Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD Sharp & Dohme GmbH

Modul 4A Anhang 4-G

Neoadjuvante und anschließende adjuvante Behandlung des resezierbaren lokal fortgeschrittenen Plattenepithelkarzinoms der Kopf-Hals-Region mit PD-L1 exprimierenden Tumoren (CPS ≥ 1)

Medizinischer Nutzen und
medizinischer Zusatznutzen,
Patientengruppen mit therapeutisch
bedeutsamem Zusatznutzen

Stand: 20.11.2025

Inhaltsverzeichnis

Seite

Tabellenverzeichnis

Seite

Abbildungsverzeichnis

Seite

Anhang 4-G1: Zuordnung Messzeitpunkte zu Visiten

Die folgenden Tabellen geben eine Übersicht wie die Messzeitpunkte den Visiten in der neoadjuvanten Phase und der adjuvanten Phase zugeordnet wurden.

Tabelle 4G-1: Erhebungszeitplan der patientenberichteten Daten und Zuordnung der Messzeitpunkte zu einzelnen Visiten während der neoadjuvanten Behandlungsphase

		Participants with neoadjuvant treatment		**Participants without neoadjuvant treatment**	
Analysis Visit	**Study Visit**	**Target Day**	**Range**	**Target Day**	**Range**
Baseline	Neoadjuvant Cycle 1 Day 1 (Pembro)/Presurgery (SoC)	1	[-3,11]	NLD	-
Neoadjuvant Week 4	Neoadjuvant Cycle 2	22	[12, NLD-1]	-	-
Neoadjuvant Week 6	Presurgery	NLD	-	-	-
Note: For participants with in-study surgery, NLD = last ePRO assessment day prior to surgery. For participants who do not have in-study surgery, but have in-study CRT/RT, NLD = last ePRO assessment day prior to in-study CRT/RT. For participants with neoadjuvant treatment and do not have in-study surgery or CRT/RT, NLD = last ePRO assessment day prior to day 52 (latest day for scheduled surgery).					

Tabelle 4G-2: Erhebungszeitplan der patientenberichteten Daten und Zuordnung der Messzeitpunkte zu einzelnen Visiten während der adjuvanten Behandlungsphase

		Participants with neoadjuvant treatment		**Participants without neoadjuvant treatment**	
Analysis Visit	**Study Visit**	**Target Day**	**Range**	**Target Day**	**Range**
Adjuvant RT Week 1	Adjuvant Week 1	ART	[NLD+1, ART+14]	NLD+72	[NLD+1, NLD+86]
Adjuvant RT Week 4	Adjuvant Week 4	ART+28	[ART+15, ART+73]	NLD+72	[NLD+87, NLD+149]
Post-Adjuvant CRT/RT Week 12	RT 12-week follow-up	LRT+77	[ART+74, LRT+122]	NLD+198	[NLD+150, NLD+243]
Post-Adjuvant CRT/RT Week 25	Year 1 follow-up 1	LRT+168	[LRT+123, LRT+213]	NLD+289	[NLD+244, NLD+334]

		Participants with neoadjuvant treatment		Participants without neoadjuvant treatment	
Analysis Visit	**Study Visit**	**Target Day**	**Range**	**Target Day**	**Range**
Post-Adjuvant CRT/RT Week 38	Year 1 follow-up 2	LRT+259	[LRT+214, LRT+304]	NLD+380	[NLD+335, NLD+425]
Post-Adjuvant CRT/RT Week 51	Year 2 follow-up 1	LRT+350	[LRT+305, LRT+395]	NLD+471	[NLD+426, NLD+516]
Post-Adjuvant CRT/RT Week 64	Year 2 follow-up 2	LRT+441	[LRT+396, LRT+486]	NLD+562	[NLD+517, NLD+607]
Post-Adjuvant CRT/RT Week 77	Year 2 follow-up 3	LRT+532	[LRT+487, LRT+577]	NLD+653	[NLD+608, NLD+698]
Post-Adjuvant CRT/RT Week 90	Year 2 follow-up 4	LRT+623	[LRT+578, LRT+668]	NLD+744	[NLD+699, NLD+789]
Post-Adjuvant CRT/RT Week 103	Year 3 follow-up 1	LRT+714	[LRT+669, LRT+759]	NLD+835	[NLD+790, NLD+880]
Post-Adjuvant CRT/RT Week 116	Year 3 follow-up 2	LRT+805	[LRT+760, LRT+850]	NLD+926	[NLD+881, NLD+971]
Post-Adjuvant CRT/RT Week 129	Year 3 follow-up 3	LRT+896	[LRT+851, LRT+941]	NLD+1017	[NLD+972, NLD+1062]
Post-Adjuvant CRT/RT Week 142	Year 3 follow-up 4	LRT+987	[LRT+942, LRT+1169]	NLD+1108	[NLD+1063, NLD+1290]
Post-Adjuvant CRT/RT Week 194	Year 4 follow-up	LRT+1352	[LRT+1170, LRT+1534]	NLD+1473	[NLD+1291, NLD+1655]
Post-Adjuvant CRT/RT Week 246	Year 5 follow-up	LRT+1717	[LRT+1535, LRT+1808]	NLD+1838	[NLD+1656, NLD+1929]

Abbreviations: ART = first day of adjuvant RT, CRT/RT = RT ± cisplatin; LRT = last day of adjuvant CRT/RT.

Anhang 4-G2: Behandlungsdauer und Beobachtungsdauer

Im Folgenden werden die Behandlungs- und Beobachtungsdauer deskriptiv dargestellt.

Alle Ergebnisse beziehen sich auf das zulassungsbegründende Database Cutoff Date (25. Juli 2024).

Tabelle 4G-3: Behandlungsdauer und Beobachtungsdauer

Study: KEYNOTE 689[a]	Pembrolizumab	SoC
Duration of Treatment (Months)[b]		
N[c]	344	301
Mean (SD)	8.0 (5.1)	2.7 (1.2)
Median (Q1; Q3)	9.1 (3.4; 12.6)	2.9 (2.6; 3.3)
Min; Max	0.0; 22.3	0.0; 7.2
Observation Period		
Overall Survival (Months)[d]		
N[e]	347	335
Mean (SD)	30.6 (18.0)	27.1 (18.3)
Median (Q1; Q3)	29.2 (14.7; 45.3)	23.0 (11.8; 40.7)
Min; Max	0.1; 64.8	0.5; 66.5
Adverse Event (Months)[f]		
N[c]	344	301
Mean (SD)	9.0 (5.1)	3.7 (1.2)
Median (Q1; Q3)	9.9 (4.1; 13.6)	3.9 (3.6; 4.2)
Min; Max	0.0; 23.3	0.3; 8.2
Serious Adverse Event (Months)[f]		
N[c]	344	301
Mean (SD)	10.7 (5.2)	5.5 (1.4)
Median (Q1; Q3)	10.9 (5.5; 15.5)	5.8 (5.6; 6.2)
Min; Max	0.0; 25.3	0.3; 10.2
EORTC QLQ-C30 (Months)[g]		
N[h]	340	291
Mean (SD)	18.4 (16.2)	17.4 (15.4)
Median (Q1; Q3)	13.3 (4.3; 31.2)	12.1 (5.4; 29.5)
Min; Max	0.0; 59.3	0.0; 61.3
EQ-5D VAS (Months)[g]		
N[h]	340	290
Mean (SD)	18.4 (16.2)	17.5 (15.4)
Median (Q1; Q3)	13.4 (4.3; 31.2)	12.2 (5.4; 29.5)
Min; Max	0.0; 59.3	0.0; 61.3
EORTC QLQ-H&N35 (Months)[g]		
N[h]	340	291
Mean (SD)	19.2 (16.1)	18.0 (15.3)
Median (Q1; Q3)	13.6 (5.0; 31.3)	13.2 (5.5; 29.5)
Min; Max	0.2; 59.6	0.0; 61.3
Event-Free Survival (IRC Primary Censoring Rule) (Months)[i]		
N[e]	347	335
Mean (SD)	22.3 (17.4)	18.6 (16.7)
Median (Q1; Q3)	18.9 (7.2; 34.5)	12.3 (5.7; 29.9)
Min; Max	0.0; 64.8	0.0; 64.6

a: Database Cutoff Date: 25JUL2024

b: Calculated from date of first dose until date of last dose

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

d: Calculated from date of randomization until date of death, date of last contact, or the database cutoff date if the participant is still alive

e: Number of participants: intention-to-treat population with CPS ≥ 1

f: Adverse event follow-up duration is defined as the time from first dose to the earliest of the last dose + planned safety follow-up time, date of death, date of last contact or the database cutoff date if the participant is still alive

g: Calculated from date of first dose until date of last questionnaire assessment. For participants without post-baseline assessments, the observation period is set to 1 day

h: Number of participants: full-analysis-set population with CPS ≥ 1

i: Calculated from date of randomization until date of last disease assessment or death

CPS: Combined Positive Score; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Head and Neck 35 items; EQ-5D: European Quality of Life 5 Dimensions; IRC: Independent Review Committee; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation; SoC: Standard of Care; VAS: Visual Analogue Scale

Anhang 4-G3: Rücklaufquoten des EORTC QLQ-C30, EORTC QLQ-H&N35 und EQ-5D VAS

Im Folgenden werden ergänzend die Rücklaufquoten des EORTC QLQ-C30, die Rücklaufquoten des EORTC QLQ-H&N35 und die Rücklaufquoten der EQ-5D VAS dargestellt.

Alle Ergebnisse beziehen sich auf das zulassungsbegründende Database Cutoff Date (25. Juli 2024).

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

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

		Pembrolizumab N=340		SoC N=291	
Treatment Visit	Category	n	(%)	n	(%)
Baseline	**Expected to Complete Questionnaires**	**339**	**(99.7)**	**266**	**(91.4)**
	Completed	324	(95.3)	265	(91.1)
	Compliance (% in those expected to complete questionnaires)	324	(95.6)	265	(99.6)
	Not completed	15	(4.4)	1	(0.3)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	6	(1.8)	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	6	(1.8)	0	(0.0)
	With visit, no record	3	(0.9)	0	(0.0)
	Missing by Design	**1**	**(0.3)**	**25**	**(8.6)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	0	(0.0)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to lost to follow-up	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340 n	(%)	SoC N=291 n	(%)
Baseline	Discontinued due to non-study anti-cancer therapy	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 progressive disease	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)
	Completed treatment and visit not scheduled	0	(0.0)	24	(8.2)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	1	(0.3)	1	(0.3)
Neoadjuvant Week 4	**Expected to Complete Questionnaires**	**296**	**(87.1)**	**1**	**(0.3)**
	Completed	278	(81.8)	1	(0.3)
	Compliance (% in those expected to complete questionnaires)	278	(93.9)	1	(100.0)
	Not completed	18	(5.3)	0	(0.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	5	(1.5)	0	(0.0)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.3)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	4	(1.2)	0	(0.0)
	Other	6	(1.8)	0	(0.0)
	With visit, no record	2	(0.6)	0	(0.0)
	Missing by Design	**44**	**(12.9)**	**1**	**(0.3)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	1	(0.3)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Neoadjuvant Week 4	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 progressive disease	1	(0.3)	0	(0.0)
	Discontinued due to withdrawal by subject	3	(0.9)	0	(0.0)
	Completed treatment and visit not scheduled	16	(4.7)	1	(0.3)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	22	(6.5)	0	(0.0)
Neoadjuvant Week 6	**Expected to Complete Questionnaires**	**324**	**(95.3)**	**2**	**(0.7)**
	Completed	324	(95.3)	2	(0.7)
	Compliance (% in those expected to complete questionnaires)	324	(100.0)	2	(100.0)
	Not completed	0	(0.0)	0	(0.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	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)	0	(0.0)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**16**	**(4.7)**	**0**	**(0.0)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	1	(0.3)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Neoadjuvant Week 6	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 progressive disease	1	(0.3)	0	(0.0)
	Discontinued due to withdrawal by subject	2	(0.6)	0	(0.0)
	Completed treatment and visit not scheduled	4	(1.2)	0	(0.0)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	7	(2.1)	0	(0.0)
Adjuvant RT Week 1	**Expected to Complete Questionnaires**	**314**	**(92.4)**	**277**	**(95.2)**
	Completed	265	(77.9)	230	(79.0)
	Compliance (% in those expected to complete questionnaires)	265	(84.4)	230	(83.0)
	Not completed	49	(14.4)	47	(16.2)
	Subject did not complete due to disease under study	2	(0.6)	2	(0.7)
	Not completed due to site staff error	4	(1.2)	14	(4.8)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	3	(0.9)	0	(0.0)
	Subject lost to follow-up/unable to contact	2	(0.6)	1	(0.3)
	Subject did not complete due to side effects of treatment	2	(0.6)	0	(0.0)
	Subject refused for other reasons	16	(4.7)	9	(3.1)
	Other	16	(4.7)	14	(4.8)
	With visit, no record	4	(1.2)	7	(2.4)
	Missing by Design	**26**	**(7.6)**	**14**	**(4.8)**
	Subject died	5	(1.5)	4	(1.4)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	2	(0.6)	5	(1.7)
	Discontinued due to clinical progression	0	(0.0)	1	(0.3)
	Discontinued due to lost to follow-up	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Adjuvant RT Week 1	Discontinued due to non-compliance with study drug	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	1	(0.3)	1	(0.3)
	Discontinued due to progressive disease	12	(3.5)	1	(0.3)
	Discontinued due to withdrawal by subject	1	(0.3)	2	(0.7)
	Completed treatment and visit not scheduled	1	(0.3)	0	(0.0)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	4	(1.2)	0	(0.0)
Adjuvant RT Week 4	**Expected to Complete Questionnaires**	**275**	**(80.9)**	**261**	**(89.7)**
	Completed	230	(67.6)	237	(81.4)
	Compliance (% in those expected to complete questionnaires)	230	(83.6)	237	(90.8)
	Not completed	45	(13.2)	24	(8.2)
	Subject did not complete due to disease under study	1	(0.3)	0	(0.0)
	Not completed due to site staff error	9	(2.6)	7	(2.4)
	Subject in hospital or hospice	0	(0.0)	1	(0.3)
	Subject was physically unable to complete	1	(0.3)	1	(0.3)
	Subject lost to follow-up/unable to contact	1	(0.3)	0	(0.0)
	Subject did not complete due to side effects of treatment	3	(0.9)	2	(0.7)
	Subject refused for other reasons	6	(1.8)	5	(1.7)
	Other	16	(4.7)	5	(1.7)
	With visit, no record	8	(2.4)	3	(1.0)
	Missing by Design	**65**	**(19.1)**	**30**	**(10.3)**
	Subject died	3	(0.9)	2	(0.7)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	11	(3.2)	8	(2.7)
	Discontinued due to clinical progression	2	(0.6)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	1	(0.3)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Adjuvant RT Week 4	Discontinued due to non-compliance with study drug	1	(0.3)	1	(0.3)
	Discontinued due to physician decision	7	(2.1)	1	(0.3)
	Discontinued due to progressive disease	27	(7.9)	7	(2.4)
	Discontinued due to withdrawal by subject	12	(3.5)	10	(3.4)
	Completed treatment and visit not scheduled	0	(0.0)	0	(0.0)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 12	**Expected to Complete Questionnaires**	**244**	**(71.8)**	**241**	**(82.8)**
	Completed	217	(63.8)	218	(74.9)
	Compliance (% in those expected to complete questionnaires)	217	(88.9)	218	(90.5)
	Not completed	27	(7.9)	23	(7.9)
	Subject did not complete due to disease under study	2	(0.6)	0	(0.0)
	Not completed due to site staff error	13	(3.8)	9	(3.1)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.3)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	3	(0.9)	4	(1.4)
	Other	7	(2.1)	4	(1.4)
	With visit, no record	1	(0.3)	5	(1.7)
	Missing by Design	**96**	**(28.2)**	**50**	**(17.2)**
	Subject died	1	(0.3)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.3)
	Subject died, after end of treatment	0	(0.0)	9	(3.1)
	Discontinued due to adverse event	16	(4.7)	11	(3.8)
	Discontinued due to clinical progression	2	(0.6)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	3	(0.9)	2	(0.7)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 12	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	8	(2.4)	3	(1.0)
	Discontinued due to progressive disease	44	(12.9)	9	(3.1)
	Discontinued due to withdrawal by subject	18	(5.3)	9	(3.1)
	Completed treatment and visit not scheduled	0	(0.0)	2	(0.7)
	Completed treatment and visit not reached	1	(0.3)	2	(0.7)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 25	**Expected to Complete Questionnaires**	**209**	**(61.5)**	**177**	**(60.8)**
	Completed	170	(50.0)	162	(55.7)
	Compliance (% in those expected to complete questionnaires)	170	(81.3)	162	(91.5)
	Not completed	39	(11.5)	15	(5.2)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	10	(2.9)	4	(1.4)
	Subject in hospital or hospice	2	(0.6)	0	(0.0)
	Subject was physically unable to complete	1	(0.3)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	4	(1.2)	4	(1.4)
	Other	13	(3.8)	5	(1.7)
	With visit, no record	9	(2.6)	1	(0.3)
	Missing by Design	**131**	**(38.5)**	**114**	**(39.2)**
	Subject died	2	(0.6)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	31	(10.7)
	Discontinued due to adverse event	26	(7.6)	12	(4.1)
	Discontinued due to clinical progression	2	(0.6)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 25	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	8	(2.4)	4	(1.4)
	Discontinued due to progressive disease	60	(17.6)	9	(3.1)
	Discontinued due to withdrawal by subject	22	(6.5)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	2	(0.7)
	Completed treatment and visit not reached	2	(0.6)	40	(13.7)
	Visit not reached	2	(0.6)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 38	**Expected to Complete Questionnaires**	**189**	**(55.6)**	**150**	**(51.5)**
	Completed	168	(49.4)	137	(47.1)
	Compliance (% in those expected to complete questionnaires)	168	(88.9)	137	(91.3)
	Not completed	21	(6.2)	13	(4.5)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	7	(2.1)	3	(1.0)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	2	(0.6)	0	(0.0)
	Subject lost to follow-up/unable to contact	1	(0.3)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	2	(0.7)
	Other	3	(0.9)	7	(2.4)
	With visit, no record	7	(2.1)	0	(0.0)
	Missing by Design	**151**	**(44.4)**	**141**	**(48.5)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	41	(14.1)
	Discontinued due to adverse event	33	(9.7)	12	(4.1)
	Discontinued due to clinical progression	2	(0.6)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 38	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	7	(2.1)	5	(1.7)
	Discontinued due to progressive disease	69	(20.3)	9	(3.1)
	Discontinued due to withdrawal by subject	23	(6.8)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	4	(1.4)
	Completed treatment and visit not reached	2	(0.6)	54	(18.6)
	Visit not reached	8	(2.4)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 51	**Expected to Complete Questionnaires**	**158**	**(46.5)**	**139**	**(47.8)**
	Completed	139	(40.9)	125	(43.0)
	Compliance (% in those expected to complete questionnaires)	139	(88.0)	125	(89.9)
	Not completed	19	(5.6)	14	(4.8)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	6	(1.8)	3	(1.0)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	1	(0.3)	2	(0.7)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	3	(0.9)	2	(0.7)
	Other	5	(1.5)	6	(2.1)
	With visit, no record	4	(1.2)	1	(0.3)
	Missing by Design	**182**	**(53.5)**	**152**	**(52.2)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	51	(17.5)
	Discontinued due to adverse event	36	(10.6)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 51	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	11	(3.2)	5	(1.7)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	26	(7.6)	12	(4.1)
	Completed treatment and visit not scheduled	2	(0.6)	0	(0.0)
	Completed treatment and visit not reached	13	(3.8)	59	(20.3)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 64	**Expected to Complete Questionnaires**	**146**	**(42.9)**	**118**	**(40.5)**
	Completed	132	(38.8)	106	(36.4)
	Compliance (% in those expected to complete questionnaires)	132	(90.4)	106	(89.8)
	Not completed	14	(4.1)	12	(4.1)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	6	(1.8)	4	(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)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	2	(0.7)
	Other	5	(1.5)	5	(1.7)
	With visit, no record	2	(0.6)	0	(0.0)
	Missing by Design	**194**	**(57.1)**	**173**	**(59.5)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	2	(0.6)	53	(18.2)
	Discontinued due to adverse event	36	(10.6)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 64	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	11	(3.2)	5	(1.7)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	25	(7.4)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	3	(1.0)
	Completed treatment and visit not reached	26	(7.6)	75	(25.8)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 77	**Expected to Complete Questionnaires**	**126**	**(37.1)**	**105**	**(36.1)**
	Completed	116	(34.1)	94	(32.3)
	Compliance (% in those expected to complete questionnaires)	116	(92.1)	94	(89.5)
	Not completed	10	(2.9)	11	(3.8)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	2	(0.6)	4	(1.4)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.3)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	1	(0.3)
	Other	6	(1.8)	5	(1.7)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**214**	**(62.9)**	**186**	**(63.9)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	3	(0.9)	56	(19.2)
	Discontinued due to adverse event	40	(11.8)	13	(4.5)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 77	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	11	(3.2)	5	(1.7)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	25	(7.4)	12	(4.1)
	Completed treatment and visit not scheduled	4	(1.2)	2	(0.7)
	Completed treatment and visit not reached	37	(10.9)	85	(29.2)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 90	**Expected to Complete Questionnaires**	**111**	**(32.6)**	**94**	**(32.3)**
	Completed	104	(30.6)	90	(30.9)
	Compliance (% in those expected to complete questionnaires)	104	(93.7)	90	(95.7)
	Not completed	7	(2.1)	4	(1.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.3)	0	(0.0)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.3)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	0	(0.0)
	Other	4	(1.2)	2	(0.7)
	With visit, no record	0	(0.0)	1	(0.3)
	Missing by Design	**229**	**(67.4)**	**197**	**(67.7)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	6	(1.8)	60	(20.6)
	Discontinued due to adverse event	43	(12.6)	13	(4.5)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 90	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	12	(3.5)	6	(2.1)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	26	(7.6)	12	(4.1)
	Completed treatment and visit not scheduled	3	(0.9)	1	(0.3)
	Completed treatment and visit not reached	45	(13.2)	92	(31.6)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 103	**Expected to Complete Questionnaires**	**99**	**(29.1)**	**80**	**(27.5)**
	Completed	88	(25.9)	78	(26.8)
	Compliance (% in those expected to complete questionnaires)	88	(88.9)	78	(97.5)
	Not completed	11	(3.2)	2	(0.7)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	4	(1.2)	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	3	(0.9)	1	(0.3)
	Other	4	(1.2)	1	(0.3)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**241**	**(70.9)**	**211**	**(72.5)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	7	(2.1)	62	(21.3)
	Discontinued due to adverse event	45	(13.2)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 103	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	12	(3.5)	6	(2.1)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	2	(0.6)	1	(0.3)
	Completed treatment and visit not reached	54	(15.9)	105	(36.1)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 116	**Expected to Complete Questionnaires**	**91**	**(26.8)**	**71**	**(24.4)**
	Completed	88	(25.9)	64	(22.0)
	Compliance (% in those expected to complete questionnaires)	88	(96.7)	64	(90.1)
	Not completed	3	(0.9)	7	(2.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.3)	2	(0.7)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	2	(0.7)
	Other	1	(0.3)	3	(1.0)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**249**	**(73.2)**	**220**	**(75.6)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	10	(2.9)	65	(22.3)
	Discontinued due to adverse event	44	(12.9)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 116	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	6	(2.1)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	3	(0.9)	2	(0.7)
	Completed treatment and visit not reached	59	(17.4)	109	(37.5)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 129	**Expected to Complete Questionnaires**	**77**	**(22.6)**	**59**	**(20.3)**
	Completed	75	(22.1)	53	(18.2)
	Compliance (% in those expected to complete questionnaires)	75	(97.4)	53	(89.8)
	Not completed	2	(0.6)	6	(2.1)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	2	(0.7)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.6)	3	(1.0)
	Other	0	(0.0)	1	(0.3)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**263**	**(77.4)**	**232**	**(79.7)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	11	(3.2)	70	(24.1)
	Discontinued due to adverse event	46	(13.5)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 129	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	7	(2.4)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	2	(0.7)
	Completed treatment and visit not reached	73	(21.5)	115	(39.5)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 142	**Expected to Complete Questionnaires**	**63**	**(18.5)**	**53**	**(18.2)**
	Completed	48	(14.1)	44	(15.1)
	Compliance (% in those expected to complete questionnaires)	48	(76.2)	44	(83.0)
	Not completed	15	(4.4)	9	(3.1)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	2	(0.6)	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	1	(0.3)	1	(0.3)
	Other	0	(0.0)	3	(1.0)
	With visit, no record	12	(3.5)	4	(1.4)
	Missing by Design	**277**	**(81.5)**	**238**	**(81.8)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	12	(3.5)	73	(25.1)
	Discontinued due to adverse event	52	(15.3)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 142	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	7	(2.4)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	26	(7.6)	12	(4.1)
	Completed treatment and visit not scheduled	1	(0.3)	0	(0.0)
	Completed treatment and visit not reached	80	(23.5)	120	(41.2)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 194	**Expected to Complete Questionnaires**	**41**	**(12.1)**	**35**	**(12.0)**
	Completed	36	(10.6)	27	(9.3)
	Compliance (% in those expected to complete questionnaires)	36	(87.8)	27	(77.1)
	Not completed	5	(1.5)	8	(2.7)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.3)	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	(0.3)
	With visit, no record	4	(1.2)	7	(2.4)
	Missing by Design	**299**	**(87.9)**	**256**	**(88.0)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	15	(4.4)	76	(26.1)
	Discontinued due to adverse event	52	(15.3)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 194	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	8	(2.7)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	0	(0.0)
	Completed treatment and visit not reached	99	(29.1)	134	(46.0)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 246	**Expected to Complete Questionnaires**	**12**	**(3.5)**	**10**	**(3.4)**
	Completed	7	(2.1)	8	(2.7)
	Compliance (% in those expected to complete questionnaires)	7	(58.3)	8	(80.0)
	Not completed	5	(1.5)	2	(0.7)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.3)	1	(0.3)
	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	(0.3)	0	(0.0)
	Other	1	(0.3)	0	(0.0)
	With visit, no record	2	(0.6)	1	(0.3)
	Missing by Design	**328**	**(96.5)**	**281**	**(96.6)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	15	(4.4)	79	(27.1)
	Discontinued due to adverse event	59	(17.4)	13	(4.5)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 246	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	8	(2.7)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	0	(0.0)
	Completed treatment and visit not reached	121	(35.6)	155	(53.3)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)

Expected to complete questionnaire includes all participants who do not have missing data due to a missing by design reason. Compliance is the proportion of participants who completed the PRO questionnaire among those who are **expected to complete the questionnaire** at this time point, excluding those missing by design. All the other categories are defined as the proportion of participants in the analysis population (N). Missing by design includes: death, disease progression, other discontinuations (reasons may include unacceptable AEs, withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment), and translation not available. Database Cutoff Date: 25JUL2024

Anhang 4-G3.2: Rücklaufquoten des EORTC QLQ-H&N35

Tabelle 4G-5: Gründe für das Fehlen von Werten im EORTC QLQ-H&N35

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Baseline	**Expected to Complete Questionnaires**	**339**	**(99.7)**	**266**	**(91.4)**
	Completed	324	(95.3)	265	(91.1)
	Compliance (% in those expected to complete questionnaires)	324	(95.6)	265	(99.6)
	Not completed	15	(4.4)	1	(0.3)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	5	(1.5)	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	7	(2.1)	0	(0.0)
	With visit, no record	3	(0.9)	0	(0.0)
	Missing by Design	**1**	**(0.3)**	**25**	**(8.6)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	0	(0.0)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to lost to follow-up	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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 progressive disease	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)
	Completed treatment and visit not scheduled	0	(0.0)	24	(8.2)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Baseline	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	1	(0.3)	1	(0.3)
Neoadjuvant Week 4	**Expected to Complete Questionnaires**	**296**	**(87.1)**	**1**	**(0.3)**
	Completed	277	(81.5)	1	(0.3)
	Compliance (% in those expected to complete questionnaires)	277	(93.6)	1	(100.0)
	Not completed	19	(5.6)	0	(0.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	5	(1.5)	0	(0.0)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	2	(0.6)	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	4	(1.2)	0	(0.0)
	Other	6	(1.8)	0	(0.0)
	With visit, no record	2	(0.6)	0	(0.0)
	Missing by Design	**44**	**(12.9)**	**1**	**(0.3)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	1	(0.3)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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 progressive disease	1	(0.3)	0	(0.0)
	Discontinued due to withdrawal by subject	3	(0.9)	0	(0.0)
	Completed treatment and visit not scheduled	16	(4.7)	1	(0.3)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Neoadjuvant Week 4	Visit not scheduled	22	(6.5)	0	(0.0)
Neoadjuvant Week 6	**Expected to Complete Questionnaires**	**324**	**(95.3)**	**2**	**(0.7)**
	Completed	323	(95.0)	2	(0.7)
	Compliance (% in those expected to complete questionnaires)	323	(99.7)	2	(100.0)
	Not completed	1	(0.3)	0	(0.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	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	1	(0.3)	0	(0.0)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**16**	**(4.7)**	**0**	**(0.0)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	1	(0.3)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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 progressive disease	1	(0.3)	0	(0.0)
	Discontinued due to withdrawal by subject	2	(0.6)	0	(0.0)
	Completed treatment and visit not scheduled	4	(1.2)	0	(0.0)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Neoadjuvant Week 6	Visit not scheduled	7	(2.1)	0	(0.0)
Adjuvant RT Week 1	**Expected to Complete Questionnaires**	**314**	**(92.4)**	**277**	**(95.2)**
	Completed	264	(77.6)	228	(78.4)
	Compliance (% in those expected to complete questionnaires)	264	(84.1)	228	(82.3)
	Not completed	50	(14.7)	49	(16.8)
	Subject did not complete due to disease under study	2	(0.6)	2	(0.7)
	Not completed due to site staff error	4	(1.2)	14	(4.8)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	3	(0.9)	0	(0.0)
	Subject lost to follow-up/unable to contact	2	(0.6)	1	(0.3)
	Subject did not complete due to side effects of treatment	2	(0.6)	0	(0.0)
	Subject refused for other reasons	17	(5.0)	10	(3.4)
	Other	16	(4.7)	15	(5.2)
	With visit, no record	4	(1.2)	7	(2.4)
	Missing by Design	**26**	**(7.6)**	**14**	**(4.8)**
	Subject died	5	(1.5)	4	(1.4)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	2	(0.6)	5	(1.7)
	Discontinued due to clinical progression	0	(0.0)	1	(0.3)
	Discontinued due to lost to follow-up	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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	1	(0.3)	1	(0.3)
	Discontinued due to progressive disease	12	(3.5)	1	(0.3)
	Discontinued due to withdrawal by subject	1	(0.3)	2	(0.7)
	Completed treatment and visit not scheduled	1	(0.3)	0	(0.0)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Adjuvant RT Week 1	Visit not scheduled	4	(1.2)	0	(0.0)
Adjuvant RT Week 4	**Expected to Complete Questionnaires**	**275**	**(80.9)**	**261**	**(89.7)**
	Completed	229	(67.4)	236	(81.1)
	Compliance (% in those expected to complete questionnaires)	229	(83.3)	236	(90.4)
	Not completed	46	(13.5)	25	(8.6)
	Subject did not complete due to disease under study	1	(0.3)	0	(0.0)
	Not completed due to site staff error	9	(2.6)	7	(2.4)
	Subject in hospital or hospice	0	(0.0)	1	(0.3)
	Subject was physically unable to complete	1	(0.3)	1	(0.3)
	Subject lost to follow-up/unable to contact	1	(0.3)	0	(0.0)
	Subject did not complete due to side effects of treatment	2	(0.6)	2	(0.7)
	Subject refused for other reasons	6	(1.8)	6	(2.1)
	Other	18	(5.3)	5	(1.7)
	With visit, no record	8	(2.4)	3	(1.0)
	Missing by Design	**65**	**(19.1)**	**30**	**(10.3)**
	Subject died	3	(0.9)	2	(0.7)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	11	(3.2)	8	(2.7)
	Discontinued due to clinical progression	2	(0.6)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	1	(0.3)	0	(0.0)
	Discontinued due to non-compliance with study drug	1	(0.3)	1	(0.3)
	Discontinued due to physician decision	7	(2.1)	1	(0.3)
	Discontinued due to progressive disease	27	(7.9)	7	(2.4)
	Discontinued due to withdrawal by subject	12	(3.5)	10	(3.4)
	Completed treatment and visit not scheduled	0	(0.0)	0	(0.0)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Adjuvant RT Week 4	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 12	**Expected to Complete Questionnaires**	**244**	**(71.8)**	**241**	**(82.8)**
	Completed	216	(63.5)	217	(74.6)
	Compliance (% in those expected to complete questionnaires)	216	(88.5)	217	(90.0)
	Not completed	28	(8.2)	24	(8.2)
	Subject did not complete due to disease under study	2	(0.6)	0	(0.0)
	Not completed due to site staff error	13	(3.8)	10	(3.4)
	Subject in hospital or hospice	1	(0.3)	0	(0.0)
	Subject was physically unable to complete	1	(0.3)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	3	(0.9)	4	(1.4)
	Other	7	(2.1)	4	(1.4)
	With visit, no record	1	(0.3)	5	(1.7)
	Missing by Design	**96**	**(28.2)**	**50**	**(17.2)**
	Subject died	1	(0.3)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.3)
	Subject died, after end of treatment	0	(0.0)	9	(3.1)
	Discontinued due to adverse event	16	(4.7)	11	(3.8)
	Discontinued due to clinical progression	2	(0.6)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	3	(0.9)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	8	(2.4)	3	(1.0)
	Discontinued due to progressive disease	44	(12.9)	9	(3.1)
	Discontinued due to withdrawal by subject	18	(5.3)	9	(3.1)
	Completed treatment and visit not scheduled	0	(0.0)	2	(0.7)
	Completed treatment and visit not reached	1	(0.3)	2	(0.7)
	Visit not reached	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 12	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 25	**Expected to Complete Questionnaires**	**209**	**(61.5)**	**177**	**(60.8)**
	Completed	169	(49.7)	161	(55.3)
	Compliance (% in those expected to complete questionnaires)	169	(80.9)	161	(91.0)
	Not completed	40	(11.8)	16	(5.5)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	10	(2.9)	4	(1.4)
	Subject in hospital or hospice	2	(0.6)	0	(0.0)
	Subject was physically unable to complete	1	(0.3)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	4	(1.2)	5	(1.7)
	Other	14	(4.1)	5	(1.7)
	With visit, no record	9	(2.6)	1	(0.3)
	Missing by Design	**131**	**(38.5)**	**114**	**(39.2)**
	Subject died	2	(0.6)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	31	(10.7)
	Discontinued due to adverse event	26	(7.6)	12	(4.1)
	Discontinued due to clinical progression	2	(0.6)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	8	(2.4)	4	(1.4)
	Discontinued due to progressive disease	60	(17.6)	9	(3.1)
	Discontinued due to withdrawal by subject	22	(6.5)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	2	(0.7)
	Completed treatment and visit not reached	2	(0.6)	40	(13.7)
	Visit not reached	2	(0.6)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 25	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 38	**Expected to Complete Questionnaires**	**189**	**(55.6)**	**150**	**(51.5)**
	Completed	168	(49.4)	136	(46.7)
	Compliance (% in those expected to complete questionnaires)	168	(88.9)	136	(90.7)
	Not completed	21	(6.2)	14	(4.8)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	7	(2.1)	3	(1.0)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	2	(0.6)	0	(0.0)
	Subject lost to follow-up/unable to contact	1	(0.3)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	3	(1.0)
	Other	3	(0.9)	7	(2.4)
	With visit, no record	7	(2.1)	0	(0.0)
	Missing by Design	**151**	**(44.4)**	**141**	**(48.5)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	41	(14.1)
	Discontinued due to adverse event	33	(9.7)	12	(4.1)
	Discontinued due to clinical progression	2	(0.6)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	7	(2.1)	5	(1.7)
	Discontinued due to progressive disease	69	(20.3)	9	(3.1)
	Discontinued due to withdrawal by subject	23	(6.8)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	4	(1.4)
	Completed treatment and visit not reached	2	(0.6)	54	(18.6)
	Visit not reached	8	(2.4)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 38	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 51	**Expected to Complete Questionnaires**	**158**	**(46.5)**	**139**	**(47.8)**
	Completed	139	(40.9)	125	(43.0)
	Compliance (% in those expected to complete questionnaires)	139	(88.0)	125	(89.9)
	Not completed	19	(5.6)	14	(4.8)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	6	(1.8)	3	(1.0)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	1	(0.3)	2	(0.7)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	3	(0.9)	2	(0.7)
	Other	5	(1.5)	6	(2.1)
	With visit, no record	4	(1.2)	1	(0.3)
	Missing by Design	**182**	**(53.5)**	**152**	**(52.2)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	51	(17.5)
	Discontinued due to adverse event	36	(10.6)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	11	(3.2)	5	(1.7)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	26	(7.6)	12	(4.1)
	Completed treatment and visit not scheduled	2	(0.6)	0	(0.0)
	Completed treatment and visit not reached	13	(3.8)	59	(20.3)
	Visit not reached	11	(3.2)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 51	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 64	**Expected to Complete Questionnaires**	**146**	**(42.9)**	**118**	**(40.5)**
	Completed	130	(38.2)	104	(35.7)
	Compliance (% in those expected to complete questionnaires)	130	(89.0)	104	(88.1)
	Not completed	16	(4.7)	14	(4.8)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	7	(2.1)	4	(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)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	2	(0.7)
	Other	6	(1.8)	7	(2.4)
	With visit, no record	2	(0.6)	0	(0.0)
	Missing by Design	**194**	**(57.1)**	**173**	**(59.5)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	2	(0.6)	53	(18.2)
	Discontinued due to adverse event	36	(10.6)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	11	(3.2)	5	(1.7)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	25	(7.4)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	3	(1.0)
	Completed treatment and visit not reached	26	(7.6)	75	(25.8)
	Visit not reached	11	(3.2)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 64	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 77	**Expected to Complete Questionnaires**	**126**	**(37.1)**	**105**	**(36.1)**
	Completed	115	(33.8)	94	(32.3)
	Compliance (% in those expected to complete questionnaires)	115	(91.3)	94	(89.5)
	Not completed	11	(3.2)	11	(3.8)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	3	(0.9)	4	(1.4)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.3)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	1	(0.3)
	Other	6	(1.8)	5	(1.7)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**214**	**(62.9)**	**186**	**(63.9)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	3	(0.9)	56	(19.2)
	Discontinued due to adverse event	40	(11.8)	13	(4.5)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	11	(3.2)	5	(1.7)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	25	(7.4)	12	(4.1)
	Completed treatment and visit not scheduled	4	(1.2)	2	(0.7)
	Completed treatment and visit not reached	37	(10.9)	85	(29.2)
	Visit not reached	11	(3.2)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 77	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 90	**Expected to Complete Questionnaires**	**111**	**(32.6)**	**94**	**(32.3)**
	Completed	104	(30.6)	90	(30.9)
	Compliance (% in those expected to complete questionnaires)	104	(93.7)	90	(95.7)
	Not completed	7	(2.1)	4	(1.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.3)	0	(0.0)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.3)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	0	(0.0)
	Other	4	(1.2)	2	(0.7)
	With visit, no record	0	(0.0)	1	(0.3)
	Missing by Design	**229**	**(67.4)**	**197**	**(67.7)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	6	(1.8)	60	(20.6)
	Discontinued due to adverse event	43	(12.6)	13	(4.5)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	12	(3.5)	6	(2.1)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	26	(7.6)	12	(4.1)
	Completed treatment and visit not scheduled	3	(0.9)	1	(0.3)
	Completed treatment and visit not reached	45	(13.2)	92	(31.6)
	Visit not reached	11	(3.2)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 90	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 103	**Expected to Complete Questionnaires**	**99**	**(29.1)**	**80**	**(27.5)**
	Completed	87	(25.6)	78	(26.8)
	Compliance (% in those expected to complete questionnaires)	87	(87.9)	78	(97.5)
	Not completed	12	(3.5)	2	(0.7)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	4	(1.2)	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	3	(0.9)	1	(0.3)
	Other	5	(1.5)	1	(0.3)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**241**	**(70.9)**	**211**	**(72.5)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	7	(2.1)	62	(21.3)
	Discontinued due to adverse event	45	(13.2)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	12	(3.5)	6	(2.1)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	2	(0.6)	1	(0.3)
	Completed treatment and visit not reached	54	(15.9)	105	(36.1)
	Visit not reached	11	(3.2)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 103	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 116	**Expected to Complete Questionnaires**	**91**	**(26.8)**	**71**	**(24.4)**
	Completed	88	(25.9)	64	(22.0)
	Compliance (% in those expected to complete questionnaires)	88	(96.7)	64	(90.1)
	Not completed	3	(0.9)	7	(2.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.3)	2	(0.7)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	2	(0.7)
	Other	1	(0.3)	3	(1.0)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**249**	**(73.2)**	**220**	**(75.6)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	10	(2.9)	65	(22.3)
	Discontinued due to adverse event	44	(12.9)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	6	(2.1)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	3	(0.9)	2	(0.7)
	Completed treatment and visit not reached	59	(17.4)	109	(37.5)
	Visit not reached	11	(3.2)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340 n	(%)	SoC N=291 n	(%)
Post-Adjuvant CRT/RT Week 116	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 129	**Expected to Complete Questionnaires**	**77**	**(22.6)**	**59**	**(20.3)**
	Completed	74	(21.8)	53	(18.2)
	Compliance (% in those expected to complete questionnaires)	74	(96.1)	53	(89.8)
	Not completed	3	(0.9)	6	(2.1)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.3)	2	(0.7)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.6)	3	(1.0)
	Other	0	(0.0)	1	(0.3)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**263**	**(77.4)**	**232**	**(79.7)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	11	(3.2)	70	(24.1)
	Discontinued due to adverse event	46	(13.5)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	7	(2.4)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	2	(0.7)
	Completed treatment and visit not reached	73	(21.5)	115	(39.5)
	Visit not reached	11	(3.2)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 129	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 142	**Expected to Complete Questionnaires**	**63**	**(18.5)**	**53**	**(18.2)**
	Completed	48	(14.1)	44	(15.1)
	Compliance (% in those expected to complete questionnaires)	48	(76.2)	44	(83.0)
	Not completed	15	(4.4)	9	(3.1)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	2	(0.6)	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	1	(0.3)	1	(0.3)
	Other	0	(0.0)	3	(1.0)
	With visit, no record	12	(3.5)	4	(1.4)
	Missing by Design	**277**	**(81.5)**	**238**	**(81.8)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	12	(3.5)	73	(25.1)
	Discontinued due to adverse event	52	(15.3)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	7	(2.4)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	26	(7.6)	12	(4.1)
	Completed treatment and visit not scheduled	1	(0.3)	0	(0.0)
	Completed treatment and visit not reached	80	(23.5)	120	(41.2)
	Visit not reached	11	(3.2)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 142	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 194	**Expected to Complete Questionnaires**	**41**	**(12.1)**	**35**	**(12.0)**
	Completed	36	(10.6)	27	(9.3)
	Compliance (% in those expected to complete questionnaires)	36	(87.8)	27	(77.1)
	Not completed	5	(1.5)	8	(2.7)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.3)	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	(0.3)
	With visit, no record	4	(1.2)	7	(2.4)
	Missing by Design	**299**	**(87.9)**	**256**	**(88.0)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	15	(4.4)	76	(26.1)
	Discontinued due to adverse event	52	(15.3)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	8	(2.7)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	0	(0.0)
	Completed treatment and visit not reached	99	(29.1)	134	(46.0)
	Visit not reached	11	(3.2)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=291	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 194	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 246	**Expected to Complete Questionnaires**	**12**	**(3.5)**	**10**	**(3.4)**
	Completed	7	(2.1)	8	(2.7)
	Compliance (% in those expected to complete questionnaires)	7	(58.3)	8	(80.0)
	Not completed	5	(1.5)	2	(0.7)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.3)	1	(0.3)
	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	(0.3)	0	(0.0)
	Other	1	(0.3)	0	(0.0)
	With visit, no record	2	(0.6)	1	(0.3)
	Missing by Design	**328**	**(96.5)**	**281**	**(96.6)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	15	(4.4)	79	(27.1)
	Discontinued due to adverse event	59	(17.4)	13	(4.5)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	8	(2.7)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	0	(0.0)
	Completed treatment and visit not reached	121	(35.6)	155	(53.3)
	Visit not reached	11	(3.2)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340 n	(%)	SoC N=291 n	(%)
Post-Adjuvant CRT/RT Week 246	Visit not scheduled	0	(0.0)	0	(0.0)

