	64 (100.0)	0.3 [0.3; 0.6]	0.46 [0.32; 0.65]	< 0.001	
Geographic Region									
Asia	22	22 (100.0)	0.8 [0.1; 3.7]	25	25 (100.0)	0.4 [0.3; 0.6]	0.61 [0.34; 1.12]	0.110	0.439
Western Europe/North America	109	105 (96.3)	1.4 [0.6; 2.3]	105	105 (100.0)	0.3 [0.3; 0.4]	0.45 [0.34; 0.61]	< 0.001	
Rest of World	22	22 (100.0)	0.4 [0.3; 1.1]	13	12 (92.3)	0.3 [0.1; 0.9]	0.74 [0.35; 1.53]	0.414	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

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

d: Number of patients: all-subjects-as-treated population

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 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; ECOG: Eastern Cooperative Oncology Group

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-46: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
Serious Adverse Events	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio[e] [95 %-CI]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	82	37 (45.1)	85.7 [44.7; -]	68	38 (55.9)	16.1 [11.9; -]	0.64 [0.40; 1.01]	0.053	0.804
Male	71	25 (35.2)	Not reached [57.0; -]	75	37 (49.3)	43.7 [29.6; 91.1]	0.56 [0.34; 0.93]	0.026	
Age									
≤70	105	37 (35.2)	Not reached [80.0; -]	103	52 (50.5)	43.7 [19.0; 91.1]	0.54 [0.35; 0.83]	0.005	0.507
>70	48	25 (52.1)	45.9 [21.9; -]	40	23 (57.5)	18.1 [10.6; -]	0.72 [0.40; 1.27]	0.256	
ECOG									
0	75	29 (38.7)	Not reached [51.1; -]	79	44 (55.7)	29.9 [14.6; 89.6]	0.50 [0.31; 0.81]	0.005	0.284
1	78	33 (42.3)	75.7 [44.7; -]	64	31 (48.4)	39.0 [14.0; -]	0.75 [0.46; 1.23]	0.251	
Geographic Region									
Asia	22	6 (27.3)	Not reached [30.1; -]	25	11 (44.0)	89.6 [14.6; -]	0.53 [0.19; 1.46]	0.219	0.533
Western Europe/North America	109	47 (43.1)	75.9 [51.1; -]	105	55 (52.4)	33.6 [14.6; 91.1]	0.64 [0.43; 0.96]	0.029	
Rest of World	22	9 (40.9)	85.7 [24.1; -]	13	9 (69.2)	18.1 [2.9; -]	0.34 [0.13; 0.89]	0.027	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

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

d: Number of patients: all-subjects-as-treated population

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 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; ECOG: Eastern Cooperative Oncology Group

Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2)

Tabelle 4G-47: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio[e] [95 %-CI]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	82	76 (92.7)	1.4 [0.6; 2.1]	68	68 (100.0)	0.4 [0.3; 0.6]	0.48 [0.34; 0.68]	< 0.001	0.848
Male	71	68 (95.8)	1.4 [0.4; 3.0]	75	72 (96.0)	0.3 [0.3; 0.6]	0.54 [0.38; 0.76]	< 0.001	
Age									
≤70	105	101 (96.2)	1.0 [0.4; 1.9]	103	101 (98.1)	0.3 [0.3; 0.4]	0.55 [0.42; 0.74]	< 0.001	0.838
>70	48	43 (89.6)	2.1 [1.3; 3.3]	40	39 (97.5)	0.8 [0.6; 2.0]	0.45 [0.28; 0.73]	0.001	
ECOG									
0	75	73 (97.3)	1.7 [0.3; 3.0]	79	77 (97.5)	0.3 [0.1; 0.7]	0.57 [0.41; 0.80]	0.001	0.595
1	78	71 (91.0)	1.3 [0.9; 2.4]	64	63 (98.4)	0.3 [0.3; 0.6]	0.48 [0.34; 0.68]	< 0.001	
Geographic Region									
Asia	22	22 (100.0)	0.8 [0.1; 3.7]	25	25 (100.0)	0.4 [0.3; 0.6]	0.61 [0.34; 1.12]	0.110	0.414
Western Europe/North America	109	100 (91.7)	1.9 [1.1; 3.0]	105	103 (98.1)	0.3 [0.3; 0.7]	0.48 [0.36; 0.64]	< 0.001	
Rest of World	22	22 (100.0)	0.4 [0.3; 2.0]	13	12 (92.3)	0.6 [0.1; 2.0]	0.77 [0.37; 1.61]	0.485	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

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

d: Number of patients: all-subjects-as-treated population

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 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; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

Tabelle 4G-48: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio[e] [95 %-CI]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	82	52 (63.4)	30.1 [17.0; 52.1]	68	56 (82.4)	7.6 [4.4; 10.1]	0.42 [0.28; 0.62]	< 0.001	0.631
Male	71	34 (47.9)	60.7 [32.9; -]	75	55 (73.3)	12.1 [6.1; 14.0]	0.36 [0.23; 0.57]	< 0.001	
Age									
≤70	105	53 (50.5)	52.1 [30.1; -]	103	77 (74.8)	9.3 [7.3; 12.4]	0.40 [0.28; 0.57]	< 0.001	0.706
>70	48	33 (68.8)	29.7 [15.1; 55.1]	40	34 (85.0)	5.9 [2.3; 12.7]	0.41 [0.25; 0.68]	< 0.001	
ECOG									
0	75	40 (53.3)	52.1 [29.9; 137.3]	79	63 (79.7)	8.1 [4.4; 11.3]	0.34 [0.23; 0.52]	< 0.001	0.178
1	78	46 (59.0)	30.1 [17.0; 60.7]	64	48 (75.0)	10.4 [6.4; 13.9]	0.50 [0.33; 0.77]	0.001	
Geographic Region									
Asia	22	10 (45.5)	38.7 [20.9; -]	25	22 (88.0)	10.4 [3.1; 13.9]	0.31 [0.15; 0.68]	0.003	0.051
Western Europe/North America	109	63 (57.8)	44.1 [24.4; 72.0]	105	77 (73.3)	9.3 [6.1; 12.9]	0.47 [0.33; 0.66]	< 0.001	
Rest of World	22	13 (59.1)	49.4 [14.1; 137.3]	13	12 (92.3)	3.1 [0.3; 10.6]	0.14 [0.06; 0.37]	< 0.001	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

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

d: Number of patients: all-subjects-as-treated population

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 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; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-49: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
Adverse Events Leading to Treatment Discontinuation	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio[e] [95 %-CI]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	82	14 (17.1)	Not reached [-; -]	68	10 (14.7)	Not reached [-; -]	0.92 [0.41; 2.10]	0.849	0.902
Male	71	7 (9.9)	Not reached [-; -]	75	7 (9.3)	Not reached [119.7; -]	0.69 [0.23; 2.04]	0.501	
Age									
≤70	105	12 (11.4)	Not reached [-; -]	103	10 (9.7)	Not reached [119.7; -]	0.88 [0.37; 2.08]	0.774	0.798
>70	48	9 (18.8)	Not reached [-; -]	40	7 (17.5)	Not reached [51.1; -]	0.84 [0.31; 2.31]	0.740	
ECOG									
0	75	10 (13.3)	Not reached [-; -]	79	13 (16.5)	Not reached [119.7; -]	0.55 [0.24; 1.29]	0.170	0.129
1	78	11 (14.1)	Not reached [-; -]	64	4 (6.3)	Not reached [-; -]	1.96 [0.62; 6.23]	0.253	
Geographic Region									
Asia	22	2 (9.1)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.231	0.070
Western Europe/North America	109	17 (15.6)	Not reached [-; -]	105	14 (13.3)	119.7 [119.7; -]	0.82 [0.40; 1.70]	0.600	
Rest of World	22	2 (9.1)	Not reached [-; -]	13	3 (23.1)	Not reached [18.1; -]	0.39 [0.07; 2.34]	0.303	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

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

d: Number of patients: all-subjects-as-treated population

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 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; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible)

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-50: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC)

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC: Blood and lymphatic system disorders									
Gender									
Female	82	23 (28.0)	Not reached [110.1; -]	68	32 (47.1)	42.0 [12.1; -]	0.49 [0.28; 0.84]	0.010	0.154
Male	71	11 (15.5)	Not reached [-; -]	75	31 (41.3)	Not reached [14.1; -]	0.29 [0.14; 0.58]	< 0.001	
Age									
≤70	105	22 (21.0)	Not reached [-; -]	103	42 (40.8)	Not reached [15.6; -]	0.39 [0.23; 0.66]	< 0.001	0.877
>70	48	12 (25.0)	Not reached [-; -]	40	21 (52.5)	17.4 [8.0; -]	0.39 [0.19; 0.80]	0.010	
ECOG									
0	75	14 (18.7)	Not reached [-; -]	79	36 (45.6)	Not reached [12.1; -]	0.32 [0.17; 0.59]	< 0.001	0.235
1	78	20 (25.6)	Not reached [-; -]	64	27 (42.2)	70.1 [14.1; -]	0.47 [0.25; 0.85]	0.013	
Geographic Region									
Asia	22	6 (27.3)	110.1 [27.3; 110.1]	25	8 (32.0)	Not reached [14.1; -]	0.90 [0.31; 2.61]	0.843	0.324
Western Europe/North America	109	22 (20.2)	Not reached [-; -]	105	49 (46.7)	42.0 [13.3; -]	0.33 [0.20; 0.56]	< 0.001	
Rest of World	22	6 (27.3)	Not reached [98.4; -]	13	6 (46.2)	15.6 [4.1; -]	0.37 [0.11; 1.18]	0.092	
SOC: Endocrine disorders									
Age									
≤70	105	23 (21.9)	Not reached [-; -]	103	2 (1.9)	Not reached [-; -]	10.42 [2.45; 44.30]	0.002	0.471
>70	48	5 (10.4)	Not reached [-; -]	40	1 (2.5)	Not reached [41.9; -]	3.81 [0.44; 32.89]	0.224	
ECOG									
0	75	16 (21.3)	Not reached [-; -]	79	1 (1.3)	Not reached [-; -]	16.03 [2.12; 121.26]	0.007	0.313
1	78	12 (15.4)	Not reached [-; -]	64	2 (3.1)	Not reached [-; -]	4.39 [0.98; 19.73]	0.054	
Geographic Region									
Asia	22	4 (18.2)	Not reached [26.1; -]	25	1 (4.0)	Not reached [-; -]	5.64 [0.63; 50.57]	0.122	0.728
Western Europe/North America	109	20 (18.3)	Not reached [-; -]	105	2 (1.9)	Not reached [-; -]	8.02 [1.87; 34.49]	0.005	

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Rest of World	22	4 (18.2)	Not reached [-; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.114	
SOC: Gastrointestinal disorders									
Gender									
Female	82	72 (87.8)	4.7 [3.1; 6.3]	68	65 (95.6)	0.9 [0.4; 2.1]	0.45 [0.32; 0.64]	< 0.001	0.082
Male	71	48 (67.6)	18.0 [8.7; 48.1]	75	69 (92.0)	1.0 [0.6; 2.1]	0.32 [0.22; 0.47]	< 0.001	
Age									
≤70	105	85 (81.0)	8.3 [3.3; 16.9]	103	98 (95.1)	0.7 [0.4; 1.6]	0.38 [0.28; 0.52]	< 0.001	0.633
>70	48	35 (72.9)	6.3 [3.3; 16.4]	40	36 (90.0)	1.6 [0.7; 2.6]	0.42 [0.26; 0.69]	< 0.001	
ECOG									
0	75	61 (81.3)	8.7 [5.0; 18.0]	79	70 (88.6)	1.0 [0.6; 2.3]	0.46 [0.32; 0.65]	< 0.001	0.184
1	78	59 (75.6)	8.3 [3.0; 15.9]	64	64 (100.0)	0.9 [0.4; 1.4]	0.31 [0.21; 0.45]	< 0.001	
Geographic Region									
Asia	22	19 (86.4)	4.9 [2.7; 11.1]	25	24 (96.0)	1.0 [0.6; 5.0]	0.48 [0.25; 0.91]	0.024	0.070
Western Europe/North America	109	82 (75.2)	8.9 [6.0; 18.0]	105	100 (95.2)	0.9 [0.4; 2.1]	0.35 [0.26; 0.48]	< 0.001	
Rest of World	22	19 (86.4)	3.1 [0.7; 17.7]	13	10 (76.9)	2.6 [0.3; 17.6]	0.67 [0.30; 1.49]	0.324	
SOC: General disorders and administration site conditions									
Gender									
Female	82	57 (69.5)	9.1 [3.4; 14.7]	68	58 (85.3)	3.3 [2.1; 4.7]	0.61 [0.42; 0.88]	0.008	0.272
Male	71	49 (69.0)	16.9 [6.1; 32.4]	75	69 (92.0)	2.7 [2.1; 5.4]	0.40 [0.27; 0.59]	< 0.001	
Age									
≤70	105	71 (67.6)	9.4 [3.4; 24.0]	103	93 (90.3)	2.9 [2.3; 4.0]	0.48 [0.35; 0.66]	< 0.001	0.365
>70	48	35 (72.9)	12.3 [6.0; 24.6]	40	34 (85.0)	3.2 [2.0; 12.4]	0.57 [0.35; 0.92]	0.022	
ECOG									
0	75	52 (69.3)	10.9 [3.3; 24.6]	79	68 (86.1)	3.0 [2.4; 5.3]	0.55 [0.38; 0.80]	0.002	0.654
1	78	54 (69.2)	12.1 [6.0; 24.0]	64	59 (92.2)	2.4 [1.1; 4.7]	0.44 [0.30; 0.65]	< 0.001	
Geographic Region									
Asia	22	12 (54.5)	14.1 [0.7; -]	25	23 (92.0)	8.7 [2.9; 12.3]	0.51 [0.25; 1.04]	0.063	0.121
Western Europe/North America	109	78 (71.6)	9.3 [4.1; 24.1]	105	96 (91.4)	2.4 [2.0; 3.3]	0.42 [0.30; 0.57]	< 0.001	
Rest of World	22	16 (72.7)	6.1 [1.0; 27.1]	13	8 (61.5)	12.4 [0.6; -]	1.06 [0.45; 2.51]	0.892	
SOC: Injury, poisoning and procedural complications									

