Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD Sharp & Dohme GmbH

Modul 4 A

Anhang 4-G: Weitere Ergebnisse

Monotherapie zur adjuvanten Behandlung des Melanoms in den Tumorstadien IIB, IIC oder III nach vollständiger Resektion bei Kindern und Jugendlichen ab 12 Jahren und bei Erwachsenen

Stand: 18.07.2022

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Anhang 4-G1: Rücklaufquoten des EORTC QLQ-C30 und der EQ-5D VAS (KEYNOTE 716)

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.1.4 bzw. Abschnitt 4.3.1.3.1.2.1 die Rücklaufquoten des EORTC QLQ-C30 und die Rücklaufquoten des EQ-5D VAS der Studie KEYNOTE 716 dargestellt.

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 04.01.2022 (Interimsanalyse III).

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

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

		Pembrolizumab		Placebo	
		N=483		N=486	
Treatment Visit	Category	n	(%)	n	(%)
BASELINE	Discontinued due to relapse/recurrence	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	1	(0.2)	3	(0.6)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 12	**Expected to Complete Questionnaires**	**482**	**(99.8)**	**486**	**(100.0)**
	Completed	409	(84.7)	440	(90.5)
	Compliance (% in those expected to complete questionnaires)	409	(84.9)	440	(90.5)
	Not completed	73	(15.1)	46	(9.5)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	19	(3.9)	11	(2.3)
	Subject in hospital or hospice	1	(0.2)	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)	1	(0.2)
	Subject did not complete due to side effects of treatment	3	(0.6)	0	(0.0)
	Subject refused for other reasons	6	(1.2)	2	(0.4)

		Pembrolizumab		Placebo	
		N=483		N=486	
Treatment Visit	Category	n	(%)	n	(%)
WEEK 12	Other	30	(6.2)	22	(4.5)
	With visit, no record	14	(2.9)	10	(2.1)
	Missing by Design	**1**	**(0.2)**	**0**	**(0.0)**
	Discontinued due to adverse event	0	(0.0)	0	(0.0)
	Discontinued due to lost to follow-up	0	(0.0)	0	(0.0)
	Discontinued due to non-compliance with study drug	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	0	(0.0)	0	(0.0)
	Discontinued due to protocol violation	0	(0.0)	0	(0.0)
	Discontinued due to relapse/recurrence	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	1	(0.2)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 24	**Expected to Complete Questionnaires**	**460**	**(95.2)**	**469**	**(96.5)**
	Completed	384	(79.5)	393	(80.9)
	Compliance (% in those expected to complete questionnaires)	384	(83.5)	393	(83.8)
	Not completed	76	(15.7)	76	(15.6)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	25	(5.2)	23	(4.7)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.2)
	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)
	Subject refused for other reasons	6	(1.2)	8	(1.6)
	Other	27	(5.6)	24	(4.9)
	With visit, no record	16	(3.3)	20	(4.1)
	Missing by Design	**23**	**(4.8)**	**17**	**(3.5)**

		Pembrolizumab		Placebo	
		N=483		N=486	
Treatment Visit	Category	n	(%)	n	(%)
WEEK 24	Discontinued due to adverse event	6	(1.2)	2	(0.4)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	0	(0.0)	0	(0.0)
	Discontinued due to protocol violation	4	(0.8)	1	(0.2)
	Discontinued due to relapse/recurrence	1	(0.2)	8	(1.6)
	Discontinued due to withdrawal by subject	11	(2.3)	3	(0.6)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	1	(0.2)	1	(0.2)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	1	(0.2)
WEEK 36	**Expected to Complete Questionnaires**	**439**	**(90.9)**	**442**	**(90.9)**
	Completed	351	(72.7)	366	(75.3)
	Compliance (% in those expected to complete questionnaires)	351	(80.0)	366	(82.8)
	Not completed	88	(18.2)	76	(15.6)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	30	(6.2)	31	(6.4)
	Subject in hospital or hospice	1	(0.2)	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)	1	(0.2)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	9	(1.9)	5	(1.0)
	Other	23	(4.8)	22	(4.5)
	With visit, no record	25	(5.2)	17	(3.5)
	Missing by Design	**44**	**(9.1)**	**44**	**(9.1)**
	Discontinued due to adverse event	12	(2.5)	2	(0.4)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	0	(0.0)

		Pembrolizumab		Placebo	
		N=483		N=486	
Treatment Visit	Category	n	(%)	n	(%)
WEEK 36	Discontinued due to physician decision	1	(0.2)	0	(0.0)
	Discontinued due to protocol violation	3	(0.6)	1	(0.2)
	Discontinued due to relapse/recurrence	9	(1.9)	25	(5.1)
	Discontinued due to withdrawal by subject	15	(3.1)	14	(2.9)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	1	(0.2)	1	(0.2)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	3	(0.6)	0	(0.0)
WEEK 48	**Expected to Complete Questionnaires**	**413**	**(85.5)**	**415**	**(85.4)**
	Completed	353	(73.1)	379	(78.0)
	Compliance (% in those expected to complete questionnaires)	353	(85.5)	379	(91.3)
	Not completed	60	(12.4)	36	(7.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	10	(2.1)	5	(1.0)
	Subject in hospital or hospice	1	(0.2)	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	1	(0.2)	0	(0.0)
	Subject refused for other reasons	6	(1.2)	4	(0.8)
	Other	24	(5.0)	16	(3.3)
	With visit, no record	18	(3.7)	11	(2.3)
	Missing by Design	**70**	**(14.5)**	**71**	**(14.6)**
	Discontinued due to adverse event	20	(4.1)	4	(0.8)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	1	(0.2)	0	(0.0)
	Discontinued due to protocol violation	4	(0.8)	1	(0.2)
	Discontinued due to relapse/recurrence	20	(4.1)	42	(8.6)

		Pembrolizumab		Placebo	
		N=483		N=486	
Treatment Visit	Category	n	(%)	n	(%)
WEEK 48	Discontinued due to withdrawal by subject	23	(4.8)	17	(3.5)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	1	(0.2)	1	(0.2)
	Subject died	0	(0.0)	3	(0.6)
	Visit not scheduled	1	(0.2)	2	(0.4)
WEEK 60	**Expected to Complete Questionnaires**	**376**	**(77.8)**	**363**	**(74.7)**
	Completed	311	(64.4)	304	(62.6)
	Compliance (% in those expected to complete questionnaires)	311	(82.7)	304	(83.7)
	Not completed	65	(13.5)	59	(12.1)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	17	(3.5)	20	(4.1)
	Subject in hospital or hospice	1	(0.2)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	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	(0.4)	3	(0.6)
	Other	37	(7.7)	33	(6.8)
	With visit, no record	7	(1.4)	3	(0.6)
	Missing by Design	**107**	**(22.2)**	**123**	**(25.3)**
	Discontinued due to adverse event	30	(6.2)	8	(1.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	1	(0.2)
	Discontinued due to physician decision	3	(0.6)	1	(0.2)
	Discontinued due to protocol violation	4	(0.8)	1	(0.2)
	Discontinued due to relapse/recurrence	23	(4.8)	58	(11.9)
	Discontinued due to withdrawal by subject	27	(5.6)	16	(3.3)
	Completed study treatment	17	(3.5)	36	(7.4)
	Translation not available in subjects language	2	(0.4)	1	(0.2)

		Pembrolizumab		Placebo	
		N=483		N=486	
Treatment Visit	Category	n	(%)	n	(%)
WEEK 60	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	1	(0.2)	0	(0.0)
WEEK 72	**Expected to Complete Questionnaires**	**337**	**(69.8)**	**336**	**(69.1)**
	Completed	289	(59.8)	292	(60.1)
	Compliance (% in those expected to complete questionnaires)	289	(85.8)	292	(86.9)
	Not completed	48	(9.9)	44	(9.1)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)
	Not completed due to site staff error	10	(2.1)	19	(3.9)
	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	1	(0.2)	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	7	(1.4)	4	(0.8)
	Other	28	(5.8)	18	(3.7)
	With visit, no record	2	(0.4)	1	(0.2)
	Missing by Design	**146**	**(30.2)**	**150**	**(30.9)**
	Discontinued due to adverse event	32	(6.6)	11	(2.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	1	(0.2)
	Discontinued due to physician decision	3	(0.6)	1	(0.2)
	Discontinued due to protocol violation	4	(0.8)	1	(0.2)
	Discontinued due to relapse/recurrence	22	(4.6)	61	(12.6)
	Discontinued due to withdrawal by subject	30	(6.2)	19	(3.9)
	Completed study treatment	54	(11.2)	54	(11.1)
	Translation not available in subjects language	1	(0.2)	1	(0.2)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 84	**Expected to Complete Questionnaires**	**294**	**(60.9)**	**285**	**(58.6)**

		Pembrolizumab		Placebo	
		N=483		N=486	
Treatment Visit	Category	n	(%)	n	(%)
WEEK 84	Completed	254	(52.6)	249	(51.2)
	Compliance (% in those expected to complete questionnaires)	254	(86.4)	249	(87.4)
	Not completed	40	(8.3)	36	(7.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	14	(2.9)	10	(2.1)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	1	(0.2)
	Subject lost to follow-up/unable to contact	1	(0.2)	1	(0.2)
	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)
	Subject refused for other reasons	8	(1.7)	1	(0.2)
	Other	16	(3.3)	22	(4.5)
	With visit, no record	0	(0.0)	1	(0.2)
	Missing by Design	**189**	**(39.1)**	**201**	**(41.4)**
	Discontinued due to adverse event	43	(8.9)	15	(3.1)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	1	(0.2)
	Discontinued due to physician decision	8	(1.7)	3	(0.6)
	Discontinued due to protocol violation	4	(0.8)	1	(0.2)
	Discontinued due to relapse/recurrence	23	(4.8)	61	(12.6)
	Discontinued due to withdrawal by subject	30	(6.2)	24	(4.9)
	Completed study treatment	80	(16.6)	95	(19.5)
	Translation not available in subjects language	1	(0.2)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 96	**Expected to Complete Questionnaires**	**265**	**(54.9)**	**263**	**(54.1)**
	Completed	236	(48.9)	236	(48.6)
	Compliance (% in those expected to complete questionnaires)	236	(89.1)	236	(89.7)
	Not completed	29	(6.0)	27	(5.6)

		Pembrolizumab		Placebo	
		N=483		N=486	
Treatment Visit	Category	n	(%)	n	(%)
WEEK 96	Subject did not complete due to disease under study	1	(0.2)	0	(0.0)
	Not completed due to site staff error	9	(1.9)	9	(1.9)
	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)	1	(0.2)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	5	(1.0)
	Other	16	(3.3)	12	(2.5)
	With visit, no record	1	(0.2)	0	(0.0)
	Missing by Design	**218**	**(45.1)**	**223**	**(45.9)**
	Discontinued due to adverse event	43	(8.9)	11	(2.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	1	(0.2)
	Discontinued due to physician decision	7	(1.4)	2	(0.4)
	Discontinued due to protocol violation	3	(0.6)	1	(0.2)
	Discontinued due to relapse/recurrence	24	(5.0)	61	(12.6)
	Discontinued due to withdrawal by subject	33	(6.8)	23	(4.7)
	Completed study treatment	107	(22.2)	121	(24.9)
	Translation not available in subjects language	1	(0.2)	2	(0.4)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
MONTH 30	**Expected to Complete Questionnaires**	**124**	**(25.7)**	**125**	**(25.7)**
	Completed	110	(22.8)	115	(23.7)
	Compliance (% in those expected to complete questionnaires)	110	(88.7)	115	(92.0)
	Not completed	14	(2.9)	10	(2.1)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	7	(1.4)	3	(0.6)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)

		Pembrolizumab		Placebo	
		N=483		N=486	
Treatment Visit	Category	n	(%)	n	(%)
MONTH 30	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	(0.2)	1	(0.2)
	Other	6	(1.2)	6	(1.2)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**359**	**(74.3)**	**361**	**(74.3)**
	Discontinued due to adverse event	67	(13.9)	19	(3.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	1	(0.2)
	Discontinued due to physician decision	9	(1.9)	3	(0.6)
	Discontinued due to protocol violation	4	(0.8)	1	(0.2)
	Discontinued due to relapse/recurrence	24	(5.0)	61	(12.6)
	Discontinued due to withdrawal by subject	38	(7.9)	24	(4.9)
	Completed study treatment	216	(44.7)	251	(51.6)
	Translation not available in subjects language	1	(0.2)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
MONTH 36	**Expected to Complete Questionnaires**	**26**	**(5.4)**	**28**	**(5.8)**
	Completed	25	(5.2)	27	(5.6)
	Compliance (% in those expected to complete questionnaires)	25	(96.2)	27	(96.4)
	Not completed	1	(0.2)	1	(0.2)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.2)	0	(0.0)
	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	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)

		Pembrolizumab		Placebo	
		N=483		N=486	
Treatment Visit	Category	n	(%)	n	(%)
MONTH 36	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	0	(0.0)	1	(0.2)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**457**	**(94.6)**	**458**	**(94.2)**
	Discontinued due to adverse event	84	(17.4)	22	(4.5)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	1	(0.2)
	Discontinued due to physician decision	10	(2.1)	4	(0.8)
	Discontinued due to protocol violation	4	(0.8)	1	(0.2)
	Discontinued due to relapse/recurrence	24	(5.0)	61	(12.6)
	Discontinued due to withdrawal by subject	40	(8.3)	27	(5.6)
	Completed study treatment	295	(61.1)	341	(70.2)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)

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

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

Number of participants: full-analysis-set population

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

Database Cutoff Date: 04JAN2022

Anhang 4-G1.2: Rücklaufquoten der EQ-5D VAS

Tabelle 4G-2: Gründe für das Fehlen von Werten in der EQ-5D VAS

Treatment Visit	Category	Pembrolizumab N=483		Placebo N=486	
		n	(%)	n	(%)
BASELINE	**Expected to Complete Questionnaires**	**482**	**(99.8)**	**483**	**(99.4)**
	Completed	456	(94.4)	466	(95.9)
	Compliance (% in those expected to complete questionnaires)	456	(94.6)	466	(96.5)
	Not completed	26	(5.4)	17	(3.5)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	14	(2.9)	7	(1.4)
	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	0	(0.0)	0	(0.0)
	Other	11	(2.3)	5	(1.0)
	With visit, no record	1	(0.2)	5	(1.0)
	Missing by Design	**1**	**(0.2)**	**3**	**(0.6)**
	Discontinued due to adverse event	0	(0.0)	0	(0.0)
	Discontinued due to lost to follow-up	0	(0.0)	0	(0.0)
	Discontinued due to non-compliance with study drug	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	0	(0.0)	0	(0.0)
	Discontinued due to protocol violation	0	(0.0)	0	(0.0)
	Discontinued due to relapse/recurrence	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	1	(0.2)	3	(0.6)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=483		Placebo N=486	
		n	(%)	n	(%)
WEEK 12	**Expected to Complete Questionnaires**	**482**	**(99.8)**	**486**	**(100.0)**
	Completed	420	(87.0)	442	(90.9)
	Compliance (% in those expected to complete questionnaires)	420	(87.1)	442	(90.9)
	Not completed	62	(12.8)	44	(9.1)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	18	(3.7)	10	(2.1)
	Subject in hospital or hospice	1	(0.2)	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)	1	(0.2)
	Subject did not complete due to side effects of treatment	3	(0.6)	0	(0.0)
	Subject refused for other reasons	4	(0.8)	2	(0.4)
	Other	23	(4.8)	22	(4.5)
	With visit, no record	13	(2.7)	9	(1.9)
	Missing by Design	**1**	**(0.2)**	**0**	**(0.0)**
	Discontinued due to adverse event	0	(0.0)	0	(0.0)
	Discontinued due to lost to follow-up	0	(0.0)	0	(0.0)
	Discontinued due to non-compliance with study drug	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	0	(0.0)	0	(0.0)
	Discontinued due to protocol violation	0	(0.0)	0	(0.0)
	Discontinued due to relapse/recurrence	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	1	(0.2)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 24	**Expected to Complete Questionnaires**	**460**	**(95.2)**	**471**	**(96.9)**
	Completed	395	(81.8)	407	(83.7)
	Compliance (% in those expected to complete questionnaires)	395	(85.9)	407	(86.4)

Treatment Visit	Category	Pembrolizumab N=483		Placebo N=486	
		n	(%)	n	(%)
WEEK 24	Not completed	65	(13.5)	64	(13.2)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	24	(5.0)	18	(3.7)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.2)
	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)
	Subject refused for other reasons	6	(1.2)	7	(1.4)
	Other	18	(3.7)	19	(3.9)
	With visit, no record	15	(3.1)	19	(3.9)
	Missing by Design	**23**	**(4.8)**	**15**	**(3.1)**
	Discontinued due to adverse event	6	(1.2)	2	(0.4)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	0	(0.0)	0	(0.0)
	Discontinued due to protocol violation	4	(0.8)	1	(0.2)
	Discontinued due to relapse/recurrence	1	(0.2)	6	(1.2)
	Discontinued due to withdrawal by subject	11	(2.3)	3	(0.6)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	1	(0.2)	1	(0.2)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	1	(0.2)
WEEK 36	**Expected to Complete Questionnaires**	**439**	**(90.9)**	**449**	**(92.4)**
	Completed	355	(73.5)	385	(79.2)
	Compliance (% in those expected to complete questionnaires)	355	(80.9)	385	(85.7)
	Not completed	84	(17.4)	64	(13.2)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	28	(5.8)	25	(5.1)

Treatment Visit	Category	Pembrolizumab N=483		Placebo N=486	
		n	(%)	n	(%)
WEEK 36	Subject in hospital or hospice	1	(0.2)	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)	1	(0.2)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	9	(1.9)	4	(0.8)
	Other	22	(4.6)	18	(3.7)
	With visit, no record	24	(5.0)	16	(3.3)
	Missing by Design	**44**	**(9.1)**	**37**	**(7.6)**
	Discontinued due to adverse event	12	(2.5)	2	(0.4)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	1	(0.2)	0	(0.0)
	Discontinued due to protocol violation	3	(0.6)	1	(0.2)
	Discontinued due to relapse/recurrence	9	(1.9)	18	(3.7)
	Discontinued due to withdrawal by subject	15	(3.1)	14	(2.9)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	1	(0.2)	1	(0.2)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	3	(0.6)	0	(0.0)
WEEK 48	**Expected to Complete Questionnaires**	**413**	**(85.5)**	**426**	**(87.7)**
	Completed	356	(73.7)	391	(80.5)
	Compliance (% in those expected to complete questionnaires)	356	(86.2)	391	(91.8)
	Not completed	57	(11.8)	35	(7.2)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	10	(2.1)	5	(1.0)
	Subject in hospital or hospice	1	(0.2)	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)

Treatment Visit	Category	Pembrolizumab N=483		Placebo N=486	
		n	(%)	n	(%)
WEEK 48	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)
	Subject refused for other reasons	6	(1.2)	3	(0.6)
	Other	22	(4.6)	17	(3.5)
	With visit, no record	17	(3.5)	10	(2.1)
	Missing by Design	**70**	**(14.5)**	**60**	**(12.3)**
	Discontinued due to adverse event	20	(4.1)	4	(0.8)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	1	(0.2)	0	(0.0)
	Discontinued due to protocol violation	4	(0.8)	1	(0.2)
	Discontinued due to relapse/recurrence	20	(4.1)	31	(6.4)
	Discontinued due to withdrawal by subject	23	(4.8)	17	(3.5)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	1	(0.2)	1	(0.2)
	Subject died	0	(0.0)	3	(0.6)
	Visit not scheduled	1	(0.2)	2	(0.4)
WEEK 60	**Expected to Complete Questionnaires**	**376**	**(77.8)**	**380**	**(78.2)**
	Completed	315	(65.2)	322	(66.3)
	Compliance (% in those expected to complete questionnaires)	315	(83.8)	322	(84.7)
	Not completed	61	(12.6)	58	(11.9)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	16	(3.3)	19	(3.9)
	Subject in hospital or hospice	1	(0.2)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	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	(0.4)	3	(0.6)
	Other	35	(7.2)	34	(7.0)