Expected to complete questionnaire includes all participants who do not have missing data due to a missing by design reason. Compliance is the proportion of participants who completed the PRO questionnaire among those who are **expected to complete the questionnaire** at this time point, excluding those missing by design. All the other categories are defined as the proportion of participants in the analysis population (N). Missing by design includes: death, disease progression, other discontinuations (reasons may include unacceptable AEs, withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment), and translation not available. Database Cutoff Date: 25JUL2024

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

Tabelle 4G-6: Gründe für das Fehlen von Werten in der EQ-5D VAS

Treatment Visit	Category	Pembrolizumab N=340 n	(%)	SoC N=290 n	(%)
Baseline	**Expected to Complete Questionnaires**	**339**	**(99.7)**	**265**	**(91.4)**
	Completed	325	(95.6)	265	(91.4)
	Compliance (% in those expected to complete questionnaires)	325	(95.9)	265	(100.0)
	Not completed	14	(4.1)	0	(0.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	5	(1.5)	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	6	(1.8)	0	(0.0)
	With visit, no record	3	(0.9)	0	(0.0)
	Missing by Design	**1**	**(0.3)**	**25**	**(8.6)**
	Subject died	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Baseline	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	0	(0.0)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to lost to follow-up	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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 progressive disease	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)
	Completed treatment and visit not scheduled	0	(0.0)	24	(8.3)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	1	(0.3)	1	(0.3)
Neoadjuvant Week 4	**Expected to Complete Questionnaires**	**296**	**(87.1)**	**1**	**(0.3)**
	Completed	279	(82.1)	1	(0.3)
	Compliance (% in those expected to complete questionnaires)	279	(94.3)	1	(100.0)
	Not completed	17	(5.0)	0	(0.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	5	(1.5)	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	4	(1.2)	0	(0.0)
	Other	6	(1.8)	0	(0.0)
	With visit, no record	2	(0.6)	0	(0.0)
	Missing by Design	**44**	**(12.9)**	**1**	**(0.3)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Neoadjuvant Week 4	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	1	(0.3)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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 progressive disease	1	(0.3)	0	(0.0)
	Discontinued due to withdrawal by subject	3	(0.9)	0	(0.0)
	Completed treatment and visit not scheduled	16	(4.7)	1	(0.3)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	22	(6.5)	0	(0.0)
Neoadjuvant Week 6	**Expected to Complete Questionnaires**	**324**	**(95.3)**	**2**	**(0.7)**
	Completed	324	(95.3)	2	(0.7)
	Compliance (% in those expected to complete questionnaires)	324	(100.0)	2	(100.0)
	Not completed	0	(0.0)	0	(0.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	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)	0	(0.0)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**16**	**(4.7)**	**0**	**(0.0)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Neoadjuvant Week 6	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	1	(0.3)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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 progressive disease	1	(0.3)	0	(0.0)
	Discontinued due to withdrawal by subject	2	(0.6)	0	(0.0)
	Completed treatment and visit not scheduled	4	(1.2)	0	(0.0)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	7	(2.1)	0	(0.0)
Adjuvant RT Week 1	**Expected to Complete Questionnaires**	**314**	**(92.4)**	**277**	**(95.5)**
	Completed	265	(77.9)	232	(80.0)
	Compliance (% in those expected to complete questionnaires)	265	(84.4)	232	(83.8)
	Not completed	49	(14.4)	45	(15.5)
	Subject did not complete due to disease under study	2	(0.6)	2	(0.7)
	Not completed due to site staff error	4	(1.2)	13	(4.5)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	3	(0.9)	0	(0.0)
	Subject lost to follow-up/unable to contact	2	(0.6)	1	(0.3)
	Subject did not complete due to side effects of treatment	2	(0.6)	0	(0.0)
	Subject refused for other reasons	16	(4.7)	9	(3.1)
	Other	16	(4.7)	13	(4.5)
	With visit, no record	4	(1.2)	7	(2.4)
	Missing by Design	**26**	**(7.6)**	**13**	**(4.5)**
	Subject died	5	(1.5)	4	(1.4)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Adjuvant RT Week 1	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	2	(0.6)	4	(1.4)
	Discontinued due to clinical progression	0	(0.0)	1	(0.3)
	Discontinued due to lost to follow-up	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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	1	(0.3)	1	(0.3)
	Discontinued due to progressive disease	12	(3.5)	1	(0.3)
	Discontinued due to withdrawal by subject	1	(0.3)	2	(0.7)
	Completed treatment and visit not scheduled	1	(0.3)	0	(0.0)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	4	(1.2)	0	(0.0)
Adjuvant RT Week 4	**Expected to Complete Questionnaires**	**275**	**(80.9)**	**261**	**(90.0)**
	Completed	231	(67.9)	238	(82.1)
	Compliance (% in those expected to complete questionnaires)	231	(84.0)	238	(91.2)
	Not completed	44	(12.9)	23	(7.9)
	Subject did not complete due to disease under study	1	(0.3)	0	(0.0)
	Not completed due to site staff error	9	(2.6)	7	(2.4)
	Subject in hospital or hospice	0	(0.0)	1	(0.3)
	Subject was physically unable to complete	1	(0.3)	1	(0.3)
	Subject lost to follow-up/unable to contact	1	(0.3)	0	(0.0)
	Subject did not complete due to side effects of treatment	2	(0.6)	2	(0.7)
	Subject refused for other reasons	6	(1.8)	5	(1.7)
	Other	16	(4.7)	4	(1.4)
	With visit, no record	8	(2.4)	3	(1.0)
	Missing by Design	**65**	**(19.1)**	**29**	**(10.0)**
	Subject died	3	(0.9)	1	(0.3)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Adjuvant RT Week 4	Subject died, after end of treatment	0	(0.0)	0	(0.0)
	Discontinued due to adverse event	11	(3.2)	8	(2.8)
	Discontinued due to clinical progression	2	(0.6)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	1	(0.3)	0	(0.0)
	Discontinued due to non-compliance with study drug	1	(0.3)	1	(0.3)
	Discontinued due to physician decision	7	(2.1)	1	(0.3)
	Discontinued due to progressive disease	27	(7.9)	7	(2.4)
	Discontinued due to withdrawal by subject	12	(3.5)	10	(3.4)
	Completed treatment and visit not scheduled	0	(0.0)	0	(0.0)
	Completed treatment and visit not reached	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 12	**Expected to Complete Questionnaires**	**244**	**(71.8)**	**241**	**(83.1)**
	Completed	217	(63.8)	218	(75.2)
	Compliance (% in those expected to complete questionnaires)	217	(88.9)	218	(90.5)
	Not completed	27	(7.9)	23	(7.9)
	Subject did not complete due to disease under study	2	(0.6)	0	(0.0)
	Not completed due to site staff error	13	(3.8)	9	(3.1)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.3)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	3	(0.9)	4	(1.4)
	Other	7	(2.1)	4	(1.4)
	With visit, no record	1	(0.3)	5	(1.7)
	Missing by Design	**96**	**(28.2)**	**49**	**(16.9)**
	Subject died	1	(0.3)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.3)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 12	Subject died, after end of treatment	0	(0.0)	9	(3.1)
	Discontinued due to adverse event	16	(4.7)	10	(3.4)
	Discontinued due to clinical progression	2	(0.6)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	3	(0.9)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	8	(2.4)	3	(1.0)
	Discontinued due to progressive disease	44	(12.9)	9	(3.1)
	Discontinued due to withdrawal by subject	18	(5.3)	9	(3.1)
	Completed treatment and visit not scheduled	0	(0.0)	2	(0.7)
	Completed treatment and visit not reached	1	(0.3)	2	(0.7)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 25	**Expected to Complete Questionnaires**	**209**	**(61.5)**	**177**	**(61.0)**
	Completed	170	(50.0)	164	(56.6)
	Compliance (% in those expected to complete questionnaires)	170	(81.3)	164	(92.7)
	Not completed	39	(11.5)	13	(4.5)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	10	(2.9)	4	(1.4)
	Subject in hospital or hospice	2	(0.6)	0	(0.0)
	Subject was physically unable to complete	1	(0.3)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	4	(1.2)	4	(1.4)
	Other	13	(3.8)	3	(1.0)
	With visit, no record	9	(2.6)	1	(0.3)
	Missing by Design	**131**	**(38.5)**	**113**	**(39.0)**
	Subject died	2	(0.6)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 25	Subject died, after end of treatment	0	(0.0)	31	(10.7)
	Discontinued due to adverse event	26	(7.6)	11	(3.8)
	Discontinued due to clinical progression	2	(0.6)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	8	(2.4)	4	(1.4)
	Discontinued due to progressive disease	60	(17.6)	9	(3.1)
	Discontinued due to withdrawal by subject	22	(6.5)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	2	(0.7)
	Completed treatment and visit not reached	2	(0.6)	40	(13.8)
	Visit not reached	2	(0.6)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 38	**Expected to Complete Questionnaires**	**189**	**(55.6)**	**150**	**(51.7)**
	Completed	168	(49.4)	136	(46.9)
	Compliance (% in those expected to complete questionnaires)	168	(88.9)	136	(90.7)
	Not completed	21	(6.2)	14	(4.8)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	7	(2.1)	3	(1.0)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	2	(0.6)	0	(0.0)
	Subject lost to follow-up/unable to contact	1	(0.3)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	2	(0.7)
	Other	3	(0.9)	7	(2.4)
	With visit, no record	7	(2.1)	0	(0.0)
	Missing by Design	**151**	**(44.4)**	**140**	**(48.3)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 38	Subject died, after end of treatment	0	(0.0)	41	(14.1)
	Discontinued due to adverse event	33	(9.7)	11	(3.8)
	Discontinued due to clinical progression	2	(0.6)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	7	(2.1)	5	(1.7)
	Discontinued due to progressive disease	69	(20.3)	9	(3.1)
	Discontinued due to withdrawal by subject	23	(6.8)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	4	(1.4)
	Completed treatment and visit not reached	2	(0.6)	54	(18.6)
	Visit not reached	8	(2.4)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 51	**Expected to Complete Questionnaires**	**158**	**(46.5)**	**139**	**(47.9)**
	Completed	140	(41.2)	125	(43.1)
	Compliance (% in those expected to complete questionnaires)	140	(88.6)	125	(89.9)
	Not completed	18	(5.3)	14	(4.8)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	6	(1.8)	3	(1.0)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	1	(0.3)	2	(0.7)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.6)	2	(0.7)
	Other	5	(1.5)	6	(2.1)
	With visit, no record	4	(1.2)	1	(0.3)
	Missing by Design	**182**	**(53.5)**	**151**	**(52.1)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 51	Subject died, after end of treatment	0	(0.0)	51	(17.6)
	Discontinued due to adverse event	36	(10.6)	11	(3.8)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	11	(3.2)	5	(1.7)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	26	(7.6)	12	(4.1)
	Completed treatment and visit not scheduled	2	(0.6)	0	(0.0)
	Completed treatment and visit not reached	13	(3.8)	59	(20.3)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 64	**Expected to Complete Questionnaires**	**146**	**(42.9)**	**118**	**(40.7)**
	Completed	132	(38.8)	106	(36.6)
	Compliance (% in those expected to complete questionnaires)	132	(90.4)	106	(89.8)
	Not completed	14	(4.1)	12	(4.1)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	6	(1.8)	4	(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)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	2	(0.7)
	Other	5	(1.5)	5	(1.7)
	With visit, no record	2	(0.6)	0	(0.0)
	Missing by Design	**194**	**(57.1)**	**172**	**(59.3)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 64	Subject died, after end of treatment	2	(0.6)	53	(18.3)
	Discontinued due to adverse event	36	(10.6)	11	(3.8)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	11	(3.2)	5	(1.7)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	25	(7.4)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	3	(1.0)
	Completed treatment and visit not reached	26	(7.6)	75	(25.9)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 77	**Expected to Complete Questionnaires**	**126**	**(37.1)**	**105**	**(36.2)**
	Completed	116	(34.1)	94	(32.4)
	Compliance (% in those expected to complete questionnaires)	116	(92.1)	94	(89.5)
	Not completed	10	(2.9)	11	(3.8)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	2	(0.6)	4	(1.4)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.3)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	1	(0.3)
	Other	6	(1.8)	5	(1.7)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**214**	**(62.9)**	**185**	**(63.8)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 77	Subject died, after end of treatment	3	(0.9)	56	(19.3)
	Discontinued due to adverse event	40	(11.8)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	11	(3.2)	5	(1.7)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	25	(7.4)	12	(4.1)
	Completed treatment and visit not scheduled	4	(1.2)	2	(0.7)
	Completed treatment and visit not reached	37	(10.9)	85	(29.3)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 90	**Expected to Complete Questionnaires**	**111**	**(32.6)**	**94**	**(32.4)**
	Completed	104	(30.6)	90	(31.0)
	Compliance (% in those expected to complete questionnaires)	104	(93.7)	90	(95.7)
	Not completed	7	(2.1)	4	(1.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.3)	0	(0.0)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.3)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	0	(0.0)
	Other	4	(1.2)	2	(0.7)
	With visit, no record	0	(0.0)	1	(0.3)
	Missing by Design	**229**	**(67.4)**	**196**	**(67.6)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 90	Subject died, after end of treatment	6	(1.8)	60	(20.7)
	Discontinued due to adverse event	43	(12.6)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	12	(3.5)	6	(2.1)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	26	(7.6)	12	(4.1)
	Completed treatment and visit not scheduled	3	(0.9)	1	(0.3)
	Completed treatment and visit not reached	45	(13.2)	92	(31.7)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 103	**Expected to Complete Questionnaires**	**99**	**(29.1)**	**80**	**(27.6)**
	Completed	87	(25.6)	78	(26.9)
	Compliance (% in those expected to complete questionnaires)	87	(87.9)	78	(97.5)
	Not completed	12	(3.5)	2	(0.7)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	4	(1.2)	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	4	(1.2)	1	(0.3)
	Other	4	(1.2)	1	(0.3)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**241**	**(70.9)**	**210**	**(72.4)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 103	Subject died, after end of treatment	7	(2.1)	62	(21.4)
	Discontinued due to adverse event	45	(13.2)	11	(3.8)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	1	(0.3)
	Discontinued due to physician decision	12	(3.5)	6	(2.1)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	2	(0.6)	1	(0.3)
	Completed treatment and visit not reached	54	(15.9)	105	(36.2)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 116	**Expected to Complete Questionnaires**	**91**	**(26.8)**	**71**	**(24.5)**
	Completed	88	(25.9)	64	(22.1)
	Compliance (% in those expected to complete questionnaires)	88	(96.7)	64	(90.1)
	Not completed	3	(0.9)	7	(2.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.3)	2	(0.7)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.3)	2	(0.7)
	Other	1	(0.3)	3	(1.0)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**249**	**(73.2)**	**219**	**(75.5)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 116	Subject died, after end of treatment	10	(2.9)	65	(22.4)
	Discontinued due to adverse event	44	(12.9)	11	(3.8)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	6	(2.1)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	3	(0.9)	2	(0.7)
	Completed treatment and visit not reached	59	(17.4)	109	(37.6)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 129	**Expected to Complete Questionnaires**	**77**	**(22.6)**	**59**	**(20.3)**
	Completed	75	(22.1)	54	(18.6)
	Compliance (% in those expected to complete questionnaires)	75	(97.4)	54	(91.5)
	Not completed	2	(0.6)	5	(1.7)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	2	(0.7)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.6)	3	(1.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**263**	**(77.4)**	**231**	**(79.7)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 129	Subject died, after end of treatment	11	(3.2)	70	(24.1)
	Discontinued due to adverse event	46	(13.5)	11	(3.8)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	7	(2.4)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	2	(0.7)
	Completed treatment and visit not reached	73	(21.5)	115	(39.7)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 142	**Expected to Complete Questionnaires**	**63**	**(18.5)**	**53**	**(18.3)**
	Completed	48	(14.1)	44	(15.2)
	Compliance (% in those expected to complete questionnaires)	48	(76.2)	44	(83.0)
	Not completed	15	(4.4)	9	(3.1)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	2	(0.6)	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	1	(0.3)	1	(0.3)
	Other	0	(0.0)	3	(1.0)
	With visit, no record	12	(3.5)	4	(1.4)
	Missing by Design	**277**	**(81.5)**	**237**	**(81.7)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 142	Subject died, after end of treatment	12	(3.5)	73	(25.2)
	Discontinued due to adverse event	52	(15.3)	11	(3.8)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	7	(2.4)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	26	(7.6)	12	(4.1)
	Completed treatment and visit not scheduled	1	(0.3)	0	(0.0)
	Completed treatment and visit not reached	80	(23.5)	120	(41.4)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 194	**Expected to Complete Questionnaires**	**41**	**(12.1)**	**35**	**(12.1)**
	Completed	36	(10.6)	27	(9.3)
	Compliance (% in those expected to complete questionnaires)	36	(87.8)	27	(77.1)
	Not completed	5	(1.5)	8	(2.8)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.3)	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	(0.3)
	With visit, no record	4	(1.2)	7	(2.4)
	Missing by Design	**299**	**(87.9)**	**255**	**(87.9)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 194	Subject died, after end of treatment	15	(4.4)	76	(26.2)
	Discontinued due to adverse event	52	(15.3)	11	(3.8)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	8	(2.8)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	0	(0.0)
	Completed treatment and visit not reached	99	(29.1)	134	(46.2)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Post-Adjuvant CRT/RT Week 246	**Expected to Complete Questionnaires**	**12**	**(3.5)**	**10**	**(3.4)**
	Completed	7	(2.1)	8	(2.8)
	Compliance (% in those expected to complete questionnaires)	7	(58.3)	8	(80.0)
	Not completed	5	(1.5)	2	(0.7)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	1	(0.3)	1	(0.3)
	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	(0.3)	0	(0.0)
	Other	1	(0.3)	0	(0.0)
	With visit, no record	2	(0.6)	1	(0.3)
	Missing by Design	**328**	**(96.5)**	**280**	**(96.6)**
	Subject died	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=340		SoC N=290	
		n	(%)	n	(%)
Post-Adjuvant CRT/RT Week 246	Subject died, after end of treatment	15	(4.4)	79	(27.2)
	Discontinued due to adverse event	59	(17.4)	12	(4.1)
	Discontinued due to clinical progression	3	(0.9)	1	(0.3)
	Discontinued due to lost to follow-up	1	(0.3)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	4	(1.2)	2	(0.7)
	Discontinued due to non-compliance with study drug	2	(0.6)	2	(0.7)
	Discontinued due to physician decision	12	(3.5)	8	(2.8)
	Discontinued due to progressive disease	73	(21.5)	9	(3.1)
	Discontinued due to withdrawal by subject	27	(7.9)	12	(4.1)
	Completed treatment and visit not scheduled	0	(0.0)	0	(0.0)
	Completed treatment and visit not reached	121	(35.6)	155	(53.4)
	Visit not reached	11	(3.2)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)

Expected to complete questionnaire includes all participants who do not have missing data due to a missing by design reason. Compliance is the proportion of participants who completed the PRO questionnaire among those who are **expected to complete the questionnaire** at this time point, excluding those missing by design. All the other categories are defined as the proportion of participants in the analysis population (N). Missing by design includes: death, disease progression, other discontinuations (reasons may include unacceptable AEs, withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment), and translation not available. Database Cutoff Date: 25JUL2024

Anhang 4-G4: Kaplan-Meier-Kurven der Subgruppen mit signifikantem Interaktionstest (p < 0,05)

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

Alle Ergebnisse beziehen sich auf das zulassungsbegründende Database Cutoff Date (25. Juli 2024).

Mortalität

Gesamtmortalität

Nicht zutreffend.

Morbidität

Ereignisfreies Überleben

Ereignisfreies Überleben gemäß BICR

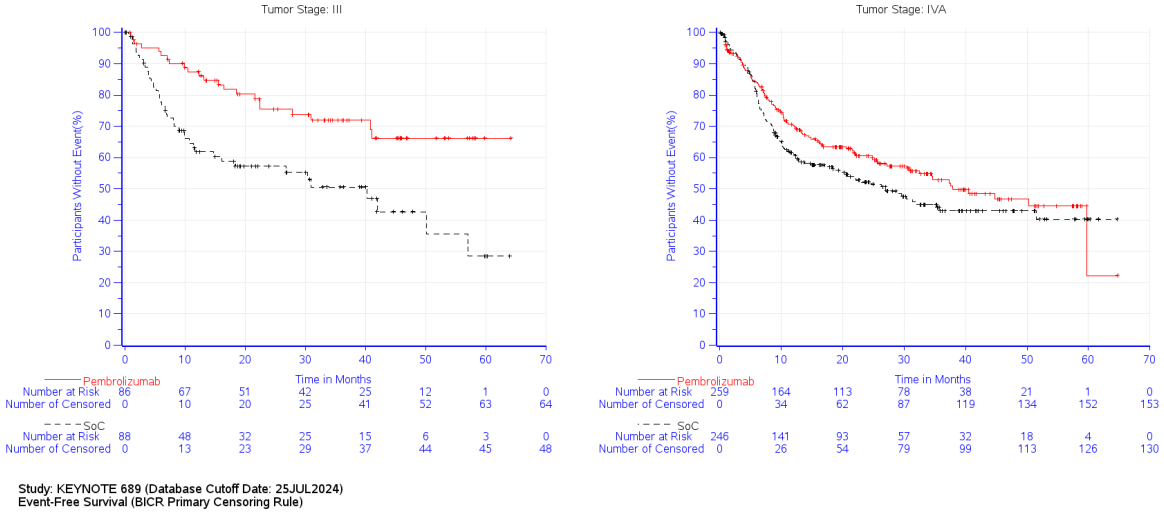
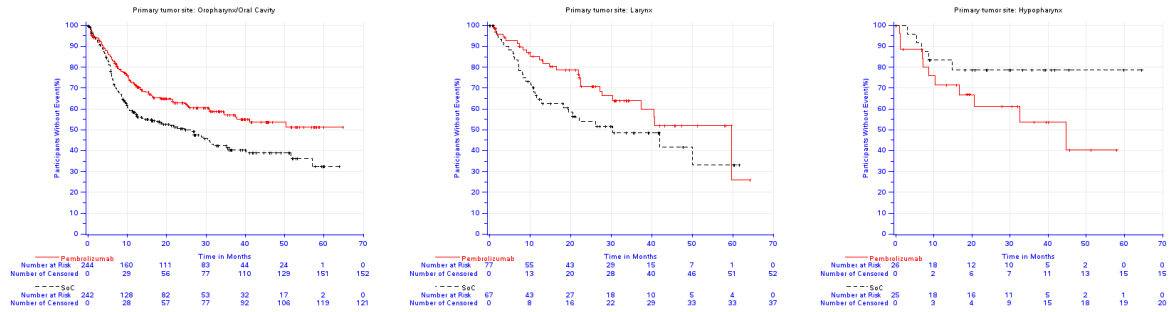


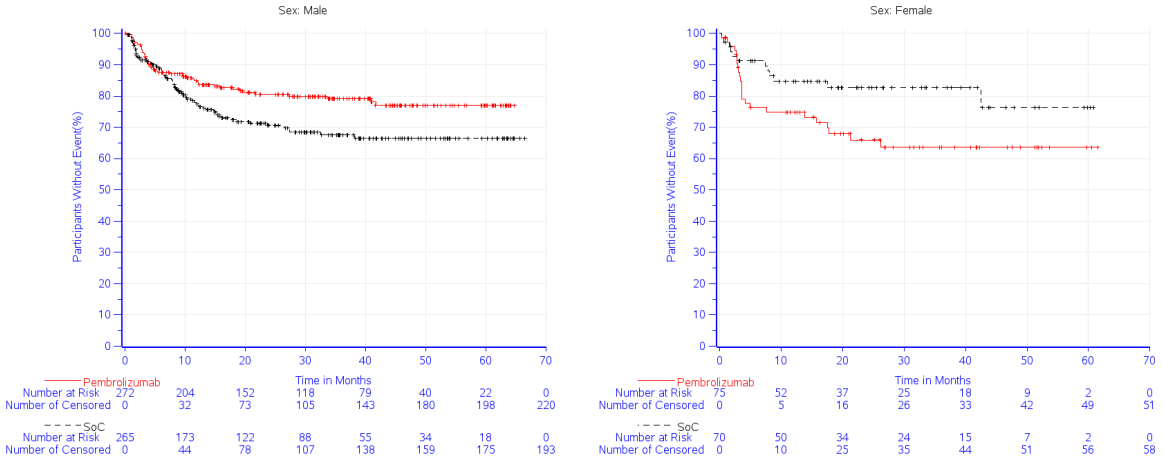
Abbildung 4G-1: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Tumorstadium für den Endpunkt Ereignisfreies Überleben gemäß BICR der Studie KEYNOTE 689



Study: KEYNOTE 689 (Database Cutoff Date: 25JUL2024)
Event-Free Survival (BICR Primary Censoring Rule)

Abbildung 4G-2: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Lokalisation des Primärtumors für den Endpunkt Ereignisfreies Überleben gemäß BICR der Studie KEYNOTE 689

Zeit bis zur ersten Folgetherapie



Study: KEYNOTE 689 (Database Cutoff Date: 25JUL2024)
Time to First Subsequent Oncologic Therapy

Abbildung 4G-3: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Zeit bis zur ersten Folgetherapie der Studie KEYNOTE 689

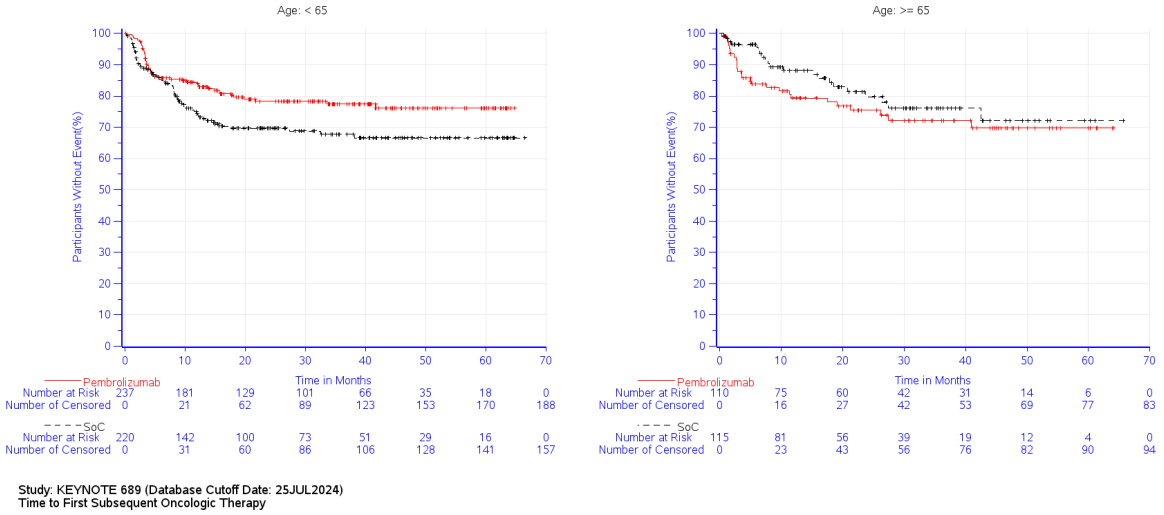


Abbildung 4G-4: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für den Endpunkt Zeit bis zur ersten Folgetherapie der Studie KEYNOTE 689

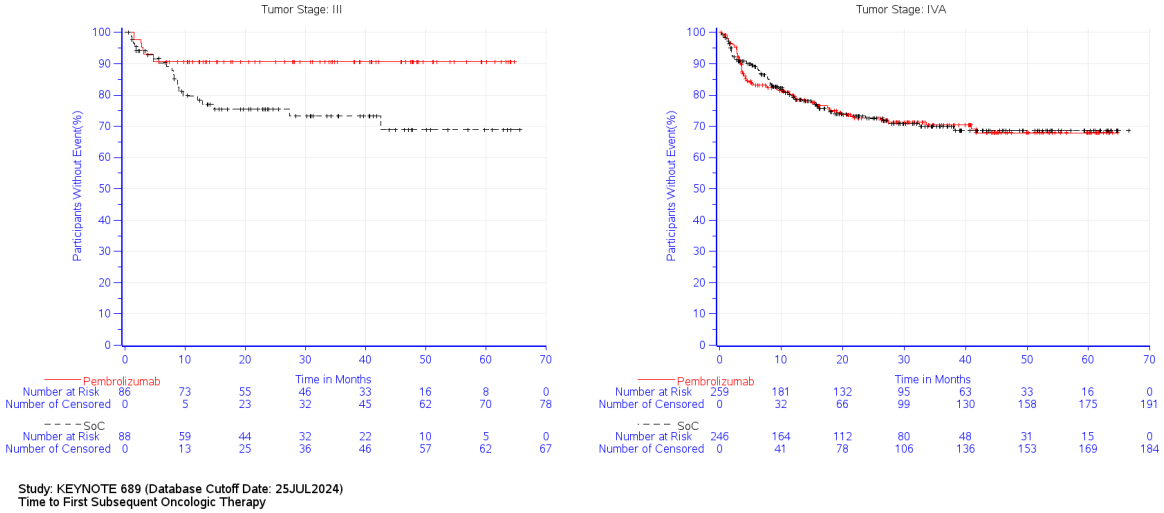


Abbildung 4G-5: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Tumorstadium für den Endpunkt Zeit bis zur ersten Folgetherapie der Studie KEYNOTE 689

Krankheitssymptomatik und Gesundheitszustand

Nicht zutreffend, da keine Ereigniszeitanalyse durchgeführt wurde.

Gesundheitsbezogene Lebensqualität

Nicht zutreffend, da keine Ereigniszeitanalyse durchgeführt wurde.

Nebenwirkungen

Unerwünschte Ereignisse gesamt

Nicht zutreffend.

Schwerwiegende unerwünschte Ereignisse

Nicht zutreffend.

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

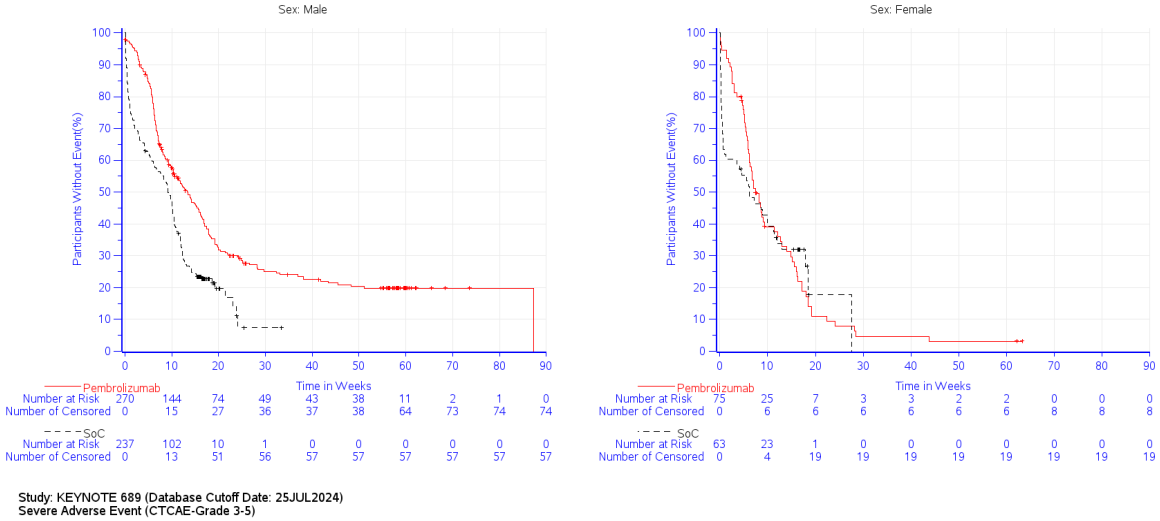
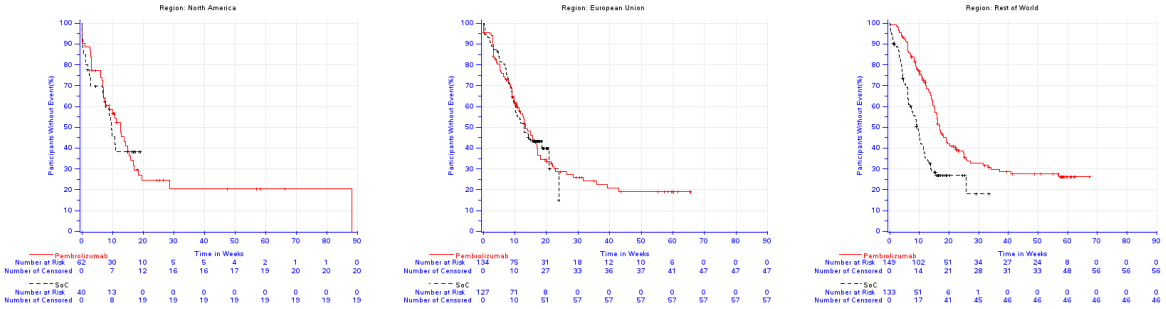


Abbildung 4G-6: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) der Studie KEYNOTE 689

Therapieabbruch wegen unerwünschter Ereignisse

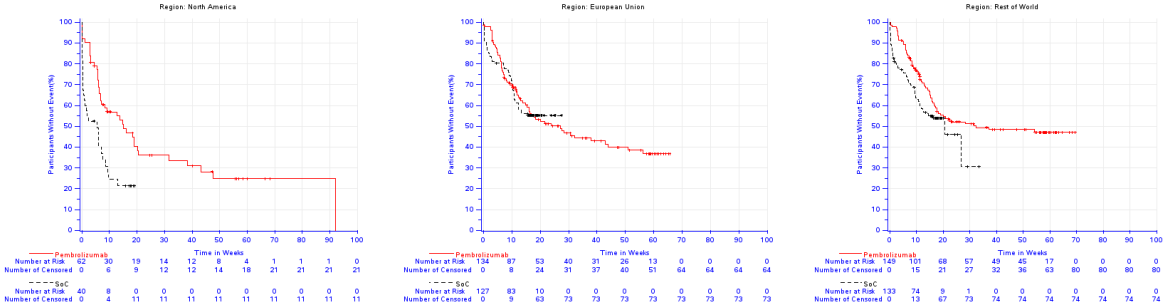
Nicht zutreffend.

Unerwünschte Ereignisse gesamt (SOC und PT)



Study: KEYNOTE 689 (Database Cutoff Date: 25JUL2024)
Adverse Event - System Organ Class: Investigations

Abbildung 4G-7: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC: Untersuchungen) der Studie KEYNOTE 689



Study: KEYNOTE 689 (Database Cutoff Date: 25JUL2024)
Adverse Event - System Organ Class: Metabolism and nutrition disorders

Abbildung 4G-8: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC: Stoffwechsel- und Ernährungsstörungen) der Studie KEYNOTE 689

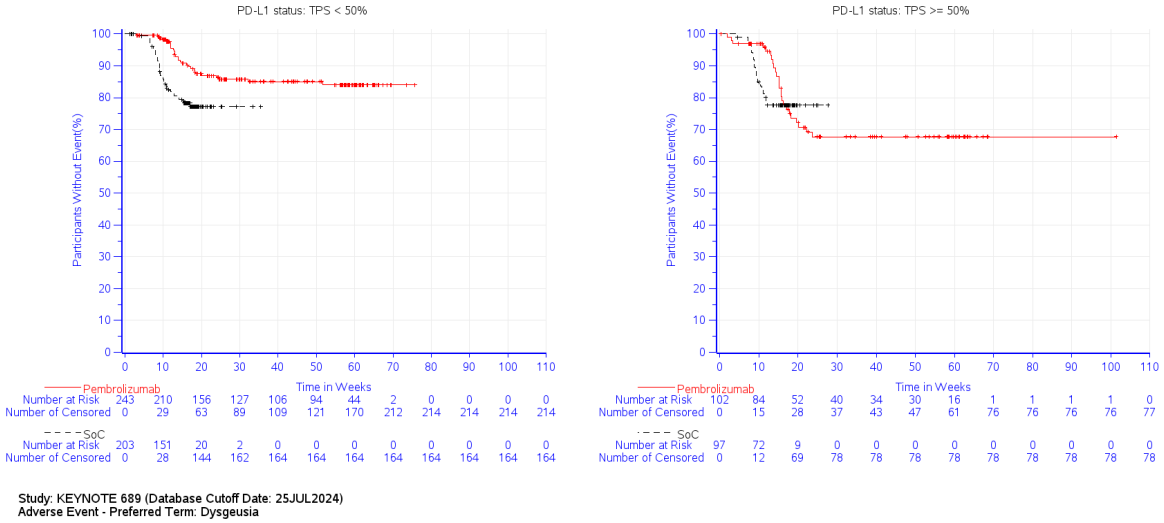


Abbildung 4G-9: Kaplan-Meier-Kurve für die Subgruppenanalyse nach PD-L1 TPS-Status für den Endpunkt Unerwünschte Ereignisse gesamt (PT: Dysgeusie) der Studie KEYNOTE 689

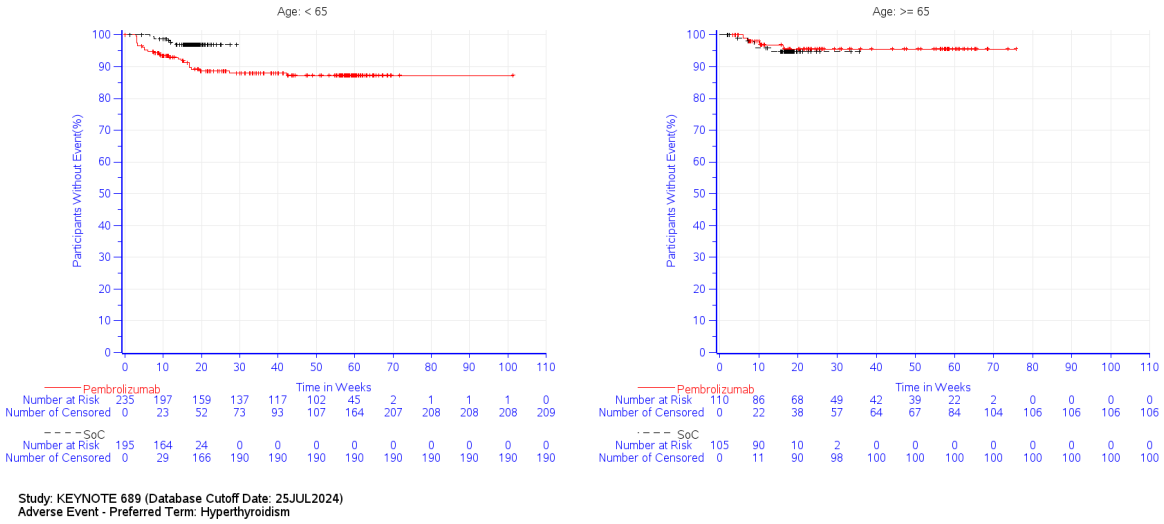


Abbildung 4G-10: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für den Endpunkt Unerwünschte Ereignisse gesamt (PT: Hyperthyreose) der Studie KEYNOTE 689

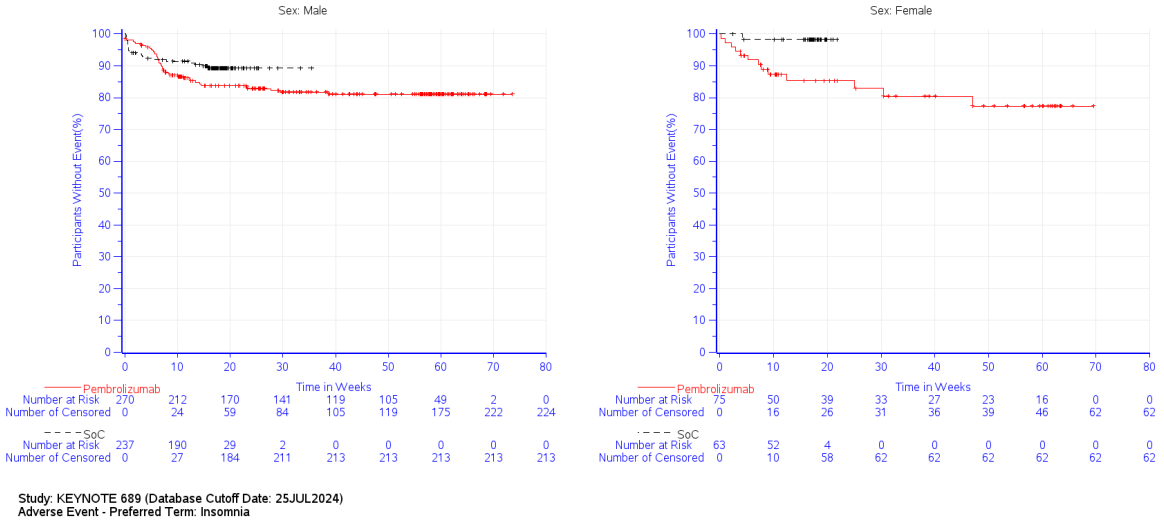


Abbildung 4G-11: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Unerwünschte Ereignisse gesamt (PT: Schlaflosigkeit) der Studie KEYNOTE 689

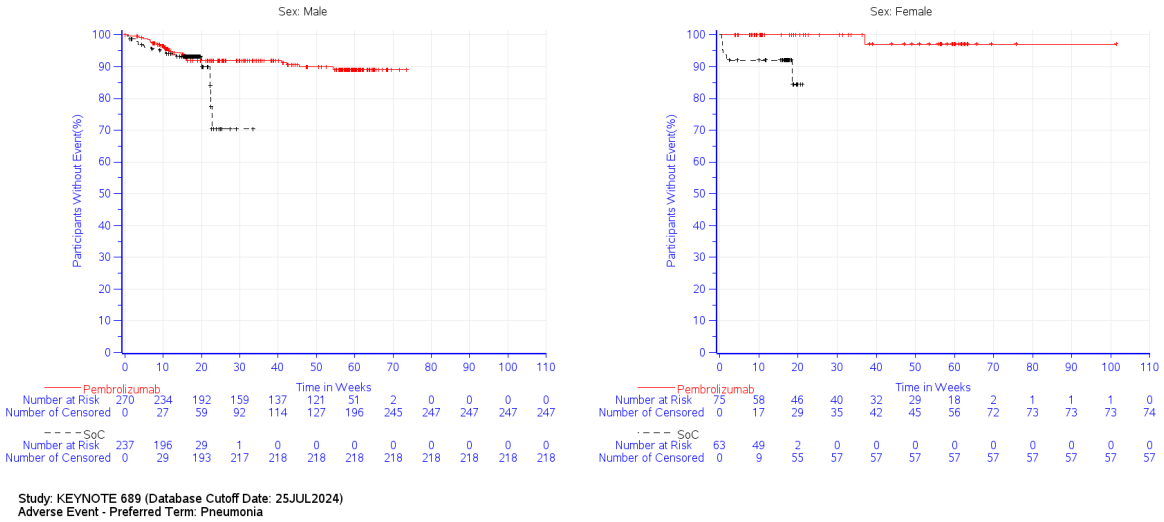


Abbildung 4G-12: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Unerwünschte Ereignisse gesamt (PT: Pneumonie) der Studie KEYNOTE 689