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	82	14 (17.1)	Not reached [-; -]	68	20 (29.4)	68.1 [30.0; -]	0.43 [0.22; 0.88]	0.020	0.106
Male	71	16 (22.5)	Not reached [-; -]	75	14 (18.7)	Not reached [-; -]	0.84 [0.41; 1.75]	0.648	
Age									
≤70	105	20 (19.0)	Not reached [-; -]	103	23 (22.3)	Not reached [-; -]	0.63 [0.34; 1.16]	0.136	0.840
>70	48	10 (20.8)	Not reached [72.0; -]	40	11 (27.5)	68.1 [44.3; -]	0.51 [0.21; 1.23]	0.134	
ECOG									
0	75	17 (22.7)	Not reached [-; -]	79	17 (21.5)	Not reached [-; -]	0.74 [0.37; 1.47]	0.389	0.310
1	78	13 (16.7)	Not reached [-; -]	64	17 (26.6)	68.1 [36.4; -]	0.46 [0.22; 0.97]	0.040	
Geographic Region									
Asia	22	5 (22.7)	Not reached [50.4; -]	25	4 (16.0)	Not reached [48.0; -]	1.20 [0.32; 4.51]	0.785	0.144
Western Europe/North America	109	19 (17.4)	Not reached [-; -]	105	23 (21.9)	Not reached [-; -]	0.58 [0.31; 1.07]	0.081	
Rest of World	22	6 (27.3)	Not reached [72.0; -]	13	7 (53.8)	39.6 [2.0; -]	0.21 [0.06; 0.74]	0.015	
SOC: Investigations									
Gender									
Female	82	28 (34.1)	Not reached [41.0; -]	68	35 (51.5)	11.9 [8.0; -]	0.47 [0.28; 0.79]	0.004	0.346
Male	71	26 (36.6)	Not reached [41.1; -]	75	34 (45.3)	37.9 [18.1; -]	0.62 [0.37; 1.05]	0.074	
Age									
≤70	105	42 (40.0)	81.3 [41.0; -]	103	50 (48.5)	37.0 [16.0; -]	0.64 [0.42; 0.97]	0.036	0.146
>70	48	12 (25.0)	Not reached [60.0; -]	40	19 (47.5)	25.0 [6.3; -]	0.35 [0.17; 0.74]	0.006	
ECOG									
0	75	29 (38.7)	Not reached [40.9; -]	79	34 (43.0)	Not reached [17.0; -]	0.74 [0.45; 1.22]	0.234	0.130
1	78	25 (32.1)	Not reached [41.1; -]	64	35 (54.7)	15.1 [10.1; 37.9]	0.36 [0.21; 0.62]	< 0.001	
SOC: Metabolism and nutrition disorders									
Gender									
Female	82	38 (46.3)	60.4 [18.0; -]	68	43 (63.2)	10.7 [5.7; 30.1]	0.57 [0.37; 0.89]	0.013	0.564
Male	71	34 (47.9)	82.1 [23.7; -]	75	40 (53.3)	18.6 [12.0; 64.7]	0.66 [0.41; 1.05]	0.081	
Age									
≤70	105	50 (47.6)	80.3 [23.7; -]	103	59 (57.3)	18.0 [10.6; 39.4]	0.64 [0.43; 0.93]	0.021	0.779
>70	48	22 (45.8)	43.4 [17.3; -]	40	24 (60.0)	12.7 [3.0; -]	0.56 [0.31; 1.01]	0.056	

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
ECOG									
0	75	38 (50.7)	60.4 [20.9; -]	79	44 (55.7)	23.0 [10.6; 42.1]	0.70 [0.45; 1.09]	0.115	0.404
1	78	34 (43.6)	78.0 [24.7; -]	64	39 (60.9)	12.0 [4.7; 30.1]	0.52 [0.32; 0.83]	0.006	
Geographic Region									
Asia	22	12 (54.5)	59.9 [8.4; -]	25	17 (68.0)	10.7 [2.9; 64.7]	0.53 [0.25; 1.14]	0.105	0.704
Western Europe/North America	109	52 (47.7)	78.0 [23.7; -]	105	62 (59.0)	14.9 [8.3; 26.0]	0.63 [0.44; 0.92]	0.016	
Rest of World	22	8 (36.4)	Not reached [15.3; -]	13	4 (30.8)	39.4 [3.9; -]	0.86 [0.25; 2.98]	0.809	
SOC: Nervous system disorders									
Age									
≤70	105	38 (36.2)	Not reached [30.7; -]	103	76 (73.8)	5.4 [3.1; 8.6]	0.27 [0.18; 0.40]	< 0.001	0.869
>70	48	13 (27.1)	114.9 [63.6; -]	40	25 (62.5)	17.0 [5.1; 23.4]	0.25 [0.12; 0.51]	< 0.001	
ECOG									
0	75	20 (26.7)	Not reached [114.9; -]	79	54 (68.4)	6.3 [3.1; 16.0]	0.23 [0.14; 0.39]	< 0.001	0.159
1	78	31 (39.7)	63.6 [30.1; -]	64	47 (73.4)	6.9 [4.3; 10.0]	0.29 [0.18; 0.47]	< 0.001	
Geographic Region									
Asia	22	6 (27.3)	Not reached [25.1; -]	25	23 (92.0)	2.9 [2.3; 15.1]	0.11 [0.04; 0.31]	< 0.001	0.098
Western Europe/North America	109	35 (32.1)	Not reached [63.6; -]	105	71 (67.6)	6.9 [4.6; 9.1]	0.27 [0.18; 0.41]	< 0.001	
Rest of World	22	10 (45.5)	114.9 [3.9; -]	13	7 (53.8)	42.1 [0.9; -]	0.61 [0.23; 1.66]	0.337	
SOC: Respiratory, thoracic and mediastinal disorders									
Gender									
Female	82	34 (41.5)	70.7 [28.1; -]	68	38 (55.9)	22.4 [13.7; 33.1]	0.50 [0.31; 0.80]	0.004	0.223
Male	71	36 (50.7)	47.1 [35.0; 95.6]	75	37 (49.3)	35.0 [15.7; 50.3]	0.75 [0.47; 1.19]	0.225	
Age									
≤70	105	46 (43.8)	60.0 [35.9; -]	103	51 (49.5)	27.0 [16.1; 44.3]	0.65 [0.43; 0.97]	0.034	0.818
>70	48	24 (50.0)	50.4 [21.1; 74.7]	40	24 (60.0)	22.4 [6.0; 50.3]	0.48 [0.26; 0.88]	0.018	
ECOG									
0	75	38 (50.7)	50.4 [35.0; -]	79	37 (46.8)	35.0 [22.4; -]	0.81 [0.51; 1.28]	0.356	0.087
1	78	32 (41.0)	64.7 [35.9; -]	64	38 (59.4)	16.0 [14.0; 33.1]	0.42 [0.26; 0.69]	< 0.001	
Geographic Region									
Asia	22	10 (45.5)	39.7 [17.0; -]	25	15 (60.0)	27.0 [14.0; 113.0]	0.64 [0.29; 1.44]	0.284	0.962

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Western Europe/North America	109	51 (46.8)	60.0 [37.4; 84.3]	105	55 (52.4)	24.3 [14.0; 44.3]	0.62 [0.42; 0.91]	0.015	
Rest of World	22	9 (40.9)	54.1 [15.1; -]	13	5 (38.5)	Not reached [6.0; -]	0.86 [0.28; 2.64]	0.792	
SOC: Vascular disorders									
Gender									
Female	82	15 (18.3)	Not reached [107.1; -]	68	22 (32.4)	75.6 [28.3; -]	0.40 [0.21; 0.80]	0.009	0.429
Male	71	16 (22.5)	Not reached [-; -]	75	20 (26.7)	136.1 [56.9; 136.1]	0.76 [0.39; 1.49]	0.423	
Age									
≤70	105	19 (18.1)	Not reached [-; -]	103	29 (28.2)	Not reached [56.9; -]	0.50 [0.28; 0.89]	0.020	0.590
>70	48	12 (25.0)	Not reached [42.0; -]	40	13 (32.5)	136.1 [18.1; 136.1]	0.67 [0.30; 1.53]	0.345	
ECOG									
0	75	16 (21.3)	Not reached [-; -]	79	26 (32.9)	Not reached [54.4; -]	0.50 [0.27; 0.94]	0.032	0.529
1	78	15 (19.2)	Not reached [-; -]	64	16 (25.0)	136.1 [38.9; 136.1]	0.63 [0.30; 1.31]	0.215	
Geographic Region									
Asia	22	2 (9.1)	Not reached [-; -]	25	8 (32.0)	136.1 [32.1; -]	0.30 [0.06; 1.43]	0.130	0.666
Western Europe/North America	109	25 (22.9)	Not reached [-; -]	105	31 (29.5)	Not reached [56.9; -]	0.59 [0.34; 1.01]	0.055	
Rest of World	22	4 (18.2)	Not reached [56.4; -]	13	3 (23.1)	Not reached [9.0; -]	0.61 [0.13; 2.79]	0.525	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: all-subjects-as-treated population

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

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 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; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); SOC: System Organ Class

Tabelle 4G-51: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (PT)

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC: Blood and lymphatic system disorders, PT: Neutropenia									
Gender									
Female	82	0 (0.0)	Not reached [-; -]	68	13 (19.1)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.057
Male	71	3 (4.2)	Not reached [-; -]	75	17 (22.7)	Not reached [-; -]	0.15 [0.04; 0.51]	0.002	
Age									
≤70	105	3 (2.9)	Not reached [-; -]	103	20 (19.4)	Not reached [-; -]	0.12 [0.04; 0.41]	< 0.001	0.102
>70	48	0 (0.0)	Not reached [-; -]	40	10 (25.0)	Not reached [42.0; -]	n.a. [n.a.; n.a.]	< 0.001	
ECOG									
0	75	2 (2.7)	Not reached [-; -]	79	18 (22.8)	Not reached [-; -]	0.10 [0.02; 0.42]	0.002	0.706
1	78	1 (1.3)	Not reached [-; -]	64	12 (18.8)	Not reached [-; -]	0.05 [0.01; 0.40]	0.005	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	3 (12.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.108	0.829
Western Europe/North America	109	2 (1.8)	Not reached [-; -]	105	22 (21.0)	Not reached [-; -]	0.07 [0.02; 0.29]	< 0.001	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	5 (38.5)	Not reached [4.1; -]	0.07 [0.01; 0.68]	0.021	
SOC: Endocrine disorders, PT: Hypothyroidism									
Gender									
Female	82	10 (12.2)	Not reached [-; -]	68	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.004	0.059
Male	71	9 (12.7)	Not reached [-; -]	75	3 (4.0)	Not reached [-; -]	2.29 [0.61; 8.61]	0.221	
Age									
≤70	105	16 (15.2)	Not reached [-; -]	103	2 (1.9)	Not reached [-; -]	6.61 [1.51; 28.91]	0.012	0.422
>70	48	3 (6.3)	Not reached [-; -]	40	1 (2.5)	Not reached [41.9; -]	2.16 [0.22; 21.17]	0.509	
ECOG									
0	75	10 (13.3)	Not reached [-; -]	79	1 (1.3)	Not reached [-; -]	9.69 [1.24; 75.88]	0.031	0.410
1	78	9 (11.5)	Not reached [-; -]	64	2 (3.1)	Not reached [-; -]	2.79 [0.59; 13.21]	0.197	
Geographic Region									
Asia	22	3 (13.6)	Not reached [-; -]	25	1 (4.0)	Not reached [-; -]	4.01 [0.42; 38.58]	0.229	0.644
Western	109	12	Not reached	105	2	Not reached	4.16	0.064	

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Europe/North America		(11.0)	[-; -]		(1.9)	[-; -]	[0.92; 18.87]		
Rest of World	22	4 (18.2)	Not reached [-; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.114	
SOC: Gastrointestinal disorders, PT: Constipation									
Gender									
Female	82	9 (11.0)	Not reached [-; -]	68	18 (26.5)	88.3 [44.7; -]	0.29 [0.13; 0.66]	0.003	0.421
Male	71	17 (23.9)	Not reached [-; -]	75	27 (36.0)	Not reached [43.3; -]	0.49 [0.27; 0.91]	0.024	
Age									
≤70	105	21 (20.0)	Not reached [-; -]	103	40 (38.8)	88.3 [35.4; -]	0.37 [0.22; 0.63]	< 0.001	0.431
>70	48	5 (10.4)	Not reached [-; -]	40	5 (12.5)	Not reached [-; -]	0.65 [0.18; 2.34]	0.507	
ECOG									
0	75	15 (20.0)	Not reached [-; -]	79	27 (34.2)	88.3 [43.7; -]	0.40 [0.21; 0.75]	0.005	0.989
1	78	11 (14.1)	Not reached [-; -]	64	18 (28.1)	Not reached [43.3; -]	0.40 [0.18; 0.85]	0.018	
SOC: Gastrointestinal disorders, PT: Diarrhoea									
Gender									
Female	82	40 (48.8)	43.7 [27.6; 106.7]	68	47 (69.1)	5.1 [3.6; 11.4]	0.43 [0.28; 0.66]	< 0.001	0.826
Male	71	28 (39.4)	Not reached [57.1; -]	75	42 (56.0)	25.4 [6.1; 41.4]	0.48 [0.29; 0.78]	0.003	
Age									
≤70	105	48 (45.7)	57.1 [37.1; -]	103	62 (60.2)	14.9 [6.1; 34.7]	0.51 [0.35; 0.75]	< 0.001	0.373
>70	48	20 (41.7)	76.0 [18.7; -]	40	27 (67.5)	5.0 [3.0; 8.6]	0.37 [0.20; 0.68]	0.001	
ECOG									
0	75	34 (45.3)	57.6 [31.1; -]	79	48 (60.8)	11.6 [4.0; 40.1]	0.48 [0.31; 0.75]	0.001	0.894
1	78	34 (43.6)	75.7 [22.3; -]	64	41 (64.1)	6.1 [4.3; 27.4]	0.44 [0.27; 0.71]	< 0.001	
Geographic Region									
Asia	22	8 (36.4)	Not reached [11.1; -]	25	12 (48.0)	34.7 [4.6; -]	0.62 [0.25; 1.51]	0.291	0.783
Western Europe/North America	109	51 (46.8)	57.6 [28.1; 106.7]	105	70 (66.7)	6.1 [4.0; 12.9]	0.43 [0.30; 0.63]	< 0.001	
Rest of World	22	9 (40.9)	82.9 [10.7; -]	13	7 (53.8)	27.6 [2.9; 93.9]	0.51 [0.18; 1.42]	0.199	
SOC: Gastrointestinal disorders, PT: Dyspepsia									
Gender									
Female	82	5 (6.1)	Not reached [-; -]	68	7 (10.3)	Not reached [-; -]	0.52 [0.16; 1.66]	0.271	0.739
Male	71	4 (5.6)	Not reached [-; -]	75	9 (12.0)	Not reached [-; -]	0.30 [0.09; 1.00]	0.049	

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Age									
≤70	105	9 (8.6)	Not reached [-; -]	103	13 (12.6)	Not reached [-; -]	0.52 [0.22; 1.24]	0.140	0.066
>70	48	0 (0.0)	Not reached [-; -]	40	3 (7.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.047	
ECOG									
0	75	4 (5.3)	Not reached [-; -]	79	9 (11.4)	Not reached [-; -]	0.35 [0.11; 1.17]	0.088	0.750
1	78	5 (6.4)	Not reached [-; -]	64	7 (10.9)	Not reached [-; -]	0.41 [0.12; 1.36]	0.145	
Geographic Region									
Asia	22	2 (9.1)	Not reached [-; -]	25	3 (12.0)	Not reached [-; -]	0.68 [0.11; 4.11]	0.672	0.399
Western Europe/North America	109	6 (5.5)	Not reached [-; -]	105	13 (12.4)	Not reached [-; -]	0.32 [0.12; 0.87]	0.026	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.442	
SOC: Gastrointestinal disorders, PT: Haemorrhoids									
Gender									
Female	82	0 (0.0)	n.c.	68	4 (5.9)	n.c.	n.c.	n.c.	n.c.
Male	71	2 (2.8)	n.c.	75	6 (8.0)	n.c.	n.c.	n.c.	
Age									
≤70	105	2 (1.9)	n.c.	103	7 (6.8)	n.c.	n.c.	n.c.	n.c.
>70	48	0 (0.0)	n.c.	40	3 (7.5)	n.c.	n.c.	n.c.	
ECOG									
0	75	2 (2.7)	n.c.	79	6 (7.6)	n.c.	n.c.	n.c.	n.c.
1	78	0 (0.0)	n.c.	64	4 (6.3)	n.c.	n.c.	n.c.	
Geographic Region									
Asia	22	0 (0.0)	n.c.	25	2 (8.0)	n.c.	n.c.	n.c.	n.c.
Western Europe/North America	109	2 (1.8)	n.c.	105	7 (6.7)	n.c.	n.c.	n.c.	
Rest of World	22	0 (0.0)	n.c.	13	1 (7.7)	n.c.	n.c.	n.c.	
SOC: Gastrointestinal disorders, PT: Nausea									
Age									
≤70	105	36 (34.3)	Not reached [67.6; -]	103	65 (63.1)	7.6 [2.6; 17.1]	0.34 [0.22; 0.51]	< 0.001	0.997
>70	48	11 (22.9)	Not reached [54.1; -]	40	20 (50.0)	18.9 [2.6; -]	0.35 [0.17; 0.74]	0.006	
ECOG									
0	75	21 (28.0)	Not reached [-; -]	79	47 (59.5)	13.3 [2.6; 37.7]	0.30 [0.18; 0.50]	< 0.001	0.440