Treatment Visit	Category	Pembrolizumab N=483		Placebo N=486	
		n	(%)	n	(%)
WEEK 60	With visit, no record	6	(1.2)	2	(0.4)
	Missing by Design	**107**	**(22.2)**	**106**	**(21.8)**
	Discontinued due to adverse event	30	(6.2)	8	(1.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	1	(0.2)
	Discontinued due to physician decision	3	(0.6)	1	(0.2)
	Discontinued due to protocol violation	4	(0.8)	1	(0.2)
	Discontinued due to relapse/recurrence	23	(4.8)	44	(9.1)
	Discontinued due to withdrawal by subject	27	(5.6)	16	(3.3)
	Completed study treatment	17	(3.5)	33	(6.8)
	Translation not available in subjects language	2	(0.4)	1	(0.2)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	1	(0.2)	0	(0.0)
WEEK 72	**Expected to Complete Questionnaires**	**337**	**(69.8)**	**353**	**(72.6)**
	Completed	293	(60.7)	307	(63.2)
	Compliance (% in those expected to complete questionnaires)	293	(86.9)	307	(87.0)
	Not completed	44	(9.1)	46	(9.5)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)
	Not completed due to site staff error	9	(1.9)	20	(4.1)
	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	1	(0.2)	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	6	(1.2)	5	(1.0)
	Other	27	(5.6)	18	(3.7)
	With visit, no record	1	(0.2)	1	(0.2)
	Missing by Design	**146**	**(30.2)**	**133**	**(27.4)**
	Discontinued due to adverse event	32	(6.6)	11	(2.3)

Treatment Visit	Category	Pembrolizumab N=483		Placebo N=486	
		n	(%)	n	(%)
WEEK 72	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	1	(0.2)
	Discontinued due to physician decision	3	(0.6)	1	(0.2)
	Discontinued due to protocol violation	4	(0.8)	1	(0.2)
	Discontinued due to relapse/recurrence	22	(4.6)	48	(9.9)
	Discontinued due to withdrawal by subject	30	(6.2)	19	(3.9)
	Completed study treatment	54	(11.2)	50	(10.3)
	Translation not available in subjects language	1	(0.2)	1	(0.2)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 84	**Expected to Complete Questionnaires**	**296**	**(61.3)**	**299**	**(61.5)**
	Completed	257	(53.2)	263	(54.1)
	Compliance (% in those expected to complete questionnaires)	257	(86.8)	263	(88.0)
	Not completed	39	(8.1)	36	(7.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	14	(2.9)	10	(2.1)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	1	(0.2)
	Subject lost to follow-up/unable to contact	1	(0.2)	1	(0.2)
	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)
	Subject refused for other reasons	8	(1.7)	1	(0.2)
	Other	15	(3.1)	22	(4.5)
	With visit, no record	0	(0.0)	1	(0.2)
	Missing by Design	**187**	**(38.7)**	**187**	**(38.5)**
	Discontinued due to adverse event	43	(8.9)	14	(2.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	1	(0.2)
	Discontinued due to physician decision	8	(1.7)	3	(0.6)

Treatment Visit	Category	Pembrolizumab N=483		Placebo N=486	
		n	(%)	n	(%)
WEEK 84	Discontinued due to protocol violation	4	(0.8)	1	(0.2)
	Discontinued due to relapse/recurrence	23	(4.8)	51	(10.5)
	Discontinued due to withdrawal by subject	30	(6.2)	24	(4.9)
	Completed study treatment	78	(16.1)	92	(18.9)
	Translation not available in subjects language	1	(0.2)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 96	**Expected to Complete Questionnaires**	**267**	**(55.3)**	**278**	**(57.2)**
	Completed	238	(49.3)	249	(51.2)
	Compliance (% in those expected to complete questionnaires)	238	(89.1)	249	(89.6)
	Not completed	29	(6.0)	29	(6.0)
	Subject did not complete due to disease under study	1	(0.2)	0	(0.0)
	Not completed due to site staff error	9	(1.9)	10	(2.1)
	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	0	(0.0)	1	(0.2)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	5	(1.0)
	Other	16	(3.3)	13	(2.7)
	With visit, no record	1	(0.2)	0	(0.0)
	Missing by Design	**216**	**(44.7)**	**208**	**(42.8)**
	Discontinued due to adverse event	43	(8.9)	10	(2.1)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	1	(0.2)
	Discontinued due to physician decision	7	(1.4)	2	(0.4)
	Discontinued due to protocol violation	3	(0.6)	1	(0.2)
	Discontinued due to relapse/recurrence	24	(5.0)	52	(10.7)
	Discontinued due to withdrawal by subject	33	(6.8)	23	(4.7)

Treatment Visit	Category	Pembrolizumab N=483		Placebo N=486	
		n	(%)	n	(%)
WEEK 96	Completed study treatment	105	(21.7)	116	(23.9)
	Translation not available in subjects language	1	(0.2)	2	(0.4)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
MONTH 30	**Expected to Complete Questionnaires**	**126**	**(26.1)**	**135**	**(27.8)**
	Completed	112	(23.2)	125	(25.7)
	Compliance (% in those expected to complete questionnaires)	112	(88.9)	125	(92.6)
	Not completed	14	(2.9)	10	(2.1)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	7	(1.4)	3	(0.6)
	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	1	(0.2)	1	(0.2)
	Other	6	(1.2)	6	(1.2)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**357**	**(73.9)**	**351**	**(72.2)**
	Discontinued due to adverse event	67	(13.9)	19	(3.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	1	(0.2)
	Discontinued due to physician decision	9	(1.9)	3	(0.6)
	Discontinued due to protocol violation	4	(0.8)	1	(0.2)
	Discontinued due to relapse/recurrence	24	(5.0)	55	(11.3)
	Discontinued due to withdrawal by subject	38	(7.9)	24	(4.9)
	Completed study treatment	214	(44.3)	247	(50.8)
	Translation not available in subjects language	1	(0.2)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=483		Placebo N=486	
		n	(%)	n	(%)
MONTH 30	Visit not scheduled	0	(0.0)	0	(0.0)
MONTH 36	**Expected to Complete Questionnaires**	**27**	**(5.6)**	**28**	**(5.8)**
	Completed	26	(5.4)	27	(5.6)
	Compliance (% in those expected to complete questionnaires)	26	(96.3)	27	(96.4)
	Not completed	1	(0.2)	1	(0.2)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.2)	0	(0.0)
	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	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)	0	(0.0)
	Other	0	(0.0)	1	(0.2)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**456**	**(94.4)**	**458**	**(94.2)**
	Discontinued due to adverse event	84	(17.4)	22	(4.5)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.2)
	Discontinued due to non-compliance with study drug	0	(0.0)	1	(0.2)
	Discontinued due to physician decision	10	(2.1)	4	(0.8)
	Discontinued due to protocol violation	4	(0.8)	1	(0.2)
	Discontinued due to relapse/recurrence	24	(5.0)	61	(12.6)
	Discontinued due to withdrawal by subject	40	(8.3)	27	(5.6)
	Completed study treatment	294	(60.9)	341	(70.2)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)

Expected to complete questionnaire includes all subjects who do not have missing data due to a missing by design reason.
Compliance is the proportion of subjects who completed the PRO questionnaire among those who are expected to complete the questionnaire at this time point,

		Pembrolizumab N=483		Placebo N=486	
Treatment Visit	Category	n	(%)	n	(%)
excluding those missing by design. All the other categories are defined as the proportion of subjects in the analysis population (N).					
Number of participants: full-analysis-set population					
Missing by design includes: death, discontinuation, translations not available, and no visit scheduled					
Database Cutoff Date: 04JAN2022					

Anhang 4-G2: Kaplan-Meier-Kurven der Subgruppen mit signifikantem Interaktionstest (p < 0,05) (KEYNOTE 716)

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 04.01.2022 (Interimsanalyse III).

Anhang 4-G2.1: Nebenwirkungen

Unerwünschte Ereignisse

Schwere unerwünschten Ereignissen (CTCAE-Grad 3-5)

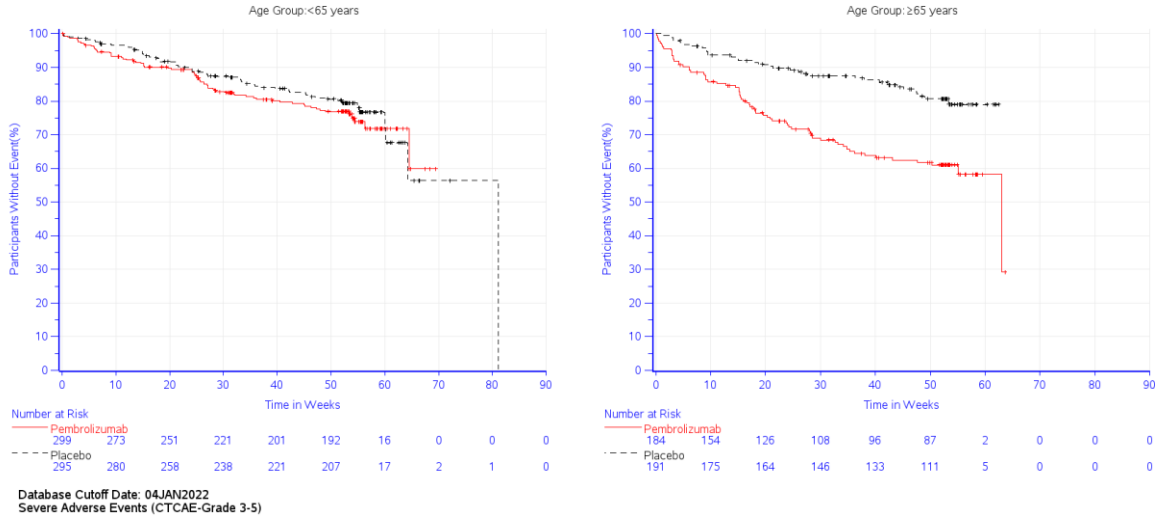

Abbildung 4G-1: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter (Jahre) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

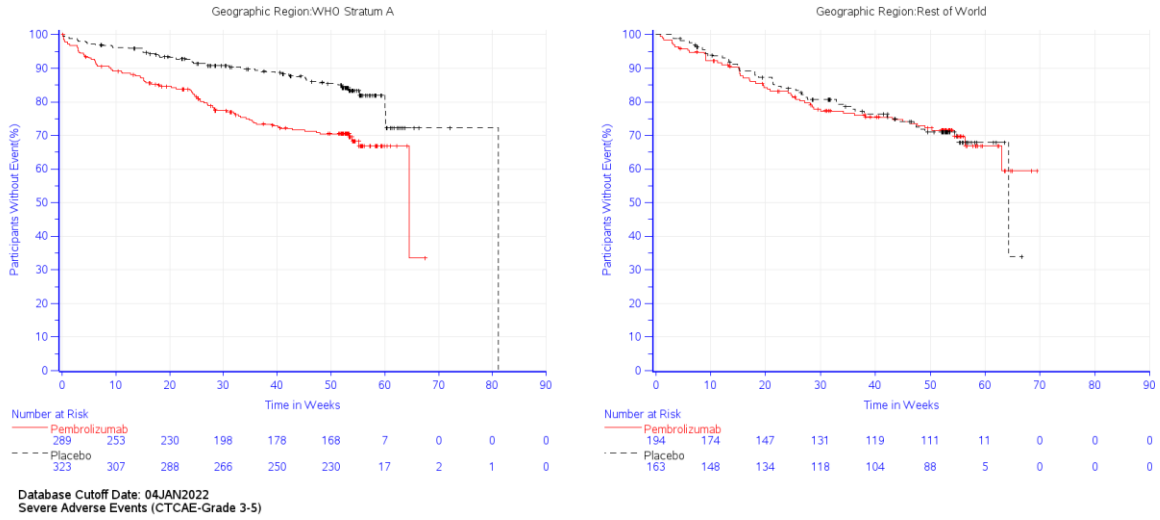

Abbildung 4G-2: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

Therapieabbruch wegen Unerwünschter Ereignisse

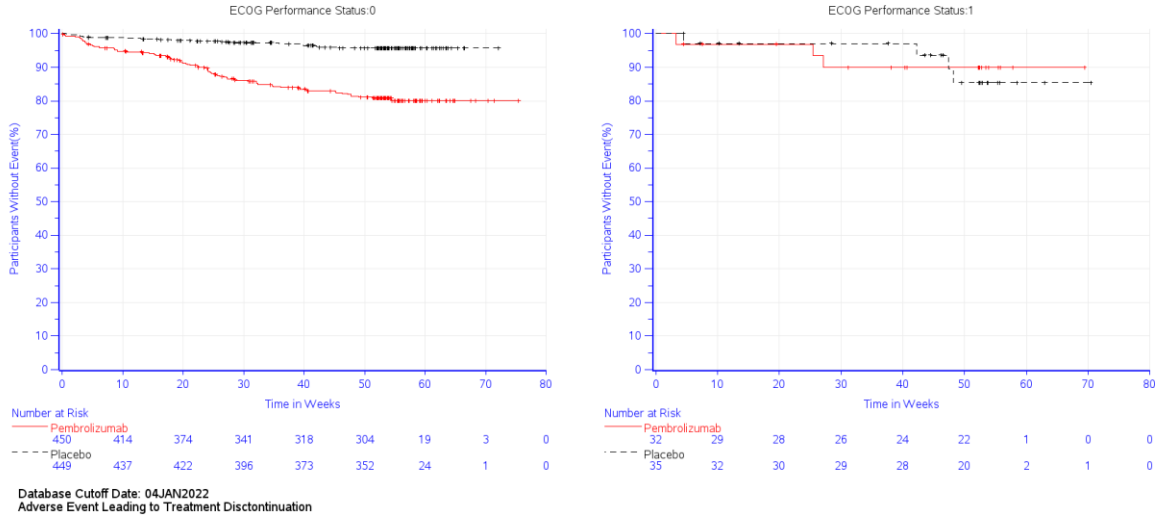

Abbildung 4G-3: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Therapieabbruch wegen Unerwünschter Ereignisse

Unerwünschte Ereignisse (SOC und PT)

Unerwünschte Ereignisse (SOC und PT)

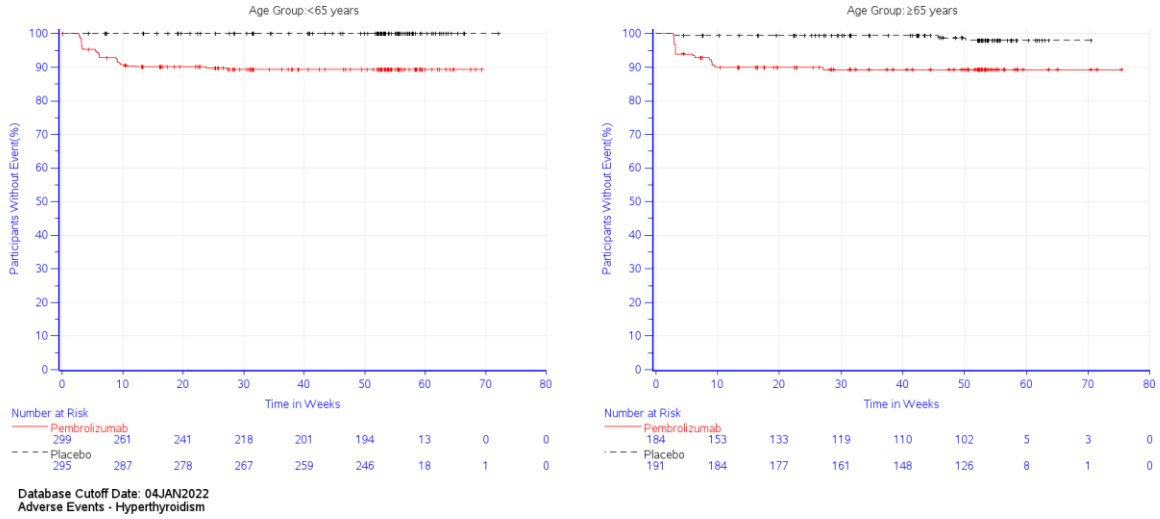

Abbildung 4G-4: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter (Jahre) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Hyperthyreose“ (SOC „Endokrine Erkrankungen“)

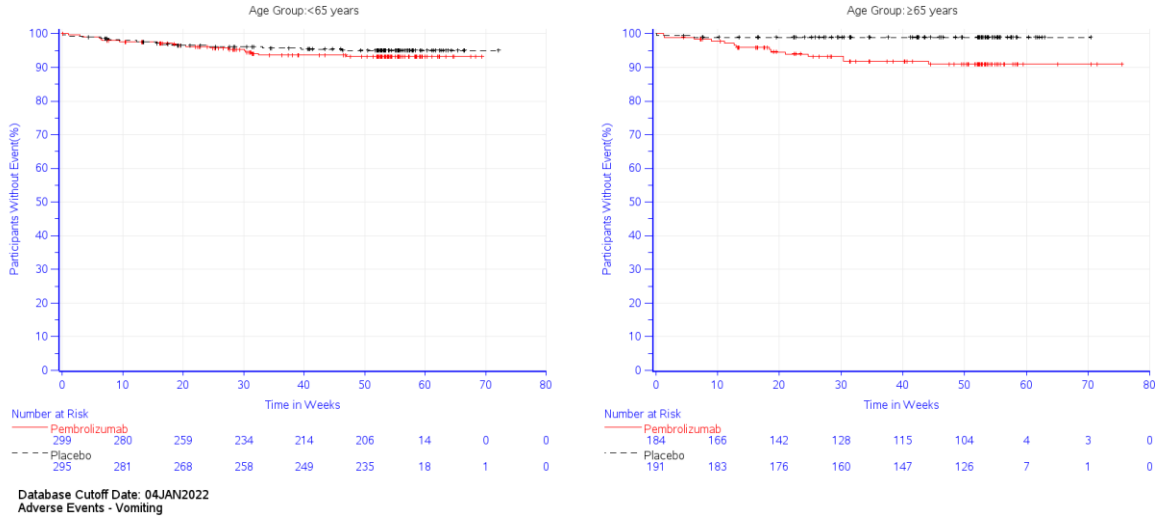

Abbildung 4G-5: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Erbrechen“ (SOC „Erkrankungen des Gastrointestinaltrakt“)

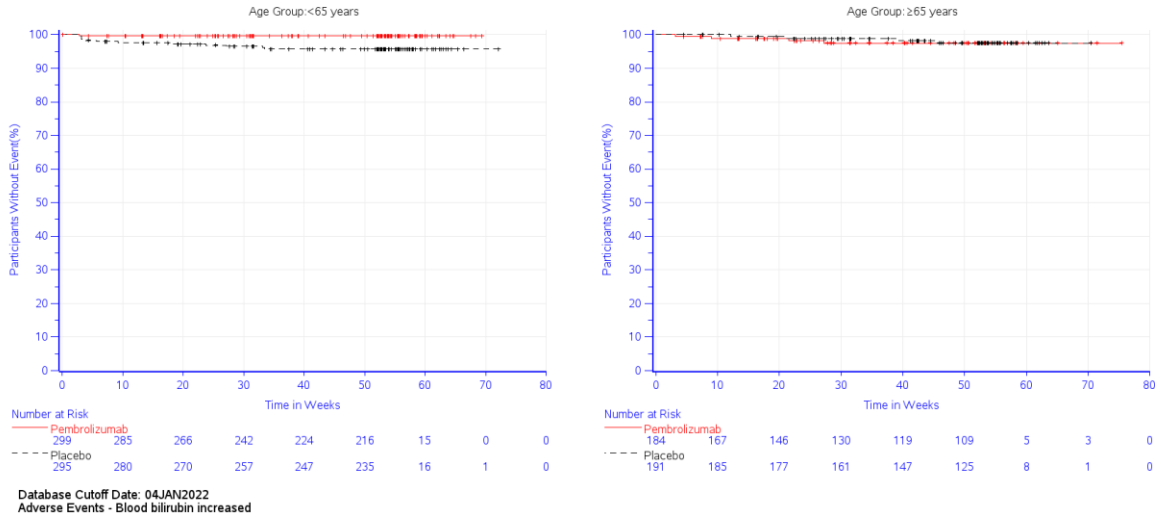

Abbildung 4G-6: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Bilirubin im Blut erhöht“ (SOC „Untersuchungen“)