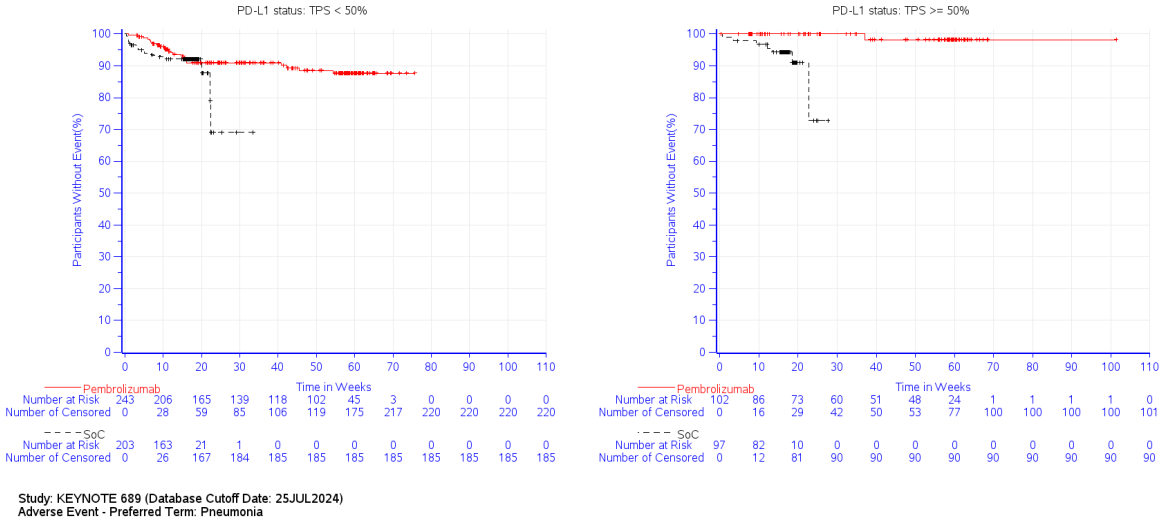


Abbildung 4G-13: Kaplan-Meier-Kurve für die Subgruppenanalyse nach PD-L1 TPS Status für den Endpunkt Unerwünschte Ereignisse gesamt (PT: Pneumonie) der Studie KEYNOTE 689

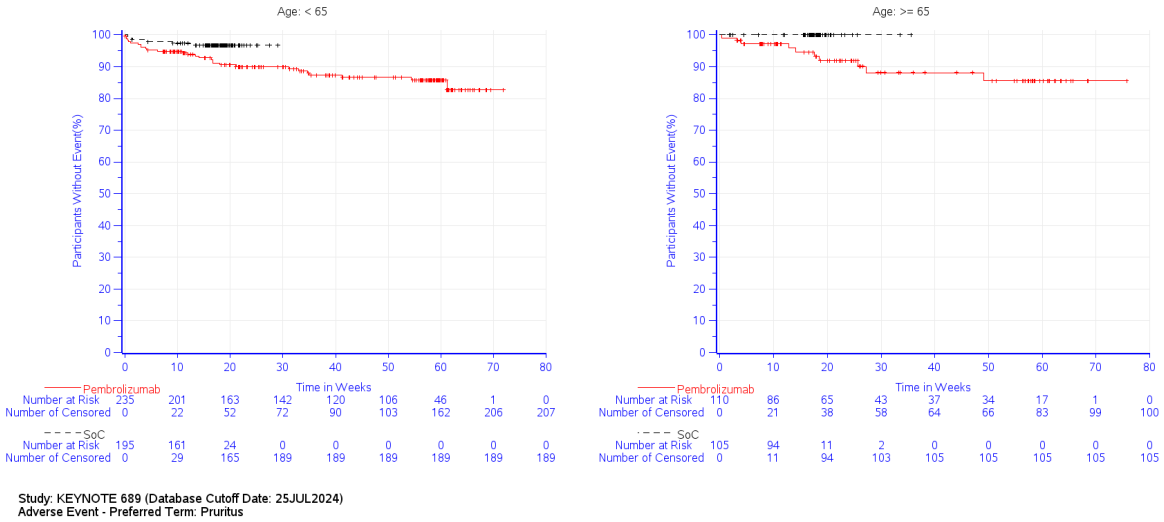


Abbildung 4G-14: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für den Endpunkt Unerwünschte Ereignisse gesamt (PT: Juckreiz) der Studie KEYNOTE 689

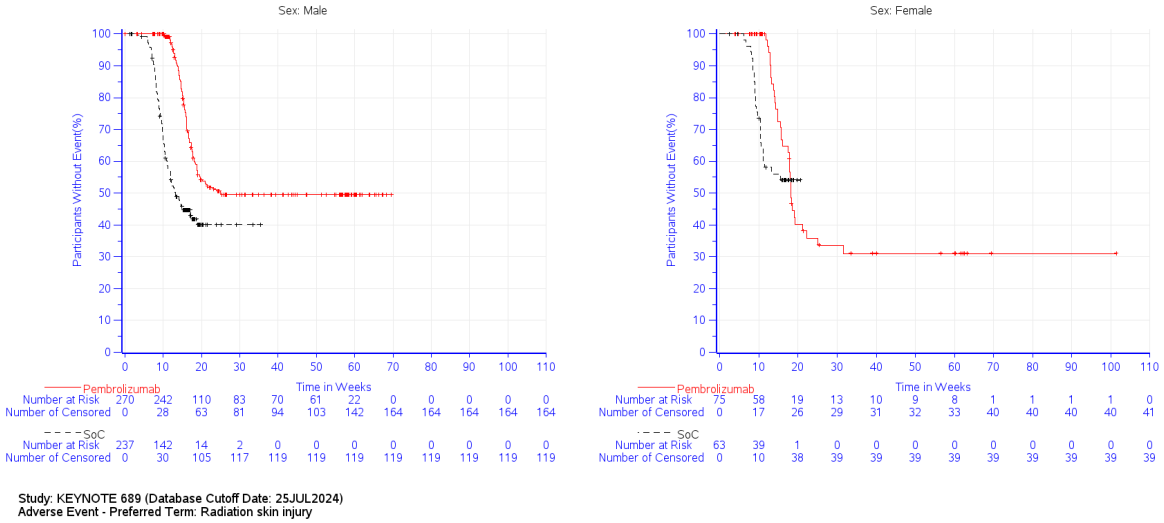


Abbildung 4G-15: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Unerwünschte Ereignisse gesamt (PT: Hautschädigung durch Strahlen) der Studie KEYNOTE 689

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Nicht zutreffend.

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

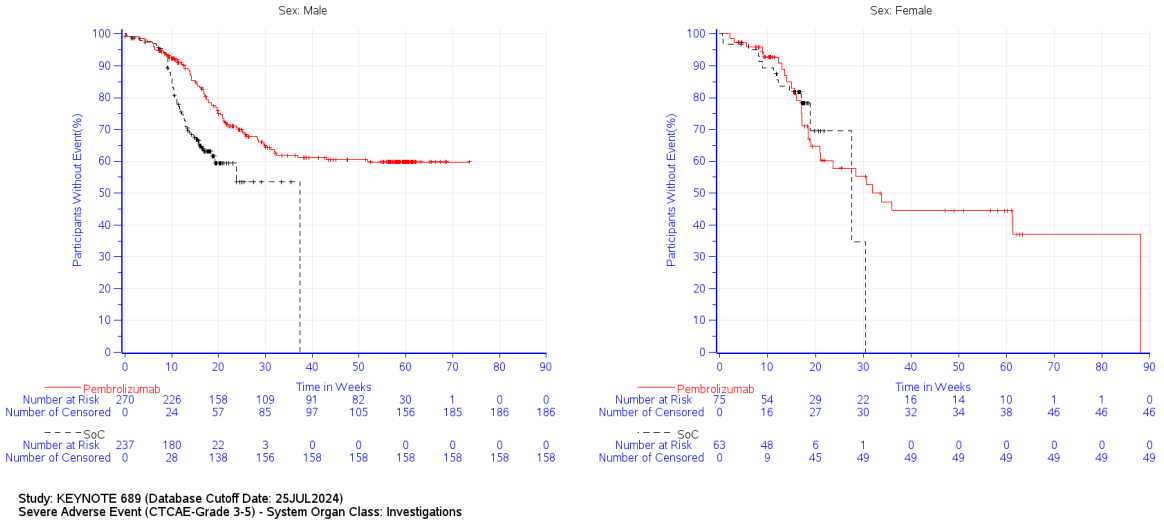


Abbildung 4G-16: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC: Untersuchungen) der Studie KEYNOTE 689

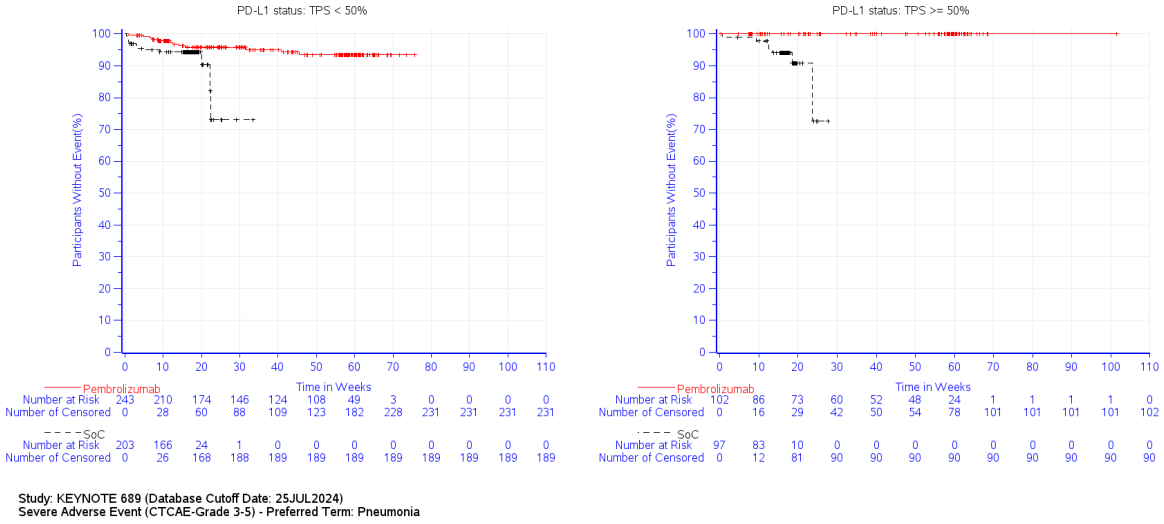


Abbildung 4G-17: Kaplan-Meier-Kurve für die Subgruppenanalyse nach PD-L1 TPS-Status für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (PT: Pneumonie) der Studie KEYNOTE 689

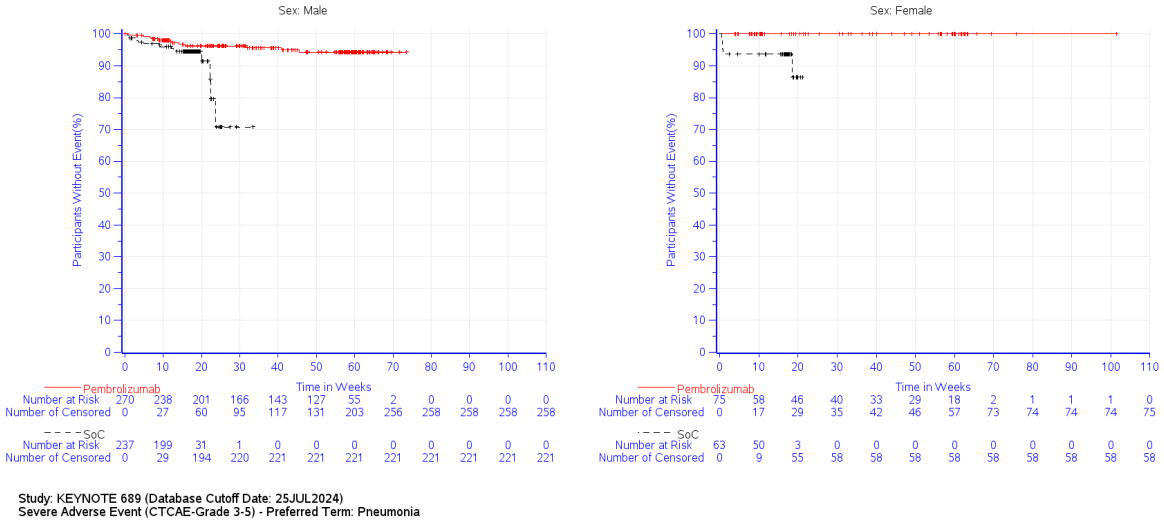


Abbildung 4G-18: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (PT: Pneumonie) der Studie KEYNOTE 689

Anhang 4-G5: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest ($p \geq 0,05$)

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

Alle Ergebnisse beziehen sich auf das zulassungsbegründende Database Cutoff Date (25. Juli 2024).

Mortalität

Gesamtüberleben

Tabelle 4G-7: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
Overall Survival	N[b]	Participants with Event n (%)	Median Time[c] in months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Sex									
Male	272	86 (31.6)	Not reached [-; -]	265	108 (40.8)	53.8 [41.9; -]	0.70 [0.53; 0.93]	0.014	0.585
Female	75	20 (26.7)	Not reached [-; -]	70	20 (28.6)	62.6 [-; -]	0.86 [0.46; 1.59]	0.622	
Age									
< 65	237	65 (27.4)	Not reached [-; -]	220	83 (37.7)	Not reached [44.3; -]	0.65 [0.47; 0.90]	0.010	0.281
≥ 65	110	41 (37.3)	Not reached [40.8; -]	115	45 (39.1)	50.1 [33.2; -]	0.87 [0.57; 1.33]	0.528	
Region									
North America	63	20 (31.7)	Not reached [34.5; -]	48	20 (41.7)	61.8 [17.1; -]	0.70 [0.37; 1.30]	0.253	0.828
European Union	134	37 (27.6)	Not reached [50.3; -]	139	45 (32.4)	62.6 [41.9; -]	0.78 [0.50; 1.20]	0.259	
Rest of World	150	49 (32.7)	Not reached [59.7; -]	148	63 (42.6)	Not reached [31.3; -]	0.67 [0.46; 0.98]	0.037	
Tumor Stage									
III	86	19 (22.1)	Not reached [-; -]	88	34 (38.6)	61.8 [41.9; -]	0.51 [0.29; 0.90]	0.019	0.145
IVA	259	87 (33.6)	Not reached [50.3; -]	246	94 (38.2)	Not reached [43.0; -]	0.80 [0.60; 1.08]	0.143	
Primary tumor site									
Oropharynx/Oral Cavity	244	73 (29.9)	Not reached [-; -]	242	97 (40.1)	61.8 [42.6; -]	0.68 [0.50; 0.92]	0.013	0.132
Larynx	77	24 (31.2)	Not reached [48.6; -]	67	27 (40.3)	49.2 [30.3; -]	0.65 [0.38; 1.14]	0.132	
Hypopharynx	26	9 (34.6)	47.4 [27.2; -]	25	4 (16.0)	Not reached [-; -]	2.03 [0.62; 6.60]	0.240	
PD-L1 status									
TPS < 50%	244	75 (30.7)	Not reached [-; -]	228	86 (37.7)	61.8 [43.0; -]	0.73 [0.53; 0.99]	0.043	0.992
TPS ≥ 50%	103	31 (30.1)	Not reached [47.4; -]	107	42 (39.3)	62.6 [33.2; -]	0.72 [0.46; 1.15]	0.174	

a: Database Cutoff Date: 25JUL2024

b: Number of participants: intention-to-treat population with CPS ≥ 1

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

d: Based on Cox regression model with treatment as a covariate. Ties are handled using Efron's method

e: Two-sided p-value using Wald test

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

CI: Confidence Interval; CPS: Combined Positive Score; PD-L1: Programmed Cell Death - Ligand 1; SoC: Standard of Care; TPS: Tumor Proportion Score

Morbidität

Ereignisfreies Überleben

Ereignisfreies Überleben gemäß BICR

Tabelle 4G-8: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Ereignisfreies Überleben gemäß BICR aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
Event-Free Survival (BICR 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	272	104 (38.2)	50.3 [37.3; -]	265	133 (50.2)	24.6 [13.8; 31.3]	0.65 [0.50; 0.84]	0.001	0.311
Female	75	24 (32.0)	Not reached [34.6; -]	70	23 (32.9)	Not reached [40.2; -]	0.91 [0.51; 1.62]	0.756	
Age									
< 65	237	82 (34.6)	59.7 [37.9; -]	220	99 (45.0)	30.4 [17.1; 57.0]	0.64 [0.48; 0.86]	0.003	0.292
≥ 65	110	46 (41.8)	40.8 [21.6; -]	115	57 (49.6)	26.8 [14.7; 40.2]	0.81 [0.55; 1.19]	0.285	
Region									
North America	63	23 (36.5)	37.9 [22.1; -]	48	22 (45.8)	21.8 [8.4; -]	0.66 [0.37; 1.19]	0.165	0.998
European Union	134	42 (31.3)	Not reached [40.8; -]	139	60 (43.2)	35.8 [22.7; -]	0.67 [0.45; 1.00]	0.047	
Rest of World	150	63 (42.0)	59.7 [25.2; -]	148	74 (50.0)	20.5 [10.7; 51.5]	0.70 [0.50; 0.98]	0.036	
PD-L1 status									
TPS < 50%	244	89 (36.5)	59.7 [37.9; -]	228	105 (46.1)	30.3 [18.8; 51.5]	0.69 [0.52; 0.92]	0.012	0.956
TPS ≥ 50%	103	39 (37.9)	Not reached [25.7; -]	107	51 (47.7)	26.3 [11.4; -]	0.69 [0.46; 1.05]	0.085	

a: Database Cutoff Date: 25JUL2024

b: Number of participants: intention-to-treat population with CPS ≥ 1

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

d: Based on Cox regression model with treatment as a covariate. Ties are handled using Efron's method

e: Two-sided p-value using Wald test

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)

BICR: Blinded Independent Central Review; CI: Confidence Interval; CPS: Combined Positive Score; PD-L1: Programmed Cell Death - Ligand 1; SoC: Standard of Care; TPS: Tumor Proportion Score

Zeit bis zur ersten Folgetherapie

Tabelle 4G-9: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Zeit bis zur ersten Folgetherapie aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	**Pembrolizumab**			**SoC**			**Pembrolizumab vs. SoC**		
Time to First Subsequent Oncologic Therapy	**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]**
Region									
North America	63	16 (25.4)	Not reached [-; -]	48	16 (33.3)	Not reached [13.5; -]	0.74 [0.37; 1.47]	0.385	0.937
European Union	134	29 (21.6)	Not reached [-; -]	139	37 (26.6)	Not reached [-; -]	0.80 [0.49; 1.30]	0.372	
Rest of World	150	31 (20.7)	Not reached [-; -]	148	31 (20.9)	Not reached [-; -]	0.87 [0.53; 1.42]	0.571	
Primary tumor site									
Oropharynx/Oral Cavity	244	58 (23.8)	Not reached [-; -]	242	72 (29.8)	Not reached [-; -]	0.76 [0.53; 1.07]	0.112	0.107
Larynx	77	11 (14.3)	Not reached [-; -]	67	9 (13.4)	Not reached [-; -]	0.96 [0.40; 2.33]	0.933	
Hypopharynx	26	7 (26.9)	Not reached [33.6; -]	25	2 (8.0)	Not reached [-; -]	3.54 [0.74; 17.07]	0.115	
PD-L1 status									
TPS < 50%	244	49 (20.1)	Not reached [-; -]	228	54 (23.7)	Not reached [-; -]	0.79 [0.54; 1.16]	0.231	0.678
TPS ≥ 50%	103	27 (26.2)	Not reached [-; -]	107	30 (28.0)	Not reached [-; -]	0.89 [0.53; 1.51]	0.674	

a: Database Cutoff Date: 25JUL2024

b: Number of participants: intention-to-treat population with CPS ≥ 1

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

d: Based on Cox regression model with treatment as a covariate. Ties are handled using Efron's method

e: Two-sided p-value using Wald test

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

CI: Confidence Interval; CPS: Combined Positive Score; PD-L1: Programmed Cell Death - Ligand 1; SoC: Standard of Care; TPS: Tumor Proportion Score

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30: Symptomskala Erschöpfung

Tabelle 4G-10: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Erschöpfung des EORTC QLQ-C30 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Fatigue	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	223	24.86 (22.92)	99	25.25 (18.84)	232	1.53 [-2.27; 5.33]	1.24	0.627	-	0.504
SoC	176	29.29 (27.28)	84	24.34 (18.61)	192	0.29 [-3.82; 4.40]	[-3.80; 6.29]			
≥ 65										
Pembrolizumab	101	28.27 (21.40)	40	27.50 (18.66)	108	5.77 [-0.49; 12.04]	5.56	0.192	-	
SoC	89	24.59 (23.00)	41	23.31 (26.15)	99	0.22 [-5.76; 6.19]	[-2.84; 13.95]			
Sex										
Female										
Pembrolizumab	72	28.40 (22.52)	30	25.19 (19.56)	75	-1.73 [-9.24; 5.78]	-1.07	0.836	-	0.748
SoC	53	29.14 (22.25)	29	26.05 (22.47)	60	-0.67 [-8.34; 7.01]	[-11.29; 9.16]			
Male										
Pembrolizumab	252	25.22 (22.46)	109	26.10 (18.60)	265	4.00 [0.44; 7.55]	3.19	0.189	-	
SoC	212	27.36 (26.86)	96	23.38 (20.99)	231	0.80 [-2.95; 4.56]	[-1.58; 7.97]			
Tumor Stage										
III										
Pembrolizumab	81	21.40 (19.15)	43	24.29 (18.82)	86	6.60 [0.83; 12.38]	8.01	0.071	-	0.380
SoC	68	29.90 (25.85)	29	25.29 (26.87)	75	-1.41 [-8.24; 5.43]	[-0.71; 16.73]			
IVA										
Pembrolizumab	241	27.11 (22.94)	96	26.62 (18.76)	252	1.83 [-1.98; 5.64]	1.45	0.563	-	
SoC	197	26.96 (26.04)	96	23.61 (19.43)	216	0.38 [-3.47; 4.23]	[-3.48; 6.38]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Fatigue	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	25.83 (22.19)	96	26.74 (18.14)	238	3.48 [-0.42; 7.38]	2.99	0.264	-	0.768
SoC	182	28.63 (26.69)	87	24.90 (22.98)	197	0.49 [-3.61; 4.58]	[-2.27; 8.25]			
TPS ≥50%										
Pembrolizumab	99	26.15 (23.24)	43	24.03 (20.13)	102	1.32 [-4.49; 7.14]	1.78	0.646	-	
SoC	83	25.70 (24.35)	38	21.93 (16.84)	94	-0.45 [-6.46; 5.55]	[-5.88; 9.43]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	29.06 (26.68)	10	31.11 (10.21)	26	8.68 [-0.03; 17.38]	1.99	0.764	-	0.852
SoC	24	18.52 (16.27)	16	25.69 (24.59)	24	6.68 [-4.87; 18.24]	[-11.06; 15.05]			
Larynx										
Pembrolizumab	67	28.52 (19.27)	34	25.49 (17.20)	74	1.33 [-5.10; 7.75]	2.08	0.636	-	
SoC	52	32.05 (27.63)	24	24.54 (21.73)	58	-0.76 [-7.25; 5.73]	[-6.56; 10.73]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	24.82 (22.83)	95	25.50 (19.97)	240	3.02 [-1.02; 7.06]	3.87	0.141	-	
SoC	189	27.69 (26.30)	85	23.53 (20.75)	209	-0.85 [-4.69; 3.00]	[-1.28; 9.02]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-C30: Übelkeit und Erbrechen

Tabelle 4G-11: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Übelkeit und Erbrechen des EORTC QLQ-C30 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Nausea and vomiting	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	223	4.78 (13.12)	99	3.87 (12.33)	232	0.29 [-2.16; 2.75]	-1.43	0.404	-	0.246
SoC	176	5.59 (12.68)	84	5.36 (11.62)	192	1.73 [-0.92; 4.37]	[-4.81; 1.94]			
≥ 65										
Pembrolizumab	101	4.46 (10.77)	40	4.58 (11.93)	108	4.12 [0.80; 7.44]	2.63	0.294	-	
SoC	89	3.00 (9.59)	41	5.28 (17.65)	99	1.48 [-2.22; 5.19]	[-2.32; 7.59]			
Sex										
Female										
Pembrolizumab	72	5.09 (11.41)	30	7.22 (21.75)	75	6.10 [-0.04; 12.23]	5.88	0.178	-	0.169
SoC	53	5.03 (10.12)	29	5.75 (12.81)	60	0.22 [-6.11; 6.55]	[-2.74; 14.50]			
Male										
Pembrolizumab	252	4.56 (12.72)	109	3.21 (7.68)	265	1.21 [-0.75; 3.16]	-1.03	0.461	-	
SoC	212	4.64 (12.17)	96	5.21 (14.17)	231	2.24 [0.16; 4.32]	[-3.79; 1.72]			
Tumor Stage										
III										
Pembrolizumab	81	3.50 (8.63)	43	5.04 (16.88)	86	6.47 [2.20; 10.74]	1.74	0.590	-	0.755
SoC	68	5.64 (13.39)	29	10.34 (21.55)	75	4.73 [-0.01; 9.46]	[-4.65; 8.14]			
IVA										
Pembrolizumab	241	4.56 (12.26)	96	3.65 (9.43)	252	-1.38 [-3.52; 0.75]	-1.37	0.324	-	
SoC	197	4.40 (11.19)	96	3.82 (10.11)	216	-0.01 [-2.24; 2.22]	[-4.11; 1.36]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	5.19 (13.37)	96	4.86 (13.87)	238	3.15 [0.54; 5.76]	-0.47	0.806	-	0.439
SoC	182	4.49 (11.87)	87	6.13 (15.06)	197	3.62 [0.86; 6.37]	[-4.22; 3.28]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Nausea and vomiting	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
TPS ≥50%										
Pembrolizumab	99	3.54 (9.90)	43	2.33 (6.88)	102	-1.83 [-5.04; 1.38]	-0.66	0.736	-	
SoC	83	5.22 (11.62)	38	3.51 (10.37)	94	-1.17 [-4.29; 1.95]	[-4.57; 3.24]			
Region										
European Union										
Pembrolizumab	124	3.09 (11.32)	54	5.56 (17.13)	132	3.53 [-0.83; 7.90]	3.10	0.199	-	0.099
SoC	113	3.24 (10.88)	55	2.73 (7.70)	126	0.44 [-2.39; 3.27]	[-1.63; 7.83]			
North America										
Pembrolizumab	56	8.93 (18.52)	11	4.55 (10.78)	59	2.48 [-3.70; 8.66]	3.62	0.344	-	
SoC	31	5.91 (12.58)	12	1.39 (4.81)	37	-1.14 [-6.18; 3.89]	[-3.90; 11.15]			
Rest of World										
Pembrolizumab	144	4.40 (9.85)	74	2.93 (6.96)	149	-0.26 [-2.40; 1.88]	-3.53	0.116	-	
SoC	121	5.79 (12.31)	58	8.62 (18.27)	128	3.27 [-0.65; 7.20]	[-7.94; 0.88]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	8.33 (19.00)	10	3.33 (7.03)	26	0.23 [-4.72; 5.18]	-3.74	0.315	-	0.273
SoC	24	2.78 (8.03)	16	7.29 (13.57)	24	3.97 [-1.72; 9.65]	[-11.04; 3.57]			
Larynx										
Pembrolizumab	67	6.47 (12.96)	34	4.90 (8.73)	74	1.78 [-1.78; 5.33]	-2.47	0.505	-	
SoC	52	7.05 (17.57)	24	9.03 (23.04)	58	4.25 [-2.16; 10.66]	[-9.75; 4.81]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	3.75 (11.22)	95	3.86 (13.63)	240	0.93 [-1.82; 3.68]	0.54	0.749	-	
SoC	189	4.32 (10.05)	85	3.92 (9.84)	209	0.39 [-1.88; 2.66]	[-2.79; 3.87]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-C30: Schmerzen

Tabelle 4G-12: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Schmerzen des EORTC QLQ-C30 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Pain	**Baseline**		**Post-Adjuvant CRT/RT Week 51**		**Change from Baseline to Post-Adjuvant CRT/RT Week 51**		**Pembrolizumab vs. SoC**			**p-Value for Interaction Test[f]**
							Mean Difference at Post-Adjuvant CRT/RT Week 51		**Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51**	
	N[b]	**Mean (SD)**	**N[b]**	**Mean (SD)**	**N[c]**	**Mean [95 %-CI][d]**	**[95 %-CI][d]**	**p-Value**	**[95 %-CI][e]**	
Age										
< 65										
Pembrolizumab	223	34.60 (29.76)	99	19.53 (20.90)	232	-12.98 [-17.42; -8.54]	-2.15	0.456	-	0.802
SoC	176	36.93 (29.33)	84	21.23 (20.75)	192	-10.83 [-15.57; -6.09]	[-7.83; 3.53]			
≥ 65										
Pembrolizumab	101	27.72 (27.31)	40	16.67 (20.67)	108	-7.06 [-14.12; -0.00]	-0.50	0.911	-	
SoC	89	27.34 (24.78)	41	16.67 (22.97)	99	-6.56 [-13.35; 0.24]	[-9.41; 8.40]			
Sex										
Female										
Pembrolizumab	72	36.34 (31.69)	30	22.22 (25.27)	75	-11.44 [-20.77; -2.11]	3.25	0.587	-	0.280
SoC	53	40.25 (29.50)	29	21.84 (24.03)	60	-14.69 [-24.19; -5.19]	[-8.63; 15.12]			
Male										
Pembrolizumab	252	31.35 (28.35)	109	17.74 (19.41)	265	-10.01 [-14.04; -5.98]	-2.15	0.416	-	
SoC	212	32.08 (27.70)	96	19.10 (20.80)	231	-7.86 [-12.10; -3.63]	[-7.34; 3.05]			
Tumor Stage										
III										
Pembrolizumab	81	28.19 (26.17)	43	18.99 (20.76)	86	-8.32 [-15.38; -1.26]	3.10	0.508	-	0.285
SoC	68	35.05 (28.96)	29	17.24 (22.49)	75	-11.42 [-19.29; -3.56]	[-6.16; 12.36]			
IVA										
Pembrolizumab	241	33.68 (29.79)	96	18.58 (20.92)	252	-11.23 [-15.64; -6.81]	-2.08	0.463	-	
SoC	197	33.25 (28.00)	96	20.49 (21.29)	216	-9.14 [-13.60; -4.69]	[-7.66; 3.49]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Pain	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	32.37 (28.92)	96	16.67 (18.89)	238	-11.19 [-15.53; -6.85]	-3.50	0.218	-	0.056
SoC	182	32.69 (27.94)	87	21.65 (22.03)	197	-7.69 [-12.24; -3.14]	[-9.09; 2.09]			
TPS ≥50%										
Pembrolizumab	99	32.66 (29.83)	43	23.26 (24.16)	102	-9.48 [-16.68; -2.28]	4.69	0.298	-	
SoC	83	35.94 (28.81)	38	15.35 (19.90)	94	-14.17 [-21.55; -6.79]	[-4.20; 13.57]			
Region										
European Union										
Pembrolizumab	124	28.63 (27.35)	54	24.07 (22.59)	132	-2.43 [-8.65; 3.78]	2.10	0.589	-	0.554
SoC	113	33.19 (26.86)	55	24.85 (23.76)	126	-4.53 [-10.34; 1.28]	[-5.52; 9.71]			
North America										
Pembrolizumab	56	44.64 (32.12)	11	22.73 (20.10)	59	-13.85 [-27.57; -0.13]	5.06	0.577	-	
SoC	31	46.77 (31.16)	12	15.28 (19.41)	37	-18.91 [-31.97; -5.86]	[-12.75; 22.87]			
Rest of World										
Pembrolizumab	144	31.02 (28.40)	74	14.19 (18.65)	149	-14.95 [-19.95; -9.95]	-2.75	0.352	-	
SoC	121	30.85 (27.94)	58	15.80 (18.84)	128	-12.20 [-17.04; -7.36]	[-8.54; 3.04]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	32.69 (35.11)	10	20.00 (21.94)	26	-2.42 [-13.67; 8.84]	-0.19	0.980	-	0.884
SoC	24	17.36 (15.91)	16	19.79 (23.74)	24	-2.22 [-15.27; 10.82]	[-15.55; 15.16]			
Larynx										
Pembrolizumab	67	24.88 (25.19)	34	12.25 (14.97)	74	-7.25 [-14.03; -0.47]	2.92	0.476	-	
SoC	52	28.53 (26.88)	24	13.89 (18.82)	58	-10.17 [-16.54; -3.80]	[-5.12; 10.97]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	34.63 (29.25)	95	20.88 (22.14)	240	-12.22 [-16.98; -7.46]	-0.71	0.809	-	
SoC	189	37.21 (28.91)	85	21.37 (21.76)	209	-11.51 [-16.04; -6.97]	[-6.49; 5.06]			

a: Database Cutoff Date: 25JUL2024
b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint
c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis
d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Pain	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero										
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction										
CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score										

EORTC QLQ-C30: Atemnot (Dyspnoe)

Tabelle 4G-13: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Atemnot (Dyspnoe) des EORTC QLQ-C30 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Dyspnea	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	223	12.56 (23.50)	99	13.80 (19.64)	232	2.24 [-1.52; 6.01]	0.58	0.824	-	0.962
SoC	176	12.50 (22.99)	84	12.70 (19.29)	192	1.67 [-2.42; 5.75]	[-4.52; 5.67]			
≥ 65										
Pembrolizumab	101	19.14 (22.78)	40	17.50 (22.63)	108	2.16 [-4.85; 9.17]	0.93	0.844	-	
SoC	89	15.36 (26.14)	41	18.70 (26.92)	99	1.23 [-5.81; 8.26]	[-8.46; 10.33]			
Sex										
Female										
Pembrolizumab	72	9.72 (19.73)	30	13.33 (18.77)	75	4.89 [-1.41; 11.18]	2.87	0.516	-	0.937
SoC	53	8.81 (20.83)	29	12.64 (25.84)	60	2.02 [-4.41; 8.45]	[-5.93; 11.67]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Dyspnea	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Male										
Pembrolizumab	252	16.01 (24.26)	109	15.29 (21.05)	265	1.80 [-2.07; 5.67]	1.35	0.609	-	
SoC	212	14.62 (24.74)	96	15.28 (21.04)	231	0.45 [-3.65; 4.56]	[-3.83; 6.53]			
Tumor Stage										
III										
Pembrolizumab	81	12.35 (21.37)	43	15.50 (22.24)	86	6.19 [0.23; 12.14]	9.50	0.039	0.47	0.054
SoC	68	13.73 (23.91)	29	10.34 (23.74)	75	-3.31 [-10.39; 3.78]	[0.48; 18.51]		[0.02; 0.92]	
IVA										
Pembrolizumab	241	15.08 (23.93)	96	14.58 (19.83)	252	1.47 [-2.55; 5.50]	-1.13	0.671	-	
SoC	197	13.37 (24.20)	96	15.97 (21.62)	216	2.60 [-1.45; 6.66]	[-6.37; 4.11]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	17.04 (24.42)	96	16.67 (21.63)	238	1.93 [-2.31; 6.18]	-0.55	0.853	-	0.239
SoC	182	14.29 (24.09)	87	17.62 (24.29)	197	2.48 [-2.00; 6.97]	[-6.36; 5.26]			
TPS ≥50%										
Pembrolizumab	99	9.09 (20.10)	43	10.85 (17.40)	102	2.93 [-2.18; 8.04]	4.27	0.211	-	
SoC	83	11.65 (24.10)	38	7.89 (14.36)	94	-1.34 [-6.98; 4.30]	[-2.48; 11.02]			
Region										
European Union										
Pembrolizumab	124	15.59 (25.30)	54	15.43 (20.18)	132	2.77 [-2.64; 8.18]	0.28	0.937	-	0.804
SoC	113	14.45 (27.05)	55	15.76 (24.72)	126	2.49 [-2.85; 7.82]	[-6.74; 7.31]			
North America										
Pembrolizumab	56	11.90 (21.49)	11	12.12 (16.82)	59	2.20 [-5.98; 10.39]	4.69	0.362	-	
SoC	31	9.68 (15.38)	12	5.56 (12.97)	37	-2.49 [-10.00; 5.03]	[-5.41; 14.79]			
Rest of World										
Pembrolizumab	144	14.81 (22.57)	74	14.86 (21.47)	149	2.13 [-2.56; 6.81]	2.10	0.513	-	
SoC	121	13.50 (23.01)	58	15.52 (20.91)	128	0.03 [-4.95; 5.02]	[-4.18; 8.37]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	23.08 (24.53)	10	23.33 (27.44)	26	-4.33 [-13.06; 4.39]	-5.23	0.411	-	0.070
SoC	24	11.11 (16.05)	16	16.67 (21.08)	24	0.90 [-8.55; 10.34]	[-17.74; 7.28]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Dyspnea	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Larynx										
Pembrolizumab	67	32.84 (29.30)	34	23.53 (26.63)	74	-5.24 [-14.89; 4.41]	11.13	0.060	-	
SoC	52	33.97 (35.85)	24	18.06 (27.77)	58	-16.37 [-25.50; -7.25]	[-0.48; 22.74]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	8.37 (17.78)	95	10.88 (15.71)	240	3.95 [0.71; 7.18]	-2.04	0.400	-	
SoC	189	8.11 (16.98)	85	13.33 (20.70)	209	5.99 [2.25; 9.72]	[-6.79; 2.71]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-C30: Schlaflosigkeit

Tabelle 4G-14: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Schlaflosigkeit des EORTC QLQ-C30 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Insomnia	**Baseline**		**Post-Adjuvant CRT/RT Week 51**		**Change from Baseline to Post-Adjuvant CRT/RT Week 51**		**Pembrolizumab vs. SoC**			**p-Value for Interaction Test[f]**
							Mean Difference at Post-Adjuvant CRT/RT Week 51		**Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51**	
	N[b]	**Mean (SD)**	**N[b]**	**Mean (SD)**	**N[c]**	**Mean [95 %-CI][d]**	**[95 %-CI][d]**	**p-Value**	**[95 %-CI][e]**	
Sex										
Female										
Pembrolizumab	72	40.74 (29.19)	30	31.11 (24.66)	75	-9.20 [-18.65; 0.26]	-0.69	0.912	-	0.580
SoC	53	40.88 (33.74)	29	31.03 (28.07)	60	-8.51 [-18.23; 1.22]	[-13.15; 11.77]			
Male										
Pembrolizumab	252	31.35 (32.05)	109	19.27 (26.17)	265	-10.27 [-15.06; -5.48]	-5.45	0.088	-	
SoC	212	32.55 (31.54)	96	24.31 (25.35)	231	-4.82 [-9.88; 0.24]	[-11.71; 0.82]			
Tumor Stage										
III										
Pembrolizumab	81	31.28 (31.77)	43	25.58 (28.02)	86	-3.85 [-11.90; 4.20]	4.92	0.388	-	0.066
SoC	68	31.37 (31.48)	29	21.84 (25.63)	75	-8.78 [-18.17; 0.62]	[-6.36; 16.21]			
IVA										
Pembrolizumab	241	34.02 (31.39)	96	20.14 (25.35)	252	-12.13 [-17.15; -7.11]	-7.54	0.022	-0.31	
SoC	197	35.19 (32.33)	96	27.08 (26.19)	216	-4.59 [-9.66; 0.48]	[-14.00; -1.08]		[-0.57; -0.04]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	34.07 (32.03)	96	22.57 (27.57)	238	-10.16 [-15.44; -4.88]	-2.09	0.555	-	0.191
SoC	182	35.53 (32.04)	87	24.52 (26.15)	197	-8.07 [-13.63; -2.52]	[-9.04; 4.87]			
TPS ≥50%										
Pembrolizumab	99	31.99 (30.83)	43	20.16 (23.16)	102	-9.13 [-16.20; -2.06]	-9.71	0.039	-0.43	
SoC	83	31.33 (32.24)	38	28.95 (25.90)	94	0.58 [-6.80; 7.97]	[-18.93; -0.50]		[-0.84; -0.02]	

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Insomnia	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Region										
European Union										
Pembrolizumab	124	33.87 (32.92)	54	27.16 (26.76)	132	-6.05 [-12.90; 0.79]	0.54	0.906	-	0.152
SoC	113	34.22 (33.17)	55	24.85 (28.12)	126	-6.59 [-13.66; 0.48]	[-8.38; 9.45]			
North America										
Pembrolizumab	56	38.69 (32.27)	11	36.36 (31.46)	59	-7.96 [-22.77; 6.85]	2.94	0.734	-	
SoC	31	47.31 (35.25)	12	22.22 (21.71)	37	-10.90 [-22.13; 0.33]	[-14.10; 19.98]			
Rest of World										
Pembrolizumab	144	31.02 (30.19)	74	15.77 (23.55)	149	-13.52 [-18.96; -8.08]	-10.36	0.004	-0.39	
SoC	121	30.85 (29.55)	58	27.59 (25.08)	128	-3.15 [-9.03; 2.72]	[-17.48; -3.25]		[-0.66; -0.12]	
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	33.33 (33.99)	10	16.67 (23.57)	26	-21.43 [-31.61; -11.24]	-17.31	0.007	-0.89	0.188
SoC	24	25.00 (24.57)	16	22.92 (29.11)	24	-4.12 [-12.46; 4.22]	[-29.88; -4.74]		[-1.53; -0.24]	
Larynx										
Pembrolizumab	67	31.34 (34.27)	34	14.71 (22.01)	74	-15.85 [-24.95; -6.76]	-13.98	0.021	-0.47	
SoC	52	39.10 (32.82)	24	30.56 (25.85)	58	-1.87 [-12.73; 8.98]	[-25.87; -2.09]		[-0.86; -0.07]	
Oropharynx/Oral Cavity										
Pembrolizumab	231	34.05 (30.68)	95	24.91 (27.49)	240	-8.50 [-13.59; -3.41]	-1.55	0.641	-	
SoC	189	34.04 (32.61)	85	25.10 (25.67)	209	-6.95 [-12.01; -1.89]	[-8.07; 4.97]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-C30: Appetitverlust