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
1	78	26 (33.3)	Not reached [47.9; -]	64	38 (59.4)	12.4 [2.3; 131.0]	0.38 [0.23; 0.64]	< 0.001	
SOC: Gastrointestinal disorders, PT: Stomatitis									
Gender									
Female	82	7 (8.5)	Not reached [-; -]	68	21 (30.9)	147.6 [147.6; -]	0.22 [0.09; 0.52]	< 0.001	0.265
Male	71	3 (4.2)	Not reached [-; -]	75	22 (29.3)	Not reached [78.0; -]	0.09 [0.03; 0.32]	< 0.001	
Age									
≤70	105	6 (5.7)	Not reached [-; -]	103	31 (30.1)	147.6 [78.0; -]	0.14 [0.06; 0.34]	< 0.001	0.594
>70	48	4 (8.3)	Not reached [-; -]	40	12 (30.0)	Not reached [16.3; -]	0.20 [0.06; 0.64]	0.007	
ECOG									
0	75	5 (6.7)	Not reached [-; -]	79	22 (27.8)	Not reached [78.0; -]	0.16 [0.06; 0.42]	< 0.001	0.799
1	78	5 (6.4)	Not reached [-; -]	64	21 (32.8)	147.6 [39.1; 147.6]	0.16 [0.06; 0.43]	< 0.001	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	11 (44.0)	147.6 [6.1; -]	n.a. [n.a.; n.a.]	0.001	0.102
Western Europe/North America	109	8 (7.3)	Not reached [-; -]	105	27 (25.7)	Not reached [78.0; -]	0.20 [0.09; 0.46]	< 0.001	
Rest of World	22	2 (9.1)	Not reached [-; -]	13	5 (38.5)	Not reached [1.0; -]	0.09 [0.01; 0.81]	0.031	
SOC: Gastrointestinal disorders, PT: Vomiting									
Gender									
Female	82	20 (24.4)	Not reached [-; -]	68	27 (39.7)	75.7 [16.3; -]	0.50 [0.28; 0.89]	0.020	0.788
Male	71	13 (18.3)	Not reached [-; -]	75	26 (34.7)	Not reached [43.0; -]	0.41 [0.21; 0.80]	0.009	
Age									
≤70	105	27 (25.7)	Not reached [-; -]	103	38 (36.9)	Not reached [43.0; -]	0.55 [0.34; 0.91]	0.020	0.161
>70	48	6 (12.5)	Not reached [-; -]	40	15 (37.5)	Not reached [16.3; -]	0.28 [0.11; 0.74]	0.009	
ECOG									
0	75	17 (22.7)	Not reached [-; -]	79	27 (34.2)	Not reached [43.0; -]	0.53 [0.29; 0.98]	0.044	0.458
1	78	16 (20.5)	Not reached [-; -]	64	26 (40.6)	Not reached [14.0; -]	0.39 [0.21; 0.74]	0.004	
Geographic Region									
Asia	22	5 (22.7)	Not reached [14.1; -]	25	11 (44.0)	Not reached [14.3; -]	0.57 [0.20; 1.65]	0.302	0.184
Western Europe/North America	109	23 (21.1)	Not reached [-; -]	105	41 (39.0)	Not reached [28.9; -]	0.41 [0.24; 0.69]	< 0.001	
Rest of World	22	5 (22.7)	Not reached [49.4; -]	13	1 (7.7)	Not reached [43.0; -]	2.01 [0.23; 17.71]	0.528	

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC: General disorders and administration site conditions, PT: Asthenia									
Gender									
Female	82	11 (13.4)	Not reached [-; -]	68	13 (19.1)	Not reached [-; -]	0.67 [0.30; 1.50]	0.329	0.429
Male	71	8 (11.3)	Not reached [-; -]	75	18 (24.0)	Not reached [-; -]	0.38 [0.16; 0.89]	0.026	
Age									
≤70	105	10 (9.5)	Not reached [-; -]	103	20 (19.4)	Not reached [-; -]	0.42 [0.19; 0.90]	0.026	0.561
>70	48	9 (18.8)	Not reached [-; -]	40	11 (27.5)	Not reached [-; -]	0.61 [0.25; 1.50]	0.286	
ECOG									
0	75	7 (9.3)	Not reached [-; -]	79	16 (20.3)	Not reached [-; -]	0.40 [0.17; 0.98]	0.046	0.495
1	78	12 (15.4)	Not reached [-; -]	64	15 (23.4)	Not reached [-; -]	0.56 [0.26; 1.22]	0.143	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	0.827
Western Europe/North America	109	18 (16.5)	Not reached [-; -]	105	29 (27.6)	Not reached [-; -]	0.50 [0.27; 0.90]	0.022	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	2 (15.4)	Not reached [11.1; -]	0.27 [0.02; 2.99]	0.286	
SOC: General disorders and administration site conditions, PT: Fatigue									
Gender									
Female	82	32 (39.0)	91.9 [36.1; -]	68	31 (45.6)	41.1 [12.3; -]	0.66 [0.40; 1.10]	0.111	0.193
Male	71	26 (36.6)	Not reached [40.7; -]	75	41 (54.7)	18.9 [4.9; 64.7]	0.45 [0.27; 0.74]	0.002	
Age									
≤70	105	40 (38.1)	Not reached [53.4; -]	103	55 (53.4)	18.9 [9.3; 64.7]	0.53 [0.35; 0.81]	0.003	0.505
>70	48	18 (37.5)	96.1 [25.9; -]	40	17 (42.5)	47.0 [13.9; -]	0.62 [0.32; 1.22]	0.167	
ECOG									
0	75	30 (40.0)	Not reached [27.1; -]	79	44 (55.7)	19.1 [6.3; 64.7]	0.51 [0.32; 0.81]	0.005	0.380
1	78	28 (35.9)	96.1 [38.0; -]	64	28 (43.8)	47.0 [15.0; -]	0.63 [0.37; 1.07]	0.086	
Geographic Region									
Asia	22	6 (27.3)	Not reached [14.1; -]	25	14 (56.0)	27.3 [12.0; -]	0.46 [0.18; 1.21]	0.115	0.155
Western Europe/North America	109	39 (35.8)	Not reached [63.1; -]	105	53 (50.5)	19.1 [9.3; -]	0.49 [0.32; 0.74]	< 0.001	
Rest of World	22	13 (59.1)	40.7 [13.4; 81.3]	13	5 (38.5)	42.1 [2.3; -]	1.14 [0.40; 3.27]	0.812	
SOC: General disorders and administration site conditions, PT: Mucosal inflammation									
Gender									
Female	82	4	Not reached	68	13	Not reached	0.20	0.006	0.850

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
		(4.9)	[-; -]		(19.1)	[-; -]	[0.06; 0.63]		
Male	71	3 (4.2)	Not reached [-; -]	75	14 (18.7)	Not reached [-; -]	0.18 [0.05; 0.64]	0.008	
Age									
≤70	105	5 (4.8)	Not reached [-; -]	103	23 (22.3)	Not reached [-; -]	0.18 [0.07; 0.48]	< 0.001	0.470
>70	48	2 (4.2)	Not reached [-; -]	40	4 (10.0)	Not reached [52.3; -]	0.21 [0.03; 1.37]	0.102	
ECOG									
0	75	3 (4.0)	Not reached [-; -]	79	20 (25.3)	Not reached [-; -]	0.13 [0.04; 0.45]	0.001	0.171
1	78	4 (5.1)	Not reached [-; -]	64	7 (10.9)	Not reached [-; -]	0.32 [0.09; 1.17]	0.084	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	1 (4.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.348	0.812
Western Europe/North America	109	6 (5.5)	Not reached [-; -]	105	23 (21.9)	Not reached [-; -]	0.18 [0.07; 0.44]	< 0.001	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	3 (23.1)	Not reached [0.6; -]	0.18 [0.02; 1.70]	0.133	
SOC: Investigations, PT: Blood alkaline phosphatase increased									
Gender									
Female	82	14 (17.1)	Not reached [-; -]	68	2 (2.9)	Not reached [-; -]	4.90 [1.10; 21.75]	0.037	0.277
Male	71	8 (11.3)	Not reached [-; -]	75	4 (5.3)	Not reached [-; -]	1.67 [0.49; 5.68]	0.408	
Age									
≤70	105	16 (15.2)	Not reached [-; -]	103	4 (3.9)	Not reached [-; -]	3.22 [1.07; 9.73]	0.038	0.630
>70	48	6 (12.5)	Not reached [-; -]	40	2 (5.0)	Not reached [-; -]	2.35 [0.47; 11.68]	0.298	
ECOG									
0	75	13 (17.3)	Not reached [-; -]	79	2 (2.5)	Not reached [-; -]	6.10 [1.37; 27.25]	0.018	0.158
1	78	9 (11.5)	Not reached [-; -]	64	4 (6.3)	Not reached [-; -]	1.46 [0.44; 4.81]	0.533	
Geographic Region									
Asia	22	2 (9.1)	Not reached [-; -]	25	1 (4.0)	Not reached [-; -]	2.36 [0.21; 26.02]	0.484	0.954
Western Europe/North America	109	13 (11.9)	Not reached [-; -]	105	4 (3.8)	Not reached [-; -]	2.67 [0.86; 8.26]	0.088	
Rest of World	22	7 (31.8)	Not reached [30.1; -]	13	1 (7.7)	Not reached [22.7; -]	3.14 [0.37; 26.37]	0.292	
SOC: Investigations, PT: Neutrophil count decreased									
Gender									

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Female	82	0 (0.0)	Not reached [-; -]	68	18 (26.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.060
Male	71	2 (2.8)	Not reached [-; -]	75	15 (20.0)	Not reached [-; -]	0.09 [0.02; 0.40]	0.002	
Age									
≤70	105	2 (1.9)	Not reached [-; -]	103	21 (20.4)	Not reached [-; -]	0.06 [0.01; 0.27]	< 0.001	0.154
>70	48	0 (0.0)	Not reached [-; -]	40	12 (30.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
ECOG									
0	75	1 (1.3)	Not reached [-; -]	79	15 (19.0)	Not reached [-; -]	0.05 [0.01; 0.37]	0.004	0.783
1	78	1 (1.3)	Not reached [-; -]	64	18 (28.1)	Not reached [-; -]	0.03 [0.00; 0.26]	0.001	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	15 (60.0)	15.1 [6.3; -]	n.a. [n.a.; n.a.]	< 0.001	0.194
Western Europe/North America	109	1 (0.9)	Not reached [-; -]	105	16 (15.2)	Not reached [-; -]	0.05 [0.01; 0.36]	0.003	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	2 (15.4)	Not reached [9.1; -]	0.13 [0.01; 1.84]	0.133	
SOC: Investigations, PT: Platelet count decreased									
Gender									
Female	82	1 (1.2)	n.c.	68	4 (5.9)	n.c.	n.c.	n.c.	n.c.
Male	71	1 (1.4)	n.c.	75	6 (8.0)	n.c.	n.c.	n.c.	
Age									
≤70	105	2 (1.9)	n.c.	103	5 (4.9)	n.c.	n.c.	n.c.	n.c.
>70	48	0 (0.0)	n.c.	40	5 (12.5)	n.c.	n.c.	n.c.	
ECOG									
0	75	1 (1.3)	n.c.	79	5 (6.3)	n.c.	n.c.	n.c.	n.c.
1	78	1 (1.3)	n.c.	64	5 (7.8)	n.c.	n.c.	n.c.	
Geographic Region									
Asia	22	0 (0.0)	n.c.	25	4 (16.0)	n.c.	n.c.	n.c.	n.c.
Western Europe/North America	109	1 (0.9)	n.c.	105	5 (4.8)	n.c.	n.c.	n.c.	
Rest of World	22	1 (4.5)	n.c.	13	1 (7.7)	n.c.	n.c.	n.c.	
SOC: Investigations, PT: Weight decreased									
Gender									
Female	82	4 (4.9)	Not reached [-; -]	68	10 (14.7)	Not reached [-; -]	0.23 [0.07; 0.78]	0.018	0.717
Male	71	3	Not reached	75	7	Not reached	0.38	0.164	

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
		(4.2)	[-; -]		(9.3)	[-; -]	[0.10; 1.49]		
Age									
≤70	105	4 (3.8)	Not reached [-; -]	103	12 (11.7)	Not reached [-; -]	0.28 [0.09; 0.88]	0.029	0.655
>70	48	3 (6.3)	Not reached [-; -]	40	5 (12.5)	Not reached [-; -]	0.31 [0.07; 1.40]	0.127	
ECOG									
0	75	3 (4.0)	Not reached [-; -]	79	9 (11.4)	Not reached [-; -]	0.26 [0.07; 0.99]	0.048	0.858
1	78	4 (5.1)	Not reached [-; -]	64	8 (12.5)	Not reached [-; -]	0.33 [0.10; 1.11]	0.072	
Geographic Region									
Asia	22	1 (4.5)	Not reached [-; -]	25	2 (8.0)	Not reached [60.7; -]	0.50 [0.04; 5.53]	0.571	0.851
Western Europe/North America	109	5 (4.6)	Not reached [-; -]	105	14 (13.3)	Not reached [-; -]	0.29 [0.10; 0.80]	0.017	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	1 (7.7)	Not reached [-; -]	0.23 [0.01; 5.05]	0.352	
SOC: Investigations, PT: White blood cell count decreased									
Gender									
Female	82	0 (0.0)	Not reached [-; -]	68	10 (14.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.156
Male	71	1 (1.4)	Not reached [-; -]	75	7 (9.3)	Not reached [-; -]	0.13 [0.02; 1.05]	0.056	
Age									
≤70	105	1 (1.0)	Not reached [-; -]	103	10 (9.7)	Not reached [-; -]	0.09 [0.01; 0.67]	0.019	0.282
>70	48	0 (0.0)	Not reached [-; -]	40	7 (17.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.004	
ECOG									
0	75	1 (1.3)	Not reached [-; -]	79	9 (11.4)	Not reached [-; -]	0.10 [0.01; 0.78]	0.028	0.236
1	78	0 (0.0)	Not reached [-; -]	64	8 (12.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	11 (44.0)	Not reached [8.1; -]	n.a. [n.a.; n.a.]	< 0.001	0.307
Western Europe/North America	109	1 (0.9)	Not reached [-; -]	105	5 (4.8)	Not reached [-; -]	0.16 [0.02; 1.43]	0.102	
Rest of World	22	0 (0.0)	Not reached [-; -]	13	1 (7.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.186	
SOC: Metabolism and nutrition disorders, PT: Decreased appetite									
Gender									
Female	82	18 (22.0)	Not reached [-; -]	68	33 (48.5)	39.4 [11.4; -]	0.39 [0.22; 0.70]	0.002	0.220
Male	71	18 (25.4)	Not reached [-; -]	75	25 (33.3)	Not reached [42.1; -]	0.61 [0.33; 1.13]	0.120	
Age									
≤70	105	24	Not reached	103	41	64.7	0.48	0.004	0.912