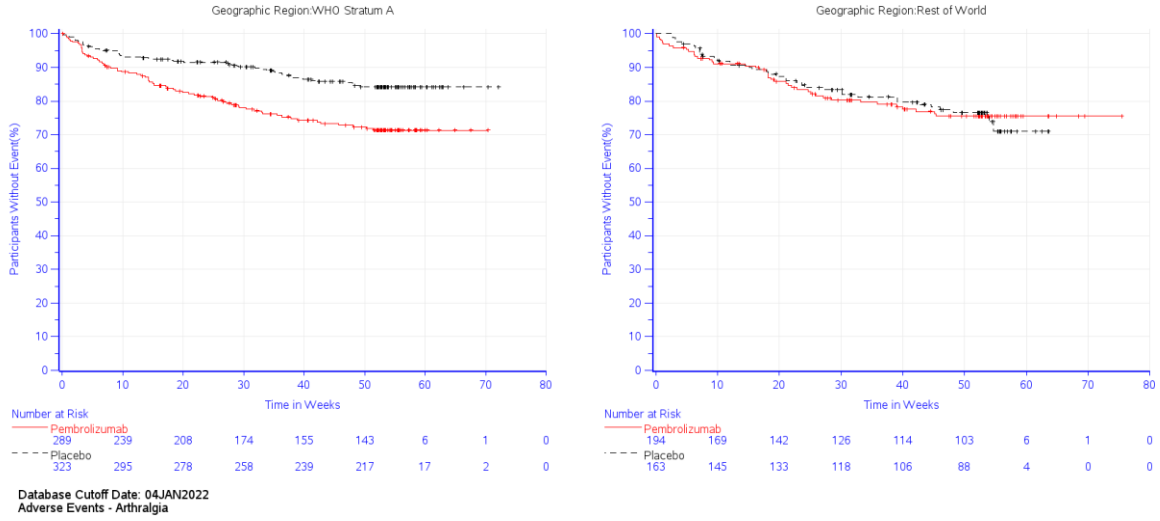

Abbildung 4G-7: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Arthralgie“ (SOC „Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen“)

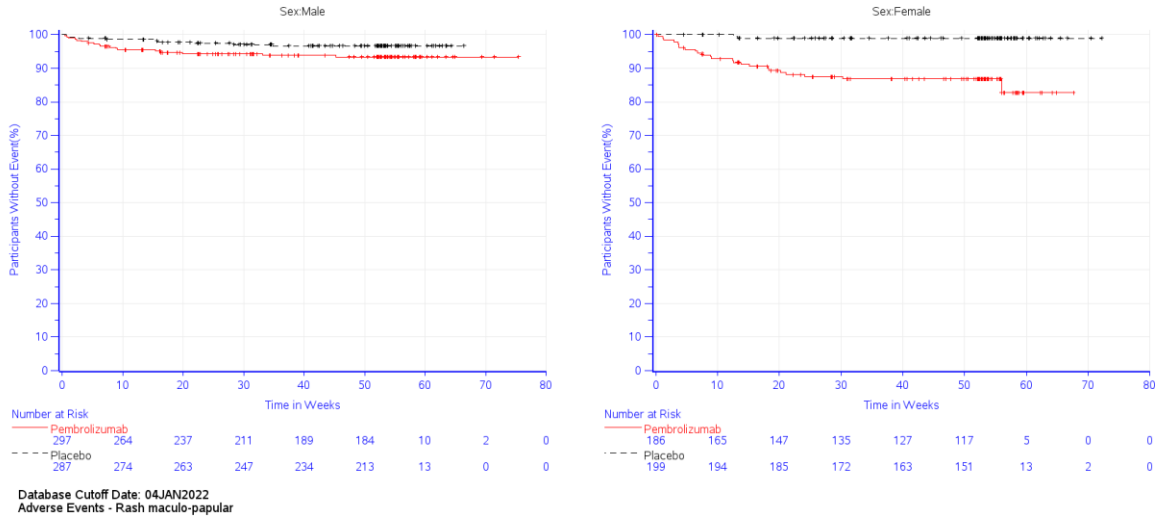

Abbildung 4G-8: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Ausschlag makulo-papuloes“ (SOC „Erkrankungen der Haut und des Unterhautzellgewebes“)

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

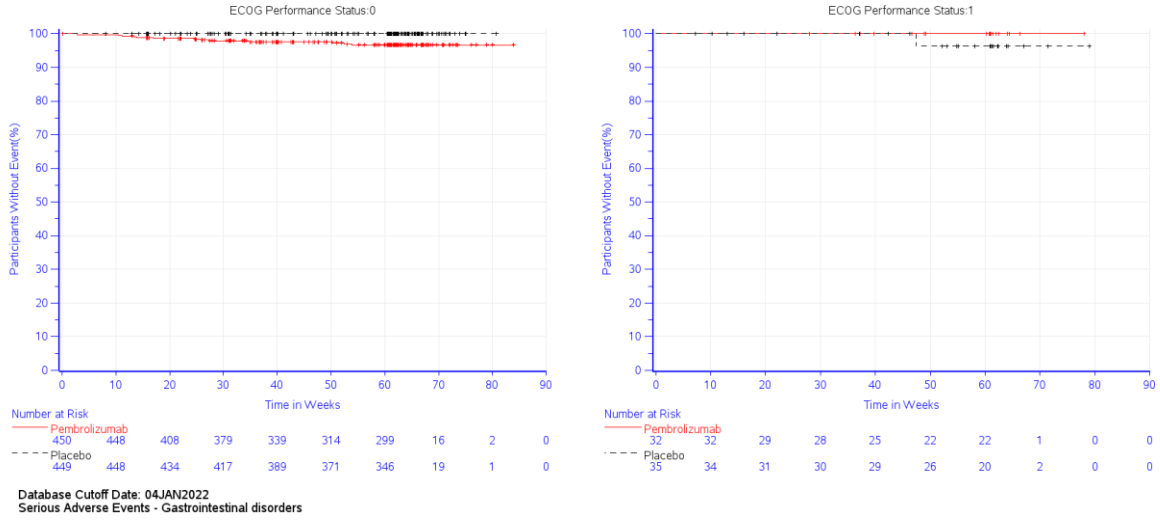

Abbildung 4G-9: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) für die SOC „Erkrankungen des Gastrointestinaltrakts“

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

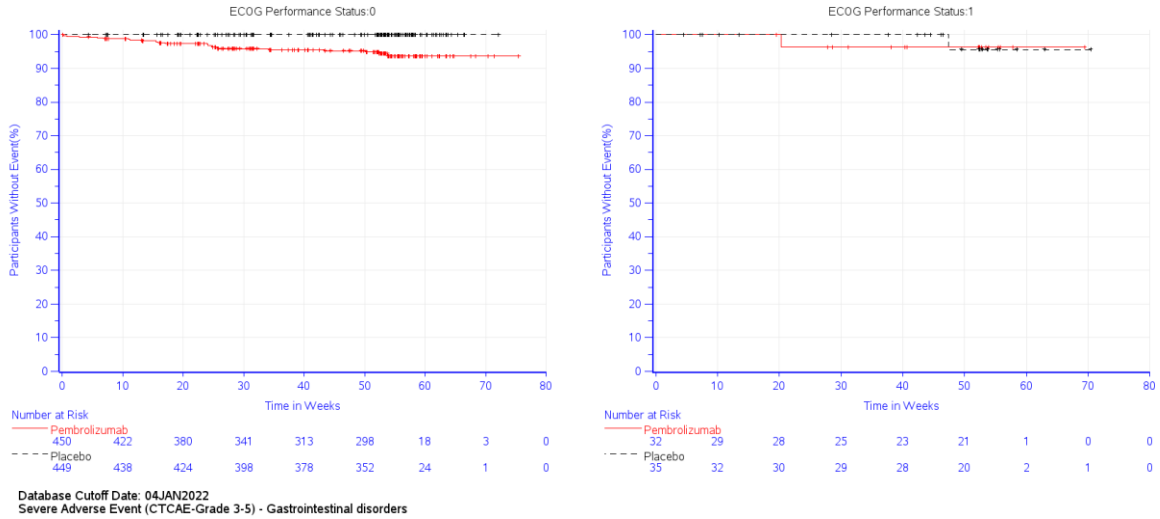

Abbildung 4G-10: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) für die SOC „Erkrankungen des Gastrointestinaltrakts“

Anhang 4-G3: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest (p ≥ 0,05) (KEYNOTE 716)

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

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 04.01.2022 (Interimsanalyse III), lediglich der ergänzende Endpunkt Progressions- /Rezidivfreies Überleben 2 basiert auf dem Datenschnitt vom 21.06.2021 (Interimsanalyse II), da für die Interimsanalyse III keine Auswertung geplant war.

Anhang 4-G3.1: Morbidität

Rezidivfreies Überleben

Tabelle 4G-3: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Rezidivfreies Überleben (INV, Hauptanalyse) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Recurrence-Free Survival (INV Primary Censoring Rule)	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Sex									
Male	300	60 (20.0)	37.2 [-; -]	289	92 (31.8)	Not reached [32.2; -]	0.57 [0.41; 0.79]	< 0.001	0.255
Female	187	35 (18.7)	Not reached [-; -]	200	47 (23.5)	Not reached [-; -]	0.78 [0.50; 1.21]	0.265	
Age Group									
< 65	303	50 (16.5)	Not reached [-; -]	295	69 (23.4)	Not reached [-; -]	0.69 [0.48; 0.99]	0.047	0.628
≥ 65	184	45 (24.5)	37.2 [-; -]	194	70 (36.1)	Not reached [29.5; -]	0.60 [0.41; 0.88]	0.009	
Severity of disease: T-Stage									
IIB T3b	200	30 (15.0)	Not reached [-; -]	200	50 (25.0)	Not reached [-; -]	0.57 [0.36; 0.89]	0.014	0.447
IIB T4a	109	16 (14.7)	37.2 [-; -]	116	31 (26.7)	Not reached [29.9; -]	0.48 [0.26; 0.90]	0.021	
IIC T4b	171	45 (26.3)	Not reached [34.3; -]	169	56 (33.1)	Not reached [33.3; -]	0.76 [0.51; 1.13]	0.173	
Geographic Region									
WHO Stratum A[g]	292	56 (19.2)	37.2 [-; -]	326	96 (29.4)	Not reached [33.3; -]	0.60 [0.43; 0.83]	0.002	0.426
Rest of World	195	39 (20.0)	Not reached [-; -]	163	43 (26.4)	Not reached [-; -]	0.73 [0.47; 1.13]	0.158	
ECOG Performance Status									
0	454	87 (19.2)	37.2 [-; -]	452	123 (27.2)	Not reached [-; -]	0.67 [0.51; 0.88]	0.005	0.546
1	32	8 (25.0)	Not reached [24.9; -]	35	16 (45.7)	25.3 [16.1; -]	0.55 [0.23; 1.28]	0.163	

Study: KEYNOTE 716[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Recurrence-Free Survival (INV Primary Censoring Rule)	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Race									
Nonwhite skin colour	10	1 (10.0)	Not reached [13.0; -]	5	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.505	0.272
White skin colour	435	88 (20.2)	37.2 [-; -]	439	124 (28.2)	Not reached [-; -]	0.69 [0.52; 0.91]	0.008	

a: Database Cutoff Date: 04JAN2022
b: Number of participants: intention-to-treat population
c: From the product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with Efron's method of tie handling with treatment as a covariate, using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom
ECOG: Eastern Cooperative Oncology Group; INV: Investigator; n.a.: not applicable (when estimation not possible); WHO: World Health Organization

Fernmetastasenfreies Überleben

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

Study: KEYNOTE 716[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Distant Metastasis-Free Survival (INV Primary Analysis)	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Sex									
Male	300	41 (13.7)	Not reached [-; -]	289	64 (22.1)	Not reached [-; -]	0.58 [0.39; 0.86]	0.007	0.417
Female	187	22 (11.8)	Not reached [-; -]	200	31 (15.5)	Not reached [-; -]	0.76 [0.44; 1.32]	0.336	
Age Group									
< 65	303	37 (12.2)	Not reached [-; -]	295	45 (15.3)	Not reached [-; -]	0.79 [0.51; 1.23]	0.300	0.188
≥ 65	184	26 (14.1)	Not reached [-; -]	194	50 (25.8)	Not reached [-; -]	0.51 [0.32; 0.82]	0.006	
Severity of disease: T-Stage									
IIB T3b	200	23 (11.5)	Not reached [-; -]	200	31 (15.5)	Not reached [-; -]	0.71 [0.41; 1.22]	0.216	0.535
IIB T4a	109	8 (7.3)	Not reached [-; -]	116	20 (17.2)	Not reached [-; -]	0.42 [0.19; 0.96]	0.040	
IIC T4b	171	30 (17.5)	Not reached [-; -]	169	41 (24.3)	Not reached [-; -]	0.70 [0.44; 1.13]	0.142	
Geographic Region									
WHO Stratum A[g]	292	44 (15.1)	Not reached [-; -]	326	67 (20.6)	Not reached [-; -]	0.70 [0.48; 1.03]	0.070	0.503
Rest of World	195	19 (9.7)	Not reached [-; -]	163	28 (17.2)	Not reached [-; -]	0.55 [0.31; 0.98]	0.044	

Study: KEYNOTE 716[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Distant Metastasis-Free Survival (INV Primary Analysis)	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
ECOG Performance Status									
0	454	60 (13.2)	Not reached [-; -]	452	85 (18.8)	Not reached [-; -]	0.69 [0.49; 0.95]	0.026	0.202
1	32	3 (9.4)	Not reached [-; -]	35	10 (28.6)	Not reached [27.6; -]	0.30 [0.08; 1.09]	0.068	

a: Database Cutoff Date: 04JAN2022
b: Number of participants: intention-to-treat population
c: From the product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with Efron's method of tie handling with treatment as a covariate, using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom
ECOG: Eastern Cooperative Oncology Group; INV: Investigator; WHO: World Health Organization

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 716[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Subsequent Oncologic Therapy or Death	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Sex									
Male	300	47 (15.7)	37.2 [-; -]	289	82 (28.4)	Not reached [30.5; -]	0.49 [0.34; 0.71]	< 0.001	0.741
Female	187	21 (11.2)	36.6 [-; -]	200	40 (20.0)	Not reached [-; -]	0.56 [0.33; 0.95]	0.031	
Age Group									
< 65	303	35 (11.6)	36.6 [-; -]	295	56 (19.0)	Not reached [-; -]	0.59 [0.39; 0.91]	0.016	0.391
≥ 65	184	33 (17.9)	37.2 [-; -]	194	66 (34.0)	33.7 [30.0; -]	0.46 [0.30; 0.70]	< 0.001	
Severity of disease: T-Stage									
IIB T3b	200	19 (9.5)	Not reached [-; -]	200	46 (23.0)	Not reached [-; -]	0.39 [0.23; 0.66]	< 0.001	0.171
IIB T4a	109	11 (10.1)	36.6 [36.6; -]	116	28 (24.1)	Not reached [30.2; -]	0.33 [0.16; 0.70]	0.004	
IIC T4b	171	34 (19.9)	Not reached [35.8; -]	169	46 (27.2)	Not reached [-; -]	0.69 [0.44; 1.08]	0.102	
Geographic Region									
WHO Stratum A[g]	292	40 (13.7)	36.6 [36.6; -]	326	82 (25.2)	Not reached [-; -]	0.49 [0.33; 0.72]	< 0.001	0.613
Rest of World	195	28 (14.4)	Not reached [-; -]	163	40 (24.5)	Not reached [33.7; -]	0.58 [0.36; 0.93]	0.026	

Study: KEYNOTE 716[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Subsequent Oncologic Therapy or Death	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
ECOG Performance Status									
0	454	63 (13.9)	36.6 [36.6; -]	452	110 (24.3)	Not reached [-; -]	0.54 [0.39; 0.73]	< 0.001	0.715
1	32	5 (15.6)	Not reached [24.9; -]	35	12 (34.3)	Not reached [21.7; -]	0.47 [0.16; 1.33]	0.152	

a: Database Cutoff Date: 04JAN2022
b: Number of participants: intention-to-treat population
c: From the product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with Efron's method of tie handling with treatment as a covariate, using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom
ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization

Progressions-/Rezidivfreies Überleben 2

Tabelle 4G-6: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Progressions-/Rezidivfreies Überleben 2 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Progression/ Recurrence-Free Survival 2 (INV Primary Censoring Rule)	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Sex									
Male	300	23 (7.7)	Not reached [-; -]	289	25 (8.7)	Not reached [-; -]	0.87 [0.50; 1.54]	0.640	0.836
Female	187	14 (7.5)	Not reached [-; -]	200	16 (8.0)	Not reached [-; -]	0.97 [0.47; 1.99]	0.937	
Age Group									
< 65	303	15 (5.0)	Not reached [-; -]	295	17 (5.8)	Not reached [-; -]	0.88 [0.44; 1.77]	0.727	0.923
≥ 65	184	22 (12.0)	Not reached [26.7; -]	194	24 (12.4)	Not reached [-; -]	0.93 [0.52; 1.65]	0.798	
Severity of disease: T-Stage									
IIB T3b	200	11 (5.5)	Not reached [-; -]	200	13 (6.5)	Not reached [-; -]	0.86 [0.39; 1.92]	0.717	0.969
IIB T4a	109	7 (6.4)	Not reached [24.9; -]	116	8 (6.9)	Not reached [-; -]	1.01 [0.37; 2.80]	0.980	
IIC T4b	171	18 (10.5)	Not reached [-; -]	169	18 (10.7)	Not reached [-; -]	0.96 [0.50; 1.84]	0.900	
Geographic Region									
WHO Stratum A[g]	292	24 (8.2)	Not reached [-; -]	326	27 (8.3)	Not reached [-; -]	0.98 [0.56; 1.69]	0.935	0.663
Rest of World	195	13 (6.7)	Not reached [-; -]	163	14 (8.6)	Not reached [-; -]	0.81 [0.38; 1.72]	0.576	

Study: KEYNOTE 716[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Progression/ Recurrence-Free Survival 2 (INV Primary Censoring Rule)	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
ECOG Performance Status									
0	454	34 (7.5)	Not reached [-; -]	452	35 (7.7)	Not reached [-; -]	0.97 [0.61; 1.56]	0.902	0.440
1	32	3 (9.4)	Not reached [24.9; -]	35	6 (17.1)	Not reached [23.8; -]	0.48 [0.12; 1.94]	0.300	

a: Database Cutoff Date: 21JUN2021

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

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

d: Based on Cox regression model with Efron's method of tie handling with treatment as a covariate, using Wald confidence interval

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

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

g: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

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Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30