Tabelle 4G-15: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Appetitverlust des EORTC QLQ-C30 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Appetite loss	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	223	19.88 (27.19)	99	15.82 (22.51)	232	-3.52 [-8.28; 1.23]	1.97	0.531	-	0.754
SoC	176	26.52 (32.72)	84	15.48 (22.82)	192	-5.50 [-10.59; -0.41]	[-4.23; 8.18]			
≥ 65										
Pembrolizumab	101	20.13 (26.28)	40	17.50 (25.02)	108	2.99 [-5.35; 11.34]	6.59	0.248	-	
SoC	89	22.85 (30.81)	41	18.70 (30.78)	99	-3.60 [-11.89; 4.69]	[-4.67; 17.86]			
Sex										
Female										
Pembrolizumab	72	25.46 (27.69)	30	15.56 (20.96)	75	-9.62 [-19.44; 0.20]	-4.04	0.536	-	0.236
SoC	53	31.45 (27.28)	29	26.44 (30.05)	60	-5.57 [-15.33; 4.19]	[-17.02; 8.93]			
Male										
Pembrolizumab	252	18.39 (26.47)	109	16.51 (23.84)	265	-0.10 [-4.66; 4.46]	4.47	0.146	-	
SoC	212	23.74 (33.05)	96	13.54 (23.48)	231	-4.57 [-9.37; 0.23]	[-1.57; 10.50]			
Tumor Stage										
III										
Pembrolizumab	81	15.23 (23.00)	43	14.73 (20.96)	86	1.74 [-6.00; 9.47]	-3.24	0.571	-	0.121
SoC	68	24.51 (31.34)	29	21.84 (32.46)	75	4.97 [-4.02; 13.97]	[-14.54; 8.07]			
IVA										
Pembrolizumab	241	21.30 (27.85)	96	17.01 (24.18)	252	-3.37 [-8.30; 1.55]	4.36	0.173	-	
SoC	197	25.55 (32.41)	96	14.93 (23.13)	216	-7.74 [-12.67; -2.80]	[-1.93; 10.66]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	19.26 (26.06)	96	18.40 (24.60)	238	1.91 [-3.29; 7.12]	2.50	0.486	-	0.706
SoC	182	24.36 (32.10)	87	18.01 (27.75)	197	-0.58 [-6.02; 4.86]	[-4.56; 9.55]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Appetite loss	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
TPS ≥50%										
Pembrolizumab	99	21.55 (28.70)	43	11.63 (19.08)	102	-10.34 [-16.77; -3.91]	2.96	0.467	-	
SoC	83	27.31 (32.15)	38	13.16 (19.82)	94	-13.30 [-19.97; -6.63]	[-5.10; 11.02]			
Region										
European Union										
Pembrolizumab	124	18.28 (25.27)	54	20.99 (27.70)	132	2.01 [-5.50; 9.52]	3.00	0.525	-	0.997
SoC	113	24.19 (32.20)	55	19.39 (26.21)	126	-0.99 [-7.82; 5.85]	[-6.25; 12.24]			
North America										
Pembrolizumab	56	24.40 (30.81)	11	15.15 (22.92)	59	-6.47 [-17.05; 4.10]	4.27	0.610	-	
SoC	31	38.71 (37.61)	12	19.44 (30.01)	37	-10.74 [-24.61; 3.13]	[-12.20; 20.74]			
Rest of World										
Pembrolizumab	144	19.68 (26.57)	74	13.06 (18.97)	149	-3.18 [-7.41; 1.04]	3.05	0.384	-	
SoC	121	22.87 (29.82)	58	13.22 (24.13)	128	-6.24 [-12.30; -0.17]	[-3.82; 9.92]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	20.51 (28.40)	10	13.33 (23.31)	26	-2.51 [-11.19; 6.17]	0.00	> 0.999	-	0.983
SoC	24	15.28 (19.61)	16	12.50 (29.50)	24	-2.51 [-16.83; 11.81]	[-15.84; 15.84]			
Larynx										
Pembrolizumab	67	15.42 (24.15)	34	13.73 (20.30)	74	3.99 [-2.33; 10.31]	7.97	0.108	-	
SoC	52	28.21 (35.78)	24	13.89 (27.66)	58	-3.98 [-11.88; 3.91]	[-1.76; 17.70]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	21.21 (27.40)	95	17.54 (24.23)	240	-2.24 [-7.28; 2.80]	3.14	0.352	-	
SoC	189	25.75 (32.18)	85	18.04 (24.43)	209	-5.38 [-10.72; -0.04]	[-3.47; 9.75]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-C30: Verstopfung

Tabelle 4G-16: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Verstopfung des EORTC QLQ-C30 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Constipation	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	223	15.40 (26.42)	99	7.74 (16.38)	232	-5.68 [-9.78; -1.59]	-2.04	0.437	-	0.947
SoC	176	15.91 (24.68)	84	11.11 (20.91)	192	-3.65 [-8.07; 0.78]	[-7.20; 3.12]			
≥ 65										
Pembrolizumab	101	15.84 (26.91)	40	10.83 (21.86)	108	-2.93 [-10.19; 4.33]	-2.47	0.599	-	
SoC	89	15.73 (23.62)	41	15.45 (23.68)	99	-0.46 [-7.48; 6.56]	[-11.77; 6.83]			
Sex										
Female										
Pembrolizumab	72	24.07 (30.76)	30	10.00 (19.87)	75	-10.75 [-19.01; -2.48]	-9.01	0.099	-	0.193
SoC	53	22.64 (24.26)	29	20.69 (27.33)	60	-1.74 [-10.36; 6.89]	[-19.76; 1.74]			
Male										
Pembrolizumab	252	13.10 (24.73)	109	8.26 (17.66)	265	-3.89 [-7.82; 0.04]	-0.99	0.691	-	
SoC	212	14.15 (24.04)	96	10.07 (19.42)	231	-2.90 [-7.05; 1.26]	[-5.89; 3.91]			
Tumor Stage										
III										
Pembrolizumab	81	12.35 (22.01)	43	9.30 (18.29)	86	-4.30 [-10.79; 2.20]	-2.65	0.555	-	0.632
SoC	68	17.65 (26.69)	29	14.94 (24.54)	75	-1.64 [-9.09; 5.80]	[-11.53; 6.22]			
IVA										
Pembrolizumab	241	16.32 (27.41)	96	8.33 (18.10)	252	-4.36 [-8.57; -0.15]	-1.69	0.530	-	
SoC	197	15.23 (23.44)	96	11.81 (21.07)	216	-2.67 [-6.97; 1.62]	[-6.97; 3.60]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	15.11 (26.52)	96	8.33 (16.75)	238	-4.20 [-8.20; -0.20]	0.06	0.980	-	0.269
SoC	182	14.10 (23.03)	87	9.96 (18.41)	197	-4.26 [-8.42; -0.10]	[-4.88; 5.00]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Constipation	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
TPS ≥50%										
Pembrolizumab	99	16.50 (26.67)	43	9.30 (20.99)	102	-6.68 [-13.90; 0.55]	-6.68	0.168	-	
SoC	83	19.68 (26.56)	38	18.42 (27.62)	94	0.01 [-7.65; 7.67]	[-16.23; 2.86]			
Region										
European Union										
Pembrolizumab	124	13.71 (25.51)	54	8.64 (17.36)	132	-3.59 [-8.60; 1.42]	-4.26	0.237	-	0.622
SoC	113	13.57 (24.25)	55	12.12 (24.31)	126	0.67 [-5.40; 6.73]	[-11.31; 2.80]			
North America										
Pembrolizumab	56	20.83 (28.11)	11	6.06 (13.48)	59	-6.81 [-16.26; 2.63]	-4.06	0.562	-	
SoC	31	23.66 (28.79)	12	13.89 (17.16)	37	-2.76 [-13.90; 8.39]	[-17.81; 9.70]			
Rest of World										
Pembrolizumab	144	15.05 (26.69)	74	9.01 (19.35)	149	-3.79 [-8.91; 1.34]	0.11	0.972	-	
SoC	121	15.98 (22.81)	58	12.64 (20.55)	128	-3.90 [-9.19; 1.40]	[-6.26; 6.49]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	20.51 (31.38)	10	20.00 (32.20)	26	0.67 [-20.19; 21.53]	0.84	0.939	-	0.785
SoC	24	11.11 (18.82)	16	12.50 (20.64)	24	-0.17 [-12.12; 11.78]	[-20.86; 22.55]			
Larynx										
Pembrolizumab	67	10.45 (21.87)	34	5.88 (15.29)	74	-2.71 [-9.12; 3.71]	1.20	0.771	-	
SoC	52	14.74 (20.25)	24	11.11 (18.82)	58	-3.91 [-11.00; 3.19]	[-6.90; 9.30]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	16.45 (27.07)	95	8.42 (16.82)	240	-5.27 [-8.98; -1.56]	-2.67	0.325	-	
SoC	189	16.75 (25.87)	85	12.94 (23.06)	209	-2.60 [-7.31; 2.10]	[-7.99; 2.65]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-C30: Diarrhö

Tabelle 4G-17: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Diarrhö des EORTC QLQ-C30 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Diarrhea	**Baseline**		**Post-Adjuvant CRT/RT Week 51**		**Change from Baseline to Post-Adjuvant CRT/RT Week 51**		**Pembrolizumab vs. SoC**			**p-Value for Interaction Test[f]**
							Mean Difference at Post-Adjuvant CRT/RT Week 51		**Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51**	
	N[b]	**Mean (SD)**	**N[b]**	**Mean (SD)**	**N[c]**	**Mean [95 %-CI][d]**	**[95 %-CI][d]**	**p-Value**	**[95 %-CI][e]**	
Age										
< 65										
Pembrolizumab	223	6.28 (15.83)	99	9.76 (21.95)	232	3.12 [-0.37; 6.61]	0.25	0.921	-	0.900
SoC	176	6.06 (16.75)	84	8.33 (15.41)	192	2.87 [-0.95; 6.70]	[-4.69; 5.19]			
≥ 65										
Pembrolizumab	101	9.24 (18.93)	40	5.83 (14.88)	108	2.60 [-2.45; 7.64]	2.22	0.513	-	
SoC	89	3.37 (10.11)	41	7.32 (17.50)	99	0.38 [-4.92; 5.68]	[-4.50; 8.93]			
Tumor Stage										
III										
Pembrolizumab	81	8.64 (17.30)	43	6.20 (16.68)	86	1.49 [-4.16; 7.14]	-3.46	0.396	-	0.129
SoC	68	3.43 (10.20)	29	10.34 (20.13)	75	4.95 [-1.72; 11.62]	[-11.52; 4.60]			
IVA										
Pembrolizumab	241	6.64 (16.73)	96	9.72 (21.58)	252	3.08 [-0.30; 6.47]	2.34	0.320	-	
SoC	197	5.75 (16.17)	96	7.29 (14.67)	216	0.75 [-2.70; 4.20]	[-2.28; 6.95]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	8.97 (20.13)	10	0.00 (0.00)	26	-8.65 [-16.47; -0.84]	-7.78	0.084	-	0.260
SoC	24	8.33 (14.74)	16	8.33 (14.91)	24	-0.87 [-8.57; 6.83]	[-16.60; 1.04]			
Larynx										
Pembrolizumab	67	7.46 (16.23)	34	3.92 (13.64)	74	-2.34 [-6.48; 1.81]	-2.77	0.459	-	
SoC	52	5.77 (14.34)	24	6.94 (16.97)	58	0.44 [-6.22; 7.09]	[-10.12; 4.57]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	6.93 (16.74)	95	11.23 (22.60)	240	5.40 [1.18; 9.63]	2.94	0.262	-	
SoC	189	4.59 (15.07)	85	8.24 (16.19)	209	2.46 [-0.83; 5.75]	[-2.20; 8.08]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Symptom Scales Diarrhea	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	

a: Database Cutoff Date: 25JUL2024
b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint
c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis
d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction
e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction
CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care

EORTC QLQ-H&N35: Symptomskala Schmerzen

Tabelle 4G-18: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Schmerzen des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Pain	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	222	35.02 (25.96)	99	17.51 (17.76)	232	-16.49 [-20.24; -12.73]	-3.90	0.112	-	0.649
SoC	176	37.93 (27.63)	84	21.13 (19.72)	192	-12.59 [-16.60; -8.57]	[-8.71; 0.91]			
≥ 65										
Pembrolizumab	102	27.78 (26.36)	40	12.71 (14.86)	108	-12.00 [-17.75; -6.26]	-1.25	0.729	-	
SoC	89	30.15 (23.42)	41	17.28 (23.53)	99	-10.75 [-16.44; -5.06]	[-8.39; 5.89]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Pain	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Sex										
Female										
Pembrolizumab	72	39.00 (25.32)	30	21.94 (18.63)	75	-15.65 [-23.11; -8.19]	-0.01	0.998	-	0.519
SoC	53	42.45 (27.55)	29	23.28 (26.58)	60	-15.64 [-23.26; -8.02]	[-9.93; 9.91]			
Male										
Pembrolizumab	252	30.95 (26.30)	109	14.53 (16.33)	265	-14.60 [-18.07; -11.13]	-3.73	0.093	-	
SoC	212	33.53 (25.99)	96	18.84 (19.09)	231	-10.87 [-14.52; -7.22]	[-8.08; 0.63]			
Tumor Stage										
III										
Pembrolizumab	81	30.66 (24.57)	43	14.92 (15.81)	86	-13.60 [-19.41; -7.79]	-3.61	0.375	-	0.744
SoC	68	35.05 (24.96)	29	22.41 (23.89)	75	-9.99 [-16.75; -3.23]	[-11.65; 4.43]			
IVA										
Pembrolizumab	241	33.40 (26.85)	96	16.67 (17.65)	252	-15.60 [-19.38; -11.82]	-3.15	0.193	-	
SoC	197	35.41 (27.07)	96	19.10 (20.16)	216	-12.46 [-16.29; -8.62]	[-7.90; 1.61]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	32.22 (25.58)	96	15.36 (16.24)	238	-13.34 [-16.93; -9.76]	-2.36	0.313	-	0.538
SoC	182	34.62 (25.92)	87	20.40 (20.20)	197	-10.98 [-14.77; -7.19]	[-6.97; 2.24]			
TPS ≥50%										
Pembrolizumab	99	33.92 (27.85)	43	17.83 (18.86)	102	-19.95 [-26.39; -13.51]	-5.91	0.153	-	
SoC	83	36.85 (27.83)	38	18.64 (23.04)	94	-14.04 [-20.67; -7.42]	[-14.05; 2.24]			
Region										
European Union										
Pembrolizumab	125	27.33 (22.98)	54	17.75 (19.09)	132	-10.34 [-15.01; -5.67]	-2.40	0.466	-	0.717
SoC	113	35.10 (24.23)	55	23.03 (22.05)	126	-7.94 [-13.38; -2.49]	[-8.87; 4.06]			
North America										
Pembrolizumab	56	48.36 (28.75)	11	18.18 (17.41)	59	-29.46 [-41.32; -17.61]	-3.85	0.590	-	
SoC	31	50.27 (31.58)	12	13.19 (17.57)	37	-25.62 [-35.31; -15.92]	[-17.88; 10.19]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Pain	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Rest of World										
Pembrolizumab	143	31.35 (25.75)	74	14.64 (15.47)	149	-16.24 [-20.22; -12.26]	-3.94	0.149	-	
SoC	121	31.68 (26.01)	58	18.25 (20.50)	128	-12.30 [-17.19; -7.40]	[-9.30; 1.42]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	22.12 (18.70)	10	11.67 (16.76)	26	-7.03 [-13.99; -0.06]	-4.95	0.317	-	0.712
SoC	24	16.32 (16.02)	16	13.02 (14.58)	24	-2.07 [-9.31; 5.16]	[-14.67; 4.77]			
Larynx										
Pembrolizumab	67	17.41 (16.01)	34	9.31 (13.10)	74	-6.58 [-11.26; -1.90]	0.14	0.971	-	
SoC	52	22.12 (18.81)	24	13.89 (20.21)	58	-6.72 [-13.88; 0.44]	[-7.49; 7.77]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	38.38 (27.27)	95	19.04 (17.68)	240	-18.95 [-22.73; -15.18]	-3.58	0.169	-	
SoC	189	41.36 (26.98)	85	22.84 (21.79)	209	-15.37 [-19.81; -10.94]	[-8.68; 1.52]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-H&N35: Symptomskala Schluckprobleme

Tabelle 4G-19: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Schluckprobleme des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Swallowing	**Baseline**		**Post-Adjuvant CRT/RT Week 51**		**Change from Baseline to Post-Adjuvant CRT/RT Week 51**		**Pembrolizumab vs. SoC**			**p-Value for Interaction Test[f]**
							Mean Difference at Post-Adjuvant CRT/RT Week 51		**Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51**	
	N[b]	**Mean (SD)**	**N[b]**	**Mean (SD)**	**N[c]**	**Mean [95 %-CI][d]**	**[95 %-CI][d]**	**p-Value**	**[95 %-CI][e]**	
Age										
< 65										
Pembrolizumab	222	25.60 (27.17)	99	23.74 (22.79)	232	0.44 [-4.09; 4.96]	0.12	0.968	-	0.978
SoC	176	27.79 (28.59)	84	22.22 (22.42)	192	0.31 [-4.59; 5.21]	[-5.93; 6.18]			
≥ 65										
Pembrolizumab	102	24.75 (29.40)	40	22.92 (24.15)	108	2.82 [-3.50; 9.13]	-0.46	0.916	-	
SoC	89	23.22 (23.92)	41	24.39 (26.96)	99	3.28 [-2.98; 9.54]	[-9.08; 8.16]			
Sex										
Female										
Pembrolizumab	72	26.27 (27.86)	30	23.06 (26.68)	75	5.47 [-3.51; 14.45]	0.23	0.971	-	0.916
SoC	53	25.00 (24.57)	29	28.74 (23.94)	60	5.24 [-4.07; 14.55]	[-12.24; 12.70]			
Male										
Pembrolizumab	252	25.07 (27.89)	109	23.62 (22.15)	265	-0.03 [-4.18; 4.11]	-0.61	0.829	-	
SoC	212	26.57 (27.80)	96	21.18 (23.75)	231	0.58 [-3.85; 5.01]	[-6.19; 4.96]			
Tumor Stage										
III										
Pembrolizumab	81	17.18 (21.90)	43	22.87 (25.01)	86	7.17 [-0.09; 14.43]	4.87	0.366	-	0.277
SoC	68	26.47 (28.14)	29	22.41 (27.10)	75	2.30 [-6.03; 10.63]	[-5.77; 15.50]			
IVA										
Pembrolizumab	241	27.73 (28.84)	96	23.78 (22.33)	252	-0.82 [-5.17; 3.53]	-1.89	0.514	-	
SoC	197	26.18 (26.87)	96	23.09 (23.02)	216	1.07 [-3.34; 5.48]	[-7.57; 3.80]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Swallowing	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	25.63 (28.54)	96	24.91 (23.74)	238	2.02 [-2.60; 6.65]	0.90	0.777	-	0.339
SoC	182	26.60 (26.43)	87	22.51 (24.71)	197	1.13 [-3.79; 6.04]	[-5.35; 7.15]			
TPS ≥50%										
Pembrolizumab	99	24.66 (26.32)	43	20.35 (21.54)	102	-0.43 [-6.78; 5.91]	-2.50	0.570	-	
SoC	83	25.50 (28.82)	38	23.90 (22.27)	94	2.07 [-4.78; 8.92]	[-11.22; 6.21]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	38.46 (36.22)	10	21.67 (22.29)	26	-7.38 [-14.19; -0.57]	-4.97	0.480	-	0.309
SoC	24	23.96 (26.84)	16	24.48 (24.81)	24	-2.41 [-15.80; 10.98]	[-18.80; 8.86]			
Larynx										
Pembrolizumab	67	24.75 (26.87)	34	19.61 (24.00)	74	-2.08 [-9.49; 5.33]	4.97	0.359	-	
SoC	52	32.53 (29.30)	24	18.40 (25.89)	58	-7.05 [-15.44; 1.34]	[-5.65; 15.59]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	24.03 (26.79)	95	25.09 (22.92)	240	2.65 [-1.88; 7.18]	-0.80	0.791	-	
SoC	189	24.82 (26.46)	85	23.92 (23.32)	209	3.46 [-1.23; 8.14]	[-6.75; 5.14]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-H&N35: Symptomskala Gefühlsstörungen

Tabelle 4G-20: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Krankheitssymptomatik für die Symptomskala Gefühlsstörungen des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Senses Problems	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	222	9.76 (18.62)	99	24.58 (26.44)	232	14.72 [10.17; 19.28]	2.50	0.446	-	0.803
SoC	176	10.89 (19.59)	84	21.03 (22.87)	192	12.23 [7.26; 17.20]	[-3.94; 8.94]			
≥ 65										
Pembrolizumab	102	11.27 (19.08)	40	23.75 (25.57)	108	13.49 [5.78; 21.20]	-1.31	0.800	-	
SoC	89	6.18 (11.89)	41	25.20 (28.66)	99	14.80 [7.38; 22.21]	[-11.49; 8.88]			
Sex										
Female										
Pembrolizumab	72	9.49 (16.03)	30	16.11 (17.77)	75	10.61 [2.05; 19.17]	-8.06	0.178	-	0.102
SoC	53	8.18 (13.72)	29	27.01 (24.16)	60	18.67 [9.95; 27.39]	[-19.86; 3.75]			
Male										
Pembrolizumab	252	10.45 (19.48)	109	26.61 (27.60)	265	15.97 [11.50; 20.45]	3.96	0.210	-	
SoC	212	9.59 (18.35)	96	21.01 (25.04)	231	12.01 [7.32; 16.70]	[-2.25; 10.18]			
Tumor Stage										
III										
Pembrolizumab	81	6.38 (14.09)	43	25.97 (26.80)	86	22.83 [15.54; 30.13]	3.54	0.524	-	0.358
SoC	68	5.64 (11.74)	29	22.99 (26.13)	75	19.30 [11.06; 27.53]	[-7.43; 14.50]			
IVA										
Pembrolizumab	241	11.55 (19.99)	96	23.61 (25.90)	252	12.20 [7.47; 16.94]	-0.07	0.983	-	
SoC	197	10.58 (18.96)	96	22.22 (24.62)	216	12.27 [7.52; 17.03]	[-6.42; 6.28]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Senses Problems	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	10.44 (18.85)	96	26.04 (27.97)	238	17.01 [11.94; 22.07]	3.70	0.299	-	0.267
SoC	182	9.43 (17.72)	87	22.61 (25.92)	197	13.31 [8.00; 18.62]	[-3.30; 10.70]			
TPS ≥50%										
Pembrolizumab	99	9.76 (18.60)	43	20.54 (21.16)	102	9.73 [3.73; 15.73]	-3.87	0.356	-	
SoC	83	9.04 (17.13)	38	21.93 (22.63)	94	13.60 [7.46; 19.74]	[-12.15; 4.41]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	9.62 (16.45)	10	30.00 (29.19)	26	29.69 [15.25; 44.12]	-0.98	0.924	-	0.569
SoC	24	2.08 (7.47)	16	35.42 (33.26)	24	30.66 [15.23; 46.09]	[-21.02; 19.07]			
Larynx										
Pembrolizumab	67	9.70 (15.39)	34	35.78 (29.63)	74	25.99 [16.29; 35.70]	6.31	0.313	-	
SoC	52	9.62 (19.90)	24	29.17 (26.12)	58	19.68 [10.15; 29.22]	[-5.97; 18.59]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	10.46 (19.90)	95	19.65 (23.19)	240	9.72 [5.56; 13.88]	1.98	0.501	-	
SoC	189	10.14 (17.57)	85	18.04 (21.55)	209	7.74 [3.39; 12.08]	[-3.79; 7.75]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-H&N35: Symptomskala Sprachprobleme

Tabelle 4G-21: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Sprachprobleme des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Speech Problems	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Sex										
Female										
Pembrolizumab	72	26.39 (27.12)	30	32.22 (30.23)	75	12.81 [3.75; 21.86]	7.69	0.231	-	0.208
SoC	53	20.13 (22.96)	29	24.52 (24.01)	60	5.12 [-4.46; 14.69]	[-5.00; 20.38]			
Male										
Pembrolizumab	252	25.40 (28.10)	109	27.83 (26.00)	265	4.56 [0.38; 8.74]	-0.53	0.855	-	
SoC	212	26.47 (28.15)	96	28.01 (24.13)	231	5.09 [0.71; 9.47]	[-6.17; 5.12]			
Tumor Stage										
III										
Pembrolizumab	81	21.95 (25.34)	43	27.39 (26.93)	86	9.05 [2.10; 15.99]	5.24	0.309	-	0.286
SoC	68	24.35 (25.27)	29	26.82 (23.48)	75	3.80 [-4.31; 11.91]	[-4.93; 15.41]			
IVA										
Pembrolizumab	241	26.51 (28.30)	96	29.40 (27.02)	252	4.53 [-0.03; 9.08]	-1.43	0.645	-	
SoC	197	25.49 (27.98)	96	27.31 (24.34)	216	5.95 [1.35; 10.56]	[-7.53; 4.67]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	26.27 (27.76)	96	29.63 (26.18)	238	6.06 [1.42; 10.69]	1.13	0.724	-	0.934
SoC	182	25.82 (26.56)	87	27.97 (24.66)	197	4.93 [0.10; 9.75]	[-5.17; 7.43]			
TPS ≥50%										
Pembrolizumab	99	24.13 (28.13)	43	26.87 (28.71)	102	7.62 [0.84; 14.39]	1.75	0.710	-	
SoC	83	23.83 (28.89)	38	25.44 (22.80)	94	5.86 [-1.24; 12.96]	[-7.59; 11.10]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Speech Problems	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Region										
European Union										
Pembrolizumab	125	20.71 (24.50)	54	28.60 (25.41)	132	10.93 [4.95; 16.92]	2.98	0.441	-	0.541
SoC	113	20.35 (25.88)	55	25.25 (23.47)	126	7.96 [2.51; 13.41]	[-4.61; 10.56]			
North America										
Pembrolizumab	56	27.98 (30.26)	11	30.30 (31.46)	59	10.26 [-3.57; 24.09]	15.26	0.077	-	
SoC	31	34.77 (31.39)	12	17.59 (21.95)	37	-5.00 [-17.13; 7.13]	[-1.68; 32.21]			
Rest of World										
Pembrolizumab	143	28.98 (29.16)	74	28.68 (27.65)	149	3.38 [-2.00; 8.76]	-1.10	0.772	-	
SoC	121	27.27 (26.72)	58	31.03 (24.61)	128	4.48 [-1.31; 10.26]	[-8.54; 6.34]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	29.91 (28.24)	10	40.00 (30.18)	26	14.51 [-0.98; 29.99]	-1.39	0.887	-	0.367
SoC	24	21.30 (29.11)	16	36.11 (27.37)	24	15.89 [3.10; 28.69]	[-20.57; 17.79]			
Larynx										
Pembrolizumab	67	45.27 (28.64)	34	41.18 (30.40)	74	-1.76 [-11.68; 8.16]	8.62	0.185	-	
SoC	52	48.29 (27.91)	24	38.43 (24.51)	58	-10.39 [-20.71; -0.06]	[-4.14; 21.39]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	19.43 (24.77)	95	23.16 (23.47)	240	7.83 [3.73; 11.93]	0.96	0.727	-	
SoC	189	19.34 (23.35)	85	22.35 (21.92)	209	6.87 [2.93; 10.81]	[-4.45; 6.38]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-H&N35: Symptomskala Probleme in der Öffentlichkeit zu Essen

Tabelle 4G-22: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Probleme in der Öffentlichkeit zu Essen des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Trouble with Social Eating	**Baseline**		**Post-Adjuvant CRT/RT Week 51**		**Change from Baseline to Post-Adjuvant CRT/RT Week 51**		**Pembrolizumab vs. SoC**			**p-Value for Interaction Test[f]**
							Mean Difference at Post-Adjuvant CRT/RT Week 51		**Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51**	
	N[b]	**Mean (SD)**	**N[b]**	**Mean (SD)**	**N[c]**	**Mean [95 %-CI][d]**	**[95 %-CI][d]**	**p-Value**	**[95 %-CI][e]**	
Age										
< 65										
Pembrolizumab	222	28.50 (28.97)	99	28.03 (27.05)	232	1.94 [-2.87; 6.76]	0.72	0.828	-	0.859
SoC	176	29.34 (30.39)	84	26.79 (25.13)	192	1.22 [-4.01; 6.45]	[-5.82; 7.27]			
≥ 65										
Pembrolizumab	102	27.70 (33.34)	40	26.88 (28.71)	108	6.00 [-0.94; 12.94]	-0.52	0.912	-	
SoC	89	21.16 (21.56)	41	27.03 (26.32)	99	6.52 [-0.24; 13.28]	[-9.78; 8.75]			
Sex										
Female										
Pembrolizumab	72	31.94 (31.02)	30	31.02 (28.38)	75	5.40 [-3.57; 14.37]	-1.28	0.835	-	0.731
SoC	53	29.93 (28.88)	29	35.25 (24.21)	60	6.68 [-2.76; 16.12]	[-13.47; 10.92]			
Male										
Pembrolizumab	252	27.19 (30.15)	109	26.78 (27.24)	265	3.89 [-0.52; 8.29]	1.38	0.649	-	
SoC	212	25.76 (27.74)	96	24.33 (25.35)	231	2.50 [-2.14; 7.15]	[-4.59; 7.36]			
Tumor Stage										
III										
Pembrolizumab	81	18.21 (23.46)	43	24.68 (26.25)	86	6.59 [-0.72; 13.89]	3.80	0.475	-	0.487
SoC	68	28.10 (29.12)	29	25.29 (27.54)	75	2.78 [-5.55; 11.11]	[-6.71; 14.31]			
IVA										
Pembrolizumab	241	31.37 (31.49)	96	29.05 (27.98)	252	3.12 [-1.59; 7.83]	-0.01	0.996	-	
SoC	197	26.07 (27.61)	96	27.34 (24.88)	216	3.14 [-1.68; 7.96]	[-6.28; 6.25]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Trouble with Social Eating	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	27.91 (30.16)	96	27.66 (27.79)	238	4.90 [0.11; 9.69]	1.80	0.591	-	0.718
SoC	182	25.93 (26.32)	87	25.54 (25.59)	197	3.10 [-2.01; 8.22]	[-4.78; 8.38]			
TPS ≥50%										
Pembrolizumab	99	29.01 (30.96)	43	27.78 (26.96)	102	1.81 [-5.20; 8.82]	-0.40	0.932	-	
SoC	83	28.05 (31.39)	38	29.90 (25.10)	94	2.22 [-5.07; 9.51]	[-9.71; 8.91]			
Region										
European Union										
Pembrolizumab	125	21.60 (25.82)	54	31.94 (31.63)	132	10.12 [3.62; 16.62]	8.39	0.043	0.34	0.125
SoC	113	25.22 (25.62)	55	23.64 (23.61)	126	1.73 [-3.63; 7.08]	[0.27; 16.52]		[0.01; 0.66]	
North America										
Pembrolizumab	56	40.03 (35.48)	11	37.12 (24.54)	59	3.28 [-11.01; 17.57]	1.14	0.893	-	
SoC	31	37.63 (31.90)	12	34.03 (19.61)	37	2.14 [-9.90; 14.19]	[-15.53; 17.81]			
Rest of World										
Pembrolizumab	143	29.45 (30.54)	74	23.20 (23.82)	149	-0.38 [-5.86; 5.10]	-4.20	0.275	-	
SoC	121	25.05 (28.59)	58	28.45 (27.93)	128	3.82 [-2.35; 10.00]	[-11.76; 3.35]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	24.79 (29.74)	10	16.94 (30.86)	26	-2.45 [-15.32; 10.43]	-10.54	0.237	-	0.329
SoC	24	17.71 (26.51)	16	26.04 (25.74)	24	8.09 [-5.89; 22.07]	[-28.04; 6.96]			
Larynx										
Pembrolizumab	67	22.01 (28.82)	34	19.61 (25.94)	74	4.04 [-3.22; 11.31]	1.76	0.709	-	
SoC	52	20.03 (22.22)	24	17.71 (23.86)	58	2.28 [-3.86; 8.43]	[-7.51; 11.03]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	30.45 (30.70)	95	31.73 (26.94)	240	3.28 [-1.71; 8.27]	1.58	0.626	-	
SoC	189	29.53 (29.11)	85	29.61 (25.45)	209	1.70 [-3.28; 6.68]	[-4.79; 7.95]			

a: Database Cutoff Date: 25JUL2024
b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint
c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Trouble with Social Eating	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction										
e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero										
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction										
CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score										

EORTC QLQ-H&N35: Symptomskala Probleme mit Sozialkontakten

Tabelle 4G-23: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Probleme mit Sozialkontakten des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Trouble with Social Contact	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	222	15.17 (22.59)	99	18.79 (22.80)	232	6.26 [2.47; 10.06]	1.57	0.563	-	0.918
SoC	176	16.29 (23.61)	84	16.98 (19.62)	192	4.70 [0.55; 8.85]	[-3.77; 6.91]			
≥ 65										
Pembrolizumab	102	13.66 (20.56)	40	15.50 (20.99)	108	6.29 [0.60; 11.98]	2.61	0.511	-	
SoC	89	12.73 (17.16)	41	16.91 (22.02)	99	3.69 [-1.86; 9.24]	[-5.23; 10.44]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Trouble with Social Contact	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Sex										
Female										
Pembrolizumab	72	14.63 (20.07)	30	22.44 (20.68)	75	10.58 [4.08; 17.07]	4.87	0.291	-	0.320
SoC	53	16.10 (20.48)	29	17.93 (18.00)	60	5.70 [-1.06; 12.46]	[-4.26; 14.01]			
Male										
Pembrolizumab	252	14.71 (22.50)	109	16.57 (22.62)	265	5.28 [1.71; 8.85]	0.93	0.715	-	
SoC	212	14.84 (22.03)	96	16.67 (21.08)	231	4.35 [0.51; 8.19]	[-4.08; 5.94]			
Tumor Stage										
III										
Pembrolizumab	81	11.28 (17.44)	43	15.97 (22.50)	86	8.23 [1.86; 14.59]	3.10	0.526	-	0.971
SoC	68	12.45 (19.51)	29	18.62 (27.16)	75	5.12 [-2.45; 12.69]	[-6.57; 12.78]			
IVA										
Pembrolizumab	241	15.77 (23.17)	96	18.68 (22.24)	252	5.82 [2.18; 9.46]	1.95	0.435	-	
SoC	197	16.01 (22.37)	96	16.46 (17.94)	216	3.87 [0.18; 7.56]	[-2.96; 6.87]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	14.13 (21.35)	96	17.01 (22.41)	238	6.25 [2.37; 10.13]	1.22	0.663	-	0.533
SoC	182	15.05 (20.83)	87	17.24 (20.70)	197	5.04 [0.85; 9.22]	[-4.27; 6.70]			
TPS ≥50%										
Pembrolizumab	99	15.96 (23.32)	43	19.69 (22.11)	102	6.43 [1.05; 11.82]	3.96	0.287	-	
SoC	83	15.18 (23.61)	38	16.32 (19.77)	94	2.47 [-3.00; 7.95]	[-3.38; 11.29]			
Region										
European Union										
Pembrolizumab	125	9.17 (15.40)	54	18.89 (24.05)	132	9.94 [4.94; 14.94]	4.09	0.236	-	0.068
SoC	113	12.63 (19.81)	55	14.67 (19.00)	126	5.84 [1.08; 10.61]	[-2.68; 10.86]			
North America										
Pembrolizumab	56	20.36 (27.60)	11	23.64 (20.52)	59	9.57 [1.09; 18.05]	17.61	0.002	0.82	
SoC	31	28.17 (31.54)	12	8.89 (11.13)	37	-8.04 [-16.00; -0.09]	[6.57; 28.65]		[0.31; 1.34]	

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Trouble with Social Contact	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Rest of World										
Pembrolizumab	143	17.30 (23.41)	74	16.22 (21.26)	149	3.69 [-0.98; 8.37]	-1.24	0.708	-	
SoC	121	14.05 (19.22)	58	20.80 (22.38)	128	4.94 [-0.17; 10.04]	[-7.76; 5.27]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	10.00 (18.01)	10	16.00 (21.59)	26	9.69 [0.28; 19.10]	1.13	0.857	-	0.794
SoC	24	5.56 (10.89)	16	13.33 (15.59)	24	8.56 [0.54; 16.58]	[-11.25; 13.51]			
Larynx										
Pembrolizumab	67	20.30 (23.16)	34	18.24 (24.64)	74	4.53 [-3.10; 12.17]	5.26	0.324	-	
SoC	52	17.95 (23.19)	24	19.17 (24.02)	58	-0.73 [-8.82; 7.36]	[-5.21; 15.73]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	13.59 (21.79)	95	17.89 (21.68)	240	6.98 [3.54; 10.41]	2.18	0.387	-	
SoC	189	15.52 (22.06)	85	17.02 (20.15)	209	4.80 [0.98; 8.61]	[-2.76; 7.12]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-H&N35: Symptomskala Verminderte Sexualität

Tabelle 4G-24: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Verminderte Sexualität des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Less Sexuality	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	220	22.95 (33.40)	97	19.59 (29.17)	232	2.00 [-3.28; 7.27]	-5.95	0.113	-	0.138
SoC	175	24.95 (33.33)	84	27.98 (29.63)	191	7.95 [2.23; 13.67]	[-13.32; 1.42]			
≥ 65										
Pembrolizumab	101	24.26 (32.70)	38	24.56 (28.67)	108	4.71 [-5.01; 14.43]	3.62	0.557	-	
SoC	89	26.97 (35.49)	41	24.39 (31.64)	99	1.09 [-8.17; 10.35]	[-8.56; 15.80]			
Sex										
Female										
Pembrolizumab	71	24.18 (35.05)	29	22.99 (32.25)	75	-0.26 [-10.50; 9.99]	-10.37	0.145	-	0.249
SoC	53	20.75 (30.99)	29	32.76 (35.77)	60	10.11 [-0.76; 20.99]	[-24.39; 3.65]			
Male										
Pembrolizumab	250	23.13 (32.65)	106	20.44 (28.20)	265	1.77 [-3.48; 7.02]	-1.04	0.772	-	
SoC	211	26.86 (34.70)	96	25.00 (28.30)	230	2.81 [-2.70; 8.31]	[-8.08; 6.01]			
Tumor Stage										
III										
Pembrolizumab	81	18.93 (27.10)	41	21.14 (32.71)	86	-1.06 [-10.31; 8.20]	-9.87	0.147	-	0.230
SoC	68	20.10 (33.77)	29	29.89 (37.90)	75	8.81 [-1.77; 19.40]	[-23.27; 3.53]			
IVA										
Pembrolizumab	238	24.37 (34.56)	94	20.92 (27.43)	252	2.75 [-2.73; 8.23]	-0.68	0.853	-	
SoC	196	27.55 (33.98)	96	25.87 (27.66)	215	3.43 [-2.09; 8.94]	[-7.86; 6.50]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Less Sexuality	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	223	23.32 (32.10)	92	21.92 (30.35)	238	2.59 [-3.27; 8.44]	-2.13	0.598	-	0.592
SoC	181	27.35 (34.10)	87	27.01 (30.42)	196	4.72 [-1.52; 10.95]	[-10.08; 5.82]			
TPS ≥50%										
Pembrolizumab	98	23.47 (35.56)	43	18.99 (26.12)	102	-3.67 [-11.17; 3.84]	-8.83	0.089	-	
SoC	83	21.89 (33.73)	38	26.32 (30.17)	94	5.16 [-2.93; 13.26]	[-19.02; 1.36]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	26.92 (31.65)	9	9.26 (14.70)	26	1.02 [-13.26; 15.31]	-15.07	0.130	-	0.288
SoC	24	17.36 (29.27)	16	33.33 (34.96)	24	16.10 [1.29; 30.91]	[-34.62; 4.47]			
Larynx										
Pembrolizumab	66	28.03 (35.71)	33	23.74 (30.06)	74	-0.22 [-11.17; 10.73]	-3.73	0.622	-	
SoC	52	27.24 (33.17)	24	29.17 (32.69)	58	3.51 [-8.77; 15.80]	[-18.59; 11.13]			
Oropharynx/Oral Cavity										
Pembrolizumab	229	21.62 (32.52)	93	21.15 (29.60)	240	3.90 [-1.24; 9.03]	-0.06	0.987	-	
SoC	188	26.24 (34.81)	85	24.90 (28.71)	208	3.95 [-1.69; 9.60]	[-7.14; 7.02]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-H&N35: Symptomskala Zahnprobleme

Tabelle 4G-25: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Krankheitssymptomatik für die Symptomskala Zahnprobleme des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Teeth	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	222	28.98 (37.06)	99	26.60 (33.66)	232	-1.22 [-7.85; 5.41]	-1.48	0.739	-	0.408
SoC	176	25.38 (33.04)	84	25.40 (32.98)	192	0.26 [-6.88; 7.40]	[-10.26; 7.29]			
≥ 65										
Pembrolizumab	102	22.88 (33.49)	40	20.83 (35.15)	108	2.29 [-7.86; 12.45]	6.14	0.370	-	
SoC	89	22.10 (32.15)	41	21.95 (30.38)	99	-3.85 [-14.30; 6.60]	[-7.40; 19.68]			
Sex										
Female										
Pembrolizumab	72	29.17 (38.33)	30	26.67 (32.04)	75	1.89 [-10.92; 14.71]	-6.48	0.443	-	0.580
SoC	53	20.13 (32.91)	29	35.63 (36.66)	60	8.37 [-4.29; 21.04]	[-23.25; 10.29]			
Male										
Pembrolizumab	252	26.46 (35.41)	109	24.46 (34.74)	265	-1.93 [-8.18; 4.33]	2.08	0.616	-	
SoC	212	25.31 (32.67)	96	20.83 (29.91)	231	-4.00 [-10.52; 2.52]	[-6.07; 10.22]			
Tumor Stage										
III										
Pembrolizumab	81	23.46 (34.74)	43	23.26 (32.15)	86	3.15 [-7.75; 14.04]	-2.52	0.739	-	0.774
SoC	68	21.57 (31.94)	29	31.03 (36.66)	75	5.67 [-6.54; 17.88]	[-17.52; 12.47]			
IVA										
Pembrolizumab	241	28.22 (36.47)	96	25.69 (35.04)	252	-2.62 [-9.21; 3.97]	-0.19	0.965	-	
SoC	197	25.21 (33.02)	96	22.22 (30.46)	216	-2.43 [-9.04; 4.18]	[-8.68; 8.30]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Teeth	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	28.44 (36.20)	96	24.31 (35.37)	238	-1.69 [-8.66; 5.29]	-0.65	0.891	-	0.673
SoC	182	24.54 (32.62)	87	24.14 (32.02)	197	-1.04 [-8.27; 6.18]	[-9.88; 8.59]			
TPS ≥50%										
Pembrolizumab	99	23.91 (35.65)	43	26.36 (31.34)	102	0.25 [-9.82; 10.33]	2.82	0.658	-	
SoC	83	23.69 (33.14)	38	24.56 (32.59)	94	-2.57 [-12.52; 7.39]	[-9.77; 15.41]			
Region										
European Union										
Pembrolizumab	125	23.20 (34.19)	54	23.46 (35.84)	132	-0.84 [-10.09; 8.41]	-1.93	0.741	-	0.900
SoC	113	23.89 (33.77)	55	24.24 (30.40)	126	1.09 [-7.64; 9.82]	[-13.43; 9.56]			
North America										
Pembrolizumab	56	31.55 (38.88)	11	12.12 (16.82)	59	-16.92 [-32.23; -1.62]	9.12	0.257	-	
SoC	31	30.11 (34.81)	12	5.56 (12.97)	37	-26.04 [-39.48; -12.60]	[-6.68; 24.92]			
Rest of World										
Pembrolizumab	143	28.67 (36.39)	74	27.93 (34.47)	149	1.74 [-6.43; 9.92]	0.66	0.903	-	
SoC	121	23.14 (31.28)	58	28.16 (35.21)	128	1.08 [-6.86; 9.02]	[-9.92; 11.23]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	16.67 (31.62)	10	6.67 (14.05)	26	-8.35 [-23.33; 6.62]	-10.11	0.129	-	0.538
SoC	24	9.72 (20.80)	16	14.58 (17.08)	24	1.76 [-9.89; 13.42]	[-23.19; 2.96]			
Larynx										
Pembrolizumab	67	16.42 (29.23)	34	20.59 (33.85)	74	2.94 [-8.58; 14.46]	-4.13	0.618	-	
SoC	52	20.51 (30.36)	24	25.00 (35.78)	58	7.07 [-6.00; 20.15]	[-20.42; 12.15]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	31.31 (37.50)	95	28.42 (35.05)	240	-1.64 [-8.74; 5.46]	2.06	0.653	-	
SoC	189	27.16 (34.08)	85	25.88 (33.08)	209	-3.70 [-10.66; 3.25]	[-6.94; 11.07]			

a: Database Cutoff Date: 25JUL2024
b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint
c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis
d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Teeth	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score									