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
		(22.9)	[-; -]		(39.8)	[30.1; -]	[0.29; 0.79]		
>70	48	12 (25.0)	Not reached [43.4; -]	40	17 (42.5)	Not reached [11.4; -]	0.51 [0.24; 1.07]	0.073	
ECOG									
0	75	20 (26.7)	Not reached [-; -]	79	28 (35.4)	Not reached [42.1; -]	0.67 [0.37; 1.19]	0.167	0.152
1	78	16 (20.5)	Not reached [-; -]	64	30 (46.9)	30.1 [11.4; -]	0.34 [0.18; 0.63]	< 0.001	
Geographic Region									
Asia	22	6 (27.3)	Not reached [17.1; -]	25	15 (60.0)	30.1 [10.4; -]	0.40 [0.16; 1.05]	0.063	0.300
Western Europe/North America	109	26 (23.9)	Not reached [-; -]	105	42 (40.0)	Not reached [23.0; -]	0.51 [0.31; 0.83]	0.007	
Rest of World	22	4 (18.2)	Not reached [49.6; -]	13	1 (7.7)	Not reached [39.4; -]	1.52 [0.16; 14.30]	0.716	
SOC: Metabolism and nutrition disorders, PT: Hypokalaemia									
Gender									
Female	82	10 (12.2)	Not reached [-; -]	68	16 (23.5)	Not reached [-; -]	0.46 [0.21; 1.03]	0.059	0.726
Male	71	3 (4.2)	Not reached [-; -]	75	8 (10.7)	Not reached [-; -]	0.33 [0.09; 1.27]	0.107	
Age									
≤70	105	8 (7.6)	Not reached [-; -]	103	12 (11.7)	Not reached [-; -]	0.56 [0.23; 1.38]	0.206	0.352
>70	48	5 (10.4)	Not reached [-; -]	40	12 (30.0)	Not reached [39.1; -]	0.32 [0.11; 0.91]	0.033	
ECOG									
0	75	5 (6.7)	Not reached [-; -]	79	14 (17.7)	Not reached [-; -]	0.31 [0.11; 0.88]	0.027	0.344
1	78	8 (10.3)	Not reached [-; -]	64	10 (15.6)	Not reached [-; -]	0.61 [0.24; 1.56]	0.303	
SOC: Musculoskeletal and connective tissue disorders, PT: Arthralgia									
Gender									
Female	82	16 (19.5)	Not reached [103.3; -]	68	2 (2.9)	Not reached [-; -]	5.29 [1.20; 23.23]	0.027	0.258
Male	71	12 (16.9)	Not reached [-; -]	75	5 (6.7)	Not reached [79.1; -]	2.08 [0.72; 5.96]	0.175	
Age									
≤70	105	23 (21.9)	Not reached [-; -]	103	5 (4.9)	Not reached [-; -]	3.93 [1.49; 10.41]	0.006	0.358
>70	48	5 (10.4)	Not reached [-; -]	40	2 (5.0)	79.1 [79.1; -]	1.40 [0.26; 7.50]	0.696	
Geographic Region									
Asia	22	3 (13.6)	Not reached [63.4; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.068	0.095
Western Europe/North America	109	18 (16.5)	Not reached [-; -]	105	7 (6.7)	Not reached [79.1; -]	1.94 [0.80; 4.70]	0.143	

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Rest of World	22	7 (31.8)	Not reached [36.3; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.077	
SOC: Nervous system disorders, PT: Dysgeusia									
Gender									
Female	82	1 (1.2)	n.c.	68	7 (10.3)	n.c.	n.c.	n.c.	n.c.
Male	71	3 (4.2)	n.c.	75	6 (8.0)	n.c.	n.c.	n.c.	
Age									
≤70	105	2 (1.9)	Not reached [-; -]	103	9 (8.7)	Not reached [-; -]	0.18 [0.04; 0.84]	0.029	0.588
>70	48	2 (4.2)	Not reached [-; -]	40	4 (10.0)	Not reached [42.1; -]	0.31 [0.05; 1.75]	0.184	
ECOG									
0	75	3 (4.0)	Not reached [-; -]	79	7 (8.9)	Not reached [-; -]	0.36 [0.09; 1.41]	0.143	0.325
1	78	1 (1.3)	Not reached [-; -]	64	6 (9.4)	Not reached [-; -]	0.12 [0.01; 1.00]	0.050	
Geographic Region									
Asia	22	1 (4.5)	Not reached [-; -]	25	2 (8.0)	Not reached [-; -]	0.59 [0.05; 6.51]	0.667	0.729
Western Europe/North America	109	2 (1.8)	Not reached [-; -]	105	9 (8.6)	Not reached [-; -]	0.16 [0.03; 0.77]	0.022	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	2 (15.4)	Not reached [28.9; -]	0.17 [0.02; 2.00]	0.160	
SOC: Nervous system disorders, PT: Neuropathy peripheral									
Gender									
Female	82	1 (1.2)	Not reached [-; -]	68	15 (22.1)	Not reached [-; -]	0.04 [0.01; 0.33]	0.002	0.335
Male	71	0 (0.0)	Not reached [-; -]	75	12 (16.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Age									
≤70	105	1 (1.0)	Not reached [-; -]	103	24 (23.3)	Not reached [-; -]	0.03 [0.00; 0.26]	< 0.001	0.633
>70	48	0 (0.0)	Not reached [-; -]	40	3 (7.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.033	
ECOG									
0	75	0 (0.0)	Not reached [-; -]	79	16 (20.3)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.217
1	78	1 (1.3)	Not reached [-; -]	64	11 (17.2)	Not reached [-; -]	0.06 [0.01; 0.50]	0.009	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	3 (12.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.111	0.762
Western Europe/North America	109	1 (0.9)	Not reached [-; -]	105	21 (20.0)	Not reached [-; -]	0.04 [0.01; 0.29]	0.002	
Rest of World	22	0 (0.0)	Not reached [-; -]	13	3 (23.1)	Not reached [22.9; -]	n.a. [n.a.; n.a.]	0.017	
SOC: Nervous system disorders, PT: Peripheral sensory neuropathy									

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	82	1 (1.2)	Not reached [-; -]	68	12 (17.6)	Not reached [-; -]	0.06 [0.01; 0.45]	0.007	0.744
Male	71	2 (2.8)	Not reached [-; -]	75	19 (25.3)	Not reached [68.1; -]	0.08 [0.02; 0.33]	< 0.001	
Age									
≤70	105	3 (2.9)	Not reached [-; -]	103	23 (22.3)	Not reached [-; -]	0.09 [0.03; 0.31]	< 0.001	0.175
>70	48	0 (0.0)	Not reached [-; -]	40	8 (20.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
ECOG									
0	75	1 (1.3)	Not reached [-; -]	79	17 (21.5)	Not reached [-; -]	0.05 [0.01; 0.34]	0.003	0.604
1	78	2 (2.6)	Not reached [-; -]	64	14 (21.9)	Not reached [34.0; -]	0.08 [0.02; 0.36]	0.001	
Geographic Region									
Asia	22	1 (4.5)	Not reached [-; -]	25	14 (56.0)	23.0 [2.6; -]	0.05 [0.01; 0.36]	0.003	0.892
Western Europe/North America	109	2 (1.8)	Not reached [-; -]	105	17 (16.2)	Not reached [-; -]	0.08 [0.02; 0.37]	0.001	
Rest of World	22	0 (0.0)	Not reached [-; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
SOC: Renal and urinary disorders, PT: Proteinuria									
Gender									
Female	82	3 (3.7)	n.c.	68	6 (8.8)	n.c.	n.c.	n.c.	n.c.
Male	71	2 (2.8)	n.c.	75	4 (5.3)	n.c.	n.c.	n.c.	
Age									
≤70	105	4 (3.8)	Not reached [-; -]	103	9 (8.7)	Not reached [-; -]	0.35 [0.11; 1.15]	0.084	0.680
>70	48	1 (2.1)	Not reached [-; -]	40	1 (2.5)	Not reached [58.0; -]	0.11 [0.01; 2.09]	0.143	
ECOG									
0	75	1 (1.3)	n.c.	79	8 (10.1)	n.c.	n.c.	n.c.	n.c.
1	78	4 (5.1)	n.c.	64	2 (3.1)	n.c.	n.c.	n.c.	
Geographic Region									
Asia	22	1 (4.5)	n.c.	25	4 (16.0)	n.c.	n.c.	n.c.	n.c.
Western Europe/North America	109	2 (1.8)	n.c.	105	4 (3.8)	n.c.	n.c.	n.c.	
Rest of World	22	2 (9.1)	n.c.	13	2 (15.4)	n.c.	n.c.	n.c.	
SOC: Respiratory, thoracic and mediastinal disorders, PT: Epistaxis									
Gender									
Female	82	0 (0.0)	Not reached [-; -]	68	11 (16.2)	Not reached [58.0; -]	n.a. [n.a.; n.a.]	< 0.001	0.089

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Male	71	2 (2.8)	Not reached [-; -]	75	12 (16.0)	Not reached [-; -]	0.16 [0.03; 0.70]	0.015	
Age									
≤70	105	2 (1.9)	Not reached [-; -]	103	18 (17.5)	Not reached [-; -]	0.09 [0.02; 0.37]	0.001	0.312
>70	48	0 (0.0)	Not reached [-; -]	40	5 (12.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.012	
ECOG									
0	75	0 (0.0)	Not reached [-; -]	79	11 (13.9)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.157
1	78	2 (2.6)	Not reached [-; -]	64	12 (18.8)	Not reached [-; -]	0.12 [0.03; 0.55]	0.006	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	5 (20.0)	Not reached [28.0; -]	n.a. [n.a.; n.a.]	0.028	0.597
Western Europe/North America	109	2 (1.8)	Not reached [-; -]	105	17 (16.2)	Not reached [-; -]	0.09 [0.02; 0.41]	0.002	
Rest of World	22	0 (0.0)	Not reached [-; -]	13	1 (7.7)	Not reached [22.4; -]	n.a. [n.a.; n.a.]	0.197	
SOC: Skin and subcutaneous tissue disorders, PT: Alopecia									
Gender									
Female	82	8 (9.8)	Not reached [-; -]	68	16 (23.5)	Not reached [-; -]	0.35 [0.15; 0.83]	0.018	0.411
Male	71	3 (4.2)	Not reached [-; -]	75	13 (17.3)	Not reached [-; -]	0.19 [0.05; 0.66]	0.010	
Age									
≤70	105	7 (6.7)	Not reached [-; -]	103	20 (19.4)	Not reached [-; -]	0.28 [0.12; 0.66]	0.004	0.936
>70	48	4 (8.3)	Not reached [108.1; -]	40	9 (22.5)	Not reached [-; -]	0.27 [0.07; 0.99]	0.049	
ECOG									
0	75	4 (5.3)	Not reached [-; -]	79	11 (13.9)	Not reached [-; -]	0.31 [0.10; 0.98]	0.046	0.727
1	78	7 (9.0)	Not reached [-; -]	64	18 (28.1)	Not reached [-; -]	0.25 [0.10; 0.62]	0.003	
Geographic Region									
Asia	22	1 (4.5)	Not reached [-; -]	25	9 (36.0)	Not reached [13.7; -]	0.12 [0.01; 0.93]	0.042	0.074
Western Europe/North America	109	8 (7.3)	Not reached [-; -]	105	20 (19.0)	Not reached [-; -]	0.32 [0.14; 0.73]	0.007	
Rest of World	22	2 (9.1)	Not reached [108.1; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.408	
SOC: Skin and subcutaneous tissue disorders, PT: Palmar-plantar erythrodysaesthesia syndrome									
Gender									
Female	82	1 (1.2)	Not reached [-; -]	68	13 (19.1)	Not reached [66.0; -]	0.05 [0.01; 0.38]	0.004	0.302
Male	71	0 (0.0)	Not reached [-; -]	75	12 (16.0)	Not reached [73.9; -]	n.a. [n.a.; n.a.]	< 0.001	
Age									

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
≤70	105	1 (1.0)	Not reached [-; -]	103	20 (19.4)	Not reached [73.9; -]	0.03 [0.00; 0.24]	< 0.001	0.489
>70	48	0 (0.0)	Not reached [-; -]	40	5 (12.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.012	
ECOG									
0	75	1 (1.3)	Not reached [-; -]	79	17 (21.5)	Not reached [66.0; -]	0.04 [0.00; 0.29]	0.002	0.355
1	78	0 (0.0)	Not reached [-; -]	64	8 (12.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Geographic Region									
Asia	22	1 (4.5)	Not reached [-; -]	25	6 (24.0)	Not reached [45.6; -]	0.18 [0.02; 1.48]	0.110	0.187
Western Europe/North America	109	0 (0.0)	Not reached [-; -]	105	18 (17.1)	Not reached [73.9; -]	n.a. [n.a.; n.a.]	< 0.001	
Rest of World	22	0 (0.0)	Not reached [-; -]	13	1 (7.7)	66.0 [-; -]	n.a. [n.a.; n.a.]	n.a.	
SOC: Skin and subcutaneous tissue disorders, PT: Pruritus									
Gender									
Female	82	13 (15.9)	Not reached [-; -]	68	4 (5.9)	144.1 [144.1; -]	4.04 [1.15; 14.22]	0.030	0.233
Male	71	12 (16.9)	Not reached [-; -]	75	8 (10.7)	Not reached [-; -]	1.46 [0.60; 3.59]	0.407	
Age									
≤70	105	19 (18.1)	Not reached [-; -]	103	10 (9.7)	144.1 [144.1; -]	2.06 [0.93; 4.57]	0.074	0.794
>70	48	6 (12.5)	Not reached [-; -]	40	2 (5.0)	Not reached [-; -]	2.31 [0.46; 11.60]	0.310	
ECOG									
0	75	14 (18.7)	Not reached [-; -]	79	7 (8.9)	144.1 [-; -]	2.33 [0.89; 6.08]	0.084	0.924
1	78	11 (14.1)	Not reached [-; -]	64	5 (7.8)	Not reached [-; -]	1.89 [0.65; 5.44]	0.240	
Geographic Region									
Asia	22	2 (9.1)	Not reached [-; -]	25	3 (12.0)	144.1 [144.1; -]	1.16 [0.16; 8.27]	0.881	0.696
Western Europe/North America	109	18 (16.5)	Not reached [-; -]	105	7 (6.7)	Not reached [-; -]	2.51 [1.05; 6.03]	0.039	
Rest of World	22	5 (22.7)	Not reached [32.1; -]	13	2 (15.4)	Not reached [11.1; -]	1.17 [0.22; 6.12]	0.854	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: all-subjects-as-treated population

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

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 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; 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; PT: Preferred Term; SOC:

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
System Organ Class									

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-52: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC)

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Serious Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC: Blood and lymphatic system disorders									
Gender									
Female	82	1 (1.2)	n.c.	68	7 (10.3)	n.c.	n.c.	n.c.	n.c.
Male	71	2 (2.8)	n.c.	75	4 (5.3)	n.c.	n.c.	n.c.	
Age									
≤70	105	2 (1.9)	n.c.	103	6 (5.8)	n.c.	n.c.	n.c.	n.c.
>70	48	1 (2.1)	n.c.	40	5 (12.5)	n.c.	n.c.	n.c.	
ECOG									
0	75	0 (0.0)	n.c.	79	7 (8.9)	n.c.	n.c.	n.c.	n.c.
1	78	3 (3.8)	n.c.	64	4 (6.3)	n.c.	n.c.	n.c.	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	1 (4.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.355	0.676
Western Europe/North America	109	2 (1.8)	Not reached [-; -]	105	9 (8.6)	Not reached [-; -]	0.21 [0.04; 0.96]	0.045	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	1 (7.7)	Not reached [-; -]	0.57 [0.04; 9.08]	0.689	
SOC: Gastrointestinal disorders									
Gender									
Female	82	14 (17.1)	Not reached [-; -]	68	15 (22.1)	Not reached [-; -]	0.64 [0.30; 1.34]	0.232	0.576
Male	71	10 (14.1)	Not reached [-; -]	75	18 (24.0)	Not reached [-; -]	0.46 [0.21; 1.00]	0.051	
Age									
≤70	105	16 (15.2)	Not reached [-; -]	103	23 (22.3)	Not reached [-; -]	0.57 [0.30; 1.08]	0.085	0.946
>70	48	8 (16.7)	Not reached [75.9; -]	40	10 (25.0)	Not reached [39.0; -]	0.49 [0.19; 1.28]	0.145	
ECOG									
0	75	12 (16.0)	Not reached [-; -]	79	16 (20.3)	Not reached [-; -]	0.64 [0.30; 1.38]	0.255	0.646