EORTC QLQ-C30: Symptomskala Erschöpfung

Tabelle 4G-7: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Erschöpfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Fatigue	**N[b]**	**N[c]**	**Mean at Baseline (SD)[d]**	**Mean Change from Baseline (SE)[e]**	**Mean Difference[e] [95 %-CI]**	**p-Value[e]**	**Standardized Mean Difference[f] [95 %-CI]**	**p-Value for Interaction Test[g]**
Sex								
Male								
Pembrolizumab	297	269	11.40 (15.07)	7.05 (0.80)	3.96	< 0.001	0.24	0.461
Placebo	287	270	11.32 (16.41)	3.09 (0.80)	[1.75; 6.18]		[0.10; 0.37]	
Female								
Pembrolizumab	186	161	14.56 (18.56)	8.03 (1.26)	2.39	0.170	-	
Placebo	199	179	19.06 (21.40)	5.64 (1.19)	[-1.03; 5.81]			
Age Group								
< 65								
Pembrolizumab	299	267	13.23 (17.39)	7.98 (0.92)	3.95	0.002	0.21	0.465
Placebo	295	270	15.19 (19.48)	4.03 (0.92)	[1.40; 6.51]		[0.07; 0.34]	
≥ 65								
Pembrolizumab	184	163	11.52 (14.96)	6.50 (1.03)	2.33	0.103	-	
Placebo	191	179	13.22 (18.05)	4.17 (0.99)	[-0.47; 5.14]			
Severity of disease: T-Stage								
IIB T3b								
Pembrolizumab	199	175	12.63 (16.69)	7.77 (1.04)	4.22	0.004	0.23	0.682
Placebo	200	184	13.10 (17.64)	3.55 (1.02)	[1.35; 7.09]		[0.07; 0.39]	
IIB T4a								
Pembrolizumab	107	99	13.58 (16.23)	7.68 (1.47)	2.23	0.273	-	
Placebo	116	108	15.23 (20.19)	5.45 (1.39)	[-1.77; 6.22]			
IIC T4b								
Pembrolizumab	170	152	11.92 (16.63)	6.99 (1.18)	3.39	0.043	0.19	
Placebo	169	156	15.31 (19.57)	3.60 (1.18)	[0.10; 6.67]		[0.01; 0.37]	
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	260	12.91 (16.53)	8.60 (0.89)	4.77	< 0.001	0.26	0.098
Placebo	323	302	15.49 (19.84)	3.83 (0.83)	[2.38; 7.15]		[0.13; 0.38]	
Rest of World								
Pembrolizumab	194	170	12.09 (16.52)	5.89 (1.10)	1.38	0.395	-	

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Fatigue	**N[b]**	**N[c]**	**Mean at Baseline (SD)[d]**	**Mean Change from Baseline (SE)[e]**	**Mean Difference[e] [95 %-CI]**	**p-Value[e]**	**Standardized Mean Difference[f] [95 %-CI]**	**p-Value for Interaction Test[g]**
Placebo	163	147	12.17 (16.72)	4.51 (1.18)	[-1.80; 4.56]			
ECOG Performance Status								
0								
Pembrolizumab	450	403	12.43 (16.39)	7.33 (0.72)	3.24	0.001	0.18	0.575
Placebo	449	417	14.23 (18.86)	4.09 (0.71)	[1.26; 5.22]		[0.07; 0.28]	
1								
Pembrolizumab	32	27	14.81 (18.49)	9.69 (2.55)	5.40	0.128	-	
Placebo	35	31	15.77 (19.62)	4.29 (2.40)	[-1.60; 12.41]			

a: Database Cutoff Date: 04JAN2022
b: Number of participants: full-analysis-set population
c: Number of participants with data available for analysis
d: Mean and SD at baseline are calculated based on number of participants with data available for analysis
e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed
f: Standardized mean difference (Hedges' g) is only calculated if confidence interval for mean difference does not include zero
g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed
h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom
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; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-8: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Übelkeit und Erbrechen des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Nausea and Vomiting	**N[b]**	**N[c]**	**Mean at Baseline (SD)[d]**	**Mean Change from Baseline (SE)[e]**	**Mean Difference[e] [95 %-CI]**	**p-Value[e]**	**Standardized Mean Difference[f] [95 %-CI]**	**p-Value for Interaction Test[g]**
Sex								
Male								
Pembrolizumab	297	269	1.05 (5.18)	1.49 (0.28)	0.54	0.177	-	0.714
Placebo	287	270	0.62 (3.47)	0.94 (0.29)	[-0.25; 1.34]			
Female								
Pembrolizumab	186	161	1.24 (6.60)	2.68 (0.61)	0.29	0.734	-	
Placebo	199	179	2.14 (7.07)	2.39 (0.58)	[-1.37; 1.94]			
Age Group								
< 65								
Pembrolizumab	299	267	1.56 (6.98)	2.11 (0.41)	0.39	0.505	-	0.977
Placebo	295	270	1.54 (5.98)	1.72 (0.41)	[-0.76; 1.54]			
≥ 65								
Pembrolizumab	184	163	0.41 (2.59)	1.59 (0.35)	0.26	0.590	-	
Placebo	191	179	0.74 (3.88)	1.33 (0.34)	[-0.70; 1.22]			

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Nausea and Vomiting	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Severity of disease: T-Stage								
IIB T3b								
Pembrolizumab	199	175	1.14 (4.59)	1.85 (0.39)	0.48	0.388	-	0.749
Placebo	200	184	1.00 (4.98)	1.37 (0.39)	[-0.61; 1.56]			
IIB T4a								
Pembrolizumab	107	99	1.35 (7.78)	1.66 (0.75)	-0.18	0.863	-	
Placebo	116	108	1.39 (6.50)	1.84 (0.71)	[-2.23; 1.87]			
IIC T4b								
Pembrolizumab	170	152	0.99 (5.50)	2.14 (0.47)	0.64	0.338	-	
Placebo	169	156	1.39 (4.62)	1.50 (0.47)	[-0.67; 1.94]			
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	260	1.22 (6.52)	2.20 (0.38)	0.41	0.431	-	0.966
Placebo	323	302	1.10 (5.14)	1.78 (0.36)	[-0.62; 1.44]			
Rest of World								
Pembrolizumab	194	170	0.98 (4.33)	1.46 (0.45)	0.42	0.523	-	
Placebo	163	147	1.47 (5.49)	1.04 (0.49)	[-0.88; 1.73]			
ECOG Performance Status								
0								
Pembrolizumab	450	403	1.20 (5.93)	1.76 (0.30)	0.27	0.519	-	0.261
Placebo	449	417	1.24 (5.21)	1.49 (0.30)	[-0.55; 1.10]			
1								
Pembrolizumab	32	27	0.00 (0.00)	4.32 (1.50)	1.71	0.412	-	
Placebo	35	31	1.08 (5.99)	2.61 (1.41)	[-2.44; 5.86]			

a: Database Cutoff Date: 04JAN2022

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

c: Number of participants with data available for analysis

d: Mean and SD at baseline are calculated based on number of participants with data available for analysis

e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

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

g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

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; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Schmerzen

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

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Pain	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex								
Male								
Pembrolizumab	297	269	10.16 (17.58)	4.59 (0.72)	3.52	< 0.001	0.21	0.243

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Pain	**N[b]**	**N[c]**	**Mean at Baseline (SD)[d]**	**Mean Change from Baseline (SE)[e]**	**Mean Difference[e] [95 %-CI]**	**p-Value[e]**	**Standardized Mean Difference[f] [95 %-CI]**	**p-Value for Interaction Test[g]**
Placebo	287	270	10.43 (17.40)	1.08 (0.72)	[1.51; 5.52]		[0.09; 0.33]	
Female								
Pembrolizumab	186	161	12.53 (19.63)	3.77 (1.24)	1.33	0.439	-	
Placebo	199	179	15.83 (21.22)	2.45 (1.18)	[-2.04; 4.70]			
Age Group								
< 65								
Pembrolizumab	299	267	11.17 (17.79)	4.50 (0.87)	3.23	0.009	0.17	0.384
Placebo	295	270	13.33 (20.10)	1.27 (0.87)	[0.81; 5.65]		[0.04; 0.30]	
≥ 65								
Pembrolizumab	184	163	10.84 (19.38)	3.81 (0.95)	1.60	0.225	-	
Placebo	191	179	11.45 (17.69)	2.20 (0.91)	[-0.99; 4.19]			
Severity of disease: T-Stage								
IIB T3b								
Pembrolizumab	199	175	12.00 (18.10)	4.33 (0.93)	3.59	0.006	0.21	0.548
Placebo	200	184	10.51 (17.02)	0.74 (0.91)	[1.03; 6.15]		[0.06; 0.35]	
IIB T4a								
Pembrolizumab	107	99	9.43 (15.46)	5.63 (1.40)	3.21	0.098	-	
Placebo	116	108	13.27 (20.09)	2.42 (1.33)	[-0.60; 7.02]			
IIC T4b								
Pembrolizumab	170	152	11.07 (20.47)	3.38 (1.17)	1.56	0.350	-	
Placebo	169	156	14.21 (20.37)	1.82 (1.18)	[-1.71; 4.83]			
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	260	10.19 (16.76)	5.09 (0.86)	2.53	0.032	0.14	0.751
Placebo	323	302	12.03 (18.49)	2.56 (0.80)	[0.22; 4.84]		[0.01; 0.26]	
Rest of World								
Pembrolizumab	194	170	12.35 (20.62)	2.87 (0.99)	3.15	0.030	0.18	
Placebo	163	147	13.72 (20.52)	-0.28 (1.06)	[0.31; 5.99]		[0.02; 0.35]	
ECOG Performance Status								
0								
Pembrolizumab	450	403	10.71 (18.22)	4.22 (0.67)	2.39	0.012	0.13	0.234
Placebo	449	417	12.23 (18.80)	1.83 (0.67)	[0.53; 4.25]		[0.03; 0.23]	
1								
Pembrolizumab	32	27	16.05 (20.40)	5.29 (2.49)	6.58	0.061	-	
Placebo	35	31	15.59 (21.92)	-1.29 (2.36)	[-0.30; 13.46]			

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Pain	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]

a: Database Cutoff Date: 04JAN2022
b: Number of participants: full-analysis-set population
c: Number of participants with data available for analysis
d: Mean and SD at baseline are calculated based on number of participants with data available for analysis
e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed
f: Standardized mean difference (Hedges' g) is only calculated if confidence interval for mean difference does not include zero
g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed
h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Dyspnoe

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

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Dyspnoea	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex								
Male								
Pembrolizumab	297	269	7.68 (16.75)	3.78 (0.70)	2.05	0.041	0.13	0.981
Placebo	287	270	5.19 (13.40)	1.73 (0.71)	[0.08; 4.01]		[0.01; 0.25]	
Female								
Pembrolizumab	186	161	6.42 (14.20)	6.05 (1.12)	1.89	0.223	-	
Placebo	199	179	6.89 (15.27)	4.16 (1.06)	[-1.15; 4.93]			
Age Group								
< 65								
Pembrolizumab	299	267	7.37 (17.10)	5.01 (0.81)	2.60	0.023	0.15	0.264
Placebo	295	270	5.56 (14.30)	2.42 (0.81)	[0.35; 4.84]		[0.02; 0.28]	
≥ 65								
Pembrolizumab	184	163	6.95 (13.59)	3.88 (0.93)	0.69	0.590	-	
Placebo	191	179	6.33 (14.03)	3.19 (0.89)	[-1.84; 3.23]			
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	260	8.59 (17.30)	4.95 (0.80)	2.41	0.028	0.14	0.382
Placebo	323	302	6.62 (15.14)	2.54 (0.75)	[0.27; 4.55]		[0.01; 0.26]	
Rest of World								
Pembrolizumab	194	170	5.10 (13.08)	4.36 (0.94)	1.22	0.380	-	
Placebo	163	147	4.31 (11.88)	3.14 (1.01)	[-1.50; 3.93]			
ECOG Performance Status								
0								
Pembrolizumab	450	403	7.28 (16.01)	4.49 (0.63)	2.02	0.022	0.12	0.463
Placebo	449	417	6.00 (14.39)	2.47 (0.62)	[0.29; 3.76]		[0.02; 0.22]	
1								
Pembrolizumab	32	27	6.17 (13.19)	6.12 (2.64)	-0.02	0.997	-	
Placebo	35	31	4.30 (11.36)	6.13 (2.50)	[-7.32; 7.29]			

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Dyspnoea	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]

a: Database Cutoff Date: 04JAN2022

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

c: Number of participants with data available for analysis

d: Mean and SD at baseline are calculated based on number of participants with data available for analysis

e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

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

g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

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; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

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

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Insomnia	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex								
Male								
Pembrolizumab	297	269	14.99 (24.14)	1.95 (0.94)	1.28	0.336	-	0.439
Placebo	287	270	14.69 (22.13)	0.67 (0.94)	[-1.33; 3.89]			
Female								
Pembrolizumab	186	161	21.95 (26.38)	1.66 (1.39)	-0.46	0.808	-	
Placebo	199	179	21.79 (26.03)	2.12 (1.32)	[-4.23; 3.30]			
Age Group								
< 65								
Pembrolizumab	299	267	19.10 (27.06)	1.74 (1.05)	0.12	0.935	-	0.684
Placebo	295	270	18.77 (25.42)	1.62 (1.05)	[-2.79; 3.03]			
≥ 65								
Pembrolizumab	184	163	15.13 (21.66)	1.90 (1.17)	1.02	0.530	-	
Placebo	191	179	15.64 (21.58)	0.88 (1.13)	[-2.18; 4.22]			
Severity of disease: T-Stage								
IIB T3b								
Pembrolizumab	199	175	18.48 (26.17)	3.35 (1.24)	2.79	0.109	-	0.217
Placebo	200	184	15.76 (20.60)	0.55 (1.22)	[-0.63; 6.21]			
IIB T4a								

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Insomnia	**N[b]**	**N[c]**	**Mean at Baseline (SD)[d]**	**Mean Change from Baseline (SE)[e]**	**Mean Difference[e] [95 %-CI]**	**p-Value[e]**	**Standardized Mean Difference[f] [95 %-CI]**	**p-Value for Interaction Test[g]**
Pembrolizumab	107	99	17.85 (22.49)	0.46 (1.74)	-1.94	0.419	-	
Placebo	116	108	21.30 (25.15)	2.40 (1.64)	[-6.66; 2.78]			
IIC T4b								
Pembrolizumab	170	152	16.67 (26.02)	0.86 (1.26)	-0.49	0.786	-	
Placebo	169	156	16.88 (26.64)	1.34 (1.27)	[-4.01; 3.04]			
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	260	19.49 (26.13)	2.04 (1.06)	1.01	0.486	-	0.532
Placebo	323	302	17.33 (24.56)	1.03 (0.99)	[-1.83; 3.85]			
Rest of World								
Pembrolizumab	194	170	14.71 (23.49)	1.37 (1.15)	-0.48	0.774	-	
Placebo	163	147	17.91 (22.84)	1.86 (1.23)	[-3.79; 2.82]			
ECOG Performance Status								
0								
Pembrolizumab	450	403	17.87 (25.44)	1.65 (0.82)	0.45	0.693	-	0.627
Placebo	449	417	17.59 (24.02)	1.20 (0.81)	[-1.80; 2.70]			
1								
Pembrolizumab	32	27	13.58 (21.20)	3.83 (3.05)	2.41	0.569	-	
Placebo	35	31	17.20 (24.15)	1.42 (2.89)	[-6.03; 10.84]			

a: Database Cutoff Date: 04JAN2022

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

c: Number of participants with data available for analysis

d: Mean and SD at baseline are calculated based on number of participants with data available for analysis

e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

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

g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

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; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Appetitverlust

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

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Appetite loss	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex								
Male								
Pembrolizumab	297	269	2.97 (10.35)	3.02 (0.58)	1.61	0.052	-	0.769
Placebo	287	270	3.21 (12.77)	1.41 (0.59)	[-0.01; 3.24]			
Female								
Pembrolizumab	186	161	3.31 (10.00)	2.09 (0.94)	0.76	0.560	-	
Placebo	199	179	8.01 (17.78)	1.33 (0.90)	[-1.81; 3.34]			
Age Group								
< 65								
Pembrolizumab	299	267	3.75 (11.31)	2.42 (0.68)	1.38	0.150	-	0.992
Placebo	295	270	5.80 (16.36)	1.04 (0.67)	[-0.50; 3.26]			
≥ 65								
Pembrolizumab	184	163	2.04 (8.02)	3.32 (0.77)	1.59	0.138	-	
Placebo	191	179	4.10 (13.05)	1.74 (0.74)	[-0.51; 3.69]			
Severity of disease: T-Stage								
IIB T3b								
Pembrolizumab	199	175	3.43 (10.77)	2.23 (0.75)	1.27	0.228	-	0.915
Placebo	200	184	3.80 (12.71)	0.96 (0.74)	[-0.80; 3.34]			
IIB T4a								
Pembrolizumab	107	99	2.69 (9.13)	4.38 (1.29)	2.47	0.171	-	
Placebo	116	108	7.41 (17.25)	1.91 (1.23)	[-1.07; 6.01]			
IIC T4b								
Pembrolizumab	170	152	3.07 (10.40)	2.32 (0.76)	1.21	0.266	-	
Placebo	169	156	5.13 (16.13)	1.11 (0.77)	[-0.93; 3.35]			
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	260	2.69 (9.56)	2.98 (0.66)	1.52	0.094	-	0.998
Placebo	323	302	4.97 (14.92)	1.46 (0.62)	[-0.26; 3.29]			
Rest of World								
Pembrolizumab	194	170	3.73 (11.14)	2.34 (0.80)	1.35	0.254	-	
Placebo	163	147	5.44 (15.63)	0.99 (0.86)	[-0.97; 3.66]			
ECOG Performance Status								
0								
Pembrolizumab	450	403	3.31 (10.52)	2.57 (0.53)	1.32	0.074	-	0.629
Placebo	449	417	5.04 (15.11)	1.24 (0.52)	[-0.13; 2.78]			
1								
Pembrolizumab	32	27	0.00 (0.00)	5.41 (2.22)	2.96	0.346	-	
Placebo	35	31	6.45 (15.91)	2.45 (2.10)	[-3.28; 9.20]			

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Appetite loss	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]

a: Database Cutoff Date: 04JAN2022

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

c: Number of participants with data available for analysis

d: Mean and SD at baseline are calculated based on number of participants with data available for analysis

e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

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

g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

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; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Verstopfung

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

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Constipation	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex								
Male								
Pembrolizumab	297	269	5.33 (14.42)	1.87 (0.65)	0.81	0.382	-	0.131
Placebo	287	270	5.19 (14.00)	1.07 (0.65)	[-1.00; 2.61]			
Female								
Pembrolizumab	186	161	9.73 (20.63)	-0.69 (1.00)	-1.53	0.265	-	
Placebo	199	179	11.55 (22.42)	0.85 (0.95)	[-4.24; 1.17]			
Severity of disease: T-Stage								
IIB T3b								
Pembrolizumab	199	175	9.14 (20.03)	0.33 (0.82)	1.06	0.357	-	0.426
Placebo	200	184	7.43 (16.32)	-0.73 (0.80)	[-1.20; 3.32]			
IIB T4a								
Pembrolizumab	107	99	4.71 (12.61)	0.53 (1.18)	-1.44	0.379	-	
Placebo	116	108	9.26 (18.70)	1.98 (1.12)	[-4.67; 1.78]			
IIC T4b								
Pembrolizumab	170	152	6.14 (16.01)	1.59 (0.97)	-0.76	0.583	-	
Placebo	169	156	7.05 (19.68)	2.35 (0.98)	[-3.48; 1.96]			
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	260	6.79 (17.60)	1.32 (0.70)	0.55	0.563	-	0.175
Placebo	323	302	6.84 (17.32)	0.77 (0.66)	[-1.33; 2.44]			
Rest of World								
Pembrolizumab	194	170	7.25 (16.41)	0.05 (0.92)	-1.59	0.241	-	
Placebo	163	147	9.52 (19.51)	1.64 (0.99)	[-4.26; 1.07]			

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Constipation	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
ECOG Performance Status								
0								
Pembrolizumab	450	403	6.53 (16.58)	0.98 (0.57)	-0.34	0.670	-	0.434
Placebo	449	417	7.67 (18.19)	1.33 (0.56)	[-1.92; 1.23]			
1								
Pembrolizumab	32	27	13.58 (23.13)	-1.52 (2.45)	1.64	0.627	-	
Placebo	35	31	8.60 (17.14)	-3.16 (2.30)	[-5.10; 8.39]			

a: Database Cutoff Date: 04JAN2022
b: Number of participants: full-analysis-set population
c: Number of participants with data available for analysis
d: Mean and SD at baseline are calculated based on number of participants with data available for analysis
e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed
f: Standardized mean difference (Hedges' g) is only calculated if confidence interval for mean difference does not include zero
g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed
h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom
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; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Diarrhö