EORTC QLQ-H&N35: Symptomskala Probleme beim Mundöffnen (Trismus)

Tabelle 4G-26: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Krankheitssymptomatik für die Symptomskala Probleme beim Mundöffnen (Trismus) des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Opening Mouth	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	222	26.73 (32.90)	99	29.63 (31.90)	232	3.37 [-1.75; 8.49]	-2.61	0.473	-	0.801
SoC	176	30.11 (34.49)	84	28.97 (30.07)	192	5.98 [0.37; 11.59]	[-9.77; 4.55]			
≥ 65										
Pembrolizumab	102	18.63 (31.67)	40	17.50 (22.63)	108	-1.31 [-9.75; 7.13]	-8.50	0.117	-	
SoC	89	20.97 (31.93)	41	26.02 (28.39)	99	7.18 [-1.12; 15.49]	[-19.17; 2.18]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Opening Mouth	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Sex										
Female										
Pembrolizumab	72	31.48 (35.77)	30	36.67 (35.40)	75	4.31 [-4.86; 13.47]	0.90	0.891	-	0.183
SoC	53	30.82 (35.11)	29	29.89 (30.01)	60	3.41 [-6.64; 13.46]	[-12.12; 13.92]			
Male										
Pembrolizumab	252	22.09 (31.51)	109	23.24 (27.78)	265	1.48 [-3.53; 6.48]	-5.08	0.134	-	
SoC	212	26.10 (33.57)	96	27.43 (29.42)	231	6.55 [1.30; 11.81]	[-11.74; 1.58]			
Tumor Stage										
III										
Pembrolizumab	81	19.75 (30.17)	43	18.60 (26.53)	86	2.14 [-5.69; 9.97]	-9.01	0.119	-	0.163
SoC	68	23.04 (31.68)	29	29.89 (31.30)	75	11.14 [1.87; 20.42]	[-20.35; 2.34]			
IVA										
Pembrolizumab	241	25.86 (33.47)	96	29.51 (30.92)	252	3.56 [-1.85; 8.97]	-0.79	0.829	-	
SoC	197	28.43 (34.56)	96	27.43 (29.02)	216	4.34 [-1.12; 9.81]	[-7.92; 6.35]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	23.70 (33.20)	96	24.31 (26.70)	238	2.28 [-2.89; 7.46]	-6.48	0.066	-	0.087
SoC	182	26.01 (32.80)	87	30.27 (29.48)	197	8.77 [3.34; 14.19]	[-13.39; 0.43]			
TPS ≥50%										
Pembrolizumab	99	25.25 (31.62)	43	30.23 (36.23)	102	5.57 [-2.58; 13.72]	5.91	0.300	-	
SoC	83	29.32 (36.22)	38	22.81 (29.11)	94	-0.34 [-8.86; 8.18]	[-5.34; 17.16]			
Region										
European Union										
Pembrolizumab	125	18.13 (28.87)	54	31.48 (33.28)	132	10.64 [3.86; 17.43]	1.13	0.813	-	0.738
SoC	113	25.96 (33.55)	55	32.12 (30.74)	126	9.51 [2.20; 16.82]	[-8.27; 10.53]			
North America										
Pembrolizumab	56	32.14 (36.50)	11	30.30 (37.87)	59	-0.55 [-11.62; 10.51]	-5.33	0.610	-	
SoC	31	44.09 (40.72)	12	25.00 (32.18)	37	4.77 [-13.86; 23.41]	[-25.82; 15.17]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Opening Mouth	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Rest of World										
Pembrolizumab	143	26.34 (33.53)	74	21.62 (25.54)	149	-0.55 [-6.19; 5.10]	-4.54	0.263	-	
SoC	121	23.69 (31.16)	58	24.71 (27.61)	128	4.00 [-2.73; 10.72]	[-12.51; 3.42]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	5.13 (12.26)	10	16.67 (17.57)	26	11.08 [1.37; 20.79]	3.54	0.598	-	0.509
SoC	24	5.56 (12.69)	16	12.50 (20.64)	24	7.54 [-2.01; 17.09]	[-9.66; 16.74]			
Larynx										
Pembrolizumab	67	4.98 (14.51)	34	10.78 (17.83)	74	6.57 [1.34; 11.80]	-2.21	0.672	-	
SoC	52	10.26 (21.43)	24	13.89 (23.91)	58	8.78 [-0.43; 17.99]	[-12.44; 8.03]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	31.89 (34.86)	95	32.63 (32.24)	240	0.88 [-4.63; 6.39]	-4.37	0.260	-	
SoC	189	34.39 (35.71)	85	34.90 (29.95)	209	5.24 [-0.97; 11.45]	[-11.96; 3.23]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-H&N35: Symptomskala Mundtrockenheit

Tabelle 4G-27: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Mundtrockenheit des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Dry Mouth	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	222	24.47 (29.52)	99	44.11 (36.21)	232	21.58 [15.08; 28.08]	7.12	0.109	-	0.767
SoC	176	22.54 (31.32)	84	39.68 (32.10)	192	14.46 [7.54; 21.39]	[-1.59; 15.82]			
≥ 65										
Pembrolizumab	102	22.55 (27.01)	40	34.17 (30.65)	108	13.03 [4.61; 21.46]	3.42	0.547	-	
SoC	89	19.48 (25.03)	41	27.64 (28.77)	99	9.61 [1.45; 17.77]	[-7.80; 14.64]			
Sex										
Female										
Pembrolizumab	72	25.93 (30.76)	30	48.89 (34.72)	75	22.06 [9.43; 34.69]	-1.40	0.870	-	0.272
SoC	53	25.79 (29.70)	29	49.43 (35.21)	60	23.46 [10.50; 36.43]	[-18.40; 15.60]			
Male										
Pembrolizumab	252	23.28 (28.16)	109	39.14 (34.80)	265	18.30 [12.46; 24.14]	8.64	0.029	0.27	
SoC	212	20.44 (29.23)	96	31.60 (29.17)	231	9.66 [3.58; 15.74]	[0.90; 16.38]		[0.03; 0.51]	
Tumor Stage										
III										
Pembrolizumab	81	21.81 (26.96)	43	39.53 (37.98)	86	22.43 [12.01; 32.84]	8.20	0.268	-	0.875
SoC	68	20.59 (27.64)	29	35.63 (28.07)	75	14.22 [2.45; 25.99]	[-6.40; 22.81]			
IVA										
Pembrolizumab	241	24.34 (28.99)	96	42.01 (33.59)	252	18.31 [12.06; 24.56]	5.61	0.181	-	
SoC	197	21.83 (29.98)	96	35.76 (32.53)	216	12.71 [6.48; 18.94]	[-2.62; 13.84]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Dry Mouth	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	24.74 (29.13)	96	36.46 (33.88)	238	15.71 [9.56; 21.87]	6.42	0.125	-	0.997
SoC	182	22.53 (29.92)	87	31.42 (29.80)	197	9.29 [2.89; 15.68]	[-1.80; 14.65]			
TPS ≥50%										
Pembrolizumab	99	21.89 (27.83)	43	51.94 (35.11)	102	28.62 [18.28; 38.97]	7.67	0.275	-	
SoC	83	19.28 (28.09)	38	45.61 (33.26)	94	20.95 [10.37; 31.53]	[-6.20; 21.54]			
Region										
European Union										
Pembrolizumab	125	25.33 (30.05)	54	45.06 (37.29)	132	19.91 [10.67; 29.15]	0.91	0.875	-	0.172
SoC	113	20.65 (31.60)	55	41.82 (31.57)	126	19.00 [10.78; 27.23]	[-10.43; 12.25]			
North America										
Pembrolizumab	56	25.00 (29.98)	11	57.58 (26.21)	59	30.38 [16.14; 44.61]	23.39	0.016	0.76	
SoC	31	32.26 (32.75)	12	36.11 (30.01)	37	6.99 [-8.56; 22.53]	[4.42; 42.37]		[0.14; 1.38]	
Rest of World										
Pembrolizumab	143	22.14 (27.10)	74	36.04 (33.45)	149	15.85 [8.48; 23.22]	8.12	0.102	-	
SoC	121	19.56 (25.70)	58	29.89 (31.03)	128	7.73 [0.29; 15.17]	[-1.63; 17.87]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	25.64 (30.27)	10	26.67 (26.29)	26	7.42 [-5.52; 20.37]	12.00	0.079	-	0.392
SoC	24	18.06 (25.97)	16	14.58 (17.08)	24	-4.57 [-12.43; 3.28]	[-1.38; 25.37]			
Larynx										
Pembrolizumab	67	22.39 (26.84)	34	23.53 (30.18)	74	7.43 [-2.51; 17.37]	13.77	0.032	0.50	
SoC	52	20.51 (28.89)	24	11.11 (21.23)	58	-6.34 [-15.53; 2.85]	[1.22; 26.31]		[0.04; 0.95]	
Oropharynx/Oral Cavity										
Pembrolizumab	231	24.10 (29.18)	95	49.12 (34.67)	240	24.84 [18.12; 31.56]	3.56	0.411	-	
SoC	189	22.22 (29.97)	85	46.67 (30.08)	209	21.28 [14.84; 27.72]	[-4.94; 12.06]			

a: Database Cutoff Date: 25JUL2024
b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint
c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis
d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Dry Mouth	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero										
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction										
CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score										

EORTC QLQ-H&N35: Symptomskala klebriger Speichel

Tabelle 4G-28: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Krankheitssymptomatik für die Symptomskala klebriger Speichel des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Sticky Saliva	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	222	30.48 (35.69)	99	38.05 (35.64)	232	9.09 [2.42; 15.75]	3.32	0.459	-	0.936
SoC	176	29.92 (34.19)	84	33.73 (29.50)	192	5.77 [-1.38; 12.92]	[-5.49; 12.12]			
≥ 65										
Pembrolizumab	102	25.16 (29.83)	40	30.83 (29.61)	108	9.92 [1.22; 18.61]	2.23	0.700	-	
SoC	89	23.60 (31.86)	41	30.89 (31.08)	99	7.69 [-0.78; 16.15]	[-9.21; 13.67]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Sticky Saliva	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Tumor Stage										
III										
Pembrolizumab	81	21.81 (27.47)	43	37.21 (37.24)	86	16.88 [6.20; 27.56]	8.87	0.222	-	0.474
SoC	68	24.51 (30.81)	29	33.33 (32.12)	75	8.01 [-3.96; 19.98]	[-5.44; 23.18]			
IVA										
Pembrolizumab	241	30.84 (35.53)	96	35.42 (32.74)	252	7.06 [0.84; 13.28]	1.75	0.668	-	
SoC	197	28.93 (34.39)	96	32.64 (29.41)	216	5.31 [-0.95; 11.57]	[-6.27; 9.77]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	28.89 (34.21)	96	35.76 (33.59)	238	10.23 [3.75; 16.71]	6.50	0.129	-	0.158
SoC	182	28.02 (33.09)	87	29.89 (30.09)	197	3.72 [-3.02; 10.47]	[-1.90; 14.91]			
TPS ≥50%										
Pembrolizumab	99	28.62 (33.68)	43	36.43 (35.50)	102	8.00 [-1.36; 17.35]	-4.11	0.526	-	
SoC	83	27.31 (34.59)	38	39.47 (28.85)	94	12.10 [2.06; 22.14]	[-16.91; 8.70]			
Region										
European Union										
Pembrolizumab	125	22.93 (30.94)	54	38.89 (38.17)	132	16.21 [7.01; 25.41]	9.27	0.115	-	0.388
SoC	113	26.55 (34.55)	55	31.52 (32.97)	126	6.94 [-1.79; 15.66]	[-2.26; 20.80]			
North America										
Pembrolizumab	56	41.07 (39.69)	11	42.42 (21.56)	59	-3.32 [-19.22; 12.58]	1.56	0.877	-	
SoC	31	37.63 (36.25)	12	27.78 (23.92)	37	-4.88 [-19.38; 9.62]	[-18.25; 21.37]			
Rest of World										
Pembrolizumab	143	29.14 (33.07)	74	32.88 (32.40)	149	5.09 [-2.49; 12.67]	-1.37	0.775	-	
SoC	121	26.45 (31.60)	58	35.06 (28.22)	128	6.47 [-1.05; 13.99]	[-10.80; 8.05]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Sticky Saliva	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	28.21 (32.24)	10	20.00 (23.31)	26	4.12 [-10.61; 18.86]	-7.10	0.428	-	0.561
SoC	24	18.06 (25.97)	16	31.25 (25.73)	24	11.22 [-2.08; 24.52]	[-24.72; 10.52]			
Larynx										
Pembrolizumab	67	24.38 (31.56)	34	21.57 (27.07)	74	1.15 [-7.56; 9.86]	3.55	0.522	-	
SoC	52	27.56 (34.75)	24	18.06 (25.97)	58	-2.40 [-10.33; 5.53]	[-7.35; 14.46]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	30.16 (34.88)	95	42.81 (35.28)	240	11.19 [4.07; 18.30]	4.34	0.335	-	
SoC	189	29.10 (33.94)	85	37.25 (30.61)	209	6.85 [-0.05; 13.74]	[-4.48; 13.16]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-H&N35: Symptomskala Husten

Tabelle 4G-29: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Husten des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Coughing	**Baseline**		**Post-Adjuvant CRT/RT Week 51**		**Change from Baseline to Post-Adjuvant CRT/RT Week 51**		**Pembrolizumab vs. SoC**			**p-Value for Interaction Test[f]**
							Mean Difference at Post-Adjuvant CRT/RT Week 51		**Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51**	
	N[b]	**Mean (SD)**	**N[b]**	**Mean (SD)**	**N[c]**	**Mean [95 %-CI][d]**	**[95 %-CI][d]**	**p-Value**	**[95 %-CI][e]**	
Age										
< 65										
Pembrolizumab	222	21.02 (24.94)	99	19.53 (23.33)	232	-1.69 [-6.28; 2.90]	-1.66	0.599	-	0.375
SoC	176	25.57 (26.60)	84	21.03 (23.59)	192	-0.02 [-4.93; 4.88]	[-7.90; 4.57]			
≥ 65										
Pembrolizumab	102	22.55 (25.33)	40	20.83 (23.49)	108	3.16 [-5.24; 11.55]	4.16	0.450	-	
SoC	89	22.85 (29.13)	41	21.95 (27.50)	99	-1.01 [-9.19; 7.18]	[-6.73; 15.06]			
Sex										
Female										
Pembrolizumab	72	18.06 (21.62)	30	25.56 (27.24)	75	7.19 [-3.48; 17.86]	3.53	0.624	-	0.486
SoC	53	20.13 (27.22)	29	22.99 (29.69)	60	3.66 [-6.73; 14.05]	[-10.77; 17.83]			
Male										
Pembrolizumab	252	22.49 (25.88)	109	18.35 (21.98)	265	-3.03 [-7.35; 1.30]	-1.21	0.678	-	
SoC	212	25.79 (27.45)	96	20.83 (23.32)	231	-1.82 [-6.33; 2.69]	[-6.92; 4.51]			
Tumor Stage										
III										
Pembrolizumab	81	16.87 (21.16)	43	19.38 (23.27)	86	7.89 [1.61; 14.17]	4.33	0.362	-	0.977
SoC	68	22.06 (24.84)	29	24.14 (25.03)	75	3.56 [-3.74; 10.87]	[-5.07; 13.73]			
IVA										
Pembrolizumab	241	22.96 (26.15)	96	20.14 (23.44)	252	-2.86 [-7.98; 2.25]	-0.29	0.931	-	
SoC	197	25.55 (28.30)	96	20.49 (24.84)	216	-2.58 [-7.65; 2.50]	[-6.81; 6.23]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Coughing	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	23.11 (25.77)	96	20.49 (23.88)	238	-1.36 [-6.20; 3.49]	-1.31	0.691	-	0.472
SoC	182	25.82 (26.89)	87	24.14 (25.26)	197	-0.05 [-5.05; 4.95]	[-7.79; 5.18]			
TPS ≥50%										
Pembrolizumab	99	17.85 (22.99)	43	18.60 (22.19)	102	-1.34 [-8.98; 6.30]	3.33	0.495	-	
SoC	83	22.09 (28.64)	38	14.91 (22.86)	94	-4.67 [-12.57; 3.22]	[-6.32; 12.99]			
Region										
European Union										
Pembrolizumab	125	23.47 (26.10)	54	20.99 (21.76)	132	-0.86 [-6.63; 4.92]	-2.22	0.586	-	0.124
SoC	113	25.07 (28.71)	55	24.24 (25.22)	126	1.36 [-5.29; 8.02]	[-10.21; 5.77]			
North America										
Pembrolizumab	56	25.60 (28.42)	11	30.30 (23.35)	59	6.78 [-5.25; 18.81]	16.50	0.053	-	
SoC	31	32.26 (30.41)	12	11.11 (21.71)	37	-9.72 [-23.70; 4.27]	[-0.23; 33.23]			
Rest of World										
Pembrolizumab	143	18.18 (22.28)	74	17.57 (24.19)	149	-0.87 [-6.30; 4.56]	-0.65	0.864	-	
SoC	121	22.31 (25.24)	58	20.69 (24.84)	128	-0.22 [-5.99; 5.56]	[-8.12; 6.82]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	32.05 (27.46)	10	20.00 (23.31)	26	-12.03 [-24.72; 0.67]	0.60	0.943	-	0.823
SoC	24	34.72 (25.02)	16	18.75 (24.25)	24	-12.62 [-25.23; -0.02]	[-15.93; 17.13]			
Larynx										
Pembrolizumab	67	37.81 (27.76)	34	19.61 (24.78)	74	-16.55 [-24.86; -8.23]	-2.47	0.673	-	
SoC	52	41.67 (33.58)	24	26.39 (25.97)	58	-14.07 [-23.78; -4.36]	[-13.98; 9.04]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	15.58 (21.25)	95	20.00 (23.01)	240	5.61 [1.10; 10.13]	0.99	0.761	-	
SoC	189	18.69 (23.39)	85	20.39 (24.72)	209	4.62 [-0.42; 9.66]	[-5.41; 7.40]			

a: Database Cutoff Date: 25JUL2024
b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint
c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis
d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Coughing	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero										
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction										
CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score										

EORTC QLQ-H&N35: Symptomskala Krankheitsgefühl

Tabelle 4G-30: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Krankheitssymptomatik für die Symptomskala Krankheitsgefühl des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Felt Ill	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	222	20.87 (27.82)	99	16.16 (21.49)	232	-4.49 [-8.99; 0.01]	-0.84	0.782	-	0.157
SoC	176	28.98 (32.66)	84	17.06 (22.25)	192	-3.64 [-8.56; 1.27]	[-6.83; 5.14]			
≥ 65										
Pembrolizumab	102	26.47 (29.42)	40	20.00 (24.81)	108	-1.70 [-9.53; 6.13]	6.19	0.226	-	
SoC	89	22.85 (29.13)	41	13.01 (23.43)	99	-7.89 [-15.46; -0.32]	[-3.89; 16.26]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Felt Ill	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Sex										
Female										
Pembrolizumab	72	16.20 (24.38)	30	15.56 (27.31)	75	3.30 [-6.54; 13.14]	6.60	0.340	-	0.339
SoC	53	20.75 (26.33)	29	12.64 (24.26)	60	-3.30 [-13.67; 7.07]	[-7.11; 20.32]			
Male										
Pembrolizumab	252	24.47 (29.24)	109	17.74 (21.07)	265	-5.88 [-10.09; -1.67]	-0.48	0.860	-	
SoC	212	28.46 (32.65)	96	16.67 (22.16)	231	-5.40 [-9.87; -0.93]	[-5.87; 4.90]			
Tumor Stage										
III										
Pembrolizumab	81	14.40 (24.12)	43	17.83 (19.72)	86	4.99 [-2.83; 12.82]	5.04	0.380	-	0.654
SoC	68	24.51 (28.57)	29	19.54 (30.23)	75	-0.05 [-9.32; 9.22]	[-6.32; 16.41]			
IVA										
Pembrolizumab	241	24.90 (28.83)	96	17.01 (23.69)	252	-6.89 [-11.49; -2.30]	0.55	0.851	-	
SoC	197	27.75 (32.60)	96	14.58 (19.83)	216	-7.44 [-12.10; -2.79]	[-5.23; 6.33]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	22.96 (29.06)	96	18.40 (21.56)	238	-2.77 [-7.37; 1.84]	1.00	0.743	-	0.909
SoC	182	26.37 (31.35)	87	17.24 (23.22)	197	-3.77 [-8.58; 1.05]	[-5.00; 7.00]			
TPS ≥50%										
Pembrolizumab	99	21.89 (27.01)	43	14.73 (24.45)	102	-5.79 [-12.96; 1.39]	1.68	0.731	-	
SoC	83	28.11 (32.29)	38	12.28 (21.11)	94	-7.46 [-15.15; 0.22]	[-7.99; 11.35]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Felt Ill	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Region										
European Union										
Pembrolizumab	125	21.07 (26.95)	54	17.28 (21.22)	132	-1.01 [-7.39; 5.38]	4.70	0.259	-	0.762
SoC	113	26.25 (30.03)	55	14.55 (24.65)	126	-5.70 [-12.07; 0.67]	[-3.47; 12.86]			
North America										
Pembrolizumab	56	16.07 (25.42)	11	6.06 (13.48)	59	-10.89 [-19.85; -1.94]	-1.72	0.734	-	
SoC	31	20.43 (32.97)	12	5.56 (12.97)	37	-9.17 [-18.31; -0.04]	[-11.68; 8.24]			
Rest of World										
Pembrolizumab	143	26.57 (30.27)	74	18.92 (24.10)	149	-5.67 [-11.61; 0.27]	-0.39	0.914	-	
SoC	121	29.20 (32.65)	58	18.97 (21.73)	128	-5.27 [-10.95; 0.40]	[-7.52; 6.73]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	35.90 (36.42)	10	13.33 (23.31)	26	-12.43 [-20.21; -4.64]	-13.73	0.012	-0.75	0.432
SoC	24	18.06 (21.93)	16	16.67 (17.21)	24	1.30 [-7.02; 9.62]	[-24.42; -3.03]		[-1.33; -0.17]	
Larynx										
Pembrolizumab	67	21.89 (25.66)	34	19.61 (18.56)	74	-1.46 [-9.15; 6.23]	4.42	0.402	-	
SoC	52	35.26 (36.40)	24	20.83 (25.66)	58	-5.89 [-14.69; 2.92]	[-5.93; 14.78]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	21.36 (27.90)	95	16.84 (23.76)	240	-3.22 [-8.38; 1.94]	2.81	0.379	-	
SoC	189	25.75 (30.87)	85	14.12 (22.64)	209	-6.03 [-10.84; -1.23]	[-3.46; 9.09]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-H&N35: Symptomskala Schmerzmitteleinnahme

Tabelle 4G-31: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Schmerzmitteleinnahme des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Pain Killers	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	222	22.82 (15.52)	99	11.45 (15.91)	232	-10.21 [-13.38; -7.03]	2.37	0.284	-	0.861
SoC	176	23.86 (15.08)	84	9.92 (15.33)	192	-12.58 [-16.01; -9.15]	[-1.98; 6.72]			
≥ 65										
Pembrolizumab	102	21.24 (16.11)	40	9.17 (15.07)	108	-9.20 [-13.87; -4.53]	3.41	0.269	-	
SoC	89	21.72 (15.97)	41	7.32 (13.97)	99	-12.61 [-17.19; -8.02]	[-2.68; 9.50]			
Sex										
Female										
Pembrolizumab	72	25.00 (14.54)	30	14.44 (16.80)	75	-8.79 [-14.56; -3.02]	4.54	0.251	-	0.468
SoC	53	25.16 (14.48)	29	11.49 (16.12)	60	-13.32 [-19.13; -7.52]	[-3.28; 12.35]			
Male										
Pembrolizumab	252	21.56 (15.96)	109	9.79 (15.25)	265	-10.18 [-13.07; -7.28]	2.43	0.220	-	
SoC	212	22.64 (15.60)	96	8.33 (14.51)	231	-12.61 [-15.71; -9.51]	[-1.47; 6.33]			
Tumor Stage										
III										
Pembrolizumab	81	18.52 (16.67)	43	10.08 (15.49)	86	-8.22 [-12.93; -3.50]	2.90	0.396	-	0.746
SoC	68	24.51 (14.82)	29	10.34 (15.69)	75	-11.11 [-16.57; -5.66]	[-3.86; 9.66]			
IVA										
Pembrolizumab	241	23.51 (15.23)	96	11.11 (15.80)	252	-10.16 [-13.28; -7.05]	3.22	0.126	-	
SoC	197	22.67 (15.59)	96	8.68 (14.71)	216	-13.39 [-16.56; -10.21]	[-0.91; 7.35]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Pain Killers	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	22.81 (15.53)	96	9.72 (15.23)	238	-10.72 [-13.79; -7.66]	1.91	0.360	-	0.324
SoC	182	22.16 (15.78)	87	8.81 (14.79)	197	-12.64 [-15.87; -9.40]	[-2.20; 6.03]			
TPS ≥50%										
Pembrolizumab	99	21.21 (16.12)	43	13.18 (16.49)	102	-7.32 [-12.14; -2.49]	5.73	0.092	-	
SoC	83	25.30 (14.34)	38	9.65 (15.32)	94	-13.04 [-18.15; -7.94]	[-0.95; 12.40]			
Region										
European Union										
Pembrolizumab	125	21.07 (16.14)	54	11.11 (15.86)	132	-9.10 [-13.20; -4.99]	0.26	0.927	-	0.372
SoC	113	23.01 (15.48)	55	12.12 (16.18)	126	-9.36 [-13.74; -4.98]	[-5.31; 5.83]			
North America										
Pembrolizumab	56	26.79 (13.36)	11	9.09 (15.57)	59	-15.54 [-24.30; -6.79]	1.25	0.819	-	
SoC	31	26.88 (13.39)	12	5.56 (12.97)	37	-16.80 [-24.22; -9.37]	[-9.50; 12.01]			
Rest of World										
Pembrolizumab	143	21.68 (15.95)	74	10.81 (15.71)	149	-9.66 [-13.29; -6.03]	5.53	0.017	0.35	
SoC	121	22.31 (15.75)	58	6.90 (13.62)	128	-15.18 [-18.60; -11.76]	[0.98; 10.07]		[0.06; 0.64]	
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	23.08 (15.69)	10	6.67 (14.05)	26	-8.70 [-17.96; 0.55]	7.26	0.122	-	0.556
SoC	24	15.28 (16.97)	16	2.08 (8.33)	24	-15.97 [-22.03; -9.91]	[-1.95; 16.47]			
Larynx										
Pembrolizumab	67	19.40 (16.56)	34	10.78 (15.83)	74	-7.62 [-12.84; -2.39]	5.53	0.093	-	
SoC	52	19.23 (16.63)	24	5.56 (12.69)	58	-13.14 [-17.99; -8.29]	[-0.93; 11.98]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	23.09 (15.41)	95	11.23 (15.84)	240	-10.99 [-14.14; -7.83]	1.14	0.606	-	
SoC	189	25.22 (14.34)	85	11.37 (15.90)	209	-12.13 [-15.55; -8.71]	[-3.20; 5.49]			

a: Database Cutoff Date: 25JUL2024
b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint
c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis
d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Pain Killers	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC				p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51			Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]		p-Value	[95 %-CI][e]	
e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score										

EORTC QLQ-H&N35: Symptomskala Nahrungsergänzungsmitteleinnahme

Tabelle 4G-32: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Krankheitssymptomatik für die Symptomskala Nahrungsergänzungsmitteleinnahme des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Nutritional Supplements	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC				p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51			Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]		p-Value	[95 %-CI][e]	
Age											
< 65											
Pembrolizumab	222	8.71 (14.68)	99	7.07 (13.70)	232	-0.98 [-3.55; 1.59]	-1.66		0.358	-	0.496
SoC	176	9.28 (14.98)	84	8.33 (14.52)	192	0.68 [-2.09; 3.45]	[-5.21; 1.89]				
≥ 65											
Pembrolizumab	102	7.84 (14.21)	40	8.33 (14.62)	108	-0.92 [-5.40; 3.56]	-0.47		0.878	-	
SoC	89	9.36 (15.07)	41	8.13 (14.49)	99	-0.45 [-5.02; 4.12]	[-6.52; 5.58]				

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Nutritional Supplements	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Sex										
Female										
Pembrolizumab	72	9.72 (15.26)	30	11.11 (15.98)	75	0.80 [-4.69; 6.29]	-2.07	0.582	-	0.784
SoC	53	9.43 (15.16)	29	10.34 (15.69)	60	2.87 [-2.61; 8.35]	[-9.54; 5.41]			
Male										
Pembrolizumab	252	8.07 (14.31)	109	6.42 (13.21)	265	-0.98 [-3.45; 1.50]	-0.47	0.785	-	
SoC	212	9.28 (14.97)	96	7.64 (14.08)	231	-0.51 [-3.15; 2.14]	[-3.84; 2.90]			
Tumor Stage										
III										
Pembrolizumab	81	7.00 (13.66)	43	8.53 (14.72)	86	0.10 [-2.98; 3.17]	-0.90	0.703	-	0.437
SoC	68	7.84 (14.24)	29	3.45 (10.33)	75	1.00 [-2.70; 4.69]	[-5.57; 3.77]			
IVA										
Pembrolizumab	241	8.85 (14.75)	96	6.94 (13.61)	252	-1.21 [-4.09; 1.66]	-1.60	0.406	-	
SoC	197	9.81 (15.23)	96	9.72 (15.23)	216	0.39 [-2.50; 3.29]	[-5.40; 2.19]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	8.89 (14.77)	96	6.60 (13.35)	238	-1.49 [-4.03; 1.06]	-0.13	0.940	-	0.434
SoC	182	9.52 (15.10)	87	6.90 (13.58)	197	-1.35 [-4.03; 1.32]	[-3.59; 3.33]			
TPS ≥50%										
Pembrolizumab	99	7.41 (13.93)	43	9.30 (15.13)	102	0.46 [-4.00; 4.92]	-2.94	0.354	-	
SoC	83	8.84 (14.80)	38	11.40 (16.03)	94	3.40 [-1.48; 8.28]	[-9.20; 3.32]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Nutritional Supplements	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Region										
European Union										
Pembrolizumab	125	5.33 (12.27)	54	6.79 (13.55)	132	-0.05 [-3.57; 3.47]	-0.01	0.997	-	0.373
SoC	113	8.26 (14.46)	55	6.67 (13.46)	126	-0.04 [-3.45; 3.37]	[-4.53; 4.51]			
North America										
Pembrolizumab	56	13.69 (16.55)	11	15.15 (17.41)	59	-0.97 [-7.81; 5.88]	-4.59	0.457	-	
SoC	31	17.20 (16.93)	12	16.67 (17.41)	37	3.62 [-6.94; 14.19]	[-16.73; 7.55]			
Rest of World										
Pembrolizumab	143	9.09 (14.90)	74	6.76 (13.49)	149	-1.10 [-4.08; 1.88]	-1.71	0.406	-	
SoC	121	8.26 (14.45)	58	8.05 (14.39)	128	0.61 [-2.45; 3.67]	[-5.76; 2.33]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	12.82 (16.54)	10	6.67 (14.05)	26	-6.54 [-15.50; 2.41]	-9.65	0.072	-	0.392
SoC	24	5.56 (12.69)	16	10.42 (15.96)	24	3.10 [-3.54; 9.75]	[-20.15; 0.85]			
Larynx										
Pembrolizumab	67	4.98 (11.97)	34	3.92 (10.90)	74	-1.22 [-3.14; 0.70]	-3.00	0.085	-	
SoC	52	7.69 (14.18)	24	5.56 (12.69)	58	1.78 [-1.11; 4.66]	[-6.41; 0.41]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	8.95 (14.80)	95	8.77 (14.76)	240	-0.52 [-3.31; 2.27]	0.17	0.930	-	
SoC	189	10.23 (15.41)	85	8.63 (14.69)	209	-0.69 [-3.74; 2.36]	[-3.68; 4.02]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-H&N35: Symptomskala Ernährungssondeneinsatz

Tabelle 4G-33: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Krankheitssymptomatik für die Symptomskala Ernährungssondeneinsatz des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Feeding Tube	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	222	2.40 (8.64)	99	6.06 (12.92)	232	3.87 [1.54; 6.21]	2.93	0.048	0.24	0.208
SoC	176	2.84 (9.33)	84	2.38 (8.64)	192	0.95 [-0.98; 2.88]	[0.03; 5.82]		[0.00; 0.48]	
≥ 65										
Pembrolizumab	102	2.61 (9.01)	40	4.17 (11.16)	108	5.44 [1.86; 9.01]	0.20	0.939	-	
SoC	89	1.12 (6.05)	41	5.69 (12.70)	99	5.24 [1.35; 9.13]	[-4.85; 5.25]			
Sex										
Female										
Pembrolizumab	72	2.31 (8.53)	30	8.89 (14.99)	75	8.14 [3.92; 12.35]	5.79	0.042	0.46	0.188
SoC	53	0.63 (4.58)	29	3.45 (10.33)	60	2.34 [-1.48; 6.17]	[0.21; 11.38]		[0.02; 0.89]	
Male										
Pembrolizumab	252	2.51 (8.82)	109	4.59 (11.54)	265	3.43 [1.28; 5.59]	0.89	0.546	-	
SoC	212	2.67 (9.07)	96	3.47 (10.24)	231	2.55 [0.42; 4.67]	[-1.99; 3.77]			
Tumor Stage										
III										
Pembrolizumab	81	0.41 (3.70)	43	3.10 (9.80)	86	3.50 [0.45; 6.56]	0.10	0.961	-	0.179
SoC	68	1.96 (7.90)	29	3.45 (10.33)	75	3.40 [-0.13; 6.93]	[-4.07; 4.27]			
IVA										
Pembrolizumab	241	3.04 (9.62)	96	6.60 (13.35)	252	4.47 [2.05; 6.90]	2.40	0.133	-	
SoC	197	2.37 (8.59)	96	3.47 (10.24)	216	2.07 [-0.15; 4.29]	[-0.73; 5.54]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Feeding Tube	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	2.81 (9.29)	96	6.25 (13.08)	238	5.10 [2.73; 7.46]	2.65	0.109	-	0.735
SoC	182	2.75 (9.19)	87	3.45 (10.21)	197	2.45 [-0.06; 4.96]	[-0.59; 5.88]			
TPS ≥50%										
Pembrolizumab	99	1.68 (7.34)	43	3.88 (10.81)	102	7.11 [4.05; 10.17]	3.51	0.145	-	
SoC	83	1.20 (6.26)	38	3.51 (10.37)	94	3.60 [-0.05; 7.25]	[-1.24; 8.26]			
Region										
European Union										
Pembrolizumab	125	1.60 (7.15)	54	8.64 (14.74)	132	7.91 [4.57; 11.26]	3.87	0.076	-	0.802
SoC	113	1.18 (6.19)	55	4.24 (11.21)	126	4.05 [1.35; 6.75]	[-0.40; 8.13]			
North America										
Pembrolizumab	56	3.57 (10.40)	11	9.09 (15.57)	59	3.90 [-2.56; 10.37]	0.01	0.998	-	
SoC	31	8.60 (14.83)	12	8.33 (15.08)	37	3.89 [-4.66; 12.43]	[-10.25; 10.28]			
Rest of World										
Pembrolizumab	143	2.80 (9.27)	74	2.70 (9.16)	149	1.56 [-0.86; 3.99]	0.74	0.621	-	
SoC	121	1.65 (7.27)	58	1.72 (7.45)	128	0.82 [-1.40; 3.03]	[-2.21; 3.70]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	6.41 (13.40)	10	0.00 (0.00)	26	-2.92 [-7.97; 2.13]	-1.86	0.566	-	0.830
SoC	24	2.78 (9.41)	16	2.08 (8.33)	24	-1.06 [-6.43; 4.31]	[-8.24; 4.52]			
Larynx										
Pembrolizumab	67	4.48 (11.45)	34	3.92 (10.90)	74	0.70 [-2.23; 3.63]	1.33	0.590	-	
SoC	52	5.13 (12.14)	24	2.78 (9.41)	58	-0.63 [-4.84; 3.58]	[-3.50; 6.16]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	1.44 (6.80)	95	6.67 (13.40)	240	6.67 [4.07; 9.27]	3.18	0.065	-	
SoC	189	1.41 (6.73)	85	3.92 (10.80)	209	3.49 [1.22; 5.76]	[-0.20; 6.56]			

a: Database Cutoff Date: 25JUL2024
b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint
c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Feeding Tube	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction										
e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero										
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction										
CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score										

EORTC QLQ-H&N35: Symptomskala Gewichtsverlust

Tabelle 4G-34: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Krankheitssymptomatik für die Symptomskala Gewichtsverlust des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Weight Loss	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	222	15.62 (16.67)	99	8.08 (14.36)	232	-7.42 [-10.58; -4.26]	2.50	0.222	-	0.263
SoC	176	16.48 (16.71)	84	5.95 (12.84)	192	-9.92 [-13.28; -6.56]	[-1.53; 6.54]			
≥ 65										
Pembrolizumab	102	15.03 (16.67)	40	10.00 (15.47)	108	-4.83 [-9.82; 0.15]	5.96	0.049	0.46	
SoC	89	13.48 (16.45)	41	3.25 (10.01)	99	-10.80 [-15.65; -5.95]	[0.03; 11.90]		[0.00; 0.92]	

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Weight Loss	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Sex										
Female										
Pembrolizumab	72	16.20 (16.78)	30	7.78 (14.34)	75	-8.95 [-15.11; -2.79]	1.59	0.671	-	0.523
SoC	53	16.98 (16.82)	29	5.75 (12.81)	60	-10.54 [-16.65; -4.43]	[-5.86; 9.05]			
Male										
Pembrolizumab	252	15.21 (16.64)	109	8.87 (14.80)	265	-5.69 [-8.66; -2.73]	4.43	0.021	0.33	
SoC	212	15.09 (16.63)	96	4.86 (11.83)	231	-10.12 [-13.22; -7.01]	[0.69; 8.17]		[0.05; 0.60]	
Tumor Stage										
III										
Pembrolizumab	81	11.11 (15.81)	43	5.43 (12.45)	86	-7.41 [-11.96; -2.87]	0.29	0.923	-	0.169
SoC	68	15.69 (16.76)	29	4.60 (11.70)	75	-7.70 [-12.96; -2.44]	[-5.64; 6.22]			
IVA										
Pembrolizumab	241	16.87 (16.70)	96	10.07 (15.39)	252	-5.73 [-8.99; -2.47]	5.41	0.008	0.39	
SoC	197	15.40 (16.66)	96	5.21 (12.17)	216	-11.14 [-14.37; -7.91]	[1.41; 9.41]		[0.10; 0.67]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	15.85 (16.68)	96	9.72 (15.23)	238	-5.01 [-8.28; -1.74]	4.91	0.018	0.35	0.387
SoC	182	14.47 (16.57)	87	5.36 (12.32)	197	-9.93 [-13.30; -6.56]	[0.85; 8.98]		[0.06; 0.64]	
TPS ≥50%										
Pembrolizumab	99	14.48 (16.61)	43	6.20 (13.12)	102	-9.08 [-13.60; -4.57]	2.24	0.432	-	
SoC	83	17.67 (16.74)	38	4.39 (11.42)	94	-11.33 [-16.02; -6.64]	[-3.41; 7.90]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Weight Loss	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Region										
European Union										
Pembrolizumab	125	12.80 (16.28)	54	9.26 (15.07)	132	-5.04 [-9.55; -0.54]	3.18	0.219	-	0.439
SoC	113	14.75 (16.63)	55	5.45 (12.45)	126	-8.23 [-12.09; -4.37]	[-1.89; 8.26]			
North America										
Pembrolizumab	56	20.83 (16.28)	11	12.12 (16.82)	59	-8.21 [-17.28; 0.86]	-1.38	0.824	-	
SoC	31	23.66 (15.38)	12	13.89 (17.16)	37	-6.83 [-16.40; 2.74]	[-13.59; 10.83]			
Rest of World										
Pembrolizumab	143	15.62 (16.69)	74	7.66 (14.12)	149	-6.72 [-10.49; -2.95]	5.10	0.013	0.33	
SoC	121	14.05 (16.53)	58	2.87 (9.44)	128	-11.82 [-15.01; -8.63]	[1.09; 9.12]		[0.07; 0.58]	
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	15.38 (16.95)	10	13.33 (17.21)	26	5.34 [-5.50; 16.18]	14.20	0.010	0.94	0.277
SoC	24	4.17 (11.26)	16	2.08 (8.33)	24	-8.87 [-15.00; -2.73]	[3.49; 24.92]		[0.23; 1.64]	
Larynx										
Pembrolizumab	67	14.93 (16.70)	34	4.90 (11.98)	74	-9.80 [-15.04; -4.56]	3.18	0.253	-	
SoC	52	14.74 (16.72)	24	2.78 (9.41)	58	-12.98 [-18.12; -7.85]	[-2.28; 8.65]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	15.58 (16.67)	95	9.47 (15.11)	240	-6.82 [-10.23; -3.41]	3.02	0.147	-	
SoC	189	17.11 (16.71)	85	6.27 (13.11)	209	-9.84 [-13.01; -6.66]	[-1.06; 7.09]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-H&N35: Symptomskala Gewichtszunahme

Tabelle 4G-35: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Krankheitssymptomatik für die Symptomskala Gewichtszunahme des EORTC QLQ-H&N35 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Weight Gain	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	222	3.75 (10.56)	99	11.45 (15.91)	232	7.72 [4.37; 11.07]	-0.91	0.702	-	0.383
SoC	176	4.55 (11.47)	84	13.10 (16.38)	192	8.63 [5.02; 12.24]	[-5.59; 3.77]			
≥ 65										
Pembrolizumab	102	5.23 (12.18)	40	10.83 (15.81)	108	5.57 [-0.04; 11.18]	-5.09	0.174	-	
SoC	89	4.49 (11.45)	41	16.26 (16.87)	99	10.66 [5.23; 16.09]	[-12.46; 2.29]			
Sex										
Female										
Pembrolizumab	72	5.09 (12.08)	30	10.00 (15.54)	75	5.51 [-0.44; 11.46]	1.23	0.760	-	0.330
SoC	53	5.66 (12.64)	29	9.20 (15.16)	60	4.28 [-1.70; 10.26]	[-6.75; 9.20]			
Male										
Pembrolizumab	252	3.97 (10.82)	109	11.62 (15.96)	265	7.37 [4.10; 10.64]	-3.76	0.100	-	
SoC	212	4.25 (11.14)	96	15.62 (16.72)	231	11.14 [7.70; 14.57]	[-8.26; 0.73]			
Tumor Stage										
III										
Pembrolizumab	81	2.88 (9.42)	43	13.18 (16.49)	86	9.58 [4.23; 14.94]	1.13	0.779	-	0.178
SoC	68	3.92 (10.82)	29	12.64 (16.46)	75	8.45 [2.13; 14.77]	[-6.89; 9.16]			
IVA										
Pembrolizumab	241	4.56 (11.48)	96	10.42 (15.53)	252	5.79 [2.37; 9.21]	-4.29	0.064	-	
SoC	197	4.74 (11.67)	96	14.58 (16.62)	216	10.08 [6.67; 13.50]	[-8.84; 0.26]			