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Serious Adverse Events	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
1	78	12 (15.4)	Not reached [-; -]	64	17 (26.6)	Not reached [43.7; -]	0.46 [0.21; 0.97]	0.042	
Geographic Region									
Asia	22	1 (4.5)	Not reached [-; -]	25	2 (8.0)	Not reached [-; -]	0.62 [0.06; 6.87]	0.698	0.398
Western Europe/North America	109	22 (20.2)	Not reached [-; -]	105	28 (26.7)	Not reached [-; -]	0.58 [0.33; 1.03]	0.063	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	3 (23.1)	Not reached [2.9; -]	0.14 [0.01; 1.39]	0.093	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: all-subjects-as-treated population

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

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 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; 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; SOC: System Organ Class

Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT)

Tabelle 4G-53: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC)

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC: Blood and lymphatic system disorders									
Gender									
Female	82	17 (20.7)	Not reached [110.1; -]	68	16 (23.5)	97.0 [70.1; -]	0.73 [0.36; 1.47]	0.374	0.169
Male	71	9 (12.7)	Not reached [-; -]	75	19 (25.3)	Not reached [-; -]	0.42 [0.19; 0.94]	0.034	
Age									
≤70	105	17 (16.2)	Not reached [-; -]	103	23 (22.3)	Not reached [97.0; -]	0.58 [0.30; 1.10]	0.093	0.781
>70	48	9 (18.8)	Not reached [-; -]	40	12 (30.0)	Not reached [19.1; -]	0.54 [0.22; 1.32]	0.175	
ECOG									
0	75	12 (16.0)	Not reached [-; -]	79	17 (21.5)	Not reached [-; -]	0.67 [0.32; 1.40]	0.283	0.839
1	78	14 (17.9)	Not reached [-; -]	64	18 (28.1)	97.0 [70.1; -]	0.45 [0.21; 0.97]	0.040	
Geographic Region									
Asia	22	4 (18.2)	110.1 [-; -]	25	5 (20.0)	Not reached [97.0; -]	0.99 [0.25; 3.82]	0.983	0.787
Western	109	18	Not reached	105	27	Not reached	0.53	0.045	

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Europe/North America		(16.5)	[-; -]		(25.7)	[70.1; -]	[0.29; 0.99]		
Rest of World	22	4 (18.2)	Not reached [98.4; -]	13	3 (23.1)	Not reached [8.0; -]	0.48 [0.10; 2.25]	0.349	
SOC: Endocrine disorders									
Age									
≤70	105	22 (21.0)	Not reached [-; -]	103	2 (1.9)	Not reached [-; -]	9.87 [2.31; 42.11]	0.002	0.405
>70	48	4 (8.3)	Not reached [-; -]	40	1 (2.5)	Not reached [41.9; -]	3.09 [0.34; 27.95]	0.316	
ECOG									
0	75	15 (20.0)	Not reached [-; -]	79	1 (1.3)	Not reached [-; -]	14.80 [1.95; 112.41]	0.009	0.311
1	78	11 (14.1)	Not reached [-; -]	64	2 (3.1)	Not reached [-; -]	4.01 [0.88; 18.22]	0.072	
Geographic Region									
Asia	22	4 (18.2)	Not reached [26.1; -]	25	1 (4.0)	Not reached [-; -]	5.64 [0.63; 50.57]	0.122	0.727
Western Europe/North America	109	18 (16.5)	Not reached [-; -]	105	2 (1.9)	Not reached [-; -]	7.13 [1.64; 30.92]	0.009	
Rest of World	22	4 (18.2)	Not reached [-; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.114	
SOC: Gastrointestinal disorders									
Gender									
Female	82	69 (84.1)	6.1 [3.1; 8.9]	68	64 (94.1)	1.1 [0.6; 2.3]	0.42 [0.29; 0.60]	< 0.001	0.167
Male	71	47 (66.2)	25.0 [10.0; 48.1]	75	66 (88.0)	1.0 [0.6; 2.6]	0.33 [0.22; 0.49]	< 0.001	
Age									
≤70	105	82 (78.1)	9.1 [6.0; 18.0]	103	96 (93.2)	0.9 [0.4; 2.1]	0.36 [0.26; 0.49]	< 0.001	0.366
>70	48	34 (70.8)	6.6 [3.3; 23.9]	40	34 (85.0)	2.3 [0.9; 3.3]	0.46 [0.28; 0.76]	0.003	
ECOG									
0	75	60 (80.0)	8.9 [5.6; 21.1]	79	70 (88.6)	1.4 [0.6; 2.4]	0.44 [0.31; 0.62]	< 0.001	0.313
1	78	56 (71.8)	9.1 [3.3; 18.0]	64	60 (93.8)	1.0 [0.6; 2.3]	0.31 [0.20; 0.46]	< 0.001	
SOC: General disorders and administration site conditions									
Gender									
Female	82	53 (64.6)	10.9 [3.4; 21.1]	68	55 (80.9)	4.0 [2.3; 8.1]	0.64 [0.44; 0.94]	0.024	0.295
Male	71	49 (69.0)	16.9 [6.1; 32.4]	75	66 (88.0)	2.9 [2.1; 8.3]	0.44 [0.30; 0.65]	< 0.001	
Age									

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in weeks [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in weeks [95 %-CI]**	**Hazard Ratio[e] [95 %-CI]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
≤70	105	70 (66.7)	10.7 [3.4; 27.1]	103	91 (88.3)	2.9 [2.3; 4.7]	0.51 [0.37; 0.70]	< 0.001	0.268
>70	48	32 (66.7)	14.7 [9.1; 27.1]	40	30 (75.0)	8.1 [2.3; 17.9]	0.64 [0.39; 1.06]	0.085	
ECOG									
0	75	51 (68.0)	10.9 [3.4; 24.6]	79	67 (84.8)	3.9 [2.6; 6.1]	0.55 [0.38; 0.81]	0.002	0.923
1	78	51 (65.4)	12.3 [6.3; 30.3]	64	54 (84.4)	3.7 [1.9; 9.1]	0.52 [0.35; 0.77]	0.001	
Geographic Region									
Asia	22	12 (54.5)	14.1 [0.7; -]	25	22 (88.0)	8.7 [2.9; 12.4]	0.55 [0.27; 1.11]	0.095	0.186
Western Europe/North America	109	74 (67.9)	12.1 [6.0; 30.3]	105	91 (86.7)	2.9 [2.1; 4.7]	0.46 [0.33; 0.63]	< 0.001	
Rest of World	22	16 (72.7)	6.1 [1.0; 27.1]	13	8 (61.5)	12.4 [0.6; -]	1.06 [0.45; 2.51]	0.892	
SOC: Injury, poisoning and procedural complications									
Gender									
Female	82	12 (14.6)	Not reached [-; -]	68	19 (27.9)	68.1 [48.0; -]	0.39 [0.19; 0.82]	0.013	0.147
Male	71	13 (18.3)	Not reached [-; -]	75	13 (17.3)	Not reached [-; -]	0.74 [0.34; 1.62]	0.459	
Age									
≤70	105	17 (16.2)	Not reached [-; -]	103	22 (21.4)	Not reached [-; -]	0.56 [0.29; 1.07]	0.078	0.895
>70	48	8 (16.7)	Not reached [72.0; -]	40	10 (25.0)	68.1 [44.3; -]	0.45 [0.17; 1.17]	0.102	
ECOG									
0	75	14 (18.7)	Not reached [-; -]	79	16 (20.3)	Not reached [-; -]	0.65 [0.32; 1.36]	0.253	0.365
1	78	11 (14.1)	Not reached [-; -]	64	16 (25.0)	68.1 [36.4; -]	0.41 [0.19; 0.90]	0.025	
Geographic Region									
Asia	22	5 (22.7)	Not reached [50.4; -]	25	4 (16.0)	Not reached [48.0; -]	1.20 [0.32; 4.51]	0.785	0.152
Western Europe/North America	109	15 (13.8)	Not reached [-; -]	105	22 (21.0)	Not reached [-; -]	0.49 [0.25; 0.95]	0.035	
Rest of World	22	5 (22.7)	Not reached [72.0; -]	13	6 (46.2)	39.6 [4.7; -]	0.17 [0.04; 0.71]	0.015	
SOC: Investigations									
Gender									
Female	82	24 (29.3)	Not reached [60.0; -]	68	30 (44.1)	104.4 [11.6; -]	0.48 [0.28; 0.83]	0.009	0.351
Male	71	24 (33.8)	Not reached [71.1; -]	75	28 (37.3)	Not reached [29.9; -]	0.63 [0.36; 1.10]	0.107	
Age									
≤70	105	40 (38.1)	103.9 [48.1; -]	103	43 (41.7)	43.0 [23.9; -]	0.68 [0.43; 1.05]	0.081	0.081
>70	48	8	Not reached	40	15	Not reached	0.29	0.007	

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
		(16.7)	[-; -]		(37.5)	[14.1; -]	[0.12; 0.71]		
ECOG									
0	75	25 (33.3)	Not reached [81.3; -]	79	31 (39.2)	104.4 [29.9; -]	0.64 [0.37; 1.10]	0.106	0.543
1	78	23 (29.5)	Not reached [48.1; -]	64	27 (42.2)	31.0 [15.1; -]	0.44 [0.25; 0.79]	0.006	
SOC: Metabolism and nutrition disorders									
Gender									
Female	82	32 (39.0)	Not reached [25.0; -]	68	40 (58.8)	15.9 [8.3; 33.0]	0.53 [0.33; 0.85]	0.008	0.365
Male	71	32 (45.1)	100.1 [26.0; -]	75	36 (48.0)	23.1 [12.7; -]	0.70 [0.43; 1.14]	0.156	
Age									
≤70	105	44 (41.9)	Not reached [26.0; -]	103	56 (54.4)	18.6 [10.7; 42.1]	0.59 [0.39; 0.88]	0.010	0.751
>70	48	20 (41.7)	62.9 [17.3; -]	40	20 (50.0)	18.1 [9.0; -]	0.67 [0.36; 1.24]	0.202	
ECOG									
0	75	34 (45.3)	94.4 [23.7; -]	79	40 (50.6)	29.0 [14.1; -]	0.70 [0.44; 1.12]	0.137	0.411
1	78	30 (38.5)	100.1 [40.6; -]	64	36 (56.3)	13.1 [8.3; 33.0]	0.51 [0.31; 0.84]	0.008	
Geographic Region									
Asia	22	10 (45.5)	80.3 [17.1; -]	25	16 (64.0)	12.7 [4.7; -]	0.48 [0.21; 1.09]	0.079	0.193
Western Europe/North America	109	46 (42.2)	Not reached [26.0; -]	105	58 (55.2)	15.9 [10.7; 42.1]	0.60 [0.41; 0.89]	0.012	
Rest of World	22	8 (36.4)	Not reached [15.3; -]	13	2 (15.4)	Not reached [39.4; -]	1.96 [0.41; 9.50]	0.402	
SOC: Nervous system disorders									
Age									
≤70	105	36 (34.3)	Not reached [65.4; -]	103	74 (71.8)	5.4 [3.1; 9.0]	0.27 [0.18; 0.41]	< 0.001	0.836
>70	48	11 (22.9)	Not reached [63.6; -]	40	25 (62.5)	17.0 [5.1; 23.4]	0.23 [0.11; 0.47]	< 0.001	
ECOG									
0	75	18 (24.0)	Not reached [-; -]	79	52 (65.8)	6.9 [3.9; 16.1]	0.23 [0.13; 0.39]	< 0.001	0.213
1	78	29 (37.2)	74.7 [39.3; -]	64	47 (73.4)	6.9 [4.3; 10.0]	0.27 [0.17; 0.44]	< 0.001	
Geographic Region									
Asia	22	6 (27.3)	Not reached [25.1; -]	25	23 (92.0)	2.9 [2.3; 15.1]	0.11 [0.04; 0.31]	< 0.001	0.193
Western Europe/North America	109	33 (30.3)	Not reached [65.4; -]	105	69 (65.7)	6.9 [5.0; 10.3]	0.27 [0.18; 0.42]	< 0.001	
Rest of World	22	8 (36.4)	Not reached [3.9; -]	13	7 (53.8)	42.1 [0.9; -]	0.54 [0.20; 1.51]	0.242	
SOC: Respiratory, thoracic and mediastinal disorders									

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	82	34 (41.5)	70.7 [28.1; -]	68	37 (54.4)	23.3 [13.7; 33.1]	0.51 [0.32; 0.83]	0.006	0.306
Male	71	34 (47.9)	54.0 [35.0; -]	75	36 (48.0)	35.0 [19.6; -]	0.73 [0.45; 1.18]	0.202	
Age									
≤70	105	44 (41.9)	64.7 [35.9; -]	103	50 (48.5)	27.0 [18.4; 44.3]	0.63 [0.42; 0.95]	0.028	0.970
>70	48	24 (50.0)	50.4 [21.1; 74.7]	40	23 (57.5)	22.4 [8.3; 50.3]	0.50 [0.27; 0.93]	0.029	
ECOG									
0	75	37 (49.3)	50.4 [24.1; -]	79	36 (45.6)	35.0 [23.3; -]	0.81 [0.51; 1.30]	0.383	0.094
1	78	31 (39.7)	64.7 [35.9; -]	64	37 (57.8)	16.1 [14.0; 44.3]	0.42 [0.25; 0.69]	< 0.001	
Geographic Region									
Asia	22	10 (45.5)	39.7 [17.0; -]	25	14 (56.0)	27.0 [14.0; 113.0]	0.70 [0.31; 1.58]	0.386	0.910
Western Europe/North America	109	49 (45.0)	70.7 [37.4; -]	105	54 (51.4)	24.3 [14.3; 44.3]	0.60 [0.41; 0.90]	0.013	
Rest of World	22	9 (40.9)	54.1 [15.1; -]	13	5 (38.5)	Not reached [6.0; -]	0.86 [0.28; 2.64]	0.792	

a: Database Cutoff Date: 19FEB2020
b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab
c: Number of patients: all-subjects-as-treated population
d: From product-limit (Kaplan-Meier) method
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 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; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); SOC: System Organ Class

Tabelle 4G-54: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (PT)

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC: Blood and lymphatic system disorders, PT: Neutropenia									
Gender									
Female	82	0 (0.0)	Not reached [-; -]	68	7 (10.3)	Not reached [97.0; -]	n.a. [n.a.; n.a.]	< 0.001	0.051
Male	71	3 (4.2)	Not reached [-; -]	75	8 (10.7)	Not reached [-; -]	0.31 [0.08; 1.18]	0.086	
ECOG									
0	75	2	Not reached	79	8	Not reached	0.23	0.060	0.544