Tabelle 4G-14: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Diarrhö des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Diarrhea	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex								
Male								
Pembrolizumab	297	269	7.43 (16.37)	1.01 (0.62)	2.77	0.002	0.19	0.134
Placebo	287	270	5.93 (14.58)	-1.76 (0.62)	[1.04; 4.50]		[0.07; 0.31]	
Female								
Pembrolizumab	186	161	4.97 (14.54)	2.29 (0.89)	0.54	0.661	-	
Placebo	199	179	4.84 (13.74)	1.75 (0.84)	[-1.88; 2.95]			
Age Group								
< 65								
Pembrolizumab	299	267	7.24 (16.01)	2.01 (0.72)	1.73	0.091	-	0.796
Placebo	295	270	6.05 (14.39)	0.28 (0.72)	[-0.28; 3.73]			
≥ 65								
Pembrolizumab	184	163	5.32 (15.24)	0.74 (0.63)	2.08	0.018	0.16	
Placebo	191	179	4.66 (14.02)	-1.35 (0.61)	[0.36; 3.81]		[0.03; 0.29]	
Severity of disease: T-Stage								
IIB T3b								
Pembrolizumab	199	175	7.81 (17.76)	1.88 (0.78)	3.37	0.002	0.22	0.133
Placebo	200	184	5.80 (15.67)	-1.49 (0.76)	[1.23; 5.51]		[0.08; 0.36]	
IIB T4a								
Pembrolizumab	107	99	6.06 (15.33)	0.31 (1.07)	-0.53	0.720	-	

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Diarrhea	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	116	108	5.86 (13.54)	0.84 (1.01)	[-3.44; 2.38]			
IIC T4b								
Pembrolizumab	170	152	5.26 (13.35)	1.92 (0.88)	1.85	0.141	-	
Placebo	169	156	4.91 (13.01)	0.07 (0.89)	[-0.62; 4.32]			
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	260	6.28 (16.01)	1.56 (0.70)	1.37	0.152	-	0.238
Placebo	323	302	5.63 (15.18)	0.19 (0.66)	[-0.51; 3.26]			
Rest of World								
Pembrolizumab	194	170	6.86 (15.34)	1.43 (0.71)	2.95	0.005	0.21	
Placebo	163	147	5.22 (12.15)	-1.52 (0.76)	[0.90; 4.99]		[0.06; 0.35]	
ECOG Performance Status								
0								
Pembrolizumab	450	403	6.29 (15.02)	1.38 (0.53)	1.71	0.022	0.11	0.286
Placebo	449	417	5.76 (14.58)	-0.33 (0.52)	[0.25; 3.17]		[0.02; 0.20]	
1								
Pembrolizumab	32	27	9.88 (24.13)	3.52 (2.06)	4.37	0.134	-	
Placebo	35	31	2.15 (8.32)	-0.85 (1.94)	[-1.38; 10.13]			

a: Database Cutoff Date: 04JAN2022

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

c: Number of participants with data available for analysis

d: Mean and SD at baseline are calculated based on number of participants with data available for analysis

e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

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

g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

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; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EQ-5D VAS

Tabelle 4G-15: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die EQ-5D VAS aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EQ-5D VAS Score	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex								
Male								
Pembrolizumab	297	272	84.24 (12.61)	-1.67 (0.52)	-1.36	0.065	-	0.924
Placebo	287	274	85.44 (12.35)	-0.32 (0.52)	[-2.79; 0.08]			
Female								
Pembrolizumab	186	165	84.70 (12.93)	-2.91 (0.83)	-1.53	0.179	-	
Placebo	199	184	84.26 (13.42)	-1.37 (0.78)	[-3.77; 0.70]			

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EQ-5D VAS Score	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Age Group								
< 65								
Pembrolizumab	299	271	83.75 (13.39)	-1.57 (0.58)	-1.65	0.044	-0.14	0.696
Placebo	295	275	84.80 (13.14)	0.08 (0.57)	[-3.25; -0.05]		[-0.27; -0.00]	
≥ 65								
Pembrolizumab	184	166	85.49 (11.51)	-3.20 (0.71)	-1.16	0.235	-	
Placebo	191	183	85.21 (12.27)	-2.04 (0.68)	[-3.09; 0.76]			
Severity of disease: T-Stage								
IIB T3b								
Pembrolizumab	199	179	84.08 (12.32)	-1.85 (0.68)	-1.56	0.102	-	0.703
Placebo	200	187	85.99 (12.68)	-0.29 (0.67)	[-3.44; 0.31]			
IIB T4a								
Pembrolizumab	107	101	84.66 (12.20)	-2.31 (0.96)	-0.86	0.514	-	
Placebo	116	112	84.09 (12.94)	-1.45 (0.90)	[-3.46; 1.73]			
IIC T4b								
Pembrolizumab	170	152	84.24 (13.58)	-2.57 (0.77)	-2.18	0.046	-0.18	
Placebo	169	158	84.38 (12.85)	-0.39 (0.77)	[-4.31; -0.04]		[-0.35; -0.00]	
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	266	83.35 (13.42)	-1.88 (0.57)	-1.38	0.079	-	0.839
Placebo	323	308	84.60 (13.05)	-0.50 (0.54)	[-2.93; 0.16]			
Rest of World								
Pembrolizumab	194	171	86.08 (11.38)	-2.73 (0.73)	-1.62	0.130	-	
Placebo	163	150	85.71 (12.24)	-1.11 (0.78)	[-3.71; 0.48]			
ECOG Performance Status								
0								
Pembrolizumab	450	408	84.66 (12.70)	-2.10 (0.47)	-1.29	0.049	-0.11	0.270
Placebo	449	424	85.08 (12.93)	-0.81 (0.46)	[-2.57; -0.01]		[-0.21; -0.00]	
1								
Pembrolizumab	32	28	80.64 (12.86)	-3.78 (1.79)	-4.21	0.095	-	
Placebo	35	32	84.00 (10.70)	0.43 (1.69)	[-9.18; 0.76]			

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EQ-5D VAS Score	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]

a: Database Cutoff Date: 04JAN2022

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

c: Number of participants with data available for analysis

d: Mean and SD at baseline are calculated based on number of participants with data available for analysis

e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

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

g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EQ-5D: European Quality of Life 5 Dimensions; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; VAS: Visual Analog Scale; WHO: World Health Organization

Anhang 4-G3.2: Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-16: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den globalen Gesundheitsstatus des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Global Health Status/QoL	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex								
Male								
Pembrolizumab	297	269	82.09 (16.37)	-4.01 (0.63)	-3.26	< 0.001	-0.23	0.196
Placebo	287	270	82.25 (15.20)	-0.76 (0.63)	[-5.00; -1.51]		[-0.35; -0.11]	
Female								
Pembrolizumab	186	161	81.31 (16.16)	-4.95 (0.95)	-1.34	0.309	-	
Placebo	199	179	79.52 (17.06)	-3.61 (0.91)	[-3.93; 1.25]			
Age Group								
< 65								
Pembrolizumab	299	267	80.87 (17.59)	-3.66 (0.70)	-2.52	0.010	-0.16	0.966
Placebo	295	270	80.96 (16.63)	-1.14 (0.69)	[-4.45; -0.60]		[-0.29; -0.04]	
≥ 65								
Pembrolizumab	184	163	83.33 (13.76)	-5.63 (0.84)	-2.56	0.028	-0.18	
Placebo	191	179	81.47 (15.06)	-3.07 (0.80)	[-4.84; -0.28]		[-0.33; -0.02]	

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Global Health Status/QoL	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Severity of disease: T-Stage								
IIB T3b								
Pembrolizumab	199	175	81.00 (17.95)	-4.05 (0.77)	-1.72	0.112	-	0.475
Placebo	200	184	83.47 (14.77)	-2.33 (0.75)	[-3.84; 0.40]			
IIB T4a								
Pembrolizumab	107	99	82.58 (15.20)	-4.70 (1.25)	-2.23	0.199	-	
Placebo	116	108	79.71 (16.64)	-2.47 (1.19)	[-5.64; 1.18]			
IIC T4b								
Pembrolizumab	170	152	81.96 (14.99)	-4.59 (0.91)	-3.78	0.004	-0.25	
Placebo	169	156	79.54 (16.73)	-0.81 (0.92)	[-6.33; -1.24]		[-0.42; -0.08]	
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	260	80.67 (16.61)	-4.17 (0.69)	-2.84	0.003	-0.18	0.502
Placebo	323	302	80.88 (16.45)	-1.33 (0.65)	[-4.70; -0.97]		[-0.31; -0.06]	
Rest of World								
Pembrolizumab	194	170	83.53 (15.65)	-4.84 (0.84)	-1.88	0.127	-	
Placebo	163	147	81.75 (15.09)	-2.96 (0.90)	[-4.30; 0.54]			
ECOG Performance Status								
0								
Pembrolizumab	450	403	81.99 (16.36)	-4.19 (0.55)	-2.43	0.002	-0.16	0.737
Placebo	449	417	81.41 (16.06)	-1.76 (0.54)	[-3.95; -0.91]		[-0.26; -0.06]	
1								
Pembrolizumab	32	27	79.01 (15.04)	-6.95 (2.21)	-3.42	0.264	-	
Placebo	35	31	77.69 (15.27)	-3.53 (2.09)	[-9.51; 2.66]			

a: Database Cutoff Date: 04JAN2022

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

c: Number of participants with data available for analysis

d: Mean and SD at baseline are calculated based on number of participants with data available for analysis

e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

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

g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

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; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-17: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Physical Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex								
Male								
Pembrolizumab	297	269	93.09 (11.25)	-2.81 (0.53)	-1.66	0.028	-0.15	0.159
Placebo	287	270	93.46 (12.32)	-1.15 (0.53)	[-3.13; -0.18]		[-0.28; -0.02]	
Female								
Pembrolizumab	186	161	90.31 (14.20)	-2.82 (0.86)	0.18	0.878	-	
Placebo	199	179	89.39 (15.43)	-3.00 (0.82)	[-2.15; 2.52]			
Age Group								
< 65								
Pembrolizumab	299	267	93.28 (10.85)	-2.93 (0.60)	-1.38	0.104	-	0.357
Placebo	295	270	92.59 (13.29)	-1.55 (0.60)	[-3.04; 0.29]			
≥ 65								
Pembrolizumab	184	163	90.02 (14.62)	-2.52 (0.73)	-0.13	0.898	-	
Placebo	191	179	90.69 (14.44)	-2.39 (0.70)	[-2.13; 1.87]			
Severity of disease: T-Stage								
IIB T3b								
Pembrolizumab	199	175	93.18 (11.83)	-3.82 (0.69)	-1.95	0.045	-0.17	0.270
Placebo	200	184	93.37 (12.06)	-1.87 (0.68)	[-3.85; -0.05]		[-0.33; -0.00]	
IIB T4a								
Pembrolizumab	107	99	91.85 (11.45)	-3.26 (1.01)	-1.14	0.412	-	
Placebo	116	108	92.41 (13.53)	-2.12 (0.96)	[-3.88; 1.60]			
IIC T4b								
Pembrolizumab	170	152	90.75 (13.90)	-1.20 (0.80)	0.50	0.659	-	
Placebo	169	156	89.96 (15.04)	-1.70 (0.80)	[-1.73; 2.73]			
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	260	92.72 (11.74)	-3.25 (0.62)	-1.37	0.108	-	0.300
Placebo	323	302	91.81 (14.43)	-1.88 (0.58)	[-3.03; 0.30]			
Rest of World								
Pembrolizumab	194	170	91.02 (13.53)	-1.94 (0.69)	0.10	0.922	-	
Placebo	163	147	91.88 (12.37)	-2.04 (0.74)	[-1.88; 2.08]			

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Physical Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
ECOG Performance Status								
0								
Pembrolizumab	450	403	92.46 (12.15)	-2.79 (0.48)	-1.05	0.117	-	0.614
Placebo	449	417	92.55 (13.27)	-1.74 (0.47)	[-2.36; 0.26]			
1								
Pembrolizumab	32	27	85.93 (15.83)	-2.98 (1.99)	0.07	0.980	-	
Placebo	35	31	82.58 (17.01)	-3.05 (1.88)	[-5.42; 5.56]			

a: Database Cutoff Date: 04JAN2022

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

c: Number of participants with data available for analysis

d: Mean and SD at baseline are calculated based on number of participants with data available for analysis

e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

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

g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

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; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-18: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Rollenfunktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Role Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex								
Male								
Pembrolizumab	297	269	91.64 (17.25)	-3.51 (0.73)	-3.68	< 0.001	-0.22	0.175
Placebo	287	270	91.11 (18.33)	0.17 (0.73)	[-5.71; -1.65]		[-0.34; -0.10]	
Female								
Pembrolizumab	186	161	87.89 (22.05)	-1.79 (1.23)	-1.14	0.503	-	
Placebo	199	179	85.85 (23.99)	-0.65 (1.17)	[-4.47; 2.20]			
Age Group								
< 65								
Pembrolizumab	299	267	89.95 (20.49)	-2.71 (0.86)	-3.50	0.004	-0.19	0.236
Placebo	295	270	87.28 (22.74)	0.79 (0.86)	[-5.89; -1.11]		[-0.32; -0.06]	
≥ 65								

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Role Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Pembrolizumab	184	163	90.70 (17.08)	-3.06 (0.98)	-1.23	0.369	-	
Placebo	191	179	91.62 (17.52)	-1.84 (0.95)	[-3.91; 1.46]			
Severity of disease: T-Stage								
IIB T3b								
Pembrolizumab	199	175	90.48 (18.86)	-3.87 (0.95)	-3.78	0.005	-0.21	0.670
Placebo	200	184	90.94 (19.93)	-0.09 (0.93)	[-6.39; -1.17]		[-0.36; -0.07]	
IIB T4a								
Pembrolizumab	107	99	91.92 (15.68)	-3.36 (1.30)	-2.80	0.121	-	
Placebo	116	108	89.04 (18.53)	-0.56 (1.23)	[-6.34; 0.74]			
IIC T4b								
Pembrolizumab	170	152	88.60 (21.82)	-1.41 (1.16)	-1.89	0.252	-	
Placebo	169	156	86.97 (23.21)	0.48 (1.17)	[-5.13; 1.35]			
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	260	89.62 (19.29)	-3.02 (0.88)	-3.10	0.011	-0.16	0.618
Placebo	323	302	88.02 (22.35)	0.09 (0.83)	[-5.48; -0.73]		[-0.29; -0.04]	
Rest of World								
Pembrolizumab	194	170	91.18 (19.20)	-2.81 (0.92)	-2.15	0.111	-	
Placebo	163	147	91.04 (17.48)	-0.67 (0.98)	[-4.79; 0.50]			
ECOG Performance Status								
0								
Pembrolizumab	450	403	90.53 (19.26)	-2.74 (0.66)	-2.58	0.005	-0.14	0.457
Placebo	449	417	89.45 (20.59)	-0.16 (0.65)	[-4.40; -0.76]		[-0.25; -0.04]	
1								
Pembrolizumab	32	27	85.80 (18.89)	-4.40 (3.30)	-5.31	0.247	-	
Placebo	35	31	82.80 (24.53)	0.91 (3.11)	[-14.43; 3.81]			

a: Database Cutoff Date: 04JAN2022

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

c: Number of participants with data available for analysis

d: Mean and SD at baseline are calculated based on number of participants with data available for analysis

e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

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

g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

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; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-19: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]					**Pembrolizumab vs. Placebo**			
EORTC QLQ-C30 Emotional Functioning	**N[b]**	**N[c]**	**Mean at Baseline (SD)[d]**	**Mean Change from Baseline (SE)[e]**	**Mean Difference[e] [95 %-CI]**	**p-Value[e]**	**Standardized Mean Difference[f] [95 %-CI]**	**p-Value for Interaction Test[g]**
Sex								
Male								
Pembrolizumab	297	269	86.03 (17.43)	0.50 (0.63)	-1.00	0.261	-	0.696
Placebo	287	270	87.96 (14.16)	1.50 (0.63)	[-2.74; 0.74]			
Female								
Pembrolizumab	186	161	82.92 (18.04)	-0.59 (1.09)	-1.66	0.268	-	
Placebo	199	179	79.84 (19.81)	1.07 (1.03)	[-4.62; 1.29]			
Age Group								
< 65								
Pembrolizumab	299	267	82.77 (19.08)	-0.04 (0.78)	-1.54	0.163	-	0.498
Placebo	295	270	82.99 (18.22)	1.50 (0.78)	[-3.70; 0.63]			
≥ 65								
Pembrolizumab	184	163	88.29 (14.60)	0.49 (0.78)	-0.38	0.724	-	
Placebo	191	179	87.34 (14.90)	0.87 (0.75)	[-2.50; 1.74]			
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	260	83.65 (18.54)	0.10 (0.71)	-1.48	0.130	-	0.564
Placebo	323	302	84.44 (16.75)	1.58 (0.67)	[-3.41; 0.44]			
Rest of World								
Pembrolizumab	194	170	86.72 (16.23)	0.14 (0.95)	-0.52	0.711	-	
Placebo	163	147	85.32 (17.81)	0.65 (1.02)	[-3.26; 2.22]			
ECOG Performance Status								
0								
Pembrolizumab	450	403	84.86 (17.77)	0.40 (0.59)	-0.81	0.327	-	0.073
Placebo	449	417	84.67 (17.20)	1.21 (0.58)	[-2.43; 0.81]			
1								
Pembrolizumab	32	27	84.88 (16.99)	-3.93 (2.26)	-6.65	0.037	-0.43	
Placebo	35	31	85.75 (15.99)	2.72 (2.13)	[-12.86; -0.43]		[-0.84; -0.03]	

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Emotional Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]

a: Database Cutoff Date: 04JAN2022

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

c: Number of participants with data available for analysis

d: Mean and SD at baseline are calculated based on number of participants with data available for analysis

e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

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

g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

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; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-20: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Kognitive Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Cognitive Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex								
Male								
Pembrolizumab	297	269	92.57 (12.82)	-3.86 (0.62)	-1.71	0.052	-	0.213
Placebo	287	270	93.02 (13.00)	-2.15 (0.62)	[-3.43; 0.01]			
Female								
Pembrolizumab	186	161	93.17 (13.63)	-3.88 (0.95)	0.10	0.942	-	
Placebo	199	179	90.50 (16.38)	-3.98 (0.90)	[-2.49; 2.68]			
Age Group								
< 65								
Pembrolizumab	299	267	92.76 (14.15)	-4.09 (0.71)	-1.47	0.145	-	0.394
Placebo	295	270	92.10 (15.32)	-2.63 (0.71)	[-3.44; 0.51]			
≥ 65								
Pembrolizumab	184	163	92.84 (11.26)	-3.41 (0.76)	-0.14	0.898	-	
Placebo	191	179	91.90 (13.14)	-3.27 (0.73)	[-2.21; 1.94]			
Severity of disease: T-Stage								
IIB T3b								
Pembrolizumab	199	175	93.24 (11.59)	-4.13 (0.81)	-0.72	0.524	-	0.936
Placebo	200	184	93.66 (10.84)	-3.40 (0.79)	[-2.96; 1.51]			
IIB T4a								

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Cognitive Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Pembrolizumab	107	99	91.25 (14.35)	-4.34 (1.22)	-1.46	0.387	-	
Placebo	116	108	89.35 (16.19)	-2.88 (1.16)	[-4.77; 1.86]			
IIC T4b								
Pembrolizumab	170	152	93.31 (13.87)	-3.29 (0.85)	-1.05	0.383	-	
Placebo	169	156	91.88 (16.67)	-2.24 (0.85)	[-3.43; 1.32]			
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	260	92.63 (13.02)	-3.49 (0.67)	-0.99	0.283	-	0.779
Placebo	323	302	91.61 (15.42)	-2.50 (0.63)	[-2.79; 0.82]			
Rest of World								
Pembrolizumab	194	170	93.04 (13.28)	-4.39 (0.85)	-0.63	0.612	-	
Placebo	163	147	92.86 (12.34)	-3.75 (0.91)	[-3.08; 1.82]			

a: Database Cutoff Date: 04JAN2022
b: Number of participants: full-analysis-set population
c: Number of participants with data available for analysis
d: Mean and SD at baseline are calculated based on number of participants with data available for analysis
e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed
f: Standardized mean difference (Hedges' g) is only calculated if confidence interval for mean difference does not include zero
g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed
h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Soziale Funktion