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Weight Gain	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	5.19 (12.11)	96	10.07 (15.39)	238	5.20 [1.72; 8.68]	-4.74	0.046	-0.30	0.126
SoC	182	5.31 (12.23)	87	15.33 (16.71)	197	9.94 [6.32; 13.57]	[-9.40; -0.08]		[-0.59; -0.01]	
TPS ≥50%										
Pembrolizumab	99	2.02 (7.99)	43	13.95 (16.64)	102	11.40 [6.65; 16.14]	2.16	0.542	-	
SoC	83	2.81 (9.32)	38	11.40 (16.03)	94	9.24 [3.95; 14.53]	[-4.85; 9.17]			
Region										
European Union										
Pembrolizumab	125	4.53 (11.47)	54	11.11 (15.86)	132	6.89 [2.60; 11.17]	-1.51	0.618	-	0.825
SoC	113	5.01 (11.97)	55	13.33 (16.48)	126	8.39 [3.78; 13.01]	[-7.45; 4.43]			
North America										
Pembrolizumab	56	4.76 (11.77)	11	9.09 (15.57)	59	0.61 [-7.09; 8.32]	-3.08	0.570	-	
SoC	31	4.30 (11.36)	12	8.33 (15.08)	37	3.70 [-4.49; 11.88]	[-13.75; 7.58]			
Rest of World										
Pembrolizumab	143	3.73 (10.54)	74	11.71 (16.02)	149	7.94 [4.03; 11.85]	-4.21	0.128	-	
SoC	121	4.13 (11.03)	58	16.09 (16.80)	128	12.15 [7.80; 16.50]	[-9.64; 1.21]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	6.41 (13.40)	10	16.67 (17.57)	26	10.94 [0.79; 21.08]	-0.23	0.970	-	0.570
SoC	24	4.17 (11.26)	16	16.67 (17.21)	24	11.17 [2.44; 19.90]	[-12.44; 11.97]			
Larynx										
Pembrolizumab	67	7.96 (14.32)	34	9.80 (15.42)	74	2.87 [-2.95; 8.68]	-6.46	0.099	-	
SoC	52	6.41 (13.27)	24	15.28 (16.97)	58	9.33 [2.43; 16.22]	[-14.13; 1.21]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	2.89 (9.39)	95	11.23 (15.84)	240	8.20 [4.98; 11.42]	-1.33	0.572	-	
SoC	189	4.06 (10.93)	85	13.33 (16.43)	209	9.53 [5.99; 13.06]	[-5.95; 3.29]			

a: Database Cutoff Date: 25JUL2024
b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint
c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis
d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

Study: KEYNOTE 689[a] EORTC QLQ-H&N35 Symptom Scales Weight Gain	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC				p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51			Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value		[95 %-CI][e]	
e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero											
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction											
CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score											

EQ-5D VAS

Tabelle 4G-36: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesundheitszustand anhand EQ-5D VAS aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EQ-5D VAS	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	223	72.82 (19.32)	100	78.51 (14.38)	232	3.42 [0.39; 6.45]	1.15	0.569	-	0.208
SoC	177	70.06 (20.50)	84	76.63 (16.51)	192	2.27 [-1.01; 5.55]	[-2.82; 5.12]			
≥ 65										
Pembrolizumab	102	69.51 (21.15)	40	72.93 (15.94)	108	-0.76 [-6.07; 4.55]	-3.48	0.302	-	
SoC	88	70.18 (19.26)	41	75.93 (18.79)	98	2.71 [-2.51; 7.94]	[-10.12; 3.16]			
Sex										
Female										
Pembrolizumab	72	69.24 (20.81)	30	73.20 (14.85)	75	3.36 [-2.32; 9.03]	-3.17	0.378	-	0.322
SoC	52	69.42 (17.01)	29	78.31 (16.14)	59	6.52 [0.77; 12.28]	[-10.28; 3.95]			
Male										
Pembrolizumab	253	72.50 (19.66)	110	77.93 (14.94)	265	2.33 [-0.66; 5.32]	0.89	0.653	-	
SoC	213	70.26 (20.77)	96	75.82 (17.57)	231	1.44 [-1.71; 4.59]	[-3.00; 4.77]			
Tumor Stage										
III										
Pembrolizumab	81	74.04 (17.90)	43	75.63 (14.57)	86	-0.98 [-6.18; 4.23]	-2.42	0.522	-	0.608
SoC	68	72.38 (19.93)	29	76.38 (21.94)	75	1.45 [-4.54; 7.44]	[-9.90; 5.06]			
IVA										
Pembrolizumab	242	71.19 (20.55)	97	77.48 (15.22)	252	3.95 [0.86; 7.04]	1.06	0.587	-	
SoC	197	69.31 (20.10)	96	76.41 (15.66)	215	2.89 [-0.23; 6.01]	[-2.78; 4.91]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	226	71.66 (20.00)	97	76.21 (15.16)	238	2.43 [-0.79; 5.65]	1.17	0.583	-	0.350
SoC	182	70.46 (20.42)	87	74.95 (17.84)	196	1.25 [-2.15; 4.65]	[-3.03; 5.38]			

Study: KEYNOTE 689[a] EQ-5D VAS	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
TPS ≥50%										
Pembrolizumab	99	72.04 (19.90)	43	78.51 (14.67)	102	3.40 [-1.17; 7.98]	-2.06	0.476	-	
SoC	83	69.30 (19.35)	38	79.71 (15.42)	94	5.46 [0.78; 10.14]	[-7.77; 3.65]			
Region										
European Union										
Pembrolizumab	125	71.78 (19.36)	54	71.98 (14.36)	132	0.01 [-3.93; 3.94]	-3.39	0.198	-	0.216
SoC	114	66.71 (21.19)	55	73.47 (17.71)	126	3.40 [-0.93; 7.74]	[-8.57; 1.78]			
North America										
Pembrolizumab	56	66.39 (20.26)	12	83.92 (12.18)	59	11.09 [3.18; 19.01]	3.01	0.529	-	
SoC	31	69.68 (16.86)	12	80.58 (8.63)	37	8.08 [1.15; 15.02]	[-6.38; 12.39]			
Rest of World										
Pembrolizumab	144	73.87 (20.05)	74	79.38 (14.97)	149	2.33 [-1.39; 6.05]	0.63	0.803	-	
SoC	120	73.43 (19.31)	58	78.31 (17.83)	127	1.70 [-2.50; 5.91]	[-4.33; 5.59]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	74.85 (17.01)	10	77.70 (14.51)	26	-0.63 [-8.05; 6.80]	1.14	0.844	-	0.491
SoC	24	78.46 (11.02)	16	77.94 (20.14)	24	-1.77 [-11.42; 7.89]	[-10.32; 12.60]			
Larynx										
Pembrolizumab	68	71.06 (20.40)	34	79.56 (14.58)	74	6.30 [0.58; 12.02]	3.72	0.362	-	
SoC	52	69.94 (20.33)	24	75.92 (20.63)	58	2.59 [-4.54; 9.71]	[-4.28; 11.71]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	71.65 (20.15)	96	75.90 (15.22)	240	2.66 [-0.43; 5.75]	-1.33	0.499	-	
SoC	189	69.08 (20.69)	85	76.25 (15.75)	208	3.99 [0.89; 7.10]	[-5.20; 2.54]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EQ-5D: European Quality of Life 5 Dimensions; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score; VAS: Visual Analog Scale

Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-37: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Gesundheitsbezogene Lebensqualität für den globalen Gesundheitsstatus des EORTC QLQ-C30 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-C30 Global Health Status/QoL	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	223	64.57 (19.65)	99	71.80 (17.89)	232	5.93 [2.55; 9.31]	2.08	0.366	-	0.087
SoC	176	61.41 (22.28)	84	70.34 (17.23)	192	3.85 [0.22; 7.48]	[-2.44; 6.59]			
≥ 65										
Pembrolizumab	101	61.88 (21.84)	40	67.08 (18.68)	108	-0.85 [-6.58; 4.88]	-6.19	0.110	-	
SoC	89	64.70 (20.41)	41	72.15 (21.94)	99	5.35 [-0.25; 10.94]	[-13.81; 1.42]			
Sex										
Female										
Pembrolizumab	72	66.78 (18.95)	30	69.17 (14.54)	75	1.18 [-4.62; 6.99]	-4.64	0.220	-	0.139
SoC	53	62.89 (18.46)	29	72.13 (16.86)	60	5.82 [-0.03; 11.67]	[-12.11; 2.84]			
Male										
Pembrolizumab	252	62.86 (20.70)	109	70.80 (19.10)	265	4.95 [1.63; 8.27]	1.43	0.530	-	
SoC	212	62.42 (22.46)	96	70.57 (19.46)	231	3.52 [0.02; 7.02]	[-3.05; 5.92]			
Tumor Stage										
III										
Pembrolizumab	81	66.05 (18.76)	43	71.12 (17.19)	86	0.73 [-5.01; 6.47]	0.04	0.992	-	0.811
SoC	68	65.81 (22.31)	29	70.69 (24.86)	75	0.69 [-6.09; 7.47]	[-8.49; 8.58]			
IVA										
Pembrolizumab	241	63.07 (20.90)	96	70.14 (18.68)	252	4.85 [1.47; 8.23]	-0.40	0.857	-	
SoC	197	61.38 (21.41)	96	71.01 (16.75)	216	5.25 [1.85; 8.65]	[-4.77; 3.97]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Global Health Status/QoL	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	62.56 (19.94)	96	69.27 (17.58)	238	3.39 [-0.19; 6.96]	0.55	0.823	-	0.459
SoC	182	63.05 (21.36)	87	69.25 (20.15)	197	2.84 [-0.95; 6.62]	[-4.27; 5.37]			
TPS ≥50%										
Pembrolizumab	99	66.41 (21.14)	43	73.06 (19.40)	102	5.27 [0.64; 9.90]	-2.74	0.372	-	
SoC	83	61.35 (22.49)	38	74.78 (14.94)	94	8.01 [3.24; 12.78]	[-8.81; 3.32]			
Region										
European Union										
Pembrolizumab	124	63.24 (20.74)	54	63.73 (17.45)	132	0.16 [-4.28; 4.61]	-3.74	0.203	-	0.201
SoC	113	59.88 (21.00)	55	68.03 (18.76)	126	3.91 [-0.55; 8.36]	[-9.51; 2.02]			
North America										
Pembrolizumab	56	61.16 (21.40)	11	74.24 (12.61)	59	4.57 [-0.86; 10.00]	-10.48	0.009	-0.81	
SoC	31	61.02 (22.09)	12	79.17 (13.53)	37	15.05 [8.85; 21.24]	[-18.33; -2.62]		[-1.41; -0.20]	
Rest of World										
Pembrolizumab	144	65.16 (19.63)	74	74.77 (18.09)	149	6.67 [2.30; 11.03]	2.30	0.435	-	
SoC	121	65.36 (22.05)	58	71.98 (19.48)	128	4.37 [-0.22; 8.96]	[-3.48; 8.07]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	60.26 (15.87)	10	74.17 (20.95)	26	5.91 [-4.65; 16.48]	3.39	0.647	-	0.692
SoC	24	67.01 (16.02)	16	69.79 (22.75)	24	2.52 [-8.45; 13.49]	[-11.18; 17.96]			
Larynx										
Pembrolizumab	67	62.81 (19.48)	34	73.04 (15.90)	74	7.72 [1.77; 13.67]	0.73	0.864	-	
SoC	52	62.02 (23.99)	24	71.87 (22.76)	58	6.98 [0.13; 13.83]	[-7.71; 9.18]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	64.39 (21.07)	95	69.12 (18.67)	240	3.25 [-0.18; 6.68]	-1.71	0.447	-	
SoC	189	62.08 (21.68)	85	70.88 (16.99)	209	4.96 [1.56; 8.36]	[-6.12; 2.70]			

a: Database Cutoff Date: 25JUL2024
b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint
c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis
d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

Study: KEYNOTE 689[a] EORTC QLQ-C30 Global Health Status/QoL	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; QoL: Quality of Life; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score									

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-38: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Emotional functioning	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	223	73.43 (22.27)	99	80.05 (20.89)	232	5.65 [2.18; 9.13]	0.66	0.786	-	0.546
SoC	176	71.16 (22.43)	84	79.46 (18.22)	192	5.00 [1.23; 8.76]	[-4.11; 5.43]			
≥ 65										
Pembrolizumab	101	75.66 (19.74)	40	83.96 (15.61)	108	5.82 [0.37; 11.26]	1.87	0.619	-	
SoC	89	71.72 (22.07)	41	78.05 (25.74)	99	3.94 [-1.35; 9.23]	[-5.58; 9.33]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Emotional functioning	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Sex										
Female										
Pembrolizumab	72	70.72 (20.89)	30	73.06 (22.60)	75	3.07 [-3.81; 9.95]	-5.02	0.297	-	0.105
SoC	53	66.35 (22.11)	29	77.01 (20.00)	60	8.10 [1.05; 15.14]	[-14.56; 4.52]			
Male										
Pembrolizumab	252	75.10 (21.63)	109	83.41 (18.09)	265	6.08 [2.92; 9.24]	2.91	0.189	-	
SoC	212	72.60 (22.19)	96	79.60 (21.22)	231	3.17 [-0.16; 6.51]	[-1.44; 7.25]			
Tumor Stage										
III										
Pembrolizumab	81	74.59 (21.04)	43	81.01 (15.03)	86	5.95 [0.26; 11.64]	0.41	0.920	-	0.514
SoC	68	74.14 (20.47)	29	79.60 (26.31)	75	5.54 [-1.10; 12.18]	[-7.78; 8.60]			
IVA										
Pembrolizumab	241	74.17 (21.63)	96	81.25 (21.32)	252	5.75 [2.35; 9.15]	1.90	0.417	-	
SoC	197	70.39 (22.83)	96	78.82 (19.11)	216	3.85 [0.42; 7.28]	[-2.71; 6.51]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	74.33 (21.28)	96	81.51 (17.78)	238	6.53 [2.95; 10.11]	2.46	0.322	-	0.489
SoC	182	71.15 (22.57)	87	79.12 (21.64)	197	4.07 [0.32; 7.82]	[-2.43; 7.35]			
TPS ≥50%										
Pembrolizumab	99	73.65 (22.13)	43	80.43 (23.21)	102	3.56 [-1.25; 8.36]	-1.22	0.717	-	
SoC	83	71.79 (21.73)	38	78.73 (19.35)	94	4.78 [-0.20; 9.76]	[-7.90; 5.45]			
Region										
European Union										
Pembrolizumab	124	72.31 (22.25)	54	75.77 (19.44)	132	3.83 [-0.89; 8.56]	-0.90	0.789	-	0.143
SoC	113	67.55 (22.89)	55	76.36 (22.55)	126	4.73 [-0.50; 9.96]	[-7.48; 5.69]			
North America										
Pembrolizumab	56	73.96 (23.20)	11	75.76 (21.56)	59	-2.09 [-10.42; 6.24]	-14.00	0.018	-0.87	
SoC	31	62.90 (24.33)	12	83.33 (15.89)	37	11.91 [3.49; 20.33]	[-25.55; -2.45]		[-1.60; -0.15]	

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Emotional functioning	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Rest of World										
Pembrolizumab	144	75.75 (20.17)	74	85.92 (18.30)	149	5.96 [2.25; 9.67]	2.93	0.278	-	
SoC	121	77.07 (19.73)	58	80.60 (20.14)	128	3.03 [-1.09; 7.15]	[-2.37; 8.23]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	72.12 (26.87)	10	80.83 (23.59)	26	2.11 [-7.04; 11.25]	-1.73	0.790	-	0.812
SoC	24	77.08 (17.42)	16	83.85 (22.25)	24	3.84 [-6.33; 14.02]	[-14.53; 11.06]			
Larynx										
Pembrolizumab	67	75.00 (18.58)	34	83.58 (15.55)	74	8.66 [2.95; 14.37]	3.38	0.481	-	
SoC	52	68.11 (24.35)	24	78.47 (25.76)	58	5.28 [-2.76; 13.32]	[-6.04; 12.80]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	74.10 (21.72)	95	80.35 (20.48)	240	5.12 [1.90; 8.33]	1.08	0.641	-	
SoC	189	71.52 (22.16)	85	78.24 (19.21)	209	4.04 [0.52; 7.56]	[-3.45; 5.61]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-39: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Kognitive Funktion des EORTC QLQ-C30 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Cognitive functioning	**Baseline**		**Post-Adjuvant CRT/RT Week 51**		**Change from Baseline to Post-Adjuvant CRT/RT Week 51**		**Pembrolizumab vs. SoC**			**p-Value for Interaction Test[f]**
							Mean Difference at Post-Adjuvant CRT/RT Week 51		**Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51**	
	N[b]	**Mean (SD)**	**N[b]**	**Mean (SD)**	**N[c]**	**Mean [95 %-CI][d]**	**[95 %-CI][d]**	**p-Value**	**[95 %-CI][e]**	
Age										
< 65										
Pembrolizumab	223	87.59 (20.82)	99	88.72 (15.94)	232	-0.46 [-3.38; 2.47]	1.71	0.408	-	0.624
SoC	176	86.17 (18.98)	84	86.51 (15.84)	192	-2.17 [-5.36; 1.02]	[-2.35; 5.77]			
≥ 65										
Pembrolizumab	101	88.61 (15.80)	40	87.92 (14.61)	108	-3.58 [-8.59; 1.44]	3.95	0.242	-	
SoC	89	89.51 (16.55)	41	84.15 (19.70)	99	-7.53 [-12.20; -2.86]	[-2.71; 10.62]			
Sex										
Female										
Pembrolizumab	72	85.42 (18.54)	30	86.67 (18.77)	75	1.84 [-4.25; 7.93]	4.46	0.303	-	0.875
SoC	53	87.42 (17.57)	29	85.63 (18.75)	60	-2.62 [-9.06; 3.82]	[-4.12; 13.04]			
Male										
Pembrolizumab	252	88.62 (19.59)	109	88.99 (14.56)	265	-2.27 [-4.96; 0.42]	1.78	0.352	-	
SoC	212	87.26 (18.44)	96	85.76 (16.75)	231	-4.05 [-6.96; -1.14]	[-1.97; 5.53]			
Tumor Stage										
III										
Pembrolizumab	81	88.89 (16.24)	43	86.82 (16.08)	86	-3.33 [-8.43; 1.77]	0.81	0.831	-	0.415
SoC	68	87.99 (18.85)	29	85.63 (21.23)	75	-4.14 [-10.09; 1.80]	[-6.76; 8.39]			
IVA										
Pembrolizumab	241	87.83 (19.88)	96	89.24 (15.29)	252	-0.49 [-3.39; 2.41]	3.51	0.077	-	
SoC	197	87.06 (18.06)	96	85.76 (15.85)	216	-3.99 [-6.96; -1.03]	[-0.39; 7.40]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Cognitive functioning	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	87.56 (19.50)	96	88.54 (15.73)	238	-1.64 [-4.71; 1.43]	2.07	0.337	-	0.944
SoC	182	86.81 (17.78)	87	85.82 (17.71)	197	-3.71 [-6.96; -0.46]	[-2.16; 6.30]			
TPS ≥50%										
Pembrolizumab	99	88.72 (19.17)	43	88.37 (15.23)	102	-1.15 [-5.56; 3.26]	2.66	0.395	-	
SoC	83	88.35 (19.26)	38	85.53 (16.06)	94	-3.81 [-8.58; 0.96]	[-3.52; 8.85]			
Region										
European Union										
Pembrolizumab	124	87.77 (20.29)	54	87.35 (16.49)	132	-2.67 [-6.80; 1.46]	1.94	0.503	-	0.375
SoC	113	88.35 (16.80)	55	86.06 (17.20)	126	-4.62 [-9.00; -0.23]	[-3.75; 7.64]			
North America										
Pembrolizumab	56	83.93 (20.59)	11	80.30 (19.46)	59	-2.57 [-10.21; 5.07]	-6.32	0.231	-	
SoC	31	84.41 (17.71)	12	91.67 (11.24)	37	3.75 [-3.72; 11.23]	[-16.69; 4.04]			
Rest of World										
Pembrolizumab	144	89.58 (17.94)	74	90.54 (13.82)	149	-0.40 [-3.64; 2.84]	4.05	0.096	-	
SoC	121	87.05 (19.66)	58	84.20 (18.05)	128	-4.45 [-8.48; -0.42]	[-0.73; 8.83]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	86.54 (21.61)	10	88.33 (13.72)	26	1.99 [-4.05; 8.03]	5.90	0.230	-	0.712
SoC	24	88.19 (14.31)	16	84.38 (16.63)	24	-3.91 [-12.27; 4.44]	[-3.77; 15.58]			
Larynx										
Pembrolizumab	67	88.06 (19.42)	34	91.18 (12.47)	74	0.41 [-4.43; 5.26]	1.62	0.657	-	
SoC	52	82.69 (23.79)	24	86.11 (20.06)	58	-1.21 [-7.13; 4.71]	[-5.55; 8.80]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	88.02 (19.18)	95	87.54 (16.66)	240	-2.79 [-5.78; 0.20]	1.59	0.467	-	
SoC	189	88.45 (16.76)	85	85.88 (16.57)	209	-4.38 [-7.75; -1.00]	[-2.69; 5.87]			

a: Database Cutoff Date: 25JUL2024
b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint
c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Cognitive functioning	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction										
e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero										
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction										
CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score										

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-40: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Physical Functioning	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	223	88.04 (16.89)	99	83.97 (15.24)	232	-6.95 [-9.78; -4.13]	-1.18	0.565	-	0.911
SoC	176	86.52 (17.62)	84	84.76 (16.58)	192	-5.77 [-8.84; -2.69]	[-5.23; 2.86]			
≥ 65										
Pembrolizumab	101	82.71 (17.52)	40	84.50 (15.57)	108	-7.23 [-12.34; -2.13]	-2.61	0.454	-	
SoC	89	86.22 (17.86)	41	85.85 (18.09)	99	-4.63 [-9.53; 0.28]	[-9.50; 4.29]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Physical Functioning	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Sex										
Female										
Pembrolizumab	72	86.02 (17.30)	30	83.56 (17.22)	75	-5.33 [-10.74; 0.08]	-1.01	0.785	-	0.627
SoC	53	83.27 (17.52)	29	83.91 (12.02)	60	-4.32 [-9.90; 1.26]	[-8.39; 6.37]			
Male										
Pembrolizumab	252	86.48 (17.25)	109	84.28 (14.78)	265	-7.05 [-9.79; -4.31]	-1.20	0.547	-	
SoC	212	87.20 (17.65)	96	85.49 (18.30)	231	-5.86 [-8.77; -2.94]	[-5.10; 2.71]			
Tumor Stage										
III										
Pembrolizumab	81	89.47 (11.97)	43	84.65 (15.36)	86	-10.06 [-15.39; -4.72]	-1.92	0.641	-	0.310
SoC	68	84.80 (18.35)	29	79.77 (25.17)	75	-8.13 [-14.31; -1.96]	[-10.10; 6.25]			
IVA										
Pembrolizumab	241	85.53 (18.54)	96	83.89 (15.31)	252	-5.82 [-8.55; -3.09]	-2.52	0.173	-	
SoC	197	86.97 (17.44)	96	86.74 (13.42)	216	-3.30 [-6.07; -0.53]	[-6.16; 1.12]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	86.16 (17.40)	96	84.10 (14.52)	238	-6.10 [-9.03; -3.17]	-1.31	0.536	-	0.918
SoC	182	86.01 (17.22)	87	84.52 (18.70)	197	-4.79 [-7.91; -1.68]	[-5.47; 2.85]			
TPS ≥50%										
Pembrolizumab	99	86.87 (16.94)	43	84.19 (17.03)	102	-7.95 [-12.68; -3.22]	-1.86	0.578	-	
SoC	83	87.31 (18.67)	38	86.49 (12.45)	94	-6.09 [-11.13; -1.06]	[-8.48; 4.77]			
Region										
European Union										
Pembrolizumab	124	86.34 (17.27)	54	82.72 (16.15)	132	-7.55 [-11.66; -3.44]	-3.20	0.232	-	0.340
SoC	113	87.55 (17.31)	55	85.58 (16.27)	126	-4.35 [-7.88; -0.83]	[-8.44; 2.05]			
North America										
Pembrolizumab	56	85.95 (17.18)	11	88.48 (11.58)	59	-3.24 [-9.20; 2.71]	-6.63	0.104	-	
SoC	31	79.57 (19.77)	12	91.67 (7.59)	37	3.38 [-3.21; 9.98]	[-14.61; 1.36]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Physical Functioning	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Rest of World										
Pembrolizumab	144	86.57 (17.34)	74	84.50 (15.13)	149	-5.81 [-9.46; -2.17]	0.73	0.767	-	
SoC	121	87.11 (17.19)	58	83.33 (18.87)	128	-6.54 [-9.99; -3.10]	[-4.10; 5.55]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	82.56 (17.90)	10	88.00 (8.78)	26	-3.04 [-9.41; 3.32]	1.77	0.681	-	0.180
SoC	24	92.22 (10.34)	16	87.92 (12.46)	24	-4.82 [-10.91; 1.28]	[-6.71; 10.26]			
Larynx										
Pembrolizumab	67	81.99 (16.29)	34	84.51 (14.47)	74	-1.13 [-6.76; 4.49]	3.58	0.374	-	
SoC	52	80.77 (21.23)	24	82.78 (19.94)	58	-4.71 [-10.70; 1.27]	[-4.32; 11.49]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	88.08 (17.21)	95	83.58 (16.12)	240	-8.52 [-11.46; -5.57]	-4.35	0.032	-0.26	
SoC	189	87.23 (17.00)	85	85.25 (16.97)	209	-4.17 [-7.02; -1.33]	[-8.31; -0.38]		[-0.50; -0.02]	

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-41: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Rollenfunktion des EORTC QLQ-C30 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Role functioning	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	223	79.67 (26.52)	99	78.79 (23.91)	232	-5.12 [-9.76; -0.48]	-0.49	0.879	-	0.983
SoC	176	80.40 (25.56)	84	78.77 (21.07)	192	-4.63 [-9.70; 0.45]	[-6.85; 5.86]			
≥ 65										
Pembrolizumab	101	82.51 (22.78)	40	80.42 (19.93)	108	-8.04 [-14.87; -1.21]	0.42	0.926	-	
SoC	89	86.70 (24.51)	41	80.89 (23.44)	99	-8.46 [-15.04; -1.87]	[-8.54; 9.37]			
Sex										
Female										
Pembrolizumab	72	81.48 (26.32)	30	77.22 (22.95)	75	-8.95 [-17.01; -0.88]	-6.68	0.214	-	0.145
SoC	53	81.13 (24.69)	29	82.18 (19.89)	60	-2.26 [-10.63; 6.10]	[-17.29; 3.93]			
Male										
Pembrolizumab	252	80.29 (25.20)	109	79.82 (22.80)	265	-4.81 [-9.13; -0.50]	2.24	0.454	-	
SoC	212	82.86 (25.55)	96	78.65 (22.39)	231	-7.06 [-11.61; -2.50]	[-3.65; 8.13]			
Tumor Stage										
III										
Pembrolizumab	81	82.72 (23.34)	43	80.62 (19.90)	86	-5.33 [-12.48; 1.82]	4.02	0.422	-	0.406
SoC	68	82.35 (26.69)	29	77.01 (23.74)	75	-9.35 [-17.51; -1.19]	[-5.89; 13.93]			
IVA										
Pembrolizumab	241	80.22 (25.65)	96	78.65 (24.03)	252	-5.90 [-10.46; -1.35]	-0.97	0.751	-	
SoC	197	82.57 (24.93)	96	80.21 (21.26)	216	-4.93 [-9.53; -0.33]	[-7.02; 5.07]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Role functioning	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	80.44 (25.20)	96	79.69 (21.52)	238	-4.40 [-8.93; 0.13]	2.91	0.351	-	0.129
SoC	182	82.23 (25.55)	87	77.78 (22.97)	197	-7.31 [-12.05; -2.58]	[-3.23; 9.05]			
TPS ≥50%										
Pembrolizumab	99	80.81 (26.01)	43	78.29 (25.60)	102	-8.82 [-15.72; -1.91]	-6.76	0.149	-	
SoC	83	83.13 (25.03)	38	83.33 (18.58)	94	-2.06 [-9.30; 5.18]	[-15.97; 2.46]			
Region										
European Union										
Pembrolizumab	124	80.91 (26.18)	54	74.38 (26.25)	132	-12.00 [-18.62; -5.38]	-3.88	0.365	-	0.583
SoC	113	82.60 (25.33)	55	76.97 (24.11)	126	-8.12 [-14.19; -2.05]	[-12.28; 4.52]			
North America										
Pembrolizumab	56	75.89 (27.69)	11	81.82 (22.92)	59	2.15 [-9.74; 14.04]	-3.29	0.645	-	
SoC	31	69.89 (27.70)	12	88.89 (14.79)	37	5.44 [-4.61; 15.48]	[-17.29; 10.72]			
Rest of World										
Pembrolizumab	144	82.06 (23.74)	74	82.43 (19.49)	149	-3.76 [-8.63; 1.11]	3.34	0.300	-	
SoC	121	85.67 (23.89)	58	79.89 (20.41)	128	-7.10 [-11.95; -2.24]	[-2.98; 9.66]			
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	78.85 (28.11)	10	81.67 (22.84)	26	-7.16 [-19.15; 4.84]	6.01	0.477	-	0.896
SoC	24	93.06 (12.93)	16	79.17 (23.96)	24	-13.17 [-25.23; -1.11]	[-10.62; 22.65]			
Larynx										
Pembrolizumab	67	75.12 (24.17)	34	78.43 (22.67)	74	-1.54 [-10.03; 6.95]	1.27	0.794	-	
SoC	52	78.53 (25.42)	24	77.08 (18.92)	58	-2.81 [-8.91; 3.30]	[-8.27; 10.81]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	82.32 (25.33)	95	79.30 (23.03)	240	-6.99 [-11.73; -2.26]	-1.14	0.714	-	
SoC	189	82.28 (26.22)	85	80.20 (22.35)	209	-5.85 [-10.58; -1.13]	[-7.26; 4.98]			

a: Database Cutoff Date: 25JUL2024
b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint
c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Role functioning	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction										
e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero										
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction										
CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score										

EORTC QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-42: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesundheitsbezogene Lebensqualität für die Funktionsskala Soziale Funktion des EORTC QLQ-C30 zur post-adjuvanten CRT/RT Woche 51 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Social functioning	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Age										
< 65										
Pembrolizumab	223	80.49 (24.29)	99	82.83 (21.22)	232	-1.74 [-5.94; 2.45]	-1.37	0.639	-	0.179
SoC	176	76.89 (26.95)	84	81.15 (21.61)	192	-0.37 [-4.95; 4.20]	[-7.12; 4.38]			
≥ 65										
Pembrolizumab	101	81.52 (24.60)	40	85.83 (18.70)	108	-3.50 [-10.47; 3.48]	5.81	0.216	-	
SoC	89	85.02 (19.79)	41	78.05 (24.56)	99	-9.31 [-16.09; -2.53]	[-3.44; 15.07]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Social functioning	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Sex										
Female										
Pembrolizumab	72	78.94 (25.33)	30	77.78 (21.59)	75	-8.47 [-16.01; -0.93]	-1.71	0.761	-	0.517
SoC	53	80.19 (21.70)	29	77.59 (23.26)	60	-6.76 [-15.98; 2.46]	[-12.75; 9.33]			
Male										
Pembrolizumab	252	81.35 (24.09)	109	85.32 (20.00)	265	-0.40 [-4.15; 3.36]	1.85	0.475	-	
SoC	212	79.48 (25.85)	96	80.90 (22.42)	231	-2.25 [-6.24; 1.75]	[-3.23; 6.93]			
Tumor Stage										
III										
Pembrolizumab	81	85.60 (21.85)	43	84.88 (19.86)	86	-7.17 [-13.69; -0.65]	-0.42	0.929	-	0.823
SoC	68	82.84 (24.60)	29	78.16 (27.13)	75	-6.75 [-14.08; 0.57]	[-9.71; 8.87]			
IVA										
Pembrolizumab	241	79.53 (24.73)	96	83.16 (20.87)	252	-0.59 [-4.86; 3.69]	1.11	0.699	-	
SoC	197	78.51 (25.16)	96	80.73 (21.13)	216	-1.70 [-6.05; 2.66]	[-4.54; 6.76]			
PD-L1 TPS Status										
TPS <50%										
Pembrolizumab	225	81.48 (22.88)	96	85.24 (19.33)	238	0.37 [-3.73; 4.48]	2.88	0.312	-	0.251
SoC	182	78.30 (25.28)	87	79.50 (23.53)	197	-2.51 [-6.91; 1.89]	[-2.73; 8.49]			
TPS ≥50%										
Pembrolizumab	99	79.29 (27.47)	43	80.23 (22.79)	102	-7.49 [-14.22; -0.76]	-2.49	0.589	-	
SoC	83	82.53 (24.40)	38	81.58 (20.43)	94	-4.99 [-12.03; 2.04]	[-11.63; 6.64]			

Study: KEYNOTE 689[a] EORTC QLQ-C30 Functional Scales Social functioning	Baseline		Post-Adjuvant CRT/RT Week 51		Change from Baseline to Post-Adjuvant CRT/RT Week 51		Pembrolizumab vs. SoC			p-Value for Interaction Test[f]
							Mean Difference at Post-Adjuvant CRT/RT Week 51		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 51	
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]	
Primary Tumor Site										
Hypopharynx										
Pembrolizumab	26	76.92 (26.70)	10	88.33 (17.66)	26	6.85 [-2.25; 15.96]	12.19	0.064	-	0.224
SoC	24	87.50 (15.73)	16	83.33 (20.18)	24	-5.34 [-15.86; 5.18]	[-0.70; 25.08]			
Larynx										
Pembrolizumab	67	80.60 (25.56)	34	86.27 (16.14)	74	0.73 [-5.99; 7.46]	5.91	0.215	-	
SoC	52	76.92 (26.23)	24	74.31 (25.05)	58	-5.18 [-13.20; 2.84]	[-3.45; 15.28]			
Oropharynx/Oral Cavity										
Pembrolizumab	231	81.31 (23.79)	95	82.28 (22.12)	240	-2.95 [-7.25; 1.35]	-1.37	0.643	-	
SoC	189	79.37 (25.56)	85	81.18 (22.24)	209	-1.58 [-6.10; 2.94]	[-7.19; 4.44]			

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction

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

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable and with covariates for treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

Nebenwirkungen

Unerwünschte Ereignisse gesamt

Tabelle 4G-43: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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	270	259 (95.9)	3.3 [3.1; 4.3]	237	230 (97.0)	0.7 [0.4; 1.0]	0.57 [0.47; 0.68]	< 0.001	0.121
Female	75	74 (98.7)	2.1 [1.0; 3.1]	63	61 (96.8)	0.7 [0.3; 1.1]	0.75 [0.54; 1.06]	0.106	
Age									
< 65	235	229 (97.4)	3.1 [2.9; 4.0]	195	188 (96.4)	0.7 [0.4; 0.9]	0.59 [0.48; 0.72]	< 0.001	0.839
≥ 65	110	104 (94.5)	3.1 [2.1; 4.0]	105	103 (98.1)	0.7 [0.3; 1.1]	0.62 [0.47; 0.82]	< 0.001	
Tumor Stage									
III	86	84 (97.7)	4.6 [3.3; 5.4]	79	74 (93.7)	1.1 [0.4; 2.9]	0.58 [0.42; 0.80]	< 0.001	0.925
IVA	257	247 (96.1)	3.1 [2.4; 3.1]	221	217 (98.2)	0.6 [0.3; 0.7]	0.60 [0.50; 0.72]	< 0.001	
Region									
North America	62	60 (96.8)	2.1 [0.9; 3.1]	40	39 (97.5)	0.2 [0.1; 0.4]	0.46 [0.30; 0.72]	< 0.001	0.339
European Union	134	129 (96.3)	3.1 [2.1; 3.4]	127	124 (97.6)	0.4 [0.3; 0.7]	0.62 [0.48; 0.79]	< 0.001	
Rest of World	149	144 (96.6)	4.1 [3.1; 5.0]	133	128 (96.2)	1.1 [0.7; 2.4]	0.60 [0.47; 0.76]	< 0.001	
Primary tumor site									
Oropharynx/Oral Cavity	243	234 (96.3)	3.1 [2.3; 3.1]	215	208 (96.7)	0.7 [0.4; 0.9]	0.64 [0.53; 0.77]	< 0.001	0.371
Larynx	76	74 (97.4)	4.0 [2.9; 5.1]	61	60 (98.4)	1.3 [0.3; 2.7]	0.59 [0.41; 0.83]	0.002	
Hypopharynx	26	25 (96.2)	5.1 [1.0; 6.0]	24	23 (95.8)	0.4 [0.1; 1.0]	0.36 [0.19; 0.69]	0.002	
PD-L1 status									
TPS < 50%	243	235 (96.7)	3.1 [3.0; 4.1]	203	195 (96.1)	0.6 [0.4; 0.9]	0.57 [0.47; 0.69]	< 0.001	0.305
TPS ≥ 50%	102	98 (96.1)	3.1 [2.1; 3.4]	97	96 (99.0)	0.9 [0.3; 1.7]	0.68 [0.51; 0.90]	0.008	

a: Database Cutoff Date: 25JUL2024

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

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

d: Based on Cox regression model with treatment as a covariate. Ties are handled using Efron's method

e: Two-sided p-value using Wald test

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

CI: Confidence Interval; CPS: Combined Positive Score; PD-L1: Programmed Cell Death - Ligand 1; SoC: Standard of Care; TPS: Tumor Proportion Score

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-44: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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	270	127 (47.0)	44.3 [30.0; -]	237	91 (38.4)	Not reached [30.9; -]	1.01 [0.76; 1.33]	0.969	0.090
Female	75	44 (58.7)	20.3 [12.7; 34.4]	63	21 (33.3)	Not reached [-; -]	1.74 [1.03; 2.95]	0.039	
Age									
< 65	235	113 (48.1)	44.3 [27.9; -]	195	73 (37.4)	Not reached [30.9; -]	1.01 [0.75; 1.37]	0.940	0.283
≥ 65	110	58 (52.7)	23.9 [14.9; -]	105	39 (37.1)	Not reached [-; -]	1.44 [0.95; 2.17]	0.086	
Tumor Stage									
III	86	38 (44.2)	Not reached [27.7; -]	79	29 (36.7)	Not reached [-; -]	0.94 [0.57; 1.54]	0.796	0.356
IVA	257	132 (51.4)	31.6 [20.3; -]	221	83 (37.6)	Not reached [30.9; -]	1.21 [0.91; 1.60]	0.190	
Region									
North America	62	30 (48.4)	31.6 [20.1; -]	40	11 (27.5)	30.9 [-; -]	1.53 [0.76; 3.10]	0.235	0.228
European Union	134	78 (58.2)	18.0 [13.3; 34.4]	127	51 (40.2)	Not reached [25.9; -]	1.31 [0.91; 1.88]	0.143	
Rest of World	149	63 (42.3)	Not reached [38.1; -]	133	50 (37.6)	Not reached [-; -]	0.90 [0.61; 1.33]	0.605	
Primary tumor site									
Oropharynx/Oral Cavity	243	121 (49.8)	34.4 [21.1; -]	215	82 (38.1)	Not reached [30.9; -]	1.12 [0.84; 1.49]	0.446	0.290
Larynx	76	34 (44.7)	Not reached [23.9; -]	61	23 (37.7)	Not reached [22.1; -]	1.00 [0.58; 1.72]	0.994	
Hypopharynx	26	16 (61.5)	21.5 [8.1; -]	24	7 (29.2)	Not reached [9.4; -]	1.81 [0.72; 4.51]	0.206	
PD-L1 status									
TPS < 50%	243	130 (53.5)	30.0 [19.1; 44.3]	203	79 (38.9)	Not reached [30.9; -]	1.16 [0.87; 1.55]	0.299	0.530
TPS ≥ 50%	102	41 (40.2)	Not reached [33.1; -]	97	33 (34.0)	Not reached [-; -]	1.02 [0.64; 1.64]	0.927	

a: Database Cutoff Date: 25JUL2024

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

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

d: Based on Cox regression model with treatment as a covariate. Ties are handled using Efron's method

e: Two-sided p-value using Wald test

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

CI: Confidence Interval; CPS: Combined Positive Score; PD-L1: Programmed Cell Death - Ligand 1; SoC: Standard of Care; TPS: Tumor Proportion Score

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

Tabelle 4G-45: 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 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age									
< 65	235	183 (77.9)	12.7 [9.3; 15.1]	195	148 (75.9)	8.7 [6.0; 10.0]	0.59 [0.47; 0.74]	< 0.001	0.308
≥ 65	110	80 (72.7)	10.1 [7.4; 14.0]	105	76 (72.4)	10.0 [5.6; 11.7]	0.74 [0.53; 1.02]	0.068	
Tumor Stage									
III	86	64 (74.4)	14.1 [12.1; 17.9]	79	55 (69.6)	10.0 [7.1; 11.9]	0.62 [0.43; 0.91]	0.014	0.886
IVA	257	198 (77.0)	9.3 [7.7; 12.4]	221	169 (76.5)	8.3 [5.6; 10.0]	0.65 [0.52; 0.80]	< 0.001	
Region									
North America	62	51 (82.3)	7.0 [5.9; 13.4]	40	29 (72.5)	4.9 [0.4; 12.0]	0.70 [0.44; 1.12]	0.140	0.080
European Union	134	112 (83.6)	8.6 [7.0; 11.6]	127	99 (78.0)	9.0 [5.1; 10.1]	0.77 [0.58; 1.01]	0.059	
Rest of World	149	100 (67.1)	16.9 [14.0; 19.1]	133	96 (72.2)	9.9 [7.6; 11.1]	0.51 [0.38; 0.69]	< 0.001	
Primary tumor site									
Oropharynx/Oral Cavity	243	194 (79.8)	10.1 [8.0; 13.0]	215	166 (77.2)	7.6 [4.9; 9.6]	0.66 [0.53; 0.81]	< 0.001	0.836
Larynx	76	49 (64.5)	16.9 [11.3; 28.3]	61	41 (67.2)	10.4 [9.7; 13.0]	0.62 [0.40; 0.96]	0.030	
Hypopharynx	26	20 (76.9)	15.4 [6.3; 19.1]	24	17 (70.8)	9.3 [2.0; 11.7]	0.64 [0.32; 1.27]	0.202	
PD-L1 status									
TPS < 50%	243	186 (76.5)	11.6 [8.6; 14.9]	203	152 (74.9)	9.0 [6.0; 10.0]	0.63 [0.51; 0.79]	< 0.001	0.851
TPS ≥ 50%	102	77 (75.5)	12.1 [7.9; 15.4]	97	72 (74.2)	9.7 [5.6; 10.4]	0.67 [0.48; 0.93]	0.017	

a: Database Cutoff Date: 25JUL2024

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

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

d: Based on Cox regression model with treatment as a covariate. Ties are handled using Efron's method

e: Two-sided p-value using Wald test

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

CI: Confidence Interval; CPS: Combined Positive Score; CTCAE: Common Terminology Criteria for Adverse Events; PD-L1: Programmed Cell Death - Ligand 1; SoC: Standard of Care; TPS: Tumor Proportion Score