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
		(2.7)	[-; -]		(10.1)	[-; -]	[0.05; 1.06]		
1	78	1 (1.3)	Not reached [-; -]	64	7 (10.9)	97.0 [97.0; -]	0.05 [0.01; 0.49]	0.009	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	2 (8.0)	Not reached [97.0; -]	n.a. [n.a.; n.a.]	0.077	0.789
Western Europe/North America	109	2 (1.8)	Not reached [-; -]	105	10 (9.5)	Not reached [-; -]	0.14 [0.03; 0.67]	0.013	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	3 (23.1)	Not reached [8.0; -]	0.13 [0.01; 1.30]	0.082	
SOC: Endocrine disorders, PT: Hypothyroidism									
Gender									
Female	82	10 (12.2)	Not reached [-; -]	68	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.004	0.059
Male	71	9 (12.7)	Not reached [-; -]	75	3 (4.0)	Not reached [-; -]	2.29 [0.61; 8.61]	0.221	
Age									
≤70	105	16 (15.2)	Not reached [-; -]	103	2 (1.9)	Not reached [-; -]	6.61 [1.51; 28.91]	0.012	0.422
>70	48	3 (6.3)	Not reached [-; -]	40	1 (2.5)	Not reached [41.9; -]	2.16 [0.22; 21.17]	0.509	
ECOG									
0	75	10 (13.3)	Not reached [-; -]	79	1 (1.3)	Not reached [-; -]	9.69 [1.24; 75.88]	0.031	0.410
1	78	9 (11.5)	Not reached [-; -]	64	2 (3.1)	Not reached [-; -]	2.79 [0.59; 13.21]	0.197	
Geographic Region									
Asia	22	3 (13.6)	Not reached [-; -]	25	1 (4.0)	Not reached [-; -]	4.01 [0.42; 38.58]	0.229	0.644
Western Europe/North America	109	12 (11.0)	Not reached [-; -]	105	2 (1.9)	Not reached [-; -]	4.16 [0.92; 18.87]	0.064	
Rest of World	22	4 (18.2)	Not reached [-; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.114	
SOC: Gastrointestinal disorders, PT: Constipation									
Gender									
Female	82	9 (11.0)	Not reached [-; -]	68	18 (26.5)	88.3 [44.7; -]	0.29 [0.13; 0.66]	0.003	0.421
Male	71	17 (23.9)	Not reached [-; -]	75	27 (36.0)	Not reached [43.3; -]	0.49 [0.27; 0.91]	0.024	
Age									
≤70	105	21 (20.0)	Not reached [-; -]	103	40 (38.8)	88.3 [35.4; -]	0.37 [0.22; 0.63]	< 0.001	0.431
>70	48	5 (10.4)	Not reached [-; -]	40	5 (12.5)	Not reached [-; -]	0.65 [0.18; 2.34]	0.507	
ECOG									

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
0	75	15 (20.0)	Not reached [-; -]	79	27 (34.2)	88.3 [43.7; -]	0.40 [0.21; 0.75]	0.005	0.989
1	78	11 (14.1)	Not reached [-; -]	64	18 (28.1)	Not reached [43.3; -]	0.40 [0.18; 0.85]	0.018	
SOC: Gastrointestinal disorders, PT: Diarrhoea									
Gender									
Female	82	38 (46.3)	49.4 [27.6; 106.7]	68	46 (67.6)	6.1 [4.3; 14.3]	0.42 [0.27; 0.65]	< 0.001	0.998
Male	71	24 (33.8)	Not reached [57.1; -]	75	40 (53.3)	27.4 [9.0; 46.9]	0.46 [0.27; 0.76]	0.003	
Age									
≤70	105	45 (42.9)	57.6 [37.6; -]	103	62 (60.2)	14.9 [6.7; 34.7]	0.48 [0.32; 0.71]	< 0.001	0.551
>70	48	17 (35.4)	Not reached [20.9; -]	40	24 (60.0)	6.9 [5.0; -]	0.41 [0.22; 0.78]	0.007	
ECOG									
0	75	31 (41.3)	57.6 [37.6; -]	79	46 (58.2)	14.3 [6.7; 40.1]	0.47 [0.29; 0.74]	0.001	0.768
1	78	31 (39.7)	76.0 [28.1; -]	64	40 (62.5)	8.1 [5.0; 33.1]	0.42 [0.26; 0.69]	< 0.001	
Geographic Region									
Asia	22	8 (36.4)	Not reached [11.1; -]	25	12 (48.0)	34.7 [4.6; -]	0.62 [0.25; 1.51]	0.291	0.765
Western Europe/North America	109	46 (42.2)	76.0 [30.3; -]	105	67 (63.8)	7.7 [5.0; 14.9]	0.42 [0.28; 0.61]	< 0.001	
Rest of World	22	8 (36.4)	Not reached [10.7; -]	13	7 (53.8)	27.6 [5.0; 93.9]	0.49 [0.17; 1.41]	0.188	
SOC: Gastrointestinal disorders, PT: Dyspepsia									
Gender									
Female	82	5 (6.1)	Not reached [-; -]	68	7 (10.3)	Not reached [-; -]	0.52 [0.16; 1.66]	0.271	0.739
Male	71	4 (5.6)	Not reached [-; -]	75	9 (12.0)	Not reached [-; -]	0.30 [0.09; 1.00]	0.049	
Age									
≤70	105	9 (8.6)	Not reached [-; -]	103	13 (12.6)	Not reached [-; -]	0.52 [0.22; 1.24]	0.140	0.066
>70	48	0 (0.0)	Not reached [-; -]	40	3 (7.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.047	
ECOG									
0	75	4 (5.3)	Not reached [-; -]	79	9 (11.4)	Not reached [-; -]	0.35 [0.11; 1.17]	0.088	0.750
1	78	5 (6.4)	Not reached [-; -]	64	7 (10.9)	Not reached [-; -]	0.41 [0.12; 1.36]	0.145	
Geographic Region									
Asia	22	2 (9.1)	Not reached [-; -]	25	3 (12.0)	Not reached [-; -]	0.68 [0.11; 4.11]	0.672	0.399
Western Europe/North America	109	6 (5.5)	Not reached [-; -]	105	13 (12.4)	Not reached [-; -]	0.32 [0.12; 0.87]	0.026	
Rest of World	22	1	Not reached	13	0	Not reached	n.a.	0.442	

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
		(4.5)	[-; -]		(0.0)	[-; -]	[n.a.; n.a.]		
SOC: Gastrointestinal disorders, PT: Haemorrhoids									
Gender									
Female	82	0 (0.0)	n.c.	68	4 (5.9)	n.c.	n.c.	n.c.	n.c.
Male	71	2 (2.8)	n.c.	75	6 (8.0)	n.c.	n.c.	n.c.	
Age									
≤70	105	2 (1.9)	n.c.	103	7 (6.8)	n.c.	n.c.	n.c.	n.c.
>70	48	0 (0.0)	n.c.	40	3 (7.5)	n.c.	n.c.	n.c.	
ECOG									
0	75	2 (2.7)	n.c.	79	6 (7.6)	n.c.	n.c.	n.c.	n.c.
1	78	0 (0.0)	n.c.	64	4 (6.3)	n.c.	n.c.	n.c.	
Geographic Region									
Asia	22	0 (0.0)	n.c.	25	2 (8.0)	n.c.	n.c.	n.c.	n.c.
Western Europe/North America	109	2 (1.8)	n.c.	105	7 (6.7)	n.c.	n.c.	n.c.	
Rest of World	22	0 (0.0)	n.c.	13	1 (7.7)	n.c.	n.c.	n.c.	
SOC: Gastrointestinal disorders, PT: Nausea									
Age									
≤70	105	35 (33.3)	Not reached [67.6; -]	103	62 (60.2)	8.0 [2.6; 33.7]	0.35 [0.23; 0.54]	< 0.001	0.866
>70	48	10 (20.8)	Not reached [-; -]	40	19 (47.5)	18.9 [4.4; -]	0.33 [0.15; 0.73]	0.006	
ECOG									
0	75	21 (28.0)	Not reached [-; -]	79	45 (57.0)	13.3 [2.6; 49.7]	0.32 [0.19; 0.54]	< 0.001	0.597
1	78	24 (30.8)	Not reached [54.1; -]	64	36 (56.3)	12.7 [4.4; 131.0]	0.37 [0.22; 0.63]	< 0.001	
SOC: Gastrointestinal disorders, PT: Stomatitis									
Gender									
Female	82	7 (8.5)	Not reached [-; -]	68	19 (27.9)	147.6 [147.6; -]	0.24 [0.10; 0.60]	0.002	0.219
Male	71	3 (4.2)	Not reached [-; -]	75	21 (28.0)	Not reached [78.0; -]	0.10 [0.03; 0.33]	< 0.001	
Age									
≤70	105	6 (5.7)	Not reached [-; -]	103	29 (28.2)	147.6 [78.0; -]	0.15 [0.06; 0.36]	< 0.001	0.564
>70	48	4 (8.3)	Not reached [-; -]	40	11 (27.5)	Not reached [-; -]	0.22 [0.07; 0.72]	0.012	
ECOG									
0	75	5 (6.7)	Not reached [-; -]	79	22 (27.8)	Not reached [78.0; -]	0.16 [0.06; 0.42]	< 0.001	0.990

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
1	78	5 (6.4)	Not reached [-; -]	64	18 (28.1)	147.6 [-; -]	0.19 [0.07; 0.52]	0.001	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	11 (44.0)	147.6 [6.1; -]	n.a. [n.a.; n.a.]	0.001	0.091
Western Europe/North America	109	8 (7.3)	Not reached [-; -]	105	26 (24.8)	Not reached [78.0; -]	0.21 [0.09; 0.48]	< 0.001	
Rest of World	22	2 (9.1)	Not reached [-; -]	13	3 (23.1)	Not reached [2.6; -]	0.16 [0.02; 1.57]	0.116	
SOC: Gastrointestinal disorders, PT: Vomiting									
Gender									
Female	82	20 (24.4)	Not reached [-; -]	68	27 (39.7)	75.7 [16.3; -]	0.50 [0.28; 0.89]	0.018	0.871
Male	71	13 (18.3)	Not reached [-; -]	75	22 (29.3)	Not reached [46.9; -]	0.50 [0.25; 0.99]	0.047	
Age									
≤70	105	27 (25.7)	Not reached [-; -]	103	35 (34.0)	Not reached [46.9; -]	0.61 [0.37; 1.02]	0.059	0.153
>70	48	6 (12.5)	Not reached [-; -]	40	14 (35.0)	Not reached [28.9; -]	0.31 [0.12; 0.80]	0.016	
ECOG									
0	75	17 (22.7)	Not reached [-; -]	79	24 (30.4)	Not reached [75.7; -]	0.62 [0.33; 1.16]	0.136	0.330
1	78	16 (20.5)	Not reached [-; -]	64	25 (39.1)	Not reached [14.0; -]	0.40 [0.21; 0.76]	0.005	
Geographic Region									
Asia	22	5 (22.7)	Not reached [14.1; -]	25	11 (44.0)	Not reached [14.3; -]	0.57 [0.20; 1.65]	0.302	0.235
Western Europe/North America	109	23 (21.1)	Not reached [-; -]	105	37 (35.2)	Not reached [46.9; -]	0.46 [0.27; 0.79]	0.004	
Rest of World	22	5 (22.7)	Not reached [49.4; -]	13	1 (7.7)	Not reached [43.0; -]	2.01 [0.23; 17.71]	0.528	
SOC: General disorders and administration site conditions, PT: Fatigue									
Gender									
Female	82	30 (36.6)	118.0 [38.0; -]	68	28 (41.2)	54.0 [23.9; -]	0.71 [0.42; 1.20]	0.201	0.165
Male	71	24 (33.8)	Not reached [63.1; -]	75	38 (50.7)	27.3 [9.1; -]	0.47 [0.28; 0.78]	0.004	
Age									
≤70	105	38 (36.2)	Not reached [57.1; -]	103	52 (50.5)	39.4 [12.0; 65.1]	0.55 [0.36; 0.85]	0.007	0.448
>70	48	16 (33.3)	118.0 [40.7; 118.0]	40	14 (35.0)	54.0 [23.9; -]	0.69 [0.33; 1.44]	0.328	
ECOG									
0	75	29 (38.7)	Not reached [40.7; -]	79	41 (51.9)	27.3 [9.7; 65.1]	0.53 [0.33; 0.87]	0.011	0.523
1	78	25 (32.1)	118.0 [57.1; -]	64	25 (39.1)	57.1 [18.9; -]	0.64 [0.36; 1.13]	0.126	

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Geographic Region									
Asia	22	6 (27.3)	Not reached [14.1; -]	25	13 (52.0)	41.1 [12.0; -]	0.50 [0.19; 1.32]	0.163	0.067
Western Europe/North America	109	35 (32.1)	118.0 [96.1; -]	105	49 (46.7)	54.0 [13.9; -]	0.48 [0.31; 0.76]	0.001	
Rest of World	22	13 (59.1)	40.7 [13.4; 81.3]	13	4 (30.8)	42.1 [2.6; -]	1.51 [0.48; 4.76]	0.478	
SOC: General disorders and administration site conditions, PT: Mucosal inflammation									
Gender									
Female	82	4 (4.9)	Not reached [-; -]	68	12 (17.6)	Not reached [-; -]	0.22 [0.07; 0.70]	0.011	0.766
Male	71	3 (4.2)	Not reached [-; -]	75	14 (18.7)	Not reached [-; -]	0.18 [0.05; 0.64]	0.008	
Age									
≤70	105	5 (4.8)	Not reached [-; -]	103	22 (21.4)	Not reached [-; -]	0.19 [0.07; 0.50]	< 0.001	0.502
>70	48	2 (4.2)	Not reached [-; -]	40	4 (10.0)	Not reached [52.3; -]	0.21 [0.03; 1.37]	0.102	
ECOG									
0	75	3 (4.0)	Not reached [-; -]	79	20 (25.3)	Not reached [-; -]	0.13 [0.04; 0.45]	0.001	0.123
1	78	4 (5.1)	Not reached [-; -]	64	6 (9.4)	Not reached [-; -]	0.36 [0.09; 1.40]	0.141	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	1 (4.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.348	0.795
Western Europe/North America	109	6 (5.5)	Not reached [-; -]	105	22 (21.0)	Not reached [-; -]	0.18 [0.07; 0.47]	< 0.001	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	3 (23.1)	Not reached [0.6; -]	0.18 [0.02; 1.70]	0.133	
SOC: Investigations, PT: Blood alkaline phosphatase increased									
Gender									
Female	82	10 (12.2)	Not reached [-; -]	68	1 (1.5)	Not reached [-; -]	6.68 [0.84; 52.76]	0.072	0.362
Male	71	8 (11.3)	Not reached [-; -]	75	3 (4.0)	Not reached [-; -]	2.26 [0.59; 8.67]	0.235	
Age									
≤70	105	15 (14.3)	Not reached [-; -]	103	2 (1.9)	Not reached [-; -]	6.00 [1.36; 26.50]	0.018	0.126
>70	48	3 (6.3)	Not reached [-; -]	40	2 (5.0)	Not reached [-; -]	1.15 [0.19; 6.93]	0.879	
Geographic Region									
Asia	22	1 (4.5)	Not reached [-; -]	25	1 (4.0)	Not reached [-; -]	1.20 [0.08; 19.21]	0.897	0.276
Western Europe/North America	109	10 (9.2)	Not reached [-; -]	105	3 (2.9)	Not reached [-; -]	2.70 [0.73; 9.92]	0.135	