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

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Social Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex								
Male								
Pembrolizumab	297	269	92.19 (15.93)	-1.36 (0.64)	-2.94	0.001	-0.21	0.470
Placebo	287	270	92.10 (16.74)	1.57 (0.64)	[-4.72; -1.15]		[-0.33; -0.08]	
Female								
Pembrolizumab	186	161	91.20 (15.37)	-1.73 (1.14)	-1.81	0.249	-	
Placebo	199	179	86.96 (22.01)	0.08 (1.08)	[-4.91; 1.28]			

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Social Functioning	**N[b]**	**N[c]**	**Mean at Baseline (SD)[d]**	**Mean Change from Baseline (SE)[e]**	**Mean Difference[e] [95 %-CI]**	**p-Value[e]**	**Standardized Mean Difference[f] [95 %-CI]**	**p-Value for Interaction Test[g]**
Age Group								
< 65								
Pembrolizumab	299	267	91.82 (16.18)	-2.03 (0.81)	-3.41	0.003	-0.20	0.129
Placebo	295	270	88.02 (21.71)	1.38 (0.81)	[-5.67; -1.15]		[-0.33; -0.07]	
≥ 65								
Pembrolizumab	184	163	91.82 (14.97)	-0.55 (0.80)	-0.73	0.514	-	
Placebo	191	179	93.11 (13.99)	0.18 (0.77)	[-2.91; 1.46]			
Severity of disease: T-Stage								
IIB T3b								
Pembrolizumab	199	175	93.33 (13.96)	-2.60 (0.82)	-3.65	0.002	-0.24	0.328
Placebo	200	184	91.39 (18.11)	1.05 (0.80)	[-5.91; -1.38]		[-0.39; -0.09]	
IIB T4a								
Pembrolizumab	107	99	91.41 (14.94)	-1.29 (1.33)	-1.18	0.520	-	
Placebo	116	108	89.35 (18.71)	-0.11 (1.26)	[-4.79; 2.43]			
IIC T4b								
Pembrolizumab	170	152	90.35 (17.95)	-0.30 (1.03)	-1.84	0.206	-	
Placebo	169	156	89.10 (20.62)	1.55 (1.03)	[-4.71; 1.02]			
Geographic Region								
WHO Stratum A[h]								
Pembrolizumab	289	260	91.67 (15.88)	-1.61 (0.78)	-2.08	0.053	-	0.457
Placebo	323	302	90.01 (19.79)	0.47 (0.73)	[-4.18; 0.03]			
Rest of World								
Pembrolizumab	194	170	92.06 (15.51)	-1.31 (0.87)	-3.25	0.011	-0.21	
Placebo	163	147	90.14 (17.85)	1.95 (0.93)	[-5.77; -0.74]		[-0.38; -0.05]	
ECOG Performance Status								
0								
Pembrolizumab	450	403	91.94 (15.87)	-1.35 (0.61)	-2.25	0.008	-0.14	0.284
Placebo	449	417	90.33 (19.02)	0.90 (0.60)	[-3.92; -0.58]		[-0.24; -0.04]	
1								
Pembrolizumab	32	27	90.12 (13.28)	-3.41 (2.38)	-6.44	0.055	-	
Placebo	35	31	86.02 (21.12)	3.03 (2.25)	[-13.03; 0.15]			

Study: KEYNOTE 716[a]					Pembrolizumab vs. Placebo			
EORTC QLQ-C30 Social Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	p-Value[e]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]

a: Database Cutoff Date: 04JAN2022

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

c: Number of participants with data available for analysis

d: Mean and SD at baseline are calculated based on number of participants with data available for analysis

e: MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

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

g: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

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; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

Anhang 4-G3.3: Nebenwirkungen

Unerwünschte Ereignisse

Unerwünschte Ereignisse gesamt

Tabelle 4G-22: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Adverse Events	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Sex									
Male	297	279 (93.9)	3.1 [3.1; 3.4]	287	259 (90.2)	6.0 [4.1; 6.3]	1.38 [1.17; 1.64]	< 0.001	0.722
Female	186	183 (98.4)	3.1 [2.9; 3.3]	199	186 (93.5)	3.4 [3.1; 5.1]	1.32 [1.08; 1.62]	0.008	
Age Group									
< 65	299	285 (95.3)	3.1 [3.1; 3.3]	295	272 (92.2)	3.4 [3.1; 4.7]	1.22 [1.04; 1.45]	0.018	0.088
≥ 65	184	177 (96.2)	3.1 [2.9; 3.3]	191	173 (90.6)	6.3 [5.0; 7.9]	1.60 [1.30; 1.98]	< 0.001	
Severity of disease: T-Stage									
IIB T3b	199	191 (96.0)	3.1 [3.1; 3.4]	200	184 (92.0)	3.5 [3.1; 6.1]	1.28 [1.04; 1.57]	0.019	0.102
IIB T4a	107	102 (95.3)	3.1 [2.7; 3.3]	116	111 (95.7)	3.6 [3.1; 6.0]	1.13 [0.86; 1.47]	0.390	
IIC T4b	170	165 (97.1)	3.1 [3.0; 3.6]	169	150 (88.8)	6.0 [4.6; 6.6]	1.64 [1.31; 2.05]	< 0.001	
Geographic Region									
WHO Stratum A[g]	289	281 (97.2)	3.1 [3.0; 3.3]	323	298 (92.3)	4.6 [3.3; 6.0]	1.49 [1.27; 1.76]	< 0.001	0.103
Rest of World	194	181 (93.3)	3.1 [3.0; 4.1]	163	147 (90.2)	5.1 [3.3; 6.7]	1.18 [0.95; 1.47]	0.138	
ECOG Performance Status									
0	450	430 (95.6)	3.1 [3.1; 3.3]	449	415 (92.4)	4.6 [3.4; 6.0]	1.32 [1.15; 1.51]	< 0.001	0.361
1	32	31 (96.9)	3.4 [1.1; 6.4]	35	29 (82.9)	9.0 [3.3; 21.4]	1.76 [1.05; 2.96]	0.033	

a: Database Cutoff Date: 04JAN2022

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

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

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

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

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

g: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-23: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Serious Adverse Events	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Sex									
Male	297	70 (23.6)	Not reached [-; -]	287	59 (20.6)	Not reached [-; -]	1.24 [0.87; 1.75]	0.230	0.556
Female	186	33 (17.7)	Not reached [-; -]	199	35 (17.6)	Not reached [-; -]	1.03 [0.64; 1.66]	0.902	
Age Group									
< 65	299	53 (17.7)	Not reached [-; -]	295	52 (17.6)	Not reached [-; -]	1.05 [0.71; 1.54]	0.813	0.362
≥ 65	184	50 (27.2)	Not reached [-; -]	191	42 (22.0)	Not reached [66.7; -]	1.34 [0.89; 2.03]	0.159	
Severity of disease: T-Stage									
IIB T3b	199	44 (22.1)	Not reached [-; -]	200	37 (18.5)	Not reached [-; -]	1.28 [0.83; 1.99]	0.265	0.687
IIB T4a	107	24 (22.4)	Not reached [-; -]	116	22 (19.0)	Not reached [-; -]	1.28 [0.72; 2.29]	0.399	
IIC T4b	170	35 (20.6)	Not reached [-; -]	169	35 (20.7)	Not reached [66.7; -]	0.99 [0.62; 1.58]	0.955	
Geographic Region									
WHO Stratum A[g]	289	64 (22.1)	Not reached [-; -]	323	61 (18.9)	Not reached [-; -]	1.26 [0.88; 1.78]	0.202	0.477
Rest of World	194	39 (20.1)	Not reached [-; -]	163	33 (20.2)	Not reached [-; -]	1.02 [0.64; 1.62]	0.927	
ECOG Performance Status									
0	450	94 (20.9)	Not reached [-; -]	449	86 (19.2)	Not reached [-; -]	1.16 [0.86; 1.55]	0.328	0.683
1	32	9 (28.1)	Not reached [55.1; -]	35	7 (20.0)	Not reached [-; -]	1.45 [0.54; 3.90]	0.461	

a: Database Cutoff Date: 04JAN2022

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

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

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

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

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

g: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization

Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5)

Tabelle 4G-24: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Sex									
Male	297	94 (31.6)	64.6 [63.0; -]	287	64 (22.3)	64.3 [60.1; -]	1.58 [1.15; 2.17]	0.005	0.879
Female	186	43 (23.1)	Not reached [-; -]	199	33 (16.6)	81.1 [-; -]	1.50 [0.95; 2.37]	0.083	
Severity of disease: T-Stage									
IIB T3b	199	55 (27.6)	64.6 [64.6; -]	200	36 (18.0)	81.1 [60.1; -]	1.72 [1.13; 2.63]	0.012	0.824
IIB T4a	107	30 (28.0)	Not reached [63.0; -]	116	26 (22.4)	64.3 [64.3; -]	1.41 [0.84; 2.39]	0.197	
IIC T4b	170	52 (30.6)	Not reached [-; -]	169	35 (20.7)	Not reached [-; -]	1.54 [1.00; 2.37]	0.048	
ECOG Performance Status									
0	450	129 (28.7)	64.6 [63.0; -]	449	89 (19.8)	81.1 [64.3; -]	1.61 [1.23; 2.12]	< 0.001	0.426
1	32	8 (25.0)	Not reached [-; -]	35	8 (22.9)	Not reached [-; -]	1.16 [0.44; 3.10]	0.764	

a: Database Cutoff Date: 04JAN2022

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

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

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

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

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

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

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-25: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 716[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Adverse Events Leading to Treatment Discontinuation	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Sex									
Male	297	56 (18.9)	Not reached [-; -]	287	15 (5.2)	Not reached [-; -]	4.04 [2.29; 7.15]	< 0.001	0.889
Female	186	27 (14.5)	Not reached [-; -]	199	7 (3.5)	Not reached [-; -]	4.38 [1.91; 10.05]	< 0.001	

Age Group									
< 65	299	46 (15.4)	Not reached [-; -]	295	11 (3.7)	Not reached [-; -]	4.49 [2.32; 8.66]	< 0.001	0.795
≥ 65	184	37 (20.1)	Not reached [-; -]	191	11 (5.8)	Not reached [-; -]	3.92 [2.00; 7.69]	< 0.001	
Severity of disease: T-Stage									
IIB T3b	199	26 (13.1)	Not reached [-; -]	200	9 (4.5)	Not reached [-; -]	3.14 [1.47; 6.70]	0.003	0.665
IIB T4a	107	19 (17.8)	Not reached [-; -]	116	5 (4.3)	Not reached [-; -]	4.72 [1.76; 12.66]	0.002	
IIC T4b	170	38 (22.4)	Not reached [-; -]	169	8 (4.7)	Not reached [-; -]	5.05 [2.36; 10.82]	< 0.001	
Geographic Region									
WHO Stratum A[g]	289	57 (19.7)	Not reached [-; -]	323	15 (4.6)	Not reached [-; -]	4.72 [2.67; 8.33]	< 0.001	0.514
Rest of World	194	26 (13.4)	Not reached [-; -]	163	7 (4.3)	Not reached [-; -]	3.38 [1.47; 7.78]	0.004	

a: Database Cutoff Date: 04JAN2022

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

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

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

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

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

g: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

CI: Confidence Interval; WHO: World Health Organization

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-26: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC)

Study: KEYNOTE 716[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Adverse Events	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
SOC[g]: Endocrine disorders									
Sex									
Male	297	71 (23.9)	Not reached [-; -]	287	9 (3.1)	Not reached [-; -]	9.28 [4.64; 18.58]	< 0.001	0.169
Female	186	56 (30.1)	Not reached [-; -]	199	15 (7.5)	Not reached [-; -]	4.76 [2.69; 8.42]	< 0.001	
Age Group									
< 65	299	84 (28.1)	Not reached [-; -]	295	15 (5.1)	Not reached [-; -]	6.62 [3.82; 11.47]	< 0.001	0.807
≥ 65	184	43 (23.4)	Not reached [-; -]	191	9 (4.7)	Not reached [-; -]	5.93 [2.89; 12.16]	< 0.001	
Severity of disease: T-Stage									
IIB T3b	199	53 (26.6)	Not reached [-; -]	200	9 (4.5)	Not reached [-; -]	7.09 [3.50; 14.39]	< 0.001	0.901
IIB T4a	107	29 (27.1)	Not reached [-; -]	116	7 (6.0)	Not reached [-; -]	5.39 [2.36; 12.31]	< 0.001	
IIC T4b	170	44 (25.9)	Not reached [-; -]	169	8 (4.7)	Not reached [-; -]	6.33 [2.98; 13.44]	< 0.001	
Geographic Region									
WHO Stratum A[h]	289	75 (26.0)	Not reached [-; -]	323	14 (4.3)	Not reached [-; -]	7.13 [4.03; 12.62]	< 0.001	0.460
Rest of World	194	52 (26.8)	Not reached [-; -]	163	10 (6.1)	Not reached [-; -]	5.27 [2.68; 10.37]	< 0.001	
ECOG Performance Status									
0	450	120 (26.7)	Not reached [-; -]	449	23 (5.1)	Not reached [-; -]	6.28 [4.02; 9.81]	< 0.001	0.752
1	32	7 (21.9)	Not reached [-; -]	35	1 (2.9)	Not reached [-; -]	8.28 [1.02; 67.36]	0.048	
SOC[g]: Eye disorders									
Sex									
Male	297	21 (7.1)	Not reached [-; -]	287	14 (4.9)	Not reached [-; -]	1.61 [0.82; 3.17]	0.166	0.352
Female	186	34 (18.3)	Not reached [-; -]	199	16 (8.0)	Not reached [-; -]	2.50 [1.38; 4.52]	0.003	
Age Group									
< 65	299	28 (9.4)	Not reached [-; -]	295	19 (6.4)	Not reached [-; -]	1.59 [0.89; 2.84]	0.120	0.186
≥ 65	184	27 (14.7)	Not reached [-; -]	191	11 (5.8)	Not reached [-; -]	2.90 [1.44; 5.86]	0.003	
Severity of disease: T-Stage									
IIB T3b	199	26 (13.1)	Not reached [-; -]	200	15 (7.5)	Not reached [-; -]	1.92 [1.02; 3.63]	0.044	0.979
IIB T4a	107	12 (11.2)	Not reached [-; -]	116	7 (6.0)	Not reached [-; -]	2.07 [0.82; 5.28]	0.125	

Study: KEYNOTE 716[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IIC T4b	170	16 (9.4)	Not reached [-; -]	169	8 (4.7)	Not reached [-; -]	2.17 [0.93; 5.08]	0.073	
Geographic Region									
WHO Stratum A[h]	289	37 (12.8)	Not reached [-; -]	323	21 (6.5)	Not reached [-; -]	2.22 [1.30; 3.79]	0.004	0.669
Rest of World	194	18 (9.3)	Not reached [-; -]	163	9 (5.5)	Not reached [-; -]	1.82 [0.82; 4.05]	0.144	
ECOG Performance Status									
0	450	50 (11.1)	Not reached [-; -]	449	27 (6.0)	Not reached [-; -]	2.06 [1.29; 3.29]	0.002	0.885
1	32	5 (15.6)	Not reached [-; -]	35	3 (8.6)	Not reached [-; -]	1.85 [0.44; 7.77]	0.399	
SOC[g]: Gastrointestinal disorders									
Sex									
Male	297	155 (52.2)	33.7 [24.9; 47.1]	287	98 (34.1)	Not reached [-; -]	1.74 [1.35; 2.24]	< 0.001	0.317
Female	186	115 (61.8)	22.4 [13.7; 32.1]	199	99 (49.7)	44.1 [28.1; -]	1.44 [1.10; 1.88]	0.008	
Age Group									
< 65	299	160 (53.5)	36.6 [24.3; 52.1]	295	124 (42.0)	Not reached [-; -]	1.41 [1.12; 1.79]	0.004	0.146
≥ 65	184	110 (59.8)	24.7 [15.4; 31.3]	191	73 (38.2)	Not reached [53.0; -]	1.89 [1.40; 2.54]	< 0.001	
Severity of disease: T-Stage									
IIB T3b	199	122 (61.3)	26.9 [18.1; 34.9]	200	78 (39.0)	Not reached [-; -]	1.87 [1.41; 2.49]	< 0.001	0.247
IIB T4a	107	60 (56.1)	26.4 [15.1; -]	116	57 (49.1)	47.3 [21.0; -]	1.25 [0.87; 1.79]	0.236	
IIC T4b	170	86 (50.6)	36.6 [24.7; -]	169	62 (36.7)	Not reached [-; -]	1.54 [1.11; 2.14]	0.009	
Geographic Region									
WHO Stratum A[h]	289	169 (58.5)	27.1 [20.9; 34.1]	323	130 (40.2)	Not reached [-; -]	1.71 [1.36; 2.15]	< 0.001	0.341
Rest of World	194	101 (52.1)	34.7 [20.4; -]	163	67 (41.1)	Not reached [42.1; -]	1.39 [1.02; 1.89]	0.039	
ECOG Performance Status									
0	450	257 (57.1)	27.6 [23.4; 34.1]	449	184 (41.0)	Not reached [-; -]	1.60 [1.33; 1.94]	< 0.001	0.401
1	32	13 (40.6)	60.6 [17.9; -]	35	13 (37.1)	Not reached [42.1; -]	1.13 [0.53; 2.45]	0.750	
SOC[g]: Musculoskeletal and connective tissue disorders									
Sex									
Male	297	121 (40.7)	Not reached [42.1; -]	287	97 (33.8)	Not reached [60.1; -]	1.38 [1.06; 1.81]	0.018	0.949
Female	186	97 (52.2)	33.1 [26.6; -]	199	86 (43.2)	Not reached [40.9; -]	1.40 [1.05; 1.88]	0.022	
Age Group									
< 65	299	132 (44.1)	Not reached [39.9; -]	295	116 (39.3)	Not reached [60.1; -]	1.25 [0.97; 1.60]	0.081	0.226

Study: KEYNOTE 716[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
≥ 65	184	86 (46.7)	37.9 [29.9; -]	191	67 (35.1)	Not reached [54.0; -]	1.63 [1.18; 2.25]	0.003	
Severity of disease: T-Stage									
IIB T3b	199	90 (45.2)	52.3 [35.6; -]	200	83 (41.5)	60.1 [45.1; -]	1.15 [0.85; 1.55]	0.364	0.108
IIB T4a	107	46 (43.0)	Not reached [31.1; -]	116	46 (39.7)	Not reached [50.1; -]	1.26 [0.84; 1.90]	0.268	
IIC T4b	170	81 (47.6)	40.4 [27.3; -]	169	54 (32.0)	Not reached [-; -]	1.85 [1.31; 2.61]	< 0.001	
Geographic Region									
WHO Stratum A[h]	289	132 (45.7)	51.4 [35.6; -]	323	112 (34.7)	Not reached [60.1; -]	1.57 [1.22; 2.02]	< 0.001	0.069
Rest of World	194	86 (44.3)	52.3 [32.9; -]	163	71 (43.6)	54.7 [39.1; -]	1.09 [0.79; 1.49]	0.606	
ECOG Performance Status									
0	450	205 (45.6)	51.0 [36.1; -]	449	173 (38.5)	Not reached [60.1; -]	1.36 [1.11; 1.66]	0.003	0.643
1	32	13 (40.6)	Not reached [18.1; -]	35	10 (28.6)	Not reached [44.6; -]	1.66 [0.73; 3.78]	0.231	
SOC[g]: Nervous system disorders									
Sex									
Male	297	75 (25.3)	Not reached [60.7; -]	287	65 (22.6)	Not reached [60.6; -]	1.20 [0.86; 1.68]	0.277	0.442
Female	186	70 (37.6)	Not reached [54.0; -]	199	55 (27.6)	Not reached [-; -]	1.45 [1.02; 2.06]	0.041	
Age Group									
< 65	299	99 (33.1)	Not reached [60.7; -]	295	75 (25.4)	Not reached [-; -]	1.40 [1.04; 1.90]	0.027	0.378
≥ 65	184	46 (25.0)	Not reached [-; -]	191	45 (23.6)	Not reached [60.6; -]	1.14 [0.76; 1.72]	0.526	
Severity of disease: T-Stage									
IIB T3b	199	61 (30.7)	60.7 [60.7; -]	200	55 (27.5)	Not reached [60.6; -]	1.21 [0.84; 1.74]	0.312	0.644
IIB T4a	107	31 (29.0)	Not reached [-; -]	116	29 (25.0)	Not reached [-; -]	1.24 [0.75; 2.06]	0.404	
IIC T4b	170	53 (31.2)	Not reached [-; -]	169	36 (21.3)	Not reached [-; -]	1.56 [1.02; 2.38]	0.041	
Geographic Region									
WHO Stratum A[h]	289	91 (31.5)	Not reached [-; -]	323	79 (24.5)	Not reached [-; -]	1.42 [1.05; 1.92]	0.022	0.355
Rest of World	194	54 (27.8)	Not reached [60.7; -]	163	41 (25.2)	Not reached [-; -]	1.13 [0.75; 1.69]	0.561	
ECOG Performance Status									
0	450	136 (30.2)	Not reached [60.7; -]	449	116 (25.8)	Not reached [-; -]	1.26 [0.98; 1.61]	0.070	0.200
1	32	9 (28.1)	Not reached [39.6; -]	35	4 (11.4)	Not reached [-; -]	2.70 [0.83; 8.79]	0.099	