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-46: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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	270	61 (22.6)	Not reached [-; -]	237	35 (14.8)	Not reached [28.0; -]	0.88 [0.56; 1.38]	0.569	0.355
Female	75	24 (32.0)	Not reached [28.9; -]	63	10 (15.9)	Not reached [-; -]	1.47 [0.68; 3.17]	0.331	
Age									
< 65	235	52 (22.1)	Not reached [-; -]	195	21 (10.8)	Not reached [-; -]	1.09 [0.63; 1.89]	0.760	0.575
≥ 65	110	33 (30.0)	Not reached [38.1; -]	105	24 (22.9)	28.0 [28.0; -]	1.03 [0.59; 1.80]	0.920	
Tumor Stage									
III	86	21 (24.4)	Not reached [-; -]	79	10 (12.7)	28.0 [-; -]	0.91 [0.39; 2.11]	0.824	0.919
IVA	257	63 (24.5)	Not reached [-; -]	221	35 (15.8)	Not reached [-; -]	1.02 [0.66; 1.59]	0.925	
Region									
North America	62	10 (16.1)	Not reached [-; -]	40	2 (5.0)	Not reached [-; -]	2.21 [0.47; 10.45]	0.316	0.376
European Union	134	43 (32.1)	Not reached [54.1; -]	127	23 (18.1)	Not reached [-; -]	1.21 [0.70; 2.08]	0.492	
Rest of World	149	32 (21.5)	Not reached [-; -]	133	20 (15.0)	Not reached [28.0; -]	0.74 [0.40; 1.39]	0.353	
Primary tumor site									
Oropharynx/Oral Cavity	243	57 (23.5)	Not reached [-; -]	215	32 (14.9)	Not reached [-; -]	0.96 [0.60; 1.54]	0.871	0.158
Larynx	76	16 (21.1)	Not reached [-; -]	61	10 (16.4)	Not reached [28.0; -]	0.80 [0.34; 1.87]	0.604	
Hypopharynx	26	12 (46.2)	28.1 [18.0; -]	24	3 (12.5)	Not reached [-; -]	2.25 [0.59; 8.54]	0.234	
PD-L1 status									
TPS < 50%	243	58 (23.9)	Not reached [-; -]	203	30 (14.8)	Not reached [28.0; -]	0.98 [0.61; 1.57]	0.925	0.823
TPS ≥ 50%	102	27 (26.5)	Not reached [-; -]	97	15 (15.5)	Not reached [-; -]	1.08 [0.55; 2.13]	0.822	

a: Database Cutoff Date: 25JUL2024

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

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

d: Based on Cox regression model with treatment as a covariate. Ties are handled using Efron's method

e: Two-sided p-value using Wald test

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

CI: Confidence Interval; CPS: Combined Positive Score; PD-L1: Programmed Cell Death - Ligand 1; SoC: Standard of Care; TPS: Tumor Proportion Score

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-47: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für SOC aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]: Blood and lymphatic system disorders									
Sex									
Male	270	89 (33.0)	Not reached [-; -]	237	77 (32.5)	Not reached [24.7; -]	0.65 [0.47; 0.91]	0.011	0.730
Female	75	38 (50.7)	20.0 [12.3; -]	63	30 (47.6)	12.9 [8.1; -]	0.77 [0.47; 1.27]	0.302	
Age									
< 65	235	88 (37.4)	Not reached [58.3; -]	195	59 (30.3)	Not reached [-; -]	0.84 [0.59; 1.19]	0.325	0.103
≥ 65	110	39 (35.5)	Not reached [32.4; -]	105	48 (45.7)	24.7 [11.7; -]	0.51 [0.33; 0.81]	0.004	
Tumor Stage									
III	86	30 (34.9)	Not reached [36.7; -]	79	23 (29.1)	24.7 [24.7; -]	0.57 [0.31; 1.05]	0.072	0.816
IVA	257	96 (37.4)	Not reached [40.3; -]	221	84 (38.0)	Not reached [-; -]	0.72 [0.53; 0.98]	0.037	
Region									
North America	62	24 (38.7)	Not reached [20.0; -]	40	19 (47.5)	15.3 [5.1; -]	0.59 [0.32; 1.11]	0.101	0.390
European Union	134	55 (41.0)	Not reached [22.3; -]	127	45 (35.4)	Not reached [-; -]	0.86 [0.57; 1.29]	0.458	
Rest of World	149	48 (32.2)	Not reached [-; -]	133	43 (32.3)	24.7 [24.7; -]	0.56 [0.36; 0.88]	0.012	
Primary tumor site									
Oropharynx/Oral Cavity	243	97 (39.9)	Not reached [31.1; -]	215	84 (39.1)	Not reached [17.7; -]	0.76 [0.56; 1.03]	0.080	0.570
Larynx	76	19 (25.0)	Not reached [-; -]	61	16 (26.2)	24.7 [24.7; -]	0.44 [0.21; 0.92]	0.030	
Hypopharynx	26	11 (42.3)	40.3 [19.3; -]	24	7 (29.2)	Not reached [11.7; -]	0.76 [0.26; 2.21]	0.614	
PD-L1 status									
TPS < 50%	243	89 (36.6)	Not reached [58.3; -]	203	69 (34.0)	Not reached [24.7; -]	0.72 [0.52; 1.01]	0.055	0.597
TPS ≥ 50%	102	38 (37.3)	Not reached [24.1; -]	97	38 (39.2)	Not reached [12.9; -]	0.65 [0.40; 1.04]	0.074	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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	270	81 (30.0)	Not reached [57.0; -]	237	23 (9.7)	Not reached [24.7; -]	1.73 [1.05; 2.85]	0.030	0.398
Female	75	26 (34.7)	46.9 [37.6; -]	63	5 (7.9)	Not reached [-; -]	2.60 [0.94; 7.24]	0.067	
Age									
< 65	235	76 (32.3)	Not reached [53.0; -]	195	15 (7.7)	Not reached [24.7; -]	2.24 [1.24; 4.05]	0.007	0.323
≥ 65	110	31 (28.2)	Not reached [46.1; -]	105	13 (12.4)	Not reached [-; -]	1.48 [0.74; 2.98]	0.272	
Tumor Stage									
III	86	33 (38.4)	64.6 [39.1; -]	79	9 (11.4)	Not reached [-; -]	1.59 [0.71; 3.56]	0.257	0.684
IVA	257	73 (28.4)	Not reached [53.0; -]	221	19 (8.6)	Not reached [24.7; -]	1.99 [1.16; 3.41]	0.013	
Region									
North America	62	15 (24.2)	Not reached [49.9; -]	40	3 (7.5)	Not reached [-; -]	1.41 [0.36; 5.45]	0.620	0.642
European Union	134	42 (31.3)	64.6 [40.0; -]	127	15 (11.8)	Not reached [24.7; -]	1.70 [0.90; 3.19]	0.100	
Rest of World	149	50 (33.6)	Not reached [43.6; -]	133	10 (7.5)	Not reached [-; -]	2.46 [1.19; 5.06]	0.015	
Primary tumor site									
Oropharynx/Oral Cavity	243	65 (26.7)	Not reached [64.6; -]	215	14 (6.5)	Not reached [24.7; -]	2.27 [1.22; 4.22]	0.009	0.497
Larynx	76	34 (44.7)	43.6 [26.4; -]	61	10 (16.4)	Not reached [-; -]	1.45 [0.68; 3.10]	0.331	
Hypopharynx	26	8 (30.8)	Not reached [16.9; -]	24	4 (16.7)	Not reached [-; -]	1.36 [0.38; 4.84]	0.632	
PD-L1 status									
TPS < 50%	243	69 (28.4)	Not reached [64.6; -]	203	18 (8.9)	Not reached [-; -]	1.91 [1.10; 3.32]	0.022	0.619
TPS ≥ 50%	102	38 (37.3)	46.9 [37.6; -]	97	10 (10.3)	Not reached [24.7; -]	1.87 [0.87; 4.00]	0.107	
SOC[g]: Gastrointestinal disorders									
Sex									
Male	270	202 (74.8)	11.1 [9.0; 12.9]	237	187 (78.9)	6.1 [5.7; 6.9]	0.61 [0.50; 0.74]	< 0.001	0.205
Female	75	63 (84.0)	7.0 [5.7; 10.6]	63	49 (77.8)	6.4 [4.1; 7.9]	0.78 [0.53; 1.14]	0.199	
Age									
< 65	235	189 (80.4)	9.0 [7.3; 11.3]	195	153 (78.5)	6.1 [5.4; 6.9]	0.66 [0.53; 0.82]	< 0.001	0.580
≥ 65	110	76 (69.1)	11.7 [8.3; 14.9]	105	83 (79.0)	6.6 [4.6; 7.7]	0.59 [0.43; 0.81]	0.001	
Tumor Stage									
III	86	66 (76.7)	10.7 [8.0; 15.6]	79	60 (75.9)	6.4 [4.9; 8.1]	0.57 [0.39; 0.81]	0.002	0.575
IVA	257	197 (76.7)	10.1 [7.4; 12.1]	221	176 (79.6)	6.1 [5.6; 7.0]	0.67 [0.54; 0.82]	< 0.001	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Region									
North America	62	52 (83.9)	6.7 [4.6; 7.0]	40	33 (82.5)	3.0 [0.4; 4.9]	0.51 [0.32; 0.80]	0.004	0.557
European Union	134	109 (81.3)	9.0 [7.1; 11.1]	127	112 (88.2)	6.4 [5.1; 7.4]	0.61 [0.47; 0.80]	< 0.001	
Rest of World	149	104 (69.8)	13.3 [10.7; 15.9]	133	91 (68.4)	6.9 [6.0; 8.9]	0.66 [0.49; 0.88]	0.004	
Primary tumor site									
Oropharynx/Oral Cavity	243	199 (81.9)	8.1 [7.0; 10.6]	215	184 (85.6)	6.0 [4.9; 6.1]	0.59 [0.48; 0.72]	< 0.001	0.313
Larynx	76	49 (64.5)	15.6 [12.6; 19.4]	61	33 (54.1)	12.0 [7.4; 22.3]	0.80 [0.51; 1.26]	0.335	
Hypopharynx	26	17 (65.4)	12.3 [5.4; 27.7]	24	19 (79.2)	7.1 [4.6; 9.3]	0.62 [0.32; 1.21]	0.162	
PD-L1 status									
TPS < 50%	243	181 (74.5)	11.0 [8.7; 12.9]	203	159 (78.3)	6.4 [5.9; 7.0]	0.60 [0.48; 0.74]	< 0.001	0.236
TPS ≥ 50%	102	84 (82.4)	8.6 [6.6; 11.0]	97	77 (79.4)	6.0 [4.6; 7.4]	0.73 [0.53; 1.00]	0.053	
SOC[g]: Injury, poisoning and procedural complications									
Sex									
Male	270	152 (56.3)	16.3 [15.6; 17.6]	237	152 (64.1)	9.7 [8.1; 10.6]	0.51 [0.41; 0.65]	< 0.001	0.421
Female	75	48 (64.0)	14.6 [12.9; 18.1]	63	40 (63.5)	8.4 [6.1; 10.6]	0.58 [0.38; 0.90]	0.014	
Age									
< 65	235	140 (59.6)	16.1 [15.3; 17.7]	195	126 (64.6)	8.9 [7.7; 10.3]	0.49 [0.39; 0.63]	< 0.001	0.343
≥ 65	110	60 (54.5)	15.9 [14.1; 18.9]	105	66 (62.9)	9.7 [8.1; 12.1]	0.59 [0.41; 0.85]	0.005	
Tumor Stage									
III	86	48 (55.8)	18.0 [15.3; 36.1]	79	47 (59.5)	9.0 [7.7; 13.1]	0.47 [0.31; 0.72]	< 0.001	0.582
IVA	257	151 (58.8)	16.0 [14.3; 16.9]	221	145 (65.6)	9.1 [8.0; 10.3]	0.55 [0.43; 0.69]	< 0.001	
Region									
North America	62	34 (54.8)	15.9 [13.4; 18.7]	40	27 (67.5)	8.4 [3.6; 9.9]	0.35 [0.20; 0.59]	< 0.001	0.267
European Union	134	89 (66.4)	15.3 [13.7; 16.1]	127	94 (74.0)	8.1 [7.3; 9.3]	0.54 [0.40; 0.72]	< 0.001	
Rest of World	149	77 (51.7)	18.9 [15.7; 30.1]	133	71 (53.4)	11.4 [9.7; 16.3]	0.57 [0.41; 0.80]	0.001	
Primary tumor site									
Oropharynx/Oral Cavity	243	148 (60.9)	15.0 [13.9; 16.6]	215	140 (65.1)	8.9 [7.9; 9.9]	0.57 [0.45; 0.72]	< 0.001	0.508
Larynx	76	36 (47.4)	23.9 [17.3; -]	61	34 (55.7)	11.1 [10.1; 17.1]	0.43 [0.26; 0.71]	< 0.001	
Hypopharynx	26	16 (61.5)	15.3 [12.1; 17.3]	24	18 (75.0)	6.0 [1.4; 8.4]	0.46 [0.23; 0.90]	0.024	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
PD-L1 status									
TPS < 50%	243	140 (57.6)	16.0 [14.7; 17.4]	203	132 (65.0)	8.9 [7.7; 10.1]	0.51 [0.40; 0.65]	< 0.001	0.402
TPS ≥ 50%	102	60 (58.8)	16.6 [15.1; 18.7]	97	60 (61.9)	10.3 [8.1; 12.3]	0.57 [0.39; 0.82]	0.003	
SOC[g]: Investigations									
Sex									
Male	270	175 (64.8)	15.0 [13.3; 16.9]	237	145 (61.2)	10.1 [9.4; 11.9]	0.71 [0.57; 0.90]	0.004	0.462
Female	75	47 (62.7)	15.9 [13.0; 17.1]	63	33 (52.4)	11.0 [7.7; -]	0.88 [0.55; 1.39]	0.581	
Age									
< 65	235	152 (64.7)	15.6 [13.9; 17.1]	195	113 (57.9)	10.4 [9.4; 12.9]	0.72 [0.56; 0.92]	0.009	0.382
≥ 65	110	70 (63.6)	14.1 [11.3; 16.1]	105	65 (61.9)	10.0 [9.0; 13.0]	0.80 [0.56; 1.13]	0.204	
Tumor Stage									
III	86	63 (73.3)	16.0 [13.0; 18.1]	79	43 (54.4)	11.0 [7.3; -]	0.78 [0.52; 1.16]	0.219	0.568
IVA	257	158 (61.5)	15.0 [13.0; 16.9]	221	135 (61.1)	10.1 [9.4; 11.9]	0.74 [0.58; 0.93]	0.011	
Primary tumor site									
Oropharynx/Oral Cavity	243	156 (64.2)	14.1 [12.7; 15.6]	215	127 (59.1)	10.4 [9.1; 12.9]	0.83 [0.65; 1.05]	0.124	0.631
Larynx	76	50 (65.8)	17.1 [15.9; 22.3]	61	35 (57.4)	10.0 [8.7; 15.1]	0.61 [0.39; 0.97]	0.035	
Hypopharynx	26	16 (61.5)	18.0 [13.4; 33.1]	24	16 (66.7)	9.9 [6.3; 14.3]	0.45 [0.21; 0.95]	0.037	
PD-L1 status									
TPS < 50%	243	158 (65.0)	15.1 [13.0; 16.9]	203	118 (58.1)	10.3 [9.1; 12.1]	0.74 [0.58; 0.95]	0.019	0.740
TPS ≥ 50%	102	64 (62.7)	16.0 [13.0; 17.0]	97	60 (61.9)	10.4 [9.0; 13.0]	0.74 [0.52; 1.07]	0.106	
SOC[g]: Metabolism and nutrition disorders									
Sex									
Male	270	134 (49.6)	28.3 [17.1; 51.0]	237	109 (46.0)	20.7 [12.3; -]	0.77 [0.59; 1.00]	0.048	0.653
Female	75	46 (61.3)	17.6 [7.3; 28.4]	63	33 (52.4)	11.3 [6.1; -]	0.83 [0.52; 1.32]	0.422	
Age									
< 65	235	122 (51.9)	20.4 [16.6; 37.9]	195	91 (46.7)	14.4 [11.1; -]	0.78 [0.59; 1.03]	0.081	0.685
≥ 65	110	58 (52.7)	30.6 [12.7; 51.0]	105	51 (48.6)	20.7 [9.7; -]	0.80 [0.53; 1.18]	0.258	
Tumor Stage									
III	86	39 (45.3)	51.0 [19.0; -]	79	33 (41.8)	20.7 [10.9; -]	0.65 [0.40; 1.06]	0.086	0.596
IVA	257	140 (54.5)	18.3 [15.3; 31.6]	221	109 (49.3)	14.1 [10.9; -]	0.82 [0.64; 1.07]	0.145	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Primary tumor site									
Oropharynx/Oral Cavity	243	137 (56.4)	17.9 [15.1; 27.1]	215	111 (51.6)	12.3 [10.6; -]	0.79 [0.61; 1.02]	0.075	0.975
Larynx	76	32 (42.1)	Not reached [23.9; -]	61	22 (36.1)	26.9 [14.4; -]	0.74 [0.41; 1.31]	0.302	
Hypopharynx	26	11 (42.3)	Not reached [8.3; -]	24	9 (37.5)	Not reached [6.6; -]	0.97 [0.40; 2.37]	0.944	
PD-L1 status									
TPS < 50%	243	126 (51.9)	23.9 [16.9; 42.9]	203	90 (44.3)	26.9 [12.3; -]	0.82 [0.62; 1.09]	0.176	0.476
TPS ≥ 50%	102	54 (52.9)	19.0 [15.0; -]	97	52 (53.6)	11.3 [9.3; -]	0.74 [0.50; 1.09]	0.130	
SOC[g]: Nervous system disorders									
Sex									
Male	270	101 (37.4)	Not reached [42.1; -]	237	91 (38.4)	24.3 [17.9; -]	0.72 [0.54; 0.97]	0.031	0.376
Female	75	31 (41.3)	25.1 [15.1; -]	63	21 (33.3)	Not reached [14.9; -]	0.95 [0.53; 1.68]	0.853	
Age									
< 65	235	93 (39.6)	Not reached [26.9; -]	195	74 (37.9)	24.3 [17.9; -]	0.72 [0.53; 1.00]	0.047	0.698
≥ 65	110	39 (35.5)	Not reached [29.4; -]	105	38 (36.2)	Not reached [-; -]	0.87 [0.55; 1.37]	0.543	
Tumor Stage									
III	86	40 (46.5)	38.3 [15.1; -]	79	30 (38.0)	Not reached [11.1; -]	0.87 [0.54; 1.42]	0.590	0.597
IVA	257	91 (35.4)	Not reached [45.3; -]	221	82 (37.1)	24.3 [24.3; -]	0.73 [0.53; 0.99]	0.044	
Region									
North America	62	36 (58.1)	15.1 [11.1; 19.3]	40	21 (52.5)	8.6 [5.9; -]	0.76 [0.44; 1.32]	0.332	0.852
European Union	134	51 (38.1)	Not reached [19.7; -]	127	50 (39.4)	24.3 [17.1; -]	0.78 [0.52; 1.17]	0.225	
Rest of World	149	45 (30.2)	Not reached [-; -]	133	41 (30.8)	Not reached [-; -]	0.65 [0.41; 1.02]	0.061	
Primary tumor site									
Oropharynx/Oral Cavity	243	95 (39.1)	Not reached [23.6; -]	215	88 (40.9)	24.3 [15.1; -]	0.73 [0.54; 0.98]	0.037	0.199
Larynx	76	25 (32.9)	Not reached [40.7; -]	61	11 (18.0)	Not reached [-; -]	1.30 [0.62; 2.72]	0.483	
Hypopharynx	26	12 (46.2)	29.7 [14.1; -]	24	13 (54.2)	15.3 [9.3; -]	0.57 [0.25; 1.30]	0.183	
PD-L1 status									
TPS < 50%	243	87 (35.8)	Not reached [42.1; -]	203	67 (33.0)	24.3 [24.3; -]	0.81 [0.58; 1.13]	0.213	0.443
TPS ≥ 50%	102	45 (44.1)	23.6 [15.1; -]	97	45 (46.4)	Not reached [9.3; -]	0.71 [0.47; 1.09]	0.119	

a: Database Cutoff Date: 25JUL2024
b: Number of participants: all-participants-as-treated population with CPS ≥ 1
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate. Ties are handled using Efron's method
e: Two-sided p-value using Wald test

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
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, and the interaction p-value is greater than or equal to 0.05 or not calculated									
CI: Confidence Interval; CPS: Combined Positive Score; PD-L1: Programmed Cell Death - Ligand 1; SOC: System Organ Class; SoC: Standard of Care; TPS: Tumor Proportion Score									