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Rest of World	22	7 (31.8)	Not reached [30.1; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.085	
SOC: Investigations, PT: Neutrophil count decreased									
Gender									
Female	82	0 (0.0)	Not reached [-; -]	68	6 (8.8)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	0.152
Male	71	2 (2.8)	Not reached [-; -]	75	10 (13.3)	Not reached [-; -]	0.13 [0.03; 0.61]	0.010	
Age									
≤70	105	2 (1.9)	Not reached [-; -]	103	12 (11.7)	Not reached [-; -]	0.09 [0.02; 0.43]	0.003	0.277
>70	48	0 (0.0)	Not reached [-; -]	40	4 (10.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.029	
ECOG									
0	75	1 (1.3)	Not reached [-; -]	79	9 (11.4)	Not reached [-; -]	0.06 [0.01; 0.53]	0.011	0.954
1	78	1 (1.3)	Not reached [-; -]	64	7 (10.9)	Not reached [-; -]	0.09 [0.01; 0.73]	0.025	
Geographic Region									
Asia	22	0 (0.0)	n.c.	25	8 (32.0)	n.c.	n.c.	n.c.	n.c.
Western Europe/North America	109	1 (0.9)	n.c.	105	7 (6.7)	n.c.	n.c.	n.c.	
Rest of World	22	1 (4.5)	n.c.	13	1 (7.7)	n.c.	n.c.	n.c.	
SOC: Investigations, PT: Weight decreased									
Gender									
Female	82	4 (4.9)	Not reached [-; -]	68	10 (14.7)	Not reached [-; -]	0.23 [0.07; 0.78]	0.018	0.938
Male	71	2 (2.8)	Not reached [-; -]	75	6 (8.0)	Not reached [-; -]	0.28 [0.06; 1.41]	0.122	
Age									
≤70	105	3 (2.9)	Not reached [-; -]	103	11 (10.7)	Not reached [-; -]	0.22 [0.06; 0.81]	0.023	0.530
>70	48	3 (6.3)	Not reached [-; -]	40	5 (12.5)	Not reached [-; -]	0.31 [0.07; 1.40]	0.127	
ECOG									
0	75	2 (2.7)	Not reached [-; -]	79	9 (11.4)	Not reached [-; -]	0.17 [0.03; 0.79]	0.024	0.475
1	78	4 (5.1)	Not reached [-; -]	64	7 (10.9)	Not reached [-; -]	0.37 [0.11; 1.29]	0.117	
Geographic Region									
Asia	22	1 (4.5)	Not reached [-; -]	25	2 (8.0)	Not reached [60.7; -]	0.50 [0.04; 5.53]	0.571	0.311
Western Europe/North America	109	4 (3.7)	Not reached [-; -]	105	14 (13.3)	Not reached [-; -]	0.22 [0.07; 0.69]	0.009	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.763	
SOC: Investigations, PT: White blood cell count decreased									

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	82	0 (0.0)	n.c.	68	6 (8.8)	n.c.	n.c.	n.c.	n.c.
Male	71	1 (1.4)	n.c.	75	6 (8.0)	n.c.	n.c.	n.c.	
Age									
≤70	105	1 (1.0)	n.c.	103	7 (6.8)	n.c.	n.c.	n.c.	n.c.
>70	48	0 (0.0)	n.c.	40	5 (12.5)	n.c.	n.c.	n.c.	
ECOG									
0	75	1 (1.3)	n.c.	79	7 (8.9)	n.c.	n.c.	n.c.	n.c.
1	78	0 (0.0)	n.c.	64	5 (7.8)	n.c.	n.c.	n.c.	
Geographic Region									
Asia	22	0 (0.0)	n.c.	25	8 (32.0)	n.c.	n.c.	n.c.	n.c.
Western Europe/North America	109	1 (0.9)	n.c.	105	3 (2.9)	n.c.	n.c.	n.c.	
Rest of World	22	0 (0.0)	n.c.	13	1 (7.7)	n.c.	n.c.	n.c.	
SOC: Metabolism and nutrition disorders, PT: Decreased appetite									
Gender									
Female	82	18 (22.0)	Not reached [-; -]	68	32 (47.1)	39.4 [13.1; -]	0.41 [0.23; 0.73]	0.003	0.264
Male	71	18 (25.4)	Not reached [-; -]	75	25 (33.3)	Not reached [42.1; -]	0.61 [0.33; 1.13]	0.119	
Age									
≤70	105	24 (22.9)	Not reached [-; -]	103	41 (39.8)	64.7 [30.1; -]	0.48 [0.29; 0.80]	0.004	0.792
>70	48	12 (25.0)	Not reached [43.4; -]	40	16 (40.0)	Not reached [12.7; -]	0.54 [0.25; 1.15]	0.112	
ECOG									
0	75	20 (26.7)	Not reached [-; -]	79	27 (34.2)	Not reached [42.1; -]	0.70 [0.39; 1.25]	0.224	0.120
1	78	16 (20.5)	Not reached [-; -]	64	30 (46.9)	30.1 [11.4; -]	0.34 [0.18; 0.63]	< 0.001	
Geographic Region									
Asia	22	6 (27.3)	Not reached [17.1; -]	25	15 (60.0)	30.1 [10.4; -]	0.41 [0.16; 1.06]	0.066	0.304
Western Europe/North America	109	26 (23.9)	Not reached [-; -]	105	41 (39.0)	Not reached [23.1; -]	0.52 [0.32; 0.86]	0.010	
Rest of World	22	4 (18.2)	Not reached [49.6; -]	13	1 (7.7)	Not reached [39.4; -]	1.52 [0.16; 14.30]	0.716	
SOC: Musculoskeletal and connective tissue disorders, PT: Arthralgia									
Gender									
Female	82	16	Not reached	68	2	Not reached	5.29	0.027	0.258

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
		(19.5)	[103.3; -]		(2.9)	[-; -]	[1.20; 23.23]		
Male	71	12 (16.9)	Not reached [-; -]	75	5 (6.7)	Not reached [79.1; -]	2.08 [0.72; 5.96]	0.175	
Age									
≤70	105	23 (21.9)	Not reached [-; -]	103	5 (4.9)	Not reached [-; -]	3.93 [1.49; 10.41]	0.006	0.358
>70	48	5 (10.4)	Not reached [-; -]	40	2 (5.0)	79.1 [79.1; -]	1.40 [0.26; 7.50]	0.696	
Geographic Region									
Asia	22	3 (13.6)	Not reached [63.4; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.068	0.095
Western Europe/North America	109	18 (16.5)	Not reached [-; -]	105	7 (6.7)	Not reached [79.1; -]	1.94 [0.80; 4.70]	0.143	
Rest of World	22	7 (31.8)	Not reached [36.3; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.077	
SOC: Nervous system disorders, PT: Dysgeusia									
Gender									
Female	82	1 (1.2)	n.c.	68	7 (10.3)	n.c.	n.c.	n.c.	n.c.
Male	71	3 (4.2)	n.c.	75	6 (8.0)	n.c.	n.c.	n.c.	
Age									
≤70	105	2 (1.9)	Not reached [-; -]	103	9 (8.7)	Not reached [-; -]	0.18 [0.04; 0.84]	0.029	0.588
>70	48	2 (4.2)	Not reached [-; -]	40	4 (10.0)	Not reached [42.1; -]	0.31 [0.05; 1.75]	0.184	
ECOG									
0	75	3 (4.0)	Not reached [-; -]	79	7 (8.9)	Not reached [-; -]	0.36 [0.09; 1.41]	0.143	0.325
1	78	1 (1.3)	Not reached [-; -]	64	6 (9.4)	Not reached [-; -]	0.12 [0.01; 1.00]	0.050	
Geographic Region									
Asia	22	1 (4.5)	Not reached [-; -]	25	2 (8.0)	Not reached [-; -]	0.59 [0.05; 6.51]	0.667	0.729
Western Europe/North America	109	2 (1.8)	Not reached [-; -]	105	9 (8.6)	Not reached [-; -]	0.16 [0.03; 0.77]	0.022	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	2 (15.4)	Not reached [28.9; -]	0.17 [0.02; 2.00]	0.160	
SOC: Nervous system disorders, PT: Neuropathy peripheral									
Gender									
Female	82	1 (1.2)	Not reached [-; -]	68	15 (22.1)	Not reached [-; -]	0.04 [0.01; 0.33]	0.002	0.354
Male	71	0 (0.0)	Not reached [-; -]	75	11 (14.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Age									
≤70	105	1 (1.0)	Not reached [-; -]	103	23 (22.3)	Not reached [-; -]	0.04 [0.00; 0.27]	0.001	0.624

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
>70	48	0 (0.0)	Not reached [-; -]	40	3 (7.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.033	
ECOG									
0	75	0 (0.0)	Not reached [-; -]	79	15 (19.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.229
1	78	1 (1.3)	Not reached [-; -]	64	11 (17.2)	Not reached [-; -]	0.06 [0.01; 0.50]	0.009	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	3 (12.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.111	0.751
Western Europe/North America	109	1 (0.9)	Not reached [-; -]	105	20 (19.0)	Not reached [-; -]	0.04 [0.01; 0.31]	0.002	
Rest of World	22	0 (0.0)	Not reached [-; -]	13	3 (23.1)	Not reached [22.9; -]	n.a. [n.a.; n.a.]	0.017	
SOC: Nervous system disorders, PT: Peripheral sensory neuropathy									
Gender									
Female	82	1 (1.2)	Not reached [-; -]	68	12 (17.6)	Not reached [-; -]	0.06 [0.01; 0.45]	0.007	0.666
Male	71	2 (2.8)	Not reached [-; -]	75	17 (22.7)	Not reached [68.1; -]	0.08 [0.02; 0.37]	0.001	
Age									
≤70	105	3 (2.9)	Not reached [-; -]	103	21 (20.4)	Not reached [-; -]	0.10 [0.03; 0.34]	< 0.001	0.158
>70	48	0 (0.0)	Not reached [-; -]	40	8 (20.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
ECOG									
0	75	1 (1.3)	Not reached [-; -]	79	15 (19.0)	Not reached [-; -]	0.05 [0.01; 0.39]	0.004	0.691
1	78	2 (2.6)	Not reached [-; -]	64	14 (21.9)	Not reached [34.0; -]	0.08 [0.02; 0.36]	0.001	
Geographic Region									
Asia	22	1 (4.5)	Not reached [-; -]	25	14 (56.0)	23.0 [2.6; -]	0.05 [0.01; 0.36]	0.003	0.835
Western Europe/North America	109	2 (1.8)	Not reached [-; -]	105	15 (14.3)	Not reached [-; -]	0.09 [0.02; 0.42]	0.002	
Rest of World	22	0 (0.0)	Not reached [-; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
SOC: Respiratory, thoracic and mediastinal disorders, PT: Epistaxis									
Gender									
Female	82	0 (0.0)	Not reached [-; -]	68	11 (16.2)	Not reached [58.0; -]	n.a. [n.a.; n.a.]	< 0.001	0.089
Male	71	2 (2.8)	Not reached [-; -]	75	12 (16.0)	Not reached [-; -]	0.16 [0.03; 0.70]	0.015	
Age									
≤70	105	2 (1.9)	Not reached [-; -]	103	18 (17.5)	Not reached [-; -]	0.09 [0.02; 0.37]	0.001	0.312
>70	48	0 (0.0)	Not reached [-; -]	40	5 (12.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.012	
ECOG									

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab vs. Chemotherapy[b]		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in weeks [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]	p-Value for Interaction Test[g]
0	75	0 (0.0)	Not reached [-; -]	79	11 (13.9)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.157
1	78	2 (2.6)	Not reached [-; -]	64	12 (18.8)	Not reached [-; -]	0.12 [0.03; 0.55]	0.006	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	5 (20.0)	Not reached [28.0; -]	n.a. [n.a.; n.a.]	0.028	0.597
Western Europe/North America	109	2 (1.8)	Not reached [-; -]	105	17 (16.2)	Not reached [-; -]	0.09 [0.02; 0.41]	0.002	
Rest of World	22	0 (0.0)	Not reached [-; -]	13	1 (7.7)	Not reached [22.4; -]	n.a. [n.a.; n.a.]	0.197	
SOC: Skin and subcutaneous tissue disorders, PT: Alopecia									
Gender									
Female	82	8 (9.8)	Not reached [-; -]	68	16 (23.5)	Not reached [-; -]	0.35 [0.15; 0.83]	0.018	0.411
Male	71	3 (4.2)	Not reached [-; -]	75	13 (17.3)	Not reached [-; -]	0.19 [0.05; 0.66]	0.010	
Age									
≤70	105	7 (6.7)	Not reached [-; -]	103	20 (19.4)	Not reached [-; -]	0.28 [0.12; 0.66]	0.004	0.936
>70	48	4 (8.3)	Not reached [108.1; -]	40	9 (22.5)	Not reached [-; -]	0.27 [0.07; 0.99]	0.049	
ECOG									
0	75	4 (5.3)	Not reached [-; -]	79	11 (13.9)	Not reached [-; -]	0.31 [0.10; 0.98]	0.046	0.727
1	78	7 (9.0)	Not reached [-; -]	64	18 (28.1)	Not reached [-; -]	0.25 [0.10; 0.62]	0.003	
Geographic Region									
Asia	22	1 (4.5)	Not reached [-; -]	25	9 (36.0)	Not reached [13.7; -]	0.12 [0.01; 0.93]	0.042	0.074
Western Europe/North America	109	8 (7.3)	Not reached [-; -]	105	20 (19.0)	Not reached [-; -]	0.32 [0.14; 0.73]	0.007	
Rest of World	22	2 (9.1)	Not reached [108.1; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.408	
SOC: Skin and subcutaneous tissue disorders, PT: Palmar-plantar erythrodysaesthesia syndrome									
Gender									
Female	82	1 (1.2)	Not reached [-; -]	68	13 (19.1)	Not reached [66.0; -]	0.04 [0.01; 0.35]	0.003	0.291
Male	71	0 (0.0)	Not reached [-; -]	75	12 (16.0)	Not reached [73.9; -]	n.a. [n.a.; n.a.]	< 0.001	
Age									
≤70	105	1 (1.0)	Not reached [-; -]	103	20 (19.4)	Not reached [69.0; -]	0.03 [0.00; 0.22]	< 0.001	0.489
>70	48	0 (0.0)	Not reached [-; -]	40	5 (12.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.012	
ECOG									
0	75	1 (1.3)	Not reached [-; -]	79	17 (21.5)	73.9 [69.0; -]	0.03 [0.00; 0.26]	0.001	0.359
1	78	0	Not reached	64	8	Not reached	n.a.	< 0.001	

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in weeks [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in weeks [95 %-CI]**	**Hazard Ratio[e] [95 %-CI]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
		(0.0)	[-; -]		(12.5)	[-; -]	[n.a.; n.a.]		
Geographic Region									
Asia	22	1 (4.5)	Not reached [-; -]	25	6 (24.0)	Not reached [45.6; -]	0.18 [0.02; 1.48]	0.110	0.190
Western Europe/North America	109	0 (0.0)	Not reached [-; -]	105	18 (17.1)	Not reached [69.0; -]	n.a. [n.a.; n.a.]	< 0.001	
Rest of World	22	0 (0.0)	Not reached [-; -]	13	1 (7.7)	66.0 [-; -]	n.a. [n.a.; n.a.]	n.a.	
SOC: Skin and subcutaneous tissue disorders, PT: Pruritus									
Gender									
Female	82	13 (15.9)	Not reached [-; -]	68	3 (4.4)	144.1 [144.1; -]	6.18 [1.39; 27.48]	0.017	0.107
Male	71	12 (16.9)	Not reached [-; -]	75	8 (10.7)	Not reached [-; -]	1.46 [0.60; 3.59]	0.407	
Age									
≤70	105	19 (18.1)	Not reached [-; -]	103	9 (8.7)	144.1 [144.1; -]	2.34 [1.02; 5.37]	0.044	0.906
>70	48	6 (12.5)	Not reached [-; -]	40	2 (5.0)	Not reached [-; -]	2.31 [0.46; 11.60]	0.310	
ECOG									
0	75	14 (18.7)	Not reached [-; -]	79	6 (7.6)	144.1 [-; -]	2.83 [1.02; 7.88]	0.047	0.752
1	78	11 (14.1)	Not reached [-; -]	64	5 (7.8)	Not reached [-; -]	1.89 [0.65; 5.44]	0.240	
Geographic Region									
Asia	22	2 (9.1)	Not reached [-; -]	25	3 (12.0)	144.1 [144.1; -]	1.16 [0.16; 8.27]	0.881	0.582
Western Europe/North America	109	18 (16.5)	Not reached [-; -]	105	6 (5.7)	Not reached [-; -]	2.96 [1.17; 7.48]	0.022	
Rest of World	22	5 (22.7)	Not reached [32.1; -]	13	2 (15.4)	Not reached [11.1; -]	1.17 [0.22; 6.12]	0.854	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: all-subjects-as-treated population

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

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 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; 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; PT: Preferred Term; SOC: System Organ Class

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

Tabelle 4G-55: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC)