Study: KEYNOTE 716[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC[g]: Renal and urinary disorders									
Sex									
Male	297	34 (11.4)	Not reached [-; -]	287	17 (5.9)	Not reached [-; -]	2.19 [1.22; 3.92]	0.008	0.360
Female	186	16 (8.6)	Not reached [-; -]	199	13 (6.5)	Not reached [-; -]	1.41 [0.68; 2.93]	0.359	
Age Group									
< 65	299	25 (8.4)	Not reached [-; -]	295	17 (5.8)	Not reached [-; -]	1.57 [0.85; 2.91]	0.152	0.387
≥ 65	184	25 (13.6)	Not reached [60.0; -]	191	13 (6.8)	Not reached [-; -]	2.34 [1.20; 4.58]	0.013	
Severity of disease: T-Stage									
IIB T3b	199	18 (9.0)	Not reached [-; -]	200	10 (5.0)	Not reached [-; -]	1.97 [0.91; 4.28]	0.085	0.968
IIB T4a	107	11 (10.3)	Not reached [60.0; -]	116	8 (6.9)	Not reached [-; -]	1.70 [0.68; 4.23]	0.254	
IIC T4b	170	21 (12.4)	Not reached [-; -]	169	12 (7.1)	Not reached [-; -]	1.86 [0.92; 3.78]	0.086	
Geographic Region									
WHO Stratum A[h]	289	21 (7.3)	Not reached [-; -]	323	20 (6.2)	Not reached [-; -]	1.29 [0.70; 2.38]	0.414	0.120
Rest of World	194	29 (14.9)	Not reached [-; -]	163	10 (6.1)	Not reached [-; -]	2.66 [1.29; 5.46]	0.008	
ECOG Performance Status									
0	450	48 (10.7)	Not reached [-; -]	449	29 (6.5)	Not reached [-; -]	1.85 [1.16; 2.93]	0.009	0.872
1	32	2 (6.3)	Not reached [-; -]	35	1 (2.9)	Not reached [57.1; -]	2.49 [0.22; 27.56]	0.458	
SOC[g]: Skin and subcutaneous tissue disorders									
Sex									
Male	297	165 (55.6)	27.1 [18.1; 33.0]	287	108 (37.6)	Not reached [-; -]	1.95 [1.53; 2.49]	< 0.001	0.640
Female	186	113 (60.8)	18.4 [12.6; 30.1]	199	86 (43.2)	Not reached [37.3; -]	1.78 [1.34; 2.35]	< 0.001	
Age Group									
< 65	299	164 (54.8)	27.1 [21.0; 41.1]	295	112 (38.0)	Not reached [-; -]	1.80 [1.42; 2.29]	< 0.001	0.572
≥ 65	184	114 (62.0)	15.1 [11.1; 24.4]	191	82 (42.9)	Not reached [37.4; -]	2.01 [1.51; 2.68]	< 0.001	
Severity of disease: T-Stage									
IIB T3b	199	109 (54.8)	27.1 [15.1; 36.4]	200	90 (45.0)	Not reached [33.4; -]	1.48 [1.12; 1.96]	0.006	0.074
IIB T4a	107	72 (67.3)	12.1 [7.3; 21.0]	116	47 (40.5)	Not reached [37.4; -]	2.41 [1.66; 3.49]	< 0.001	
IIC T4b	170	94 (55.3)	27.1 [18.1; 49.0]	169	57 (33.7)	Not reached [-; -]	2.10 [1.51; 2.92]	< 0.001	
Geographic Region									
WHO Stratum A[h]	289	172 (59.5)	19.9 [15.1; 29.9]	323	128 (39.6)	Not reached [-; -]	2.03 [1.61; 2.55]	< 0.001	0.281
Rest of World	194	106 (54.6)	27.1 [17.4; 39.1]	163	66 (40.5)	Not reached [45.0; -]	1.65 [1.21; 2.25]	0.001	

Study: KEYNOTE 716[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
ECOG Performance Status									
0	450	255 (56.7)	24.4 [17.4; 31.0]	449	177 (39.4)	Not reached [-; -]	1.85 [1.53; 2.25]	< 0.001	0.949
1	32	22 (68.8)	23.0 [8.9; 30.7]	35	16 (45.7)	38.6 [20.1; -]	2.00 [1.05; 3.82]	0.035	

a: Database Cutoff Date: 04JAN2022
b: Number of participants: all-participants-as-treated population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: A system organ class appears on this report only if its incidence ≥ 10% or (incidence ≥ 1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05 or rule of 10 is not met
h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; SOC: System Organ Class; WHO: World Health Organization

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-27: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC)

Study: KEYNOTE 716[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Serious Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC[g]: Endocrine disorders									
Sex									
Male	297	9 (3.0)	n.c.	287	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Female	186	1 (0.5)	n.c.	199	0 (0.0)	n.c.	n.c.	n.c.	
Age Group									
< 65	299	5 (1.7)	n.c.	295	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	184	5 (2.7)	n.c.	191	0 (0.0)	n.c.	n.c.	n.c.	
Severity of disease: T-Stage									
IIB T3b	199	4 (2.0)	n.c.	200	0 (0.0)	n.c.	n.c.	n.c.	n.c.
IIB T4a	107	3 (2.8)	n.c.	116	0 (0.0)	n.c.	n.c.	n.c.	
IIC T4b	170	3 (1.8)	n.c.	169	0 (0.0)	n.c.	n.c.	n.c.	
Geographic Region									
WHO Stratum A[h]	289	5 (1.7)	n.c.	323	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Rest of World	194	5 (2.6)	n.c.	163	0 (0.0)	n.c.	n.c.	n.c.	

Study: KEYNOTE 716[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Serious Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
ECOG Performance Status									
0	450	10 (2.2)	Not reached [-; -]	449	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	0.997
1	32	0 (0.0)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
SOC[g]: Gastrointestinal disorders									
Sex									
Male	297	9 (3.0)	Not reached [-; -]	287	1 (0.3)	Not reached [-; -]	9.48 [1.20; 74.86]	0.033	0.390
Female	186	4 (2.2)	Not reached [-; -]	199	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.034	
Age Group									
< 65	299	6 (2.0)	n.c.	295	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	184	7 (3.8)	n.c.	191	1 (0.5)	n.c.	n.c.	n.c.	
Severity of disease: T-Stage									
IIB T3b	199	4 (2.0)	n.c.	200	1 (0.5)	n.c.	n.c.	n.c.	n.c.
IIB T4a	107	5 (4.7)	n.c.	116	0 (0.0)	n.c.	n.c.	n.c.	
IIC T4b	170	4 (2.4)	n.c.	169	0 (0.0)	n.c.	n.c.	n.c.	
Geographic Region									
WHO Stratum A[h]	289	8 (2.8)	n.c.	323	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Rest of World	194	5 (2.6)	n.c.	163	1 (0.6)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 04JAN2022

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

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

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

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

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

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

h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 participants per subgroup and at least 10 events in one of the subgroups necessary; SOC: System Organ Class; WHO: World Health Organization

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

Tabelle 4G-28: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5) (SOC)

Study: KEYNOTE 716[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
SOC[g]: Endocrine disorders									
Sex									
Male	297	9 (3.0)	n.c.	287	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Female	186	1 (0.5)	n.c.	199	0 (0.0)	n.c.	n.c.	n.c.	
Age Group									
< 65	299	4 (1.3)	n.c.	295	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	184	6 (3.3)	n.c.	191	0 (0.0)	n.c.	n.c.	n.c.	
Severity of disease: T-Stage									
IIB T3b	199	4 (2.0)	n.c.	200	0 (0.0)	n.c.	n.c.	n.c.	n.c.
IIB T4a	107	3 (2.8)	n.c.	116	0 (0.0)	n.c.	n.c.	n.c.	
IIC T4b	170	3 (1.8)	n.c.	169	0 (0.0)	n.c.	n.c.	n.c.	
Geographic Region									
WHO Stratum A[h]	289	6 (2.1)	n.c.	323	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Rest of World	194	4 (2.1)	n.c.	163	0 (0.0)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	450	10 (2.2)	Not reached [-; -]	449	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	0.997
1	32	0 (0.0)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
SOC[g]: Gastrointestinal disorders									
Sex									
Male	297	17 (5.7)	Not reached [-; -]	287	1 (0.3)	Not reached [-; -]	18.47 [2.46; 138.74]	0.005	0.436
Female	186	6 (3.2)	Not reached [-; -]	199	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.011	
Age Group									
< 65	299	13 (4.3)	Not reached [-; -]	295	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.221
≥ 65	184	10 (5.4)	Not reached [-; -]	191	1 (0.5)	Not reached [-; -]	11.95 [1.53; 93.40]	0.018	
Severity of disease: T-Stage									
IIB T3b	199	9 (4.5)	Not reached [-; -]	200	1 (0.5)	Not reached [-; -]	9.89 [1.25; 78.09]	0.030	0.407
IIB T4a	107	5 (4.7)	Not reached [-; -]	116	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.015	
IIC T4b	170	9 (5.3)	Not reached [-; -]	169	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	

Study: KEYNOTE 716[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Geographic Region									
WHO Stratum A[h]	289	14 (4.8)	Not reached [-; -]	323	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.139
Rest of World	194	9 (4.6)	Not reached [-; -]	163	1 (0.6)	Not reached [-; -]	8.18 [1.04; 64.55]	0.046	
SOC[g]: Hepatobiliary disorders									
Sex									
Male	297	8 (2.7)	n.c.	287	1 (0.3)	n.c.	n.c.	n.c.	n.c.
Female	186	3 (1.6)	n.c.	199	1 (0.5)	n.c.	n.c.	n.c.	
Age Group									
< 65	299	7 (2.3)	n.c.	295	1 (0.3)	n.c.	n.c.	n.c.	n.c.
≥ 65	184	4 (2.2)	n.c.	191	1 (0.5)	n.c.	n.c.	n.c.	
Severity of disease: T-Stage									
IIB T3b	199	3 (1.5)	n.c.	200	0 (0.0)	n.c.	n.c.	n.c.	n.c.
IIB T4a	107	1 (0.9)	n.c.	116	1 (0.9)	n.c.	n.c.	n.c.	
IIC T4b	170	7 (4.1)	n.c.	169	1 (0.6)	n.c.	n.c.	n.c.	
Geographic Region									
WHO Stratum A[h]	289	7 (2.4)	n.c.	323	2 (0.6)	n.c.	n.c.	n.c.	n.c.
Rest of World	194	4 (2.1)	n.c.	163	0 (0.0)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	450	10 (2.2)	Not reached [-; -]	449	2 (0.4)	Not reached [-; -]	5.26 [1.15; 24.00]	0.032	0.550
1	32	1 (3.1)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.292	
SOC[g]: Skin and subcutaneous tissue disorders									
Sex									
Male	297	13 (4.4)	Not reached [-; -]	287	1 (0.3)	Not reached [-; -]	13.64 [1.78; 104.29]	0.012	0.064
Female	186	2 (1.1)	Not reached [-; -]	199	2 (1.0)	Not reached [-; -]	1.11 [0.16; 7.92]	0.913	
Age Group									
< 65	299	3 (1.0)	Not reached [-; -]	295	2 (0.7)	Not reached [-; -]	1.57 [0.26; 9.39]	0.622	0.101
≥ 65	184	12 (6.5)	Not reached [-; -]	191	1 (0.5)	Not reached [-; -]	13.82 [1.80; 106.36]	0.012	
Severity of disease: T-Stage									
IIB T3b	199	7 (3.5)	n.c.	200	2 (1.0)	n.c.	n.c.	n.c.	n.c.
IIB T4a	107	5 (4.7)	n.c.	116	0 (0.0)	n.c.	n.c.	n.c.	
IIC T4b	170	3 (1.8)	n.c.	169	1 (0.6)	n.c.	n.c.	n.c.	

Study: KEYNOTE 716[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Geographic Region									
WHO Stratum A[h]	289	10 (3.5)	Not reached [-; -]	323	2 (0.6)	Not reached [-; -]	6.18 [1.35; 28.24]	0.019	0.805
Rest of World	194	5 (2.6)	Not reached [-; -]	163	1 (0.6)	Not reached [-; -]	4.30 [0.50; 36.82]	0.183	
ECOG Performance Status									
0	450	13 (2.9)	Not reached [-; -]	449	3 (0.7)	Not reached [-; -]	4.64 [1.32; 16.28]	0.017	0.382
1	32	2 (6.3)	Not reached [54.0; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.163	

a: Database Cutoff Date: 04JAN2022

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

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

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

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

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

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

h: WHO stratum A includes following countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom

CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 participants per subgroup and at least 10 events in one of the subgroups necessary; SOC: System Organ Class; WHO: World Health Organization

Anhang 4-G4: Teil II der Studie KEYNOTE 716

Der Fokus der vorliegenden Nutzenbewertung liegt auf der Behandlung des adjuvanten Melanoms und somit auf Teil I der Studie. Im Nachfolgenden werden ergänzend zu Abschnitt 4.3.1.2.1 und Abschnitt 4.3.1.3.1.3 Daten zu Teil II der Studie KEYNOTE 716 gezeigt. Auf vergleichende Analysen mit Berechnung von Effektschätzern wird deshalb, wie auch unter 4.3.1.2.1 dargelegt, verzichtet. Zudem sind zum vorliegenden 3. Datenschnitt (04.01.2022) nur sehr wenige Patienten aus Teil I der Studie in Teil II übergegangen und hiervon ist der Großteil noch laufend. Lediglich 20,4 % der Patienten, die von Placebo in den Pembrolizumab-Arm gewechselt sind und 0 % der Patienten, die erneut Pembrolizumab erhalten haben, haben zum Zeitpunkt des 3. Datenschnitts die Studienmedikation vollständig erhalten (siehe Tabelle 4-18 in Modul 4A Charakterisierung der Studienpopulation [Therapieabbrecher, Studienabbrechern] – RCT mit dem zu bewertenden Arzneimittel). Um jedoch auch Daten zur Sicherheit aus Teil II der Studie KEYNOTE 716 zu zeigen, werden diese deskriptiv als Inzidenzen auf Basis der All-Participants-as-Treated-Population dargestellt, diese umfasst alle Patienten, die mindestens eine Dosis der Studienmedikation erhalten haben.

Anhang 4-G4.1: Studienpopulation in Teil II der Studie KEYNOTE 716

Tabelle 4G-29: Studienpopulation mit Crossover oder Rechallenge mit Pembrolizumab in Teil II der Studie KEYNOTE 716

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	487		489		976	
Participants Crossover/re-treat in Part 2	4	(0.8)	49	(10.0)	53	(5.4)
Database Cutoff Date: 04JAN2022						

Tabelle 4G-30: Charakterisierung der Studienpopulation aus Teil II der Studie KEYNOTE 716

	Pembrolizumab Rechallenge		Crossover to Pembrolizumab		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	4		49		53	
Sex						
Male	2	(50.0)	32	(65.3)	34	(64.2)
Female	2	(50.0)	17	(34.7)	19	(35.8)
Age (Years)						
12 - 17	0	(0.0)	0	(0.0)	0	(0.0)
18 - 64	4	(100.0)	23	(46.9)	27	(50.9)
≥ 65	0	(0.0)	26	(53.1)	26	(49.1)
Mean	44.3		61.4		60.1	
SD	9.5		13.1		13.6	
Median	44.0		65.0		64.0	
Range	33 to 56		20 to 79		20 to 79	

	Pembrolizumab Rechallenge		Crossover to Pembrolizumab		Total	
	n	(%)	n	(%)	n	(%)
Race						
White	3	(75.0)	43	(87.8)	46	(86.8)
Missing	1	(25.0)	6	(12.2)	7	(13.2)
Ethnicity						
Hispanic Or Latino	2	(50.0)	1	(2.0)	3	(5.7)
Not Hispanic Or Latino	1	(25.0)	42	(85.7)	43	(81.1)
Not Reported	1	(25.0)	6	(12.2)	7	(13.2)
Geographic Region						
US	0	(0.0)	7	(14.3)	7	(13.2)
Non-US	4	(100.0)	42	(85.7)	46	(86.8)
ECOG						
0	4	(100.0)	47	(95.9)	51	(96.2)
1	0	(0.0)	2	(4.1)	2	(3.8)
LDH						
≤ ULN	1	(25.0)	26	(53.1)	27	(50.9)
Missing	3	(75.0)	23	(46.9)	26	(49.1)
KPS Status						
Not Applicable	4	(100.0)	49	(100.0)	53	(100.0)
T-Stage						
T3b	0	(0.0)	19	(38.8)	19	(35.8)
T4a	2	(50.0)	14	(28.6)	16	(30.2)
T4b	2	(50.0)	16	(32.7)	18	(34.0)
Nodal Involvement						
N0	4	(100.0)	49	(100.0)	53	(100.0)
Metastatic Staging						
M0	4	(100.0)	49	(100.0)	53	(100.0)
Overall Cancer Stage						
IIB	2	(50.0)	33	(67.3)	35	(66.0)
IIC	2	(50.0)	16	(32.7)	18	(34.0)
Stratification						
IIB T3b >2.0-4.0 mm with ulceration	1	(25.0)	18	(36.7)	19	(35.8)
IIB T4a >4.0 mm without ulceration	1	(25.0)	14	(28.6)	15	(28.3)
IIC T4b >4.0 mm with ulceration	2	(50.0)	17	(34.7)	19	(35.8)

ECOG is not applicable for pediatric participants. KPS is not applicable for adult participants.
Database Cutoff Date: 04JAN2022.

Anhang 4-G4.2: Nebenwirkungen in Teil II der Studie KEYNOTE 716

Unerwünschte Ereignisse

Tabelle 4G-31: Überblick Unerwünschte Ereignisse in Teil II der Studie KEYNOTE 716

	Pembrolizumab Rechallenge		Crossover to Pembrolizumab	
	n	(%)	n	(%)
Participants in population	4		49	
with one or more adverse events	2	(50.0)	39	(79.6)
with no adverse event	2	(50.0)	10	(20.4)
with drug-related[a] adverse events	2	(50.0)	24	(49.0)
with toxicity grade 3-5 adverse events	0	(0.0)	10	(20.4)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	4	(8.2)
with serious adverse events	0	(0.0)	7	(14.3)
with serious drug-related adverse events	0	(0.0)	2	(4.1)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	5	(10.2)
discontinued drug due to a drug-related adverse event	0	(0.0)	4	(8.2)
discontinued drug due to a serious adverse event	0	(0.0)	3	(6.1)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	2	(4.1)

[a] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment in Part 2. SAEs were followed 90 days after last dose of study treatment in Part 2.
MedDRA V24.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 04JAN2022.