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab vs. Chemotherapy[b]**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in weeks [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in weeks [95 %-CI]**	**Hazard Ratio[e] [95 %-CI]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
SOC: Blood and lymphatic system disorders									
Age									
≤70	105	7 (6.7)	Not reached [-; -]	103	24 (23.3)	Not reached [-; -]	0.24 [0.11; 0.57]	0.001	0.910
>70	48	5 (10.4)	Not reached [-; -]	40	15 (37.5)	Not reached [16.1; -]	0.22 [0.08; 0.61]	0.004	
Geographic Region									
Asia	22	2 (9.1)	Not reached [-; -]	25	5 (20.0)	Not reached [-; -]	0.46 [0.09; 2.37]	0.353	0.581
Western Europe/North America	109	8 (7.3)	Not reached [-; -]	105	28 (26.7)	Not reached [-; -]	0.22 [0.10; 0.50]	< 0.001	
Rest of World	22	2 (9.1)	Not reached [-; -]	13	6 (46.2)	15.6 [10.6; -]	0.16 [0.03; 0.81]	0.027	
SOC: Gastrointestinal disorders									
Gender									
Female	82	18 (22.0)	Not reached [-; -]	68	24 (35.3)	Not reached [27.6; -]	0.50 [0.27; 0.94]	0.032	0.501
Male	71	13 (18.3)	Not reached [-; -]	75	28 (37.3)	62.9 [34.0; -]	0.32 [0.16; 0.62]	< 0.001	
Age									
≤70	105	20 (19.0)	Not reached [-; -]	103	37 (35.9)	Not reached [34.0; -]	0.39 [0.22; 0.68]	< 0.001	0.759
>70	48	11 (22.9)	Not reached [75.9; -]	40	15 (37.5)	51.1 [25.1; -]	0.41 [0.18; 0.91]	0.029	
ECOG									
0	75	14 (18.7)	Not reached [-; -]	79	29 (36.7)	Not reached [41.4; -]	0.35 [0.18; 0.67]	0.002	0.609
1	78	17 (21.8)	Not reached [-; -]	64	23 (35.9)	Not reached [34.0; -]	0.45 [0.24; 0.86]	0.016	
Geographic Region									
Asia	22	2 (9.1)	Not reached [-; -]	25	6 (24.0)	Not reached [62.9; -]	0.38 [0.08; 1.91]	0.242	0.227
Western Europe/North America	109	27 (24.8)	Not reached [-; -]	105	41 (39.0)	51.1 [34.0; -]	0.45 [0.28; 0.75]	0.002	
Rest of World	22	2 (9.1)	Not reached [83.4; -]	13	5 (38.5)	31.0 [2.9; -]	n.a. [n.a.; n.a.]	1.000	
SOC: General disorders and administration site conditions									
Gender									
Female	82	8 (9.8)	Not reached [-; -]	68	13 (19.1)	Not reached [51.1; -]	0.37 [0.15; 0.93]	0.034	0.616
Male	71	4 (5.6)	Not reached [-; -]	75	12 (16.0)	Not reached [-; -]	0.28 [0.09; 0.87]	0.028	
Age									

≤70	105	6 (5.7)	Not reached [-; -]	103	14 (13.6)	Not reached [-; -]	0.33 [0.13; 0.86]	0.024	0.943
>70	48	6 (12.5)	Not reached [-; -]	40	11 (27.5)	102.1 [47.0; -]	0.33 [0.12; 0.94]	0.037	
ECOG									
0	75	3 (4.0)	Not reached [-; -]	79	12 (15.2)	Not reached [-; -]	0.21 [0.06; 0.76]	0.017	0.272
1	78	9 (11.5)	Not reached [-; -]	64	13 (20.3)	102.1 [51.1; -]	0.41 [0.17; 0.99]	0.048	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	2 (8.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.212	0.278
Western Europe/North America	109	12 (11.0)	Not reached [-; -]	105	22 (21.0)	Not reached [57.3; -]	0.37 [0.18; 0.76]	0.007	
Rest of World	22	0 (0.0)	Not reached [-; -]	13	1 (7.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.193	
SOC: Infections and infestations									
Gender									
Female	82	9 (11.0)	Not reached [-; -]	68	9 (13.2)	Not reached [-; -]	0.84 [0.33; 2.12]	0.715	0.243
Male	71	5 (7.0)	Not reached [-; -]	75	14 (18.7)	Not reached [-; -]	0.31 [0.11; 0.86]	0.025	
Age									
≤70	105	10 (9.5)	Not reached [-; -]	103	20 (19.4)	Not reached [-; -]	0.42 [0.20; 0.90]	0.026	0.297
>70	48	4 (8.3)	Not reached [-; -]	40	3 (7.5)	Not reached [-; -]	1.18 [0.26; 5.26]	0.831	
ECOG									
0	75	6 (8.0)	Not reached [-; -]	79	14 (17.7)	Not reached [-; -]	0.40 [0.15; 1.05]	0.063	0.384
1	78	8 (10.3)	Not reached [-; -]	64	9 (14.1)	Not reached [-; -]	0.64 [0.25; 1.68]	0.368	
Geographic Region									
Asia	22	2 (9.1)	Not reached [-; -]	25	3 (12.0)	Not reached [-; -]	0.82 [0.14; 4.93]	0.831	0.465
Western Europe/North America	109	11 (10.1)	Not reached [-; -]	105	20 (19.0)	Not reached [-; -]	0.46 [0.22; 0.96]	0.038	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.480	
SOC: Investigations									
Gender									
Female	82	10 (12.2)	Not reached [-; -]	68	16 (23.5)	Not reached [-; -]	0.41 [0.18; 0.92]	0.030	0.917
Male	71	8 (11.3)	Not reached [-; -]	75	16 (21.3)	Not reached [-; -]	0.40 [0.17; 0.95]	0.038	
Age									
≤70	105	11 (10.5)	Not reached [-; -]	103	20 (19.4)	Not reached [-; -]	0.42 [0.20; 0.89]	0.024	0.749
>70	48	7 (14.6)	Not reached [-; -]	40	12 (30.0)	Not reached [25.0; -]	0.34 [0.13; 0.90]	0.031	
ECOG									
0	75	11 (14.7)	Not reached [-; -]	79	15 (19.0)	Not reached [-; -]	0.61 [0.27; 1.34]	0.214	0.154
1	78	7	Not reached	64	17	Not reached	0.25	0.003	

		(9.0)	[-; -]		(26.6)	[-; -]	[0.10; 0.62]		
Geographic Region									
Asia	22	4 (18.2)	Not reached [78.0; -]	25	10 (40.0)	Not reached [10.4; -]	0.37 [0.11; 1.20]	0.098	0.842
Western Europe/North America	109	11 (10.1)	Not reached [-; -]	105	20 (19.0)	Not reached [-; -]	0.39 [0.19; 0.83]	0.015	
Rest of World	22	3 (13.6)	Not reached [-; -]	13	2 (15.4)	Not reached [4.1; -]	0.73 [0.12; 4.45]	0.735	

a: Database Cutoff Date: 19FEB2020
b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab
c: Number of patients: all-subjects-as-treated population
d: From product-limit (Kaplan-Meier) method
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 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; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); SOC: System Organ Class

Tabelle 4G-56: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (PT)

Study: KEYNOTE-177[a]	**Pembrolizumab**			**Chemotherapy[b]**			**Pembrolizumab 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]**
Age									
<=70	105	5 (4.8)	Not reached [-; -]	103	8 (7.8)	Not reached [-; -]	0.48 [0.16; 1.50]	0.208	0.647
>70	48	4 (8.3)	Not reached [-; -]	40	8 (20.0)	Not reached [34.1; -]	0.28 [0.08; 0.98]	0.046	
ECOG									
0	75	5 (6.7)	Not reached [-; -]	79	11 (13.9)	Not reached [-; -]	0.35 [0.12; 1.03]	0.057	0.657
1	78	4 (5.1)	Not reached [-; -]	64	5 (7.8)	Not reached [-; -]	0.51 [0.13; 1.98]	0.333	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	2 (8.0)	Not reached [62.9; -]	n.a. [n.a.; n.a.]	0.139	0.492
Western Europe/North America	109	8 (7.3)	Not reached [-; -]	105	13 (12.4)	Not reached [-; -]	0.46 [0.19; 1.14]	0.093	
Rest of World	22	1 (4.5)	Not reached [-; -]	13	1 (7.7)	Not reached [-; -]	0.23 [0.01; 4.91]	0.345	
SOC: General disorders and administration site conditions, PT: Fatigue									
Gender									
Female	82	3 (3.7)	Not reached [-; -]	68	6 (8.8)	Not reached [-; -]	0.26 [0.06; 1.11]	0.068	0.876
Male	71	3 (4.2)	Not reached [-; -]	75	7 (9.3)	Not reached [-; -]	0.37 [0.09; 1.44]	0.151	
Age									
<=70	105	3 (2.9)	Not reached [-; -]	103	8 (7.8)	Not reached [-; -]	0.29 [0.07; 1.09]	0.066	0.822

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab 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]
>70	48	3 (6.3)	Not reached [-; -]	40	5 (12.5)	Not reached [47.0; -]	0.34 [0.07; 1.54]	0.160	
ECOG									
0	75	1 (1.3)	Not reached [-; -]	79	7 (8.9)	Not reached [-; -]	0.13 [0.02; 1.05]	0.056	0.156
1	78	5 (6.4)	Not reached [-; -]	64	6 (9.4)	Not reached [-; -]	0.46 [0.14; 1.57]	0.215	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	2 (8.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.212	0.270
Western Europe/North America	109	6 (5.5)	Not reached [-; -]	105	10 (9.5)	Not reached [-; -]	0.39 [0.14; 1.10]	0.075	
Rest of World	22	0 (0.0)	Not reached [-; -]	13	1 (7.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.193	
SOC: Investigations, PT: Neutrophil count decreased									
Gender									
Female	82	0 (0.0)	Not reached [-; -]	68	15 (22.1)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
Male	71	0 (0.0)	Not reached [-; -]	75	9 (12.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	
Age									
<=70	105	0 (0.0)	Not reached [-; -]	103	14 (13.6)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
>70	48	0 (0.0)	Not reached [-; -]	40	10 (25.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
ECOG									
0	75	0 (0.0)	Not reached [-; -]	79	10 (12.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	0.997
1	78	0 (0.0)	Not reached [-; -]	64	14 (21.9)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	10 (40.0)	Not reached [10.4; -]	n.a. [n.a.; n.a.]	0.002	> 0.999
Western Europe/North America	109	0 (0.0)	Not reached [-; -]	105	13 (12.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Rest of World	22	0 (0.0)	Not reached [-; -]	13	1 (7.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.186	
SOC: Metabolism and nutrition disorders, PT: Hypokalaemia									
Gender									
Female	82	2 (2.4)	n.c.	68	6 (8.8)	n.c.	n.c.	n.c.	n.c.
Male	71	0 (0.0)	n.c.	75	3 (4.0)	n.c.	n.c.	n.c.	
Age									
<=70	105	1 (1.0)	n.c.	103	2 (1.9)	n.c.	n.c.	n.c.	n.c.
>70	48	1 (2.1)	n.c.	40	7 (17.5)	n.c.	n.c.	n.c.	

Study: KEYNOTE-177[a]	Pembrolizumab			Chemotherapy[b]			Pembrolizumab 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]
ECOG									
0	75	1 (1.3)	n.c.	79	6 (7.6)	n.c.	n.c.	n.c.	n.c.
1	78	1 (1.3)	n.c.	64	3 (4.7)	n.c.	n.c.	n.c.	
Geographic Region									
Asia	22	0 (0.0)	Not reached [-; -]	25	1 (4.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.348	0.850
Western Europe/North America	109	2 (1.8)	Not reached [-; -]	105	8 (7.6)	Not reached [-; -]	0.20 [0.04; 0.96]	0.044	
Rest of World	22	0 (0.0)	Not reached [-; -]	13	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	

a: Database Cutoff Date: 19FEB2020

b: Chemotherapy: mFOLFOX6 or mFOLFOX6 + Bevacizumab or mFOLFOX6 + Cetuximab or FOLFIRI or FOLFIRI + Bevacizumab or FOLFIRI + Cetuximab

c: Number of patients: all-subjects-as-treated population

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

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 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; 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; PT: Preferred Term; SOC: System Organ Class

Anhang 4-G5: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI)

Im Folgenden wird ergänzend zu Abschnitt 4.3.1.3.1.4.3. die Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT dargestellt.

Tabelle 4G-57: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT in der Studie KEYNOTE 177 (Datenschnitt vom 19. Februar 2020)

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Pneumonitis	Acute interstitial pneumonitis, Autoimmune lung disease, Interstitial lung disease, Pneumonitis, Idiopathicpneumonia syndrome, Organising pneumonia, Immune-mediated pneumonitis	Yes
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitishaemorrhagic, Necrotising colitis, Colitis erosive,Autoimmune colitis, Immune-mediated enterocolitis	Yes
Hepatitis	Hepatitis, Immune-mediated hepatitis, Autoimmunehepatitis, Hepatitis acute, Hepatitis fulminant, Drug-induced liver injury	Yes
Nephritis	Nephritis, Autoimmune nephritis, Chronic autoimmuneglomerulonephritis, Fibrillary glomerulonephritis, Focalsegmental glomerulosclerosis, Glomerulonephritis,Glomerulonephritis acute, Glomerulonephritismembranoproliferative, Glomerulonephritis membranous,Glomerulonephritis minimal lesion, Glomerulonephritisproliferative, Glomerulonephritis rapidly progressive,Mesangioproliferative glomerulonephritis, Nephritishaemorrhagic, Tubulointerstitial nephritis, Nephroticsyndrome, Immune-mediated nephritis	Yes
Adrenal Insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute,Secondary adrenocortical insufficiency, Primary adrenalinsufficiency, Addison's disease	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis	Yes
Hyperthyroidism	Hyperthyroidism, Basedow’s disease, Thyrotoxic crisis	Yes
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema,Myxoedema coma, Primary hypothyroidism, Autoimmunehypothyroidism, Immune-mediated hypothyroidism	Yes
Thyroiditis	Thyroid disorder, Thyroiditis, Autoimmune thyroiditis,Thyroiditis acute, Silent thyroiditis, Autoimmune thyroiddisorder, Immune-mediated thyroiditis	Yes

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Type 1 Diabetes Mellitus	Diabetic ketoacidosis, Diabetic ketoacidotichyperglycaemic coma, Fulminant type 1 diabetes mellitus,Latent autoimmune diabetes in adults, Type 1 diabetesmellitus, Euglycaemic diabetic ketoacidosis, Diabeticketosis, Ketosis-prone diabetes mellitus	Yes
Severe Skin Reactions Including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): or	Dermatitis bullous, Dermatitis exfoliative, Dermatitisexfoliative generalised, Epidermal necrosis, Erythemamultiforme, Exfoliative rash, Pemphigoid, Pemphigus,Skin necrosis, Stevens-Johnson syndrome, Toxicepidermal necrolysis, Toxic skin eruption, SJS-TEN overlap	Yes
Severe Skin (continued): If grade 3 or higher:	Rash, Rash erythematous, Rash maculo-papular, Rashpruritic, Rash pustular, Pruritus, Pruritus genital, Lichenplanus, 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 Fishersyndrome, Subacute inflammatory demyelinatingpolyneuropathy	Yes
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivitymyocarditis, Immune-mediated myocarditis	Yes
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbicencephalitis, Noninfective encephalitis, Immune-mediatedencephalitis	Yes
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis,Pulmonary sarcoidosis	Yes
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylacticreaction, Anaphylactoid reaction, Cytokine releasesyndrome, Serum sickness, Serum sickness-like reaction,Infusion related reaction, Infusion related hypersensitivityreaction	No

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myastheniagravis crisis, Ocular myasthenia	Yes
Myelitis	Myelitis, Myelitis transverse	Yes