Unerwünschte Ereignisse gesamt

Tabelle 4G-32: Unerwünschte Ereignisse gesamt in Teil II der Studie KEYNOTE 716 (Inzidenz > 0 % in einer oder mehreren Behandlungsgruppen)

	Pembrolizumab Rechallenge		Crossover to Pembrolizumab	
	n	(%)	n	(%)
Participants in population	4		49	
with one or more adverse events	2	(50.0)	39	(79.6)
with no adverse events	2	(50.0)	10	(20.4)
Asthenia	1	(25.0)	4	(8.2)
Fatigue	1	(25.0)	2	(4.1)
Myalgia	1	(25.0)	1	(2.0)
Abdominal pain	0	(0.0)	3	(6.1)
Alanine aminotransferase increased	0	(0.0)	3	(6.1)
Alopecia	0	(0.0)	1	(2.0)
Anaemia	0	(0.0)	1	(2.0)
Angiodysplasia	0	(0.0)	1	(2.0)
Anxiety	0	(0.0)	2	(4.1)
Appendicitis	0	(0.0)	1	(2.0)
Arthralgia	0	(0.0)	1	(2.0)
Arthritis	0	(0.0)	1	(2.0)

	Pembrolizumab Rechallenge		Crossover to Pembrolizumab	
	n	(%)	n	(%)
Aspartate aminotransferase increased	0	(0.0)	2	(4.1)
Asthma	0	(0.0)	1	(2.0)
Back pain	0	(0.0)	1	(2.0)
Bacterial rhinitis	0	(0.0)	1	(2.0)
Balance disorder	0	(0.0)	1	(2.0)
Basal cell carcinoma	0	(0.0)	1	(2.0)
Blood thyroid stimulating hormone increased	0	(0.0)	1	(2.0)
Breast mass	0	(0.0)	1	(2.0)
Cardiac failure	0	(0.0)	1	(2.0)
Cardiac murmur	0	(0.0)	1	(2.0)
Cerebral ischaemia	0	(0.0)	1	(2.0)
Chills	0	(0.0)	2	(4.1)
Conjunctivitis	0	(0.0)	1	(2.0)
Constipation	0	(0.0)	1	(2.0)
Cough	0	(0.0)	2	(4.1)
Decreased appetite	0	(0.0)	1	(2.0)
Dehydration	0	(0.0)	1	(2.0)
Dermatitis	0	(0.0)	1	(2.0)
Diarrhoea	0	(0.0)	5	(10.2)
Dizziness	0	(0.0)	5	(10.2)
Dry eye	0	(0.0)	1	(2.0)
Dry mouth	0	(0.0)	4	(8.2)
Dry skin	0	(0.0)	1	(2.0)
Dyspepsia	0	(0.0)	1	(2.0)
Dyspnoea	0	(0.0)	2	(4.1)
Dysuria	0	(0.0)	1	(2.0)
Ear pain	0	(0.0)	1	(2.0)
Eczema	0	(0.0)	1	(2.0)
Eczema eyelids	0	(0.0)	1	(2.0)
Embolism	0	(0.0)	1	(2.0)
Eosinophil count increased	0	(0.0)	1	(2.0)
Erectile dysfunction	0	(0.0)	1	(2.0)
Erythema	0	(0.0)	1	(2.0)
Erythema of eyelid	0	(0.0)	1	(2.0)
Eye pruritus	0	(0.0)	1	(2.0)
Gastroenteritis	0	(0.0)	1	(2.0)
Gastrooesophageal reflux disease	0	(0.0)	1	(2.0)
Genital herpes	0	(0.0)	1	(2.0)
Gingival pain	0	(0.0)	1	(2.0)
Glossitis	0	(0.0)	1	(2.0)
Groin pain	0	(0.0)	1	(2.0)
Haemangioma of skin	0	(0.0)	1	(2.0)
Haematochezia	0	(0.0)	1	(2.0)
Haematoma	0	(0.0)	1	(2.0)
Haematuria	0	(0.0)	1	(2.0)
Headache	0	(0.0)	4	(8.2)
Hepatotoxicity	0	(0.0)	1	(2.0)
Herpes simplex	0	(0.0)	1	(2.0)
Hot flush	0	(0.0)	1	(2.0)
Hyperglycaemia	0	(0.0)	2	(4.1)
Hyperthyroidism	0	(0.0)	5	(10.2)
Hypokalaemia	0	(0.0)	1	(2.0)
Hypophosphataemia	0	(0.0)	3	(6.1)

	Pembrolizumab Rechallenge		Crossover to Pembrolizumab	
	n	(%)	n	(%)
Hypothyroidism	0	(0.0)	5	(10.2)
Incision site oedema	0	(0.0)	1	(2.0)
Incision site pain	0	(0.0)	2	(4.1)
Insomnia	0	(0.0)	4	(8.2)
Intermenstrual bleeding	0	(0.0)	1	(2.0)
Joint effusion	0	(0.0)	1	(2.0)
Limb injury	0	(0.0)	1	(2.0)
Lipase increased	0	(0.0)	1	(2.0)
Lung adenocarcinoma	0	(0.0)	1	(2.0)
Malaise	0	(0.0)	1	(2.0)
Mucinous adenocarcinoma of appendix	0	(0.0)	1	(2.0)
Muscle atrophy	0	(0.0)	1	(2.0)
Muscle spasms	0	(0.0)	1	(2.0)
Musculoskeletal chest pain	0	(0.0)	1	(2.0)
Musculoskeletal pain	0	(0.0)	2	(4.1)
Musculoskeletal stiffness	0	(0.0)	1	(2.0)
Myasthenia gravis	0	(0.0)	1	(2.0)
Nasal congestion	0	(0.0)	2	(4.1)
Nasopharyngitis	0	(0.0)	2	(4.1)
Nausea	0	(0.0)	1	(2.0)
Nephrolithiasis	0	(0.0)	1	(2.0)
Oral candidiasis	0	(0.0)	1	(2.0)
Osteoarthritis	0	(0.0)	1	(2.0)
Osteoporosis	0	(0.0)	2	(4.1)
Otitis media	0	(0.0)	1	(2.0)
Pain in extremity	0	(0.0)	1	(2.0)
Pancreatitis	0	(0.0)	1	(2.0)
Pelvic pain	0	(0.0)	1	(2.0)
Pharyngeal erythema	0	(0.0)	1	(2.0)
Pneumonia	0	(0.0)	1	(2.0)
Pneumonitis	0	(0.0)	1	(2.0)
Pneumonitis aspiration	0	(0.0)	1	(2.0)
Pollakiuria	0	(0.0)	1	(2.0)
Poor dental condition	0	(0.0)	1	(2.0)
Postoperative wound infection	0	(0.0)	2	(4.1)
Procedural pain	0	(0.0)	1	(2.0)
Pruritus	0	(0.0)	7	(14.3)
Pyrexia	0	(0.0)	3	(6.1)
Rash	0	(0.0)	4	(8.2)
Rash pruritic	0	(0.0)	1	(2.0)
Renal colic	0	(0.0)	1	(2.0)
Respiratory tract infection	0	(0.0)	1	(2.0)
Retinal haemorrhage	0	(0.0)	1	(2.0)
Rib fracture	0	(0.0)	1	(2.0)
Scar pain	0	(0.0)	1	(2.0)
Seborrhoeic dermatitis	0	(0.0)	1	(2.0)
Seborrhoeic keratosis	0	(0.0)	1	(2.0)
Seminoma	0	(0.0)	1	(2.0)
Skin exfoliation	0	(0.0)	1	(2.0)
Skin fissures	0	(0.0)	1	(2.0)
Skin lesion	0	(0.0)	1	(2.0)
Skin mass	0	(0.0)	1	(2.0)
Sleep disorder	0	(0.0)	1	(2.0)

	Pembrolizumab Rechallenge		Crossover to Pembrolizumab	
	n	(%)	n	(%)
Spinal compression fracture	0	(0.0)	1	(2.0)
Spinal fracture	0	(0.0)	1	(2.0)
Stomatitis	0	(0.0)	2	(4.1)
Stress	0	(0.0)	1	(2.0)
Suspected COVID-19	0	(0.0)	1	(2.0)
Swelling	0	(0.0)	1	(2.0)
Tachycardia	0	(0.0)	1	(2.0)
Tendon rupture	0	(0.0)	1	(2.0)
Thyroiditis	0	(0.0)	1	(2.0)
Tinnitus	0	(0.0)	1	(2.0)
Tonsillar hypertrophy	0	(0.0)	1	(2.0)
Tonsillitis	0	(0.0)	1	(2.0)
Tricuspid valve incompetence	0	(0.0)	1	(2.0)
Upper respiratory tract infection	0	(0.0)	1	(2.0)
Urinary tract infection	0	(0.0)	2	(4.1)
Urinary tract pain	0	(0.0)	1	(2.0)
Vaginal lesion	0	(0.0)	1	(2.0)
Vertigo	0	(0.0)	1	(2.0)
Vitamin D deficiency	0	(0.0)	1	(2.0)
Vitiligo	0	(0.0)	1	(2.0)
Vomiting	0	(0.0)	1	(2.0)
Vulval ulceration	0	(0.0)	1	(2.0)
Vulvovaginal candidiasis	0	(0.0)	1	(2.0)
Weight decreased	0	(0.0)	2	(4.1)
White blood cell count decreased	0	(0.0)	1	(2.0)

Every participant is counted a single time for each applicable row and column.
NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment in Part 2. SAEs were followed 90 days after last dose of study treatment in Part 2.
MedDRA V24.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 04JAN2022.

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-33: Schwerwiegende unerwünschte Ereignisse in Teil II der Studie KEYNOTE 716 (Inzidenz > 0 % in einer oder mehreren Behandlungsgruppen)

	Pembrolizumab Rechallenge		Crossover to Pembrolizumab	
	n	(%)	n	(%)
Participants in population	4		49	
with one or more adverse events	0	(0.0)	7	(14.3)
with no adverse events	4	(100.0)	42	(85.7)
Appendicitis	0	(0.0)	1	(2.0)
Basal cell carcinoma	0	(0.0)	1	(2.0)
Cardiac failure	0	(0.0)	1	(2.0)
Embolism	0	(0.0)	1	(2.0)
Hepatotoxicity	0	(0.0)	1	(2.0)
Lung adenocarcinoma	0	(0.0)	1	(2.0)
Mucinous adenocarcinoma of appendix	0	(0.0)	1	(2.0)

	Pembrolizumab Rechallenge		Crossover to Pembrolizumab	
	n	(%)	n	(%)
Pneumonia	0	(0.0)	1	(2.0)
Pneumonitis	0	(0.0)	1	(2.0)
Pneumonitis aspiration	0	(0.0)	1	(2.0)
Rib fracture	0	(0.0)	1	(2.0)
Seminoma	0	(0.0)	1	(2.0)
Urinary tract infection	0	(0.0)	1	(2.0)

Every participant is counted a single time for each applicable row and column.
NCI CTCAE version 4.03.
SAEs were followed 90 days after last dose of study treatment in Part 2.
MedDRA V24.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 04JAN2022

Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5)

Tabelle 4G-34: Schwere unerwünschte Ereignisse (CTCAE-Grad 3–5) in Teil II der Studie KEYNOTE 716 (Inzidenz > 0 % in einer oder mehreren Behandlungsgruppen)

	Pembrolizumab Rechallenge		Crossover to Pembrolizumab	
	n	(%)	n	(%)
Participants in population	4		49	
with one or more adverse events	0	(0.0)	10	(20.4)
with no adverse events	4	(100.0)	39	(79.6)
Appendicitis	0	(0.0)	1	(2.0)
Aspartate aminotransferase increased	0	(0.0)	1	(2.0)
Cardiac failure	0	(0.0)	1	(2.0)
Embolism	0	(0.0)	1	(2.0)
Hepatotoxicity	0	(0.0)	1	(2.0)
Hypophosphataemia	0	(0.0)	1	(2.0)
Lipase increased	0	(0.0)	1	(2.0)
Lung adenocarcinoma	0	(0.0)	1	(2.0)
Pancreatitis	0	(0.0)	1	(2.0)
Pneumonia	0	(0.0)	1	(2.0)
Pneumonitis	0	(0.0)	1	(2.0)
Pneumonitis aspiration	0	(0.0)	1	(2.0)
Urinary tract infection	0	(0.0)	1	(2.0)

Every participant is counted a single time for each applicable row and column.
NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment in Part 2. SAEs were followed 90 days after last dose of study treatment in Part 2.
MedDRA V24.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 04JAN2022

Immunvermittelte unerwünschte Ereignisse (AEOSI)

Tabelle 4G-35: Immunvermittelte unerwünschte Ereignisse (AEOSI) in Teil II der Studie KEYNOTE 716

	Pembrolizumab Rechallenge		Crossover to Pembrolizumab	
	n	(%)	n	(%)
Participants in population	4		49	
with one or more adverse events	0	(0.0)	11	(22.4)
with no adverse event	4	(100.0)	38	(77.6)
with drug-related[a] adverse events	0	(0.0)	8	(16.3)
with toxicity grade 3-5 adverse events	0	(0.0)	2	(4.1)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	2	(4.1)
with serious adverse events	0	(0.0)	1	(2.0)
with serious drug-related adverse events	0	(0.0)	1	(2.0)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	2	(4.1)
discontinued drug due to a drug-related adverse event	0	(0.0)	2	(4.1)
discontinued drug due to a serious adverse event	0	(0.0)	1	(2.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	1	(2.0)

[a] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.03.
AEs were followed 30 days after last dose of study treatment in Part 2. SAEs were followed 90 days after last dose of study treatment in Part 2.
Database Cutoff Date: 04JAN2022.

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

Tabelle 4G-36: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) Version 22 basierend auf MedDRA Version 24.1 anhand der zugeordneten PT in der Studie KEYNOTE 716

AEOSI	**Preferred Terms**	**Immune-mediated (Yes/No)**
Pneumonitis	Acute interstitial pneumonitis Autoimmune lung disease Interstitial lung disease Pneumonitis Idiopathic pneumonia syndrome Organising pneumonia Immune-mediated lung disease	Yes
Colitis	Colitis Colitis microscopic Enterocolitis Enterocolitis haemorrhagic Necrotising colitis Colitis erosive Autoimmune colitis Immune-mediated enterocolitis	Yes
Hepatitis	Hepatitis Immune-mediated hepatitis Autoimmune hepatitis Hepatitis acute Hepatitis fulminant Drug-induced liver injury	Yes

AEOSI	**Preferred Terms**	**Immune-mediated (Yes/No)**
Nephritis	Nephritis Autoimmune nephritis Chronic autoimmune glomerulonephritis Fibrillary glomerulonephritis Focal segmental glomerulosclerosis Glomerulonephritis Glomerulonephritis acute Glomerulonephritis membranoproliferative Glomerulonephritis membranous Glomerulonephritis minimal lesion Glomerulonephritis proliferative Glomerulonephritis rapidly progressive Mesangioproliferative glomerulonephritis Nephritis haemorrhagic Tubulointerstitial nephritis Nephrotic syndrome Immune-mediated nephritis	Yes
Adrenal Insufficiency	Adrenal insufficiency Adrenocortical insufficiency acute Secondary adrenocortical insufficiency Primary adrenal insufficiency Addison's disease Immune-mediated adrenal insufficiency	Yes
Hypophysitis	Hypophysitis Hypopituitarism Lymphocytic hypophysitis Immune-mediated hypophysitis	Yes
Hyperthyroidism	Hyperthyroidism Basedow's disease Thyrotoxic crisis Immune-mediated hyperthyroidism	Yes
Hypothyroidism	Hypothyroidism Hypothyroidic goitre Myxoedema Myxoedema coma Primary hypothyroidism Autoimmune hypothyroidism Immune-mediated hypothyroidism	Yes

AEOSI	**Preferred Terms**	**Immune-mediated (Yes/No)**
Thyroiditis	Thyroid disorder Thyroiditis Autoimmune thyroiditis Thyroiditis acute Silent thyroiditis Autoimmune thyroid disorder Immune-mediated thyroiditis	Yes
Type 1 Diabetes Mellitus	Diabetic ketoacidosis Diabetic ketoacidotic hyperglycaemic coma Fulminant type 1 diabetes mellitus Latent autoimmune diabetes in adults Type 1 diabetes mellitus Euglycaemic diabetic ketoacidosis Diabetic ketosis Ketosis-prone diabetes mellitus	Yes
Severe Skin Reactions Including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) or Severe Skin Reactions (CTCAE-Grade 3-5)	Dermatitis bullous Dermatitis exfoliative Dermatitis exfoliative generalised Epidermal necrosis Erythema multiforme Exfoliative rash Pemphigoid Pemphigus Skin necrosis Stevens-Johnson syndrome Toxic epidermal necrolysis Toxic skin eruption SJS-TEN overlap Rash Rash erythematous Rash maculo-papular Rash pruritic Rash pustular Pruritus Pruritus genital Lichen planus Oral lichen planus Cutaneous vasculitis Vasculitic rash	Yes

AEOSI	**Preferred Terms**	**Immune-mediated (Yes/No)**
Uveitis	Iritis Uveitis Cyclitis Autoimmune uveitis Iridocyclitis Vogt-Koyanagi-Harada disease Chorioretinitis Choroiditis Immune-mediated uveitis Choroidal effusion Choroidal detachment Serous retinal detachment	Yes
Pancreatitis	Pancreatitis Autoimmune pancreatitis Pancreatitis acute Pancreatitis haemorrhagic Pancreatitis necrotising Immune-mediated pancreatitis	Yes
Myositis	Myositis Necrotising myositis Polymyositis Immune-mediated myositis Rhabdomyolysis Myopathy Dermatomyositis Autoimmune myositis	Yes
Guillain-Barre Syndrome	Demyelinating polyneuropathy Guillain-Barre syndrome Axonal neuropathy Multifocal motor neuropathy Polyneuropathy idiopathic progressive Miller Fisher syndrome Subacute inflammatory demyelinating polyneuropathy	Yes
Myocarditis	Myocarditis Autoimmune myocarditis Hypersensitivity myocarditis Immune-mediated myocarditis	Yes
Encephalitis	Encephalitis Encephalitis autoimmune Limbic encephalitis Noninfective encephalitis Immune-mediated encephalitis	Yes

AEOSI	**Preferred Terms**	**Immune-mediated (Yes/No)**
Sarcoidosis	Sarcoidosis Cutaneous sarcoidosis Ocular sarcoidosis Pulmonary sarcoidosis	Yes
Infusion Reactions	Hypersensitivity Drug hypersensitivity Anaphylactic reaction Anaphylactoid reaction Cytokine release syndrome Serum sickness Serum sickness-like reaction Infusion related reaction Infusion related hypersensitivity reaction	No
Myasthenic Syndrome	Myasthenic syndrome Myasthenia gravis Myasthenia gravis crisis Ocular myasthenia	Yes
Myelitis	Myelitis Myelitis transverse Acute necrotizing myelitis	Yes

AEOSI	**Preferred Terms**	**Immune-mediated (Yes/No)**
Vasculitis	Anti-neutrophil cytoplasmic antibody positive vasculitis Aortitis Arteritis Arteritis coronary Behcet's syndrome Central nervous system vasculitis Cerebral arteritis Diffuse vasculitis Eosinophilic granulomatosis with polyangiitis Granulomatosis with polyangiitis Haemorrhagic vasculitis Hypersensitivity vasculitis Microscopic polyangiitis Ocular vasculitis Polyarteritis nodosa Pulmonary vasculitis Renal arteritis Renal vasculitis Retinal vasculitis Takayasu's arteritis Giant cell arteritis Vasculitis Vasculitis gastrointestinal Vasculitis necrotising	Yes
Cholangitis Sclerosing	Cholangitis sclerosing Autoimmune cholangitis Immune-mediated cholangitis	Yes