Tabelle 4G-48: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für PT aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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: Blood and lymphatic system disorders - PT[g]: Anaemia									
Sex									
Male	270	82 (30.4)	Not reached [-; -]	237	73 (30.8)	Not reached [24.7; -]	0.63 [0.45; 0.88]	0.007	0.675
Female	75	35 (46.7)	24.1 [13.3; -]	63	28 (44.4)	Not reached [9.3; -]	0.78 [0.47; 1.31]	0.345	
Age									
< 65	235	81 (34.5)	Not reached [-; -]	195	54 (27.7)	Not reached [-; -]	0.84 [0.59; 1.21]	0.361	0.081
≥ 65	110	36 (32.7)	Not reached [34.1; -]	105	47 (44.8)	24.7 [12.0; -]	0.48 [0.30; 0.76]	0.002	
Tumor Stage									
III	86	25 (29.1)	Not reached [-; -]	79	22 (27.8)	24.7 [24.7; -]	0.55 [0.29; 1.03]	0.062	0.793
IVA	257	91 (35.4)	Not reached [40.9; -]	221	79 (35.7)	Not reached [-; -]	0.70 [0.51; 0.97]	0.030	
Region									
North America	62	22 (35.5)	Not reached [24.1; -]	40	18 (45.0)	Not reached [5.1; -]	0.60 [0.32; 1.13]	0.115	0.327
European Union	134	51 (38.1)	Not reached [32.9; -]	127	42 (33.1)	Not reached [-; -]	0.84 [0.54; 1.29]	0.417	
Rest of World	149	44 (29.5)	Not reached [-; -]	133	41 (30.8)	24.7 [24.7; -]	0.53 [0.33; 0.84]	0.007	
Primary tumor site									
Oropharynx/Oral Cavity	243	89 (36.6)	Not reached [58.3; -]	215	78 (36.3)	Not reached [-; -]	0.76 [0.55; 1.04]	0.088	0.486
Larynx	76	17 (22.4)	Not reached [-; -]	61	16 (26.2)	24.7 [24.7; -]	0.39 [0.18; 0.84]	0.017	
Hypopharynx	26	11 (42.3)	40.3 [19.4; -]	24	7 (29.2)	Not reached [11.7; -]	0.65 [0.22; 1.94]	0.440	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
PD-L1 status									
TPS < 50%	243	83 (34.2)	Not reached [-; -]	203	64 (31.5)	Not reached [24.7; -]	0.71 [0.50; 1.00]	0.052	0.385
TPS ≥ 50%	102	34 (33.3)	Not reached [45.1; -]	97	37 (38.1)	Not reached [13.1; -]	0.62 [0.38; 1.01]	0.054	
SOC: General disorders and administration site conditions - PT[g]: Asthenia									
Sex									
Male	270	26 (9.6)	Not reached [-; -]	237	21 (8.9)	Not reached [-; -]	0.72 [0.39; 1.35]	0.307	0.213
Female	75	11 (14.7)	Not reached [-; -]	63	15 (23.8)	Not reached [-; -]	0.37 [0.16; 0.89]	0.026	
Age									
< 65	235	26 (11.1)	Not reached [-; -]	195	18 (9.2)	Not reached [-; -]	0.81 [0.43; 1.53]	0.521	0.241
≥ 65	110	11 (10.0)	Not reached [-; -]	105	18 (17.1)	Not reached [-; -]	0.35 [0.15; 0.84]	0.018	
Tumor Stage									
III	86	10 (11.6)	Not reached [-; -]	79	9 (11.4)	Not reached [-; -]	0.49 [0.17; 1.37]	0.172	0.961
IVA	257	26 (10.1)	Not reached [-; -]	221	27 (12.2)	Not reached [-; -]	0.60 [0.34; 1.07]	0.082	
Region									
North America	62	3 (4.8)	Not reached [-; -]	40	3 (7.5)	Not reached [-; -]	0.42 [0.07; 2.51]	0.340	0.663
European Union	134	21 (15.7)	Not reached [-; -]	127	19 (15.0)	Not reached [-; -]	0.72 [0.37; 1.40]	0.333	
Rest of World	149	13 (8.7)	Not reached [-; -]	133	14 (10.5)	Not reached [-; -]	0.53 [0.23; 1.20]	0.129	
Primary tumor site									
Oropharynx/Oral Cavity	243	28 (11.5)	Not reached [-; -]	215	34 (15.8)	Not reached [-; -]	0.46 [0.27; 0.80]	0.006	0.066
Larynx	76	7 (9.2)	Not reached [-; -]	61	1 (1.6)	Not reached [-; -]	3.62 [0.42; 30.95]	0.240	
Hypopharynx	26	2 (7.7)	Not reached [-; -]	24	1 (4.2)	Not reached [-; -]	1.62[h] [0.16; 16.82]	0.685[h]	
PD-L1 status									
TPS < 50%	243	24 (9.9)	Not reached [-; -]	203	17 (8.4)	Not reached [-; -]	0.79 [0.40; 1.53]	0.483	0.169
TPS ≥ 50%	102	13 (12.7)	Not reached [-; -]	97	19 (19.6)	Not reached [-; -]	0.42 [0.19; 0.91]	0.028	
SOC: Gastrointestinal disorders - PT[g]: Diarrhoea									
Sex									
Male	270	51 (18.9)	Not reached [-; -]	237	24 (10.1)	Not reached [-; -]	1.40 [0.84; 2.32]	0.192	0.200
Female	75	23 (30.7)	Not reached [23.7; -]	63	6 (9.5)	Not reached [-; -]	2.78 [1.11; 6.99]	0.030	
Age									
< 65	235	52 (22.1)	Not reached [-; -]	195	16 (8.2)	Not reached [-; -]	1.96 [1.10; 3.50]	0.022	0.340
≥ 65	110	22 (20.0)	Not reached [-; -]	105	14 (13.3)	Not reached [-; -]	1.32 [0.66; 2.64]	0.438	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Tumor Stage									
III	86	19 (22.1)	Not reached [-; -]	79	7 (8.9)	Not reached [-; -]	1.35 [0.53; 3.45]	0.525	0.896
IVA	257	53 (20.6)	Not reached [-; -]	221	23 (10.4)	Not reached [-; -]	1.74 [1.06; 2.88]	0.030	
Region									
North America	62	18 (29.0)	Not reached [46.7; -]	40	4 (10.0)	Not reached [-; -]	1.87 [0.60; 5.78]	0.279	0.383
European Union	134	31 (23.1)	Not reached [-; -]	127	12 (9.4)	Not reached [-; -]	2.08 [1.04; 4.15]	0.038	
Rest of World	149	25 (16.8)	Not reached [-; -]	133	14 (10.5)	Not reached [-; -]	1.25 [0.64; 2.44]	0.516	
Primary tumor site									
Oropharynx/Oral Cavity	243	58 (23.9)	Not reached [-; -]	215	25 (11.6)	Not reached [-; -]	1.56 [0.95; 2.54]	0.076	0.528
Larynx	76	10 (13.2)	Not reached [-; -]	61	4 (6.6)	Not reached [-; -]	1.71 [0.53; 5.54]	0.368	
Hypopharynx	26	6 (23.1)	Not reached [23.7; -]	24	1 (4.2)	Not reached [-; -]	4.47 [0.52; 38.75]	0.174	
PD-L1 status									
TPS < 50%	243	48 (19.8)	Not reached [-; -]	203	21 (10.3)	Not reached [-; -]	1.52 [0.89; 2.58]	0.122	0.372
TPS ≥ 50%	102	26 (25.5)	Not reached [-; -]	97	9 (9.3)	Not reached [-; -]	2.05 [0.93; 4.52]	0.074	
SOC: Gastrointestinal disorders - PT[g]: Dry mouth									
Sex									
Male	270	57 (21.1)	Not reached [-; -]	237	65 (27.4)	Not reached [-; -]	0.53 [0.37; 0.78]	< 0.001	0.119
Female	75	22 (29.3)	Not reached [22.1; -]	63	15 (23.8)	Not reached [-; -]	0.92 [0.46; 1.84]	0.816	
Age									
< 65	235	58 (24.7)	Not reached [-; -]	195	56 (28.7)	Not reached [-; -]	0.56 [0.38; 0.82]	0.003	0.522
≥ 65	110	21 (19.1)	Not reached [62.4; -]	105	24 (22.9)	Not reached [-; -]	0.67 [0.36; 1.25]	0.206	
Tumor Stage									
III	86	22 (25.6)	Not reached [-; -]	79	23 (29.1)	Not reached [-; -]	0.58 [0.32; 1.07]	0.081	0.542
IVA	257	57 (22.2)	Not reached [-; -]	221	57 (25.8)	Not reached [-; -]	0.61 [0.42; 0.91]	0.014	
Region									
North America	62	28 (45.2)	19.1 [15.0; 36.7]	40	19 (47.5)	10.6 [8.4; -]	0.48 [0.26; 0.90]	0.021	0.987
European Union	134	35 (26.1)	Not reached [62.4; -]	127	43 (33.9)	Not reached [-; -]	0.54 [0.34; 0.87]	0.011	
Rest of World	149	16 (10.7)	Not reached [-; -]	133	18 (13.5)	Not reached [-; -]	0.61 [0.30; 1.22]	0.161	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Primary tumor site									
Oropharynx/Oral Cavity	243	68 (28.0)	Not reached [62.4; -]	215	66 (30.7)	Not reached [-; -]	0.64 [0.45; 0.91]	0.014	0.511
Larynx	76	6 (7.9)	Not reached [-; -]	61	9 (14.8)	Not reached [-; -]	0.39 [0.13; 1.15]	0.088	
Hypopharynx	26	5 (19.2)	Not reached [23.1; -]	24	5 (20.8)	Not reached [-; -]	0.65[h] [0.17; 2.44]	0.524[h]	
PD-L1 status									
TPS < 50%	243	48 (19.8)	Not reached [-; -]	203	56 (27.6)	Not reached [-; -]	0.50 [0.33; 0.74]	< 0.001	0.056
TPS ≥ 50%	102	31 (30.4)	Not reached [34.1; -]	97	24 (24.7)	Not reached [-; -]	0.89 [0.51; 1.55]	0.677	
SOC: Nervous system disorders - PT[g]: Dysgeusia									
Sex									
Male	270	42 (15.6)	Not reached [-; -]	237	50 (21.1)	Not reached [-; -]	0.52 [0.34; 0.80]	0.003	0.177
Female	75	12 (16.0)	Not reached [-; -]	63	8 (12.7)	Not reached [-; -]	1.12 [0.45; 2.80]	0.808	
Age									
< 65	235	38 (16.2)	Not reached [-; -]	195	39 (20.0)	Not reached [-; -]	0.52 [0.33; 0.83]	0.006	0.535
≥ 65	110	16 (14.5)	Not reached [-; -]	105	19 (18.1)	Not reached [-; -]	0.78 [0.40; 1.54]	0.480	
Tumor Stage									
III	86	20 (23.3)	Not reached [-; -]	79	15 (19.0)	Not reached [-; -]	0.82 [0.41; 1.64]	0.578	0.285
IVA	257	34 (13.2)	Not reached [-; -]	221	43 (19.5)	Not reached [-; -]	0.52 [0.33; 0.83]	0.006	
Region									
North America	62	16 (25.8)	Not reached [20.1; -]	40	9 (22.5)	Not reached [-; -]	0.83 [0.36; 1.92]	0.669	0.549
European Union	134	20 (14.9)	Not reached [-; -]	127	31 (24.4)	Not reached [-; -]	0.48 [0.26; 0.86]	0.014	
Rest of World	149	18 (12.1)	Not reached [-; -]	133	18 (13.5)	Not reached [-; -]	0.61[h] [0.31; 1.21]	0.158[h]	
Primary tumor site									
Oropharynx/Oral Cavity	243	37 (15.2)	Not reached [-; -]	215	43 (20.0)	Not reached [-; -]	0.58 [0.37; 0.92]	0.020	0.813
Larynx	76	10 (13.2)	Not reached [-; -]	61	7 (11.5)	Not reached [-; -]	0.72 [0.26; 2.00]	0.530	
Hypopharynx	26	7 (26.9)	Not reached [17.0; -]	24	8 (33.3)	Not reached [11.9; -]	0.59 [0.21; 1.70]	0.330	
SOC: Gastrointestinal disorders - PT[g]: Dysphagia									
Sex									
Male	270	76 (28.1)	Not reached [-; -]	237	75 (31.6)	28.3 [28.3; -]	0.69 [0.50; 0.95]	0.025	0.565
Female	75	27 (36.0)	Not reached [15.1; -]	63	22 (34.9)	Not reached [9.6; -]	0.86 [0.49; 1.53]	0.611	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age									
< 65	235	72 (30.6)	Not reached [-; -]	195	58 (29.7)	Not reached [21.6; -]	0.81 [0.57; 1.15]	0.241	0.461
≥ 65	110	31 (28.2)	Not reached [-; -]	105	39 (37.1)	28.3 [18.1; -]	0.61 [0.37; 0.99]	0.046	
Tumor Stage									
III	86	24 (27.9)	Not reached [-; -]	79	27 (34.2)	28.3 [13.0; -]	0.55 [0.31; 0.98]	0.043	0.359
IVA	257	78 (30.4)	Not reached [-; -]	221	70 (31.7)	Not reached [21.6; -]	0.80 [0.57; 1.11]	0.173	
Region									
North America	62	32 (51.6)	15.9 [14.3; 33.6]	40	21 (52.5)	10.6 [8.1; -]	0.65 [0.37; 1.14]	0.130	0.351
European Union	134	47 (35.1)	Not reached [23.0; -]	127	59 (46.5)	18.1 [10.7; -]	0.62 [0.42; 0.91]	0.014	
Rest of World	149	24 (16.1)	Not reached [-; -]	133	17 (12.8)	Not reached [28.3; -]	0.91 [0.47; 1.75]	0.783	
Primary tumor site									
Oropharynx/Oral Cavity	243	82 (33.7)	Not reached [-; -]	215	78 (36.3)	Not reached [-; -]	0.75 [0.55; 1.03]	0.075	0.443
Larynx	76	14 (18.4)	Not reached [-; -]	61	15 (24.6)	28.3 [21.6; -]	0.47 [0.22; 1.04]	0.062	
Hypopharynx	26	7 (26.9)	Not reached [27.7; -]	24	4 (16.7)	Not reached [-; -]	1.47 [0.41; 5.21]	0.552	
PD-L1 status									
TPS < 50%	243	66 (27.2)	Not reached [-; -]	203	66 (32.5)	28.3 [21.6; -]	0.66 [0.47; 0.94]	0.022	0.252
TPS ≥ 50%	102	37 (36.3)	Not reached [22.7; -]	97	31 (32.0)	Not reached [-; -]	0.90 [0.55; 1.47]	0.671	
SOC: Skin and subcutaneous tissue disorders - PT[g]: Erythema									
Sex									
Male	270	9 (3.3)	Not reached [-; -]	237	13 (5.5)	Not reached [-; -]	0.35 [0.13; 0.93]	0.035	0.697
Female	75	3 (4.0)	Not reached [-; -]	63	6 (9.5)	Not reached [-; -]	0.34 [0.08; 1.43]	0.141	
Age									
< 65	235	8 (3.4)	Not reached [-; -]	195	14 (7.2)	Not reached [-; -]	0.26 [0.10; 0.71]	0.008	0.366
≥ 65	110	4 (3.6)	Not reached [-; -]	105	5 (4.8)	Not reached [-; -]	0.66 [0.16; 2.67]	0.562	
Tumor Stage									
III	86	2 (2.3)	Not reached [-; -]	79	2 (2.5)	Not reached [-; -]	0.29[h] [0.03; 3.05]	0.305[h]	0.688
IVA	257	10 (3.9)	Not reached [-; -]	221	17 (7.7)	Not reached [-; -]	0.37 [0.16; 0.86]	0.020	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Region									
North America	62	2 (3.2)	Not reached [-; -]	40	1 (2.5)	Not reached [-; -]	0.29[h] [0.01; 5.91]	0.420[h]	0.719
European Union	134	7 (5.2)	Not reached [-; -]	127	12 (9.4)	Not reached [-; -]	0.42 [0.16; 1.14]	0.090	
Rest of World	149	3 (2.0)	Not reached [-; -]	133	6 (4.5)	Not reached [-; -]	0.28 [0.06; 1.39]	0.119	
Primary tumor site									
Oropharynx/Oral Cavity	243	11 (4.5)	Not reached [-; -]	215	15 (7.0)	Not reached [-; -]	0.45 [0.19; 1.05]	0.066	0.326
Larynx	76	1 (1.3)	Not reached [-; -]	61	2 (3.3)	Not reached [-; -]	0.16[h] [0.01; 2.76]	0.207[h]	
Hypopharynx	26	0 (0.0)	Not reached [-; -]	24	2 (8.3)	Not reached [-; -]	0.18[h] [0.00; 7.43]	0.366[h]	
PD-L1 status									
TPS < 50%	243	8 (3.3)	Not reached [-; -]	203	15 (7.4)	Not reached [-; -]	0.30 [0.12; 0.79]	0.014	0.326
TPS ≥ 50%	102	4 (3.9)	Not reached [-; -]	97	4 (4.1)	Not reached [-; -]	0.53[h] [0.11; 2.48]	0.421[h]	
SOC: Investigations - PT[g]: Gamma-glutamyltransferase increased									
Sex									
Male	270	22 (8.1)	Not reached [-; -]	237	3 (1.3)	Not reached [-; -]	4.45 [1.30; 15.25]	0.018	0.082
Female	75	4 (5.3)	Not reached [-; -]	63	3 (4.8)	Not reached [-; -]	1.12 [0.25; 5.01]	0.883	
Age									
< 65	235	18 (7.7)	Not reached [-; -]	195	2 (1.0)	Not reached [-; -]	4.45[h] [1.11; 17.78]	0.035[h]	0.192
≥ 65	110	8 (7.3)	Not reached [-; -]	105	4 (3.8)	Not reached [-; -]	1.55 [0.44; 5.39]	0.492	
Tumor Stage									
III	86	3 (3.5)	Not reached [-; -]	79	2 (2.5)	Not reached [-; -]	0.95 [0.15; 6.10]	0.956	0.185
IVA	257	23 (8.9)	Not reached [-; -]	221	4 (1.8)	Not reached [-; -]	3.75 [1.27; 11.08]	0.017	
Region									
North America	62	0 (0.0)	Not reached [-; -]	40	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	0.991
European Union	134	20 (14.9)	Not reached [-; -]	127	5 (3.9)	Not reached [-; -]	3.45 [1.28; 9.32]	0.015	
Rest of World	149	6 (4.0)	Not reached [-; -]	133	1 (0.8)	Not reached [-; -]	1.93 [0.20; 18.90]	0.570	
Primary tumor site									
Oropharynx/Oral Cavity	243	18 (7.4)	Not reached [-; -]	215	4 (1.9)	Not reached [-; -]	3.33 [1.11; 10.02]	0.032	0.527
Larynx	76	6 (7.9)	Not reached [-; -]	61	2 (3.3)	Not reached [-; -]	1.55 [0.29; 8.22]	0.606	
Hypopharynx	26	2 (7.7)	Not reached [-; -]	24	0 (0.0)	Not reached [-; -]	0.29[h] [0.00; 27.25]	0.593[h]	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
PD-L1 status									
TPS < 50%	243	20 (8.2)	Not reached [-; -]	203	2 (1.0)	Not reached [-; -]	6.02 [1.38; 26.34]	0.017	0.059
TPS ≥ 50%	102	6 (5.9)	Not reached [-; -]	97	4 (4.1)	Not reached [-; -]	1.18 [0.32; 4.35]	0.801	
SOC: Endocrine disorders - PT[g]: Hyperthyroidism									
Sex									
Male	270	22 (8.1)	Not reached [-; -]	237	8 (3.4)	Not reached [-; -]	2.09 [0.92; 4.73]	0.078	0.642
Female	75	8 (10.7)	Not reached [-; -]	63	2 (3.2)	Not reached [-; -]	3.28 [0.68; 15.79]	0.139	
Tumor Stage									
III	86	9 (10.5)	Not reached [-; -]	79	4 (5.1)	Not reached [-; -]	1.93 [0.59; 6.28]	0.274	0.539
IVA	257	21 (8.2)	Not reached [-; -]	221	6 (2.7)	Not reached [-; -]	2.61 [1.04; 6.56]	0.042	
Region									
North America	62	3 (4.8)	Not reached [-; -]	40	0 (0.0)	Not reached [-; -]	4.67[h] [0.15; 143.17]	0.378[h]	0.487
European Union	134	16 (11.9)	Not reached [-; -]	127	7 (5.5)	Not reached [-; -]	1.92 [0.78; 4.72]	0.158	
Rest of World	149	11 (7.4)	Not reached [-; -]	133	3 (2.3)	Not reached [-; -]	2.93 [0.81; 10.65]	0.102	
Primary tumor site									
Oropharynx/Oral Cavity	243	20 (8.2)	Not reached [-; -]	215	7 (3.3)	Not reached [-; -]	2.17 [0.90; 5.23]	0.084	0.914
Larynx	76	6 (7.9)	Not reached [-; -]	61	2 (3.3)	Not reached [-; -]	2.18 [0.44; 10.82]	0.339	
Hypopharynx	26	4 (15.4)	Not reached [-; -]	24	1 (4.2)	Not reached [-; -]	3.58 [0.40; 32.15]	0.255	
PD-L1 status									
TPS < 50%	243	19 (7.8)	Not reached [-; -]	203	6 (3.0)	Not reached [-; -]	2.41 [0.96; 6.08]	0.062	0.961
TPS ≥ 50%	102	11 (10.8)	Not reached [-; -]	97	4 (4.1)	Not reached [-; -]	2.21 [0.69; 7.13]	0.184	
SOC: Endocrine disorders - PT[g]: Hypothyroidism									
Sex									
Male	270	62 (23.0)	Not reached [64.6; -]	237	13 (5.5)	Not reached [-; -]	1.75 [0.90; 3.37]	0.097	0.220
Female	75	21 (28.0)	Not reached [39.9; -]	63	2 (3.2)	Not reached [-; -]	4.40 [0.96; 20.11]	0.056	
Age									
< 65	235	57 (24.3)	Not reached [64.6; -]	195	7 (3.6)	Not reached [-; -]	2.58 [1.11; 6.01]	0.028	0.402
≥ 65	110	26 (23.6)	Not reached [48.3; -]	105	8 (7.6)	Not reached [-; -]	1.75 [0.74; 4.14]	0.205	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Tumor Stage									
III	86	30 (34.9)	64.6 [40.3; -]	79	4 (5.1)	Not reached [-; -]	2.66 [0.87; 8.14]	0.086	0.562
IVA	257	52 (20.2)	Not reached [-; -]	221	11 (5.0)	Not reached [-; -]	1.79 [0.87; 3.67]	0.112	
Region									
North America	62	13 (21.0)	Not reached [49.9; -]	40	2 (5.0)	Not reached [-; -]	1.10[h] [0.22; 5.45]	0.911[h]	0.803
European Union	134	28 (20.9)	Not reached [64.6; -]	127	7 (5.5)	Not reached [-; -]	2.06 [0.84; 5.05]	0.115	
Rest of World	149	42 (28.2)	Not reached [54.1; -]	133	6 (4.5)	Not reached [-; -]	2.47 [0.98; 6.24]	0.055	
Primary tumor site									
Oropharynx/Oral Cavity	243	47 (19.3)	Not reached [64.6; -]	215	5 (2.3)	Not reached [-; -]	3.40 [1.27; 9.08]	0.015	0.144
Larynx	76	31 (40.8)	43.6 [31.0; -]	61	7 (11.5)	Not reached [-; -]	1.55 [0.64; 3.78]	0.332	
Hypopharynx	26	5 (19.2)	Not reached [53.0; -]	24	3 (12.5)	Not reached [-; -]	0.94 [0.19; 4.67]	0.941	
PD-L1 status									
TPS < 50%	243	54 (22.2)	Not reached [64.6; -]	203	10 (4.9)	Not reached [-; -]	1.89 [0.91; 3.96]	0.089	0.659
TPS ≥ 50%	102	29 (28.4)	Not reached [45.6; -]	97	5 (5.2)	Not reached [-; -]	2.54 [0.91; 7.08]	0.075	
SOC: Psychiatric disorders - PT[g]: Insomnia									
Age									
< 65	235	44 (18.7)	Not reached [-; -]	195	18 (9.2)	Not reached [-; -]	1.63 [0.93; 2.87]	0.087	0.758
≥ 65	110	15 (13.6)	Not reached [-; -]	105	7 (6.7)	Not reached [-; -]	2.12 [0.85; 5.24]	0.106	
Tumor Stage									
III	86	13 (15.1)	Not reached [-; -]	79	4 (5.1)	Not reached [-; -]	2.24 [0.70; 7.12]	0.172	0.562
IVA	257	46 (17.9)	Not reached [-; -]	221	21 (9.5)	Not reached [-; -]	1.69 [1.00; 2.86]	0.050[i]	
Region									
North America	62	16 (25.8)	Not reached [47.0; -]	40	2 (5.0)	Not reached [-; -]	4.27 [0.96; 18.95]	0.056	0.257
European Union	134	17 (12.7)	Not reached [-; -]	127	9 (7.1)	Not reached [-; -]	1.70 [0.74; 3.88]	0.208	
Rest of World	149	26 (17.4)	Not reached [-; -]	133	14 (10.5)	Not reached [-; -]	1.37 [0.71; 2.66]	0.352	
Primary tumor site									
Oropharynx/Oral Cavity	243	49 (20.2)	Not reached [-; -]	215	18 (8.4)	Not reached [-; -]	2.06 [1.18; 3.58]	0.011	0.369
Larynx	76	7 (9.2)	Not reached [-; -]	61	5 (8.2)	Not reached [-; -]	1.05 [0.33; 3.30]	0.939	
Hypopharynx	26	3 (11.5)	Not reached [-; -]	24	2 (8.3)	Not reached [-; -]	1.24[h] [0.21; 7.36]	0.810[h]	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
PD-L1 status									
TPS < 50%	243	38 (15.6)	Not reached [-; -]	203	19 (9.4)	Not reached [-; -]	1.52 [0.87; 2.65]	0.143	0.161
TPS ≥ 50%	102	21 (20.6)	Not reached [-; -]	97	6 (6.2)	Not reached [-; -]	2.61 [1.02; 6.67]	0.045	
SOC: Gastrointestinal disorders - PT[g]: Nausea									
Sex									
Male	270	60 (22.2)	Not reached [-; -]	237	59 (24.9)	Not reached [25.1; -]	0.65 [0.45; 0.95]	0.025	0.585
Female	75	23 (30.7)	Not reached [23.0; -]	63	25 (39.7)	Not reached [9.9; -]	0.52 [0.28; 0.94]	0.030	
Age									
< 65	235	62 (26.4)	Not reached [-; -]	195	52 (26.7)	Not reached [-; -]	0.70 [0.48; 1.03]	0.069	0.311
≥ 65	110	21 (19.1)	Not reached [-; -]	105	32 (30.5)	25.1 [25.1; -]	0.46 [0.25; 0.82]	0.009	
Tumor Stage									
III	86	19 (22.1)	Not reached [-; -]	79	17 (21.5)	25.1 [25.1; -]	0.78 [0.40; 1.54]	0.478	0.582
IVA	257	63 (24.5)	Not reached [-; -]	221	67 (30.3)	Not reached [-; -]	0.58 [0.40; 0.83]	0.003	
Region									
North America	62	18 (29.0)	Not reached [32.0; -]	40	12 (30.0)	Not reached [11.0; -]	0.63 [0.29; 1.35]	0.232	0.694
European Union	134	31 (23.1)	Not reached [-; -]	127	33 (26.0)	Not reached [-; -]	0.64 [0.38; 1.07]	0.091	
Rest of World	149	34 (22.8)	Not reached [-; -]	133	39 (29.3)	Not reached [25.1; -]	0.57 [0.36; 0.91]	0.020	
Primary tumor site									
Oropharynx/Oral Cavity	243	66 (27.2)	Not reached [-; -]	215	66 (30.7)	Not reached [-; -]	0.63 [0.44; 0.90]	0.012	0.406
Larynx	76	11 (14.5)	Not reached [-; -]	61	8 (13.1)	Not reached [25.1; -]	0.88 [0.35; 2.24]	0.796	
Hypopharynx	26	6 (23.1)	Not reached [18.0; -]	24	10 (41.7)	Not reached [6.4; -]	0.33 [0.12; 0.95]	0.039	
PD-L1 status									
TPS < 50%	243	60 (24.7)	Not reached [-; -]	203	55 (27.1)	Not reached [25.1; -]	0.67 [0.46; 0.98]	0.038	0.582
TPS ≥ 50%	102	23 (22.5)	Not reached [-; -]	97	29 (29.9)	Not reached [-; -]	0.51 [0.29; 0.92]	0.025	
SOC: Investigations - PT[g]: Neutrophil count decreased									
Sex									
Male	270	32 (11.9)	Not reached [-; -]	237	51 (21.5)	Not reached [-; -]	0.31 [0.19; 0.51]	< 0.001	0.398
Female	75	8 (10.7)	Not reached [-; -]	63	9 (14.3)	Not reached [-; -]	0.57 [0.21; 1.55]	0.270	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age									
< 65	235	25 (10.6)	Not reached [-; -]	195	33 (16.9)	Not reached [-; -]	0.38 [0.22; 0.67]	< 0.001	0.978
≥ 65	110	15 (13.6)	Not reached [-; -]	105	27 (25.7)	Not reached [-; -]	0.33 [0.17; 0.66]	0.002	
Tumor Stage									
III	86	12 (14.0)	Not reached [-; -]	79	12 (15.2)	Not reached [-; -]	0.38 [0.15; 0.97]	0.042	0.367
IVA	257	28 (10.9)	Not reached [-; -]	221	48 (21.7)	Not reached [-; -]	0.34 [0.21; 0.56]	< 0.001	
Region									
North America	62	5 (8.1)	Not reached [-; -]	40	6 (15.0)	Not reached [-; -]	0.43[h] [0.13; 1.46]	0.177[h]	0.659
European Union	134	15 (11.2)	Not reached [-; -]	127	22 (17.3)	Not reached [-; -]	0.39 [0.19; 0.82]	0.012	
Rest of World	149	20 (13.4)	Not reached [-; -]	133	32 (24.1)	Not reached [-; -]	0.30 [0.16; 0.55]	< 0.001	
Primary tumor site									
Oropharynx/Oral Cavity	243	22 (9.1)	Not reached [-; -]	215	42 (19.5)	Not reached [-; -]	0.31 [0.18; 0.55]	< 0.001	0.396
Larynx	76	12 (15.8)	Not reached [-; -]	61	10 (16.4)	Not reached [-; -]	0.48 [0.19; 1.21]	0.122	
Hypopharynx	26	6 (23.1)	Not reached [28.1; -]	24	8 (33.3)	Not reached [12.4; -]	0.28 [0.08; 0.94]	0.039	
PD-L1 status									
TPS < 50%	243	25 (10.3)	Not reached [-; -]	203	40 (19.7)	Not reached [-; -]	0.29 [0.17; 0.50]	< 0.001	0.341
TPS ≥ 50%	102	15 (14.7)	Not reached [-; -]	97	20 (20.6)	Not reached [-; -]	0.49 [0.24; 1.00]	0.050[j]	
SOC: Investigations - PT[g]: Platelet count decreased									
Sex									
Male	270	16 (5.9)	Not reached [-; -]	237	22 (9.3)	Not reached [-; -]	0.43 [0.21; 0.86]	0.018	0.135
Female	75	1 (1.3)	Not reached [-; -]	63	6 (9.5)	Not reached [-; -]	0.19[h] [0.03; 1.27]	0.086[h]	
Age									
< 65	235	12 (5.1)	Not reached [-; -]	195	16 (8.2)	Not reached [-; -]	0.43 [0.19; 0.96]	0.039	0.670
≥ 65	110	5 (4.5)	Not reached [-; -]	105	12 (11.4)	Not reached [-; -]	0.31[h] [0.10; 0.96]	0.043[h]	
Tumor Stage									
III	86	3 (3.5)	Not reached [-; -]	79	2 (2.5)	Not reached [-; -]	0.64[h] [0.09; 4.44]	0.653[h]	0.331
IVA	257	14 (5.4)	Not reached [-; -]	221	26 (11.8)	Not reached [-; -]	0.34 [0.17; 0.69]	0.003	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Region									
North America	62	3 (4.8)	Not reached [-; -]	40	3 (7.5)	Not reached [-; -]	0.56 [0.11; 2.80]	0.484	0.677
European Union	134	9 (6.7)	Not reached [-; -]	127	14 (11.0)	Not reached [-; -]	0.48 [0.20; 1.17]	0.105	
Rest of World	149	5 (3.4)	Not reached [-; -]	133	11 (8.3)	Not reached [-; -]	0.20 [0.06; 0.72]	0.014	
Primary tumor site									
Oropharynx/Oral Cavity	243	12 (4.9)	Not reached [-; -]	215	21 (9.8)	Not reached [-; -]	0.36 [0.17; 0.78]	0.010	0.785
Larynx	76	4 (5.3)	Not reached [-; -]	61	4 (6.6)	Not reached [-; -]	0.55 [0.12; 2.46]	0.435	
Hypopharynx	26	1 (3.8)	Not reached [-; -]	24	3 (12.5)	Not reached [-; -]	0.14[h] [0.01; 2.09]	0.155[h]	
PD-L1 status									
TPS < 50%	243	10 (4.1)	Not reached [-; -]	203	19 (9.4)	Not reached [-; -]	0.23 [0.10; 0.58]	0.002	0.380
TPS ≥ 50%	102	7 (6.9)	Not reached [-; -]	97	9 (9.3)	Not reached [-; -]	0.71 [0.26; 1.90]	0.489	
SOC: Infections and infestations - PT[g]: Pneumonia									
Age									
< 65	235	14 (6.0)	Not reached [-; -]	195	14 (7.2)	Not reached [22.4; -]	0.45 [0.19; 1.05]	0.065	0.726
≥ 65	110	10 (9.1)	Not reached [-; -]	105	11 (10.5)	Not reached [22.1; -]	0.66 [0.26; 1.65]	0.374	
Tumor Stage									
III	86	5 (5.8)	Not reached [-; -]	79	6 (7.6)	22.1 [20.0; -]	0.33 [0.08; 1.37]	0.126	0.727
IVA	257	18 (7.0)	Not reached [-; -]	221	19 (8.6)	Not reached [22.7; -]	0.59 [0.29; 1.18]	0.136	
Region									
North America	62	4 (6.5)	Not reached [-; -]	40	1 (2.5)	Not reached [-; -]	2.38 [0.27; 21.37]	0.438	0.315
European Union	134	7 (5.2)	Not reached [-; -]	127	13 (10.2)	Not reached [22.4; -]	0.23 [0.07; 0.72]	0.011	
Rest of World	149	13 (8.7)	Not reached [-; -]	133	11 (8.3)	Not reached [22.1; -]	0.66 [0.27; 1.58]	0.347	
Primary tumor site									
Oropharynx/Oral Cavity	243	14 (5.8)	Not reached [-; -]	215	15 (7.0)	Not reached [22.7; -]	0.58 [0.26; 1.26]	0.168	0.062
Larynx	76	5 (6.6)	Not reached [-; -]	61	9 (14.8)	Not reached [22.1; -]	0.21 [0.06; 0.77]	0.018	
Hypopharynx	26	5 (19.2)	Not reached [42.3; -]	24	1 (4.2)	Not reached [-; -]	2.16[h] [0.25; 18.35]	0.480[h]	
SOC: Skin and subcutaneous tissue disorders - PT[g]: Pruritus									
Sex									
Male	270	24 (8.9)	Not reached [-; -]	237	5 (2.1)	Not reached [-; -]	2.88 [1.06; 7.82]	0.037	0.276
Female	75	14 (18.7)	Not reached [-; -]	63	1 (1.6)	Not reached [-; -]	8.56 [1.09; 67.12]	0.041	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Tumor Stage									
III	86	11 (12.8)	Not reached [-; -]	79	2 (2.5)	Not reached [-; -]	3.01 [0.63; 14.32]	0.166	0.742
IVA	257	27 (10.5)	Not reached [-; -]	221	4 (1.8)	Not reached [-; -]	4.20 [1.43; 12.35]	0.009	
Region									
North America	62	13 (21.0)	61.1 [61.1; -]	40	0 (0.0)	Not reached [-; -]	11.29[h] [0.55; 232.82]	0.116[h]	0.054
European Union	134	15 (11.2)	Not reached [-; -]	127	2 (1.6)	Not reached [-; -]	6.44 [1.45; 28.64]	0.014	
Rest of World	149	10 (6.7)	Not reached [-; -]	133	4 (3.0)	Not reached [-; -]	1.19 [0.34; 4.24]	0.785	
Primary tumor site									
Oropharynx/Oral Cavity	243	29 (11.9)	Not reached [-; -]	215	5 (2.3)	Not reached [-; -]	3.79 [1.43; 10.07]	0.007	0.171
Larynx	76	8 (10.5)	Not reached [-; -]	61	0 (0.0)	Not reached [-; -]	6.91[h] [0.29; 162.10]	0.230[h]	
Hypopharynx	26	1 (3.8)	Not reached [-; -]	24	1 (4.2)	Not reached [-; -]	0.94[h] [0.06; 15.01]	0.964[h]	
PD-L1 status									
TPS < 50%	243	27 (11.1)	Not reached [-; -]	203	5 (2.5)	Not reached [-; -]	3.04 [1.13; 8.14]	0.027	0.413
TPS ≥ 50%	102	11 (10.8)	Not reached [-; -]	97	1 (1.0)	Not reached [-; -]	7.54 [0.94; 60.47]	0.057	
SOC: General disorders and administration site conditions - PT[g]: Pyrexia									
Sex									
Male	270	33 (12.2)	Not reached [-; -]	237	15 (6.3)	Not reached [-; -]	1.64 [0.88; 3.05]	0.119	0.217
Female	75	11 (14.7)	Not reached [-; -]	63	2 (3.2)	Not reached [-; -]	4.15 [0.90; 19.11]	0.068	
Age									
< 65	235	35 (14.9)	Not reached [-; -]	195	11 (5.6)	Not reached [-; -]	2.17 [1.09; 4.33]	0.028	0.411
≥ 65	110	9 (8.2)	Not reached [-; -]	105	6 (5.7)	Not reached [-; -]	1.31 [0.46; 3.73]	0.616	
Tumor Stage									
III	86	12 (14.0)	Not reached [-; -]	79	5 (6.3)	Not reached [-; -]	1.60 [0.54; 4.73]	0.395	0.810
IVA	257	32 (12.5)	Not reached [-; -]	221	12 (5.4)	Not reached [-; -]	2.07 [1.06; 4.05]	0.034	
Region									
North America	62	7 (11.3)	Not reached [-; -]	40	4 (10.0)	Not reached [-; -]	1.08 [0.31; 3.69]	0.905	0.443
European Union	134	17 (12.7)	Not reached [-; -]	127	7 (5.5)	Not reached [-; -]	1.82 [0.74; 4.51]	0.194	
Rest of World	149	20 (13.4)	Not reached [-; -]	133	6 (4.5)	Not reached [-; -]	2.55 [1.01; 6.44]	0.047	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Primary tumor site									
Oropharynx/Oral Cavity	243	34 (14.0)	Not reached [-; -]	215	14 (6.5)	Not reached [-; -]	2.01 [1.07; 3.78]	0.029	0.328
Larynx	76	7 (9.2)	Not reached [-; -]	61	3 (4.9)	Not reached [-; -]	1.45 [0.36; 5.75]	0.601	
Hypopharynx	26	3 (11.5)	Not reached [-; -]	24	0 (0.0)	Not reached [-; -]	0.49[h] [0.01; 20.11]	0.705[h]	
PD-L1 status									
TPS < 50%	243	27 (11.1)	Not reached [-; -]	203	10 (4.9)	Not reached [-; -]	1.90 [0.91; 3.98]	0.088	0.940
TPS ≥ 50%	102	17 (16.7)	Not reached [-; -]	97	7 (7.2)	Not reached [-; -]	2.01 [0.82; 4.92]	0.127	
SOC: Injury, poisoning and procedural complications - PT[g]: Radiation mucositis									
Sex									
Male	270	3 (1.1)	Not reached [-; -]	237	9 (3.8)	Not reached [-; -]	0.23 [0.06; 0.89]	0.034	0.756
Female	75	1 (1.3)	Not reached [-; -]	63	2 (3.2)	Not reached [-; -]	0.55[h] [0.05; 5.66]	0.612[h]	
Age									
< 65	235	4 (1.7)	n.c.	195	5 (2.6)	n.c.	n.c.	n.c.	n.c.
≥ 65	110	0 (0.0)	n.c.	105	6 (5.7)	n.c.	n.c.	n.c.	
Tumor Stage									
III	86	2 (2.3)	Not reached [-; -]	79	1 (1.3)	Not reached [-; -]	1.37[h] [0.13; 14.17]	0.793[h]	0.113
IVA	257	2 (0.8)	Not reached [-; -]	221	10 (4.5)	Not reached [-; -]	0.14 [0.03; 0.67]	0.014	
Region									
North America	62	0 (0.0)	n.c.	40	0 (0.0)	n.c.	n.c.	n.c.	n.c.
European Union	134	1 (0.7)	n.c.	127	8 (6.3)	n.c.	n.c.	n.c.	
Rest of World	149	3 (2.0)	n.c.	133	3 (2.3)	n.c.	n.c.	n.c.	
Primary tumor site									
Oropharynx/Oral Cavity	243	3 (1.2)	n.c.	215	5 (2.3)	n.c.	n.c.	n.c.	n.c.
Larynx	76	1 (1.3)	n.c.	61	4 (6.6)	n.c.	n.c.	n.c.	
Hypopharynx	26	0 (0.0)	n.c.	24	2 (8.3)	n.c.	n.c.	n.c.	
PD-L1 status									
TPS < 50%	243	2 (0.8)	Not reached [-; -]	203	9 (4.4)	Not reached [-; -]	0.14 [0.03; 0.70]	0.016	0.181
TPS ≥ 50%	102	2 (2.0)	Not reached [-; -]	97	2 (2.1)	Not reached [-; -]	0.95[h] [0.13; 6.77]	0.962[h]	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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: Skin and subcutaneous tissue disorders - PT[g]: Rash									
Sex									
Male	270	26 (9.6)	Not reached [-; -]	237	4 (1.7)	Not reached [-; -]	4.94 [1.71; 14.30]	0.003	0.584
Female	75	12 (16.0)	Not reached [-; -]	63	1 (1.6)	Not reached [-; -]	5.21 [0.64; 42.28]	0.123	
Age									
< 65	235	29 (12.3)	Not reached [-; -]	195	4 (2.1)	Not reached [-; -]	4.19 [1.45; 12.17]	0.008	0.651
≥ 65	110	9 (8.2)	Not reached [-; -]	105	1 (1.0)	Not reached [-; -]	8.29 [1.03; 66.42]	0.046	
Tumor Stage									
III	86	11 (12.8)	Not reached [-; -]	79	2 (2.5)	Not reached [-; -]	3.52 [0.75; 16.44]	0.109	0.573
IVA	257	27 (10.5)	Not reached [-; -]	221	3 (1.4)	Not reached [-; -]	6.05 [1.81; 20.27]	0.004	
Region									
North America	62	6 (9.7)	Not reached [-; -]	40	0 (0.0)	Not reached [-; -]	6.65[h] [0.29; 155.15]	0.238[h]	0.192
European Union	134	16 (11.9)	Not reached [-; -]	127	1 (0.8)	Not reached [-; -]	9.23 [1.19; 71.81]	0.034	
Rest of World	149	16 (10.7)	Not reached [-; -]	133	4 (3.0)	Not reached [-; -]	3.09 [1.02; 9.40]	0.046	
Primary tumor site									
Oropharynx/Oral Cavity	243	29 (11.9)	Not reached [-; -]	215	5 (2.3)	Not reached [-; -]	3.77 [1.43; 9.97]	0.007	0.307
Larynx	76	6 (7.9)	Not reached [-; -]	61	0 (0.0)	Not reached [-; -]	8.59[h] [0.36; 202.97]	0.183[h]	
Hypopharynx	26	3 (11.5)	Not reached [-; -]	24	0 (0.0)	Not reached [-; -]	5.30[h] [0.16; 176.42]	0.351[h]	
PD-L1 status									
TPS < 50%	243	27 (11.1)	Not reached [-; -]	203	2 (1.0)	Not reached [-; -]	8.31 [1.95; 35.49]	0.004	0.232
TPS ≥ 50%	102	11 (10.8)	Not reached [-; -]	97	3 (3.1)	Not reached [-; -]	2.83 [0.77; 10.39]	0.116	
SOC: Gastrointestinal disorders - PT[g]: Stomatitis									
Sex									
Male	270	112 (41.5)	20.6 [17.6; -]	237	129 (54.4)	11.1 [10.3; 13.9]	0.43 [0.33; 0.56]	< 0.001	0.817
Female	75	32 (42.7)	17.9 [15.4; 23.7]	63	37 (58.7)	10.4 [9.4; 11.9]	0.37 [0.23; 0.62]	< 0.001	
Age									
< 65	235	107 (45.5)	18.1 [16.9; -]	195	109 (55.9)	10.9 [10.3; 12.3]	0.43 [0.32; 0.56]	< 0.001	0.725
≥ 65	110	37 (33.6)	25.4 [18.0; -]	105	57 (54.3)	11.3 [9.9; 18.7]	0.40 [0.26; 0.60]	< 0.001	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Tumor Stage									
III	86	40 (46.5)	20.0 [15.3; -]	79	41 (51.9)	10.9 [9.1; 15.9]	0.49 [0.31; 0.76]	0.002	0.708
IVA	257	103 (40.1)	20.0 [17.6; -]	221	125 (56.6)	11.0 [10.4; 12.3]	0.40 [0.30; 0.52]	< 0.001	
Region									
North America	62	27 (43.5)	18.1 [15.1; -]	40	24 (60.0)	9.4 [9.0; 10.3]	0.27 [0.15; 0.48]	< 0.001	0.313
European Union	134	60 (44.8)	17.6 [16.0; 23.7]	127	81 (63.8)	11.0 [10.1; 12.3]	0.40 [0.28; 0.56]	< 0.001	
Rest of World	149	57 (38.3)	Not reached [19.9; -]	133	61 (45.9)	13.7 [10.9; -]	0.49 [0.33; 0.70]	< 0.001	
Primary tumor site									
Oropharynx/Oral Cavity	243	124 (51.0)	16.3 [15.4; 17.9]	215	140 (65.1)	10.3 [9.7; 11.0]	0.41 [0.32; 0.52]	< 0.001	0.982
Larynx	76	13 (17.1)	Not reached [-; -]	61	16 (26.2)	Not reached [22.3; -]	0.33 [0.15; 0.72]	0.006	
Hypopharynx	26	7 (26.9)	Not reached [16.1; -]	24	10 (41.7)	Not reached [9.7; -]	0.47 [0.18; 1.24]	0.127	
PD-L1 status									
TPS < 50%	243	93 (38.3)	25.4 [19.1; -]	203	106 (52.2)	11.9 [10.3; 14.1]	0.41 [0.31; 0.55]	< 0.001	0.590
TPS ≥ 50%	102	51 (50.0)	16.6 [15.1; 18.3]	97	60 (61.9)	10.7 [9.6; 11.4]	0.46 [0.31; 0.67]	< 0.001	
SOC: Investigations - PT[g]: White blood cell count decreased									
Sex									
Male	270	31 (11.5)	Not reached [-; -]	237	43 (18.1)	Not reached [25.9; -]	0.36 [0.22; 0.60]	< 0.001	0.470
Female	75	9 (12.0)	Not reached [-; -]	63	9 (14.3)	Not reached [-; -]	0.43 [0.15; 1.27]	0.127	
Age									
< 65	235	28 (11.9)	Not reached [-; -]	195	33 (16.9)	Not reached [-; -]	0.39 [0.23; 0.67]	< 0.001	0.911
≥ 65	110	12 (10.9)	Not reached [-; -]	105	19 (18.1)	25.9 [25.9; -]	0.34 [0.15; 0.77]	0.010	
Tumor Stage									
III	86	12 (14.0)	Not reached [-; -]	79	13 (16.5)	25.9 [-; -]	0.29 [0.11; 0.76]	0.012	0.851
IVA	257	28 (10.9)	Not reached [-; -]	221	39 (17.6)	Not reached [-; -]	0.41 [0.25; 0.69]	< 0.001	
Region									
North America	62	4 (6.5)	Not reached [-; -]	40	6 (15.0)	Not reached [-; -]	0.37[h] [0.10; 1.32]	0.126[h]	0.244
European Union	134	17 (12.7)	Not reached [-; -]	127	18 (14.2)	Not reached [-; -]	0.54 [0.26; 1.12]	0.095	
Rest of World	149	19 (12.8)	Not reached [-; -]	133	28 (21.1)	Not reached [25.9; -]	0.29 [0.15; 0.55]	< 0.001	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Primary tumor site									
Oropharynx/Oral Cavity	243	25 (10.3)	Not reached [-; -]	215	33 (15.3)	Not reached [-; -]	0.42 [0.24; 0.74]	0.003	0.141
Larynx	76	10 (13.2)	Not reached [-; -]	61	7 (11.5)	Not reached [25.9; -]	0.48 [0.16; 1.39]	0.175	
Hypopharynx	26	5 (19.2)	Not reached [28.1; -]	24	12 (50.0)	16.1 [9.6; -]	0.15[h] [0.05; 0.49]	0.002[h]	
PD-L1 status									
TPS < 50%	243	27 (11.1)	Not reached [-; -]	203	35 (17.2)	Not reached [25.9; -]	0.37 [0.21; 0.64]	< 0.001	0.691
TPS ≥ 50%	102	13 (12.7)	Not reached [-; -]	97	17 (17.5)	Not reached [-; -]	0.40 [0.18; 0.89]	0.025	
SOC: Injury, poisoning and procedural complications - PT[g]: Radiation skin injury									
Age									
< 65	235	100 (42.6)	19.7 [18.1; -]	195	94 (48.2)	13.0 [11.3; 18.9]	0.45 [0.34; 0.60]	< 0.001	0.560
≥ 65	110	40 (36.4)	21.4 [18.3; -]	105	48 (45.7)	15.1 [11.1; -]	0.51 [0.33; 0.79]	0.003	
Tumor Stage									
III	86	40 (46.5)	21.0 [16.0; -]	79	35 (44.3)	14.6 [12.1; -]	0.55 [0.34; 0.88]	0.012	0.506
IVA	257	99 (38.5)	22.1 [18.6; -]	221	107 (48.4)	13.0 [11.0; 18.9]	0.45 [0.34; 0.59]	< 0.001	
Region									
North America	62	22 (35.5)	18.9 [18.0; -]	40	17 (42.5)	13.1 [9.9; -]	0.36 [0.19; 0.71]	0.003	0.815
European Union	134	60 (44.8)	18.3 [16.9; 25.0]	127	70 (55.1)	12.7 [10.9; 17.1]	0.49 [0.35; 0.70]	< 0.001	
Rest of World	149	58 (38.9)	Not reached [21.0; -]	133	55 (41.4)	17.4 [11.4; -]	0.50 [0.34; 0.73]	< 0.001	
Primary tumor site									
Oropharynx/Oral Cavity	243	99 (40.7)	19.1 [18.1; -]	215	100 (46.5)	14.7 [11.9; -]	0.51 [0.39; 0.68]	< 0.001	0.579
Larynx	76	26 (34.2)	Not reached [23.1; -]	61	25 (41.0)	17.1 [11.0; -]	0.38 [0.22; 0.68]	0.001	
Hypopharynx	26	15 (57.7)	15.3 [14.9; 17.3]	24	17 (70.8)	9.0 [8.0; 11.9]	0.43 [0.21; 0.88]	0.020	
PD-L1 status									
TPS < 50%	243	99 (40.7)	23.1 [18.3; -]	203	95 (46.8)	14.3 [11.3; -]	0.48 [0.36; 0.64]	< 0.001	0.954
TPS ≥ 50%	102	41 (40.2)	19.1 [17.7; -]	97	47 (48.5)	13.1 [11.0; -]	0.47 [0.31; 0.72]	< 0.001	

a: Database Cutoff Date: 25JUL2024

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

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

d: Based on Cox regression model with treatment as a covariate. Ties are handled using Efron's method

e: Two-sided p-value using Wald test

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 specific adverse event appears on this report only if its incidence ≥ 10% or (incidence ≥ 1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05, and the interaction p-value is greater than or equal to 0.05 or not calculated

h: Obtained via the Firth penalized likelihood approach to Cox regression model with treatment as a covariate. Ties are handled using Breslow's

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
method									

i: Unrounded p-value > 0.050

j: Unrounded p-value < 0.050

CI: Confidence Interval; CPS: Combined Positive Score; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup category and at least 10 participants with events in one of the subgroup categories necessary); PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term; SOC: System Organ Class; SoC: Standard of Care; TPS: Tumor Proportion Score

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Nicht zutreffend.

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

Tabelle 4G-49: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für SOC aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]: Blood and lymphatic system disorders									
Sex									
Male	270	24 (8.9)	Not reached [-; -]	237	24 (10.1)	Not reached [-; -]	0.58 [0.32; 1.07]	0.081	0.737
Female	75	16 (21.3)	Not reached [-; -]	63	17 (27.0)	22.6 [-; -]	0.47 [0.22; 1.00]	0.050[i]	
Age									
< 65	235	27 (11.5)	Not reached [-; -]	195	26 (13.3)	Not reached [22.6; -]	0.48 [0.26; 0.87]	0.015	0.791
≥ 65	110	13 (11.8)	Not reached [-; -]	105	15 (14.3)	Not reached [22.6; -]	0.73 [0.34; 1.56]	0.412	
Tumor Stage									
III	86	4 (4.7)	Not reached [-; -]	79	10 (12.7)	Not reached [22.6; -]	0.18 [0.05; 0.67]	0.010	0.067
IVA	257	35 (13.6)	Not reached [-; -]	221	31 (14.0)	Not reached [-; -]	0.69 [0.42; 1.16]	0.163	
Region									
North America	62	14 (22.6)	Not reached [-; -]	40	8 (20.0)	Not reached [-; -]	0.89 [0.36; 2.16]	0.792	0.288
European Union	134	15 (11.2)	Not reached [-; -]	127	15 (11.8)	Not reached [-; -]	0.70 [0.33; 1.50]	0.360	
Rest of World	149	11 (7.4)	Not reached [-; -]	133	18 (13.5)	Not reached [22.6; -]	0.24 [0.10; 0.56]	0.001	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Primary tumor site									
Oropharynx/Oral Cavity	243	31 (12.8)	Not reached [-; -]	215	36 (16.7)	Not reached [22.6; -]	0.57 [0.34; 0.94]	0.027	0.284
Larynx	76	5 (6.6)	Not reached [-; -]	61	4 (6.6)	Not reached [22.6; -]	0.48 [0.11; 2.02]	0.317	
Hypopharynx	26	4 (15.4)	Not reached [40.9; -]	24	1 (4.2)	Not reached [-; -]	0.90[h] [0.06; 14.41]	0.941[h]	
PD-L1 status									
TPS < 50%	243	28 (11.5)	Not reached [-; -]	203	24 (11.8)	Not reached [-; -]	0.66 [0.37; 1.18]	0.157	0.414
TPS ≥ 50%	102	12 (11.8)	Not reached [-; -]	97	17 (17.5)	Not reached [22.6; -]	0.43 [0.19; 0.97]	0.041	
SOC[g]: Injury, poisoning and procedural complications									
Sex									
Male	270	34 (12.6)	87.3 [71.7; -]	237	36 (15.2)	Not reached [26.7; -]	0.58 [0.35; 0.95]	0.031	0.386
Female	75	17 (22.7)	Not reached [-; -]	63	13 (20.6)	Not reached [-; -]	0.80 [0.38; 1.72]	0.574	
Age									
< 65	235	39 (16.6)	87.3 [71.7; -]	195	32 (16.4)	26.7 [26.7; -]	0.65 [0.39; 1.07]	0.092	0.629
≥ 65	110	12 (10.9)	Not reached [-; -]	105	17 (16.2)	Not reached [-; -]	0.62 [0.29; 1.31]	0.208	
Tumor Stage									
III	86	9 (10.5)	87.3 [71.7; -]	79	10 (12.7)	Not reached [-; -]	0.40 [0.14; 1.15]	0.090	0.342
IVA	257	42 (16.3)	Not reached [-; -]	221	39 (17.6)	Not reached [26.7; -]	0.71 [0.45; 1.12]	0.145	
Region									
North America	62	11 (17.7)	Not reached [-; -]	40	6 (15.0)	Not reached [18.3; -]	0.81 [0.28; 2.29]	0.685	0.091
European Union	134	26 (19.4)	Not reached [71.7; -]	127	21 (16.5)	26.7 [26.7; -]	0.91 [0.50; 1.66]	0.753	
Rest of World	149	14 (9.4)	87.3 [-; -]	133	22 (16.5)	Not reached [-; -]	0.36 [0.17; 0.75]	0.006	
Primary tumor site									
Oropharynx/Oral Cavity	243	42 (17.3)	87.3 [-; -]	215	35 (16.3)	26.7 [26.7; -]	0.78 [0.48; 1.25]	0.298	0.251
Larynx	76	7 (9.2)	71.7 [71.7; -]	61	10 (16.4)	Not reached [-; -]	0.34 [0.12; 0.97]	0.043	
Hypopharynx	26	2 (7.7)	Not reached [-; -]	24	4 (16.7)	Not reached [-; -]	0.47[h] [0.09; 2.48]	0.370[h]	
PD-L1 status									
TPS < 50%	243	38 (15.6)	87.3 [71.7; -]	203	32 (15.8)	Not reached [26.7; -]	0.65 [0.39; 1.08]	0.096	0.646
TPS ≥ 50%	102	13 (12.7)	Not reached [-; -]	97	17 (17.5)	Not reached [-; -]	0.63 [0.30; 1.32]	0.222	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]: Investigations									
Age									
< 65	235	85 (36.2)	88.1 [32.4; -]	195	59 (30.3)	27.6 [27.6; -]	0.58 [0.40; 0.83]	0.003	0.481
≥ 65	110	28 (25.5)	Not reached [51.9; -]	105	34 (32.4)	37.4 [18.6; -]	0.55 [0.32; 0.95]	0.032	
Tumor Stage									
III	86	32 (37.2)	61.3 [33.9; -]	79	22 (27.8)	30.4 [27.6; -]	0.66 [0.37; 1.20]	0.174	0.490
IVA	257	80 (31.1)	88.1 [37.0; -]	221	71 (32.1)	Not reached [19.3; -]	0.54 [0.38; 0.77]	< 0.001	
Region									
North America	62	19 (30.6)	88.1 [24.0; -]	40	9 (22.5)	Not reached [15.9; -]	0.56 [0.23; 1.36]	0.197	0.084
European Union	134	47 (35.1)	61.3 [31.1; -]	127	36 (28.3)	27.6 [23.9; -]	0.70 [0.43; 1.15]	0.161	
Rest of World	149	47 (31.5)	Not reached [-; -]	133	48 (36.1)	37.4 [16.9; -]	0.48 [0.31; 0.73]	< 0.001	
Primary tumor site									
Oropharynx/Oral Cavity	243	79 (32.5)	88.1 [36.0; -]	215	64 (29.8)	27.6 [27.6; -]	0.59 [0.40; 0.85]	0.005	0.737
Larynx	76	23 (30.3)	Not reached [43.0; -]	61	20 (32.8)	23.9 [16.0; -]	0.52 [0.28; 0.99]	0.046	
Hypopharynx	26	11 (42.3)	23.9 [18.4; -]	24	9 (37.5)	Not reached [11.1; -]	0.49 [0.18; 1.33]	0.164	
PD-L1 status									
TPS < 50%	243	80 (32.9)	Not reached [43.0; -]	203	67 (33.0)	27.6 [19.3; -]	0.54 [0.38; 0.77]	< 0.001	0.454
TPS ≥ 50%	102	33 (32.4)	88.1 [32.1; -]	97	26 (26.8)	30.4 [-; -]	0.65 [0.37; 1.16]	0.145	

a: Database Cutoff Date: 25JUL2024

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

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

d: Based on Cox regression model with treatment as a covariate. Ties are handled using Efron's method

e: Two-sided p-value using Wald test

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, and the interaction p-value is greater than or equal to 0.05 or not calculated

h: Obtained via the Firth penalized likelihood approach to Cox regression model with treatment as a covariate. Ties are handled using Breslow's method

i: Unrounded p-value > 0.050

CI: Confidence Interval; CPS: Combined Positive Score; CTCAE: Common Terminology Criteria for Adverse Events; PD-L1: Programmed Cell Death - Ligand 1; SOC: System Organ Class; SoC: Standard of Care; TPS: Tumor Proportion Score

Tabelle 4G-50: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für PT aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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: Blood and lymphatic system disorders - PT[g]: Anaemia									
Sex									
Male	270	22 (8.1)	Not reached [-; -]	237	20 (8.4)	Not reached [-; -]	0.61 [0.32; 1.17]	0.139	0.837
Female	75	15 (20.0)	Not reached [-; -]	63	14 (22.2)	22.6 [-; -]	0.51 [0.23; 1.16]	0.107	
Age									
< 65	235	26 (11.1)	Not reached [-; -]	195	20 (10.3)	Not reached [22.6; -]	0.58 [0.30; 1.10]	0.095	0.680
≥ 65	110	11 (10.0)	Not reached [-; -]	105	14 (13.3)	Not reached [22.6; -]	0.63 [0.28; 1.43]	0.269	
Tumor Stage									
III	86	3 (3.5)	Not reached [-; -]	79	8 (10.1)	Not reached [22.6; -]	0.13 [0.03; 0.63]	0.012	0.057
IVA	257	33 (12.8)	Not reached [-; -]	221	26 (11.8)	Not reached [-; -]	0.76 [0.44; 1.30]	0.313	
Region									
North America	62	14 (22.6)	Not reached [-; -]	40	7 (17.5)	Not reached [-; -]	0.98 [0.38; 2.50]	0.967	0.533
European Union	134	12 (9.0)	Not reached [-; -]	127	13 (10.2)	Not reached [-; -]	0.60 [0.25; 1.40]	0.234	
Rest of World	149	11 (7.4)	Not reached [-; -]	133	14 (10.5)	Not reached [22.6; -]	0.29 [0.12; 0.72]	0.008	
Primary tumor site									
Oropharynx/Oral Cavity	243	29 (11.9)	Not reached [-; -]	215	29 (13.5)	Not reached [22.6; -]	0.63 [0.37; 1.09]	0.100	0.359
Larynx	76	4 (5.3)	Not reached [-; -]	61	4 (6.6)	Not reached [22.6; -]	0.33 [0.07; 1.58]	0.166	
Hypopharynx	26	4 (15.4)	Not reached [40.9; -]	24	1 (4.2)	Not reached [-; -]	0.90[h] [0.06; 14.41]	0.941[h]	
PD-L1 status									
TPS < 50%	243	25 (10.3)	Not reached [-; -]	203	20 (9.9)	Not reached [-; -]	0.66 [0.35; 1.25]	0.201	0.623
TPS ≥ 50%	102	12 (11.8)	Not reached [-; -]	97	14 (14.4)	Not reached [22.6; -]	0.52 [0.23; 1.20]	0.125	
SOC: Metabolism and nutrition disorders - PT[g]: Hypophosphataemia									
Sex									
Male	270	5 (1.9)	Not reached [-; -]	237	9 (3.8)	Not reached [-; -]	0.31[h] [0.09; 1.12]	0.073[h]	0.963
Female	75	1 (1.3)	Not reached [-; -]	63	2 (3.2)	Not reached [-; -]	0.42 [0.04; 4.70]	0.484	
Age									
< 65	235	5 (2.1)	Not reached [-; -]	195	6 (3.1)	Not reached [-; -]	0.42[h] [0.11; 1.67]	0.220[h]	0.334
≥ 65	110	1 (0.9)	Not reached [-; -]	105	5 (4.8)	Not reached [-; -]	0.19 [0.02; 1.65]	0.133	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Tumor Stage									
III	86	1 (1.2)	Not reached [-; -]	79	2 (2.5)	Not reached [-; -]	0.18[h] [0.00; 7.52]	0.370[h]	0.900
IVA	257	5 (1.9)	Not reached [-; -]	221	9 (4.1)	Not reached [-; -]	0.37 [0.11; 1.20]	0.098	
Region									
North America	62	1 (1.6)	n.c.	40	6 (15.0)	n.c.	n.c.	n.c.	n.c.
European Union	134	4 (3.0)	n.c.	127	2 (1.6)	n.c.	n.c.	n.c.	
Rest of World	149	1 (0.7)	n.c.	133	3 (2.3)	n.c.	n.c.	n.c.	
Primary tumor site									
Oropharynx/Oral Cavity	243	3 (1.2)	Not reached [-; -]	215	10 (4.7)	Not reached [-; -]	0.26 [0.07; 0.93]	0.039	0.218
Larynx	76	3 (3.9)	Not reached [-; -]	61	1 (1.6)	Not reached [-; -]	0.74[h] [0.05; 11.90]	0.834[h]	
Hypopharynx	26	0 (0.0)	Not reached [-; -]	24	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
PD-L1 status									
TPS < 50%	243	6 (2.5)	Not reached [-; -]	203	8 (3.9)	Not reached [-; -]	0.40 [0.12; 1.33]	0.134	0.101
TPS ≥ 50%	102	0 (0.0)	Not reached [-; -]	97	3 (3.1)	Not reached [-; -]	0.14[h] [0.00; 4.17]	0.254[h]	
SOC: Investigations - PT[g]: Lymphocyte count decreased									
Sex									
Male	270	24 (8.9)	Not reached [-; -]	237	31 (13.1)	37.4 [-; -]	0.42 [0.24; 0.75]	0.003	0.102
Female	75	8 (10.7)	Not reached [-; -]	63	4 (6.3)	Not reached [-; -]	1.24[h] [0.36; 4.27]	0.737[h]	
Age									
< 65	235	26 (11.1)	Not reached [-; -]	195	23 (11.8)	Not reached [-; -]	0.54 [0.29; 0.98]	0.044	0.430
≥ 65	110	6 (5.5)	Not reached [-; -]	105	12 (11.4)	37.4 [-; -]	0.43 [0.15; 1.21]	0.111	
Tumor Stage									
III	86	12 (14.0)	Not reached [-; -]	79	8 (10.1)	37.4 [-; -]	0.88 [0.35; 2.23]	0.786	0.195
IVA	257	19 (7.4)	Not reached [-; -]	221	27 (12.2)	Not reached [-; -]	0.41 [0.22; 0.77]	0.006	
Region									
North America	62	10 (16.1)	Not reached [-; -]	40	4 (10.0)	Not reached [-; -]	1.11 [0.34; 3.63]	0.864	0.264
European Union	134	5 (3.7)	Not reached [-; -]	127	11 (8.7)	Not reached [-; -]	0.27 [0.08; 0.91]	0.034	
Rest of World	149	17 (11.4)	Not reached [-; -]	133	20 (15.0)	37.4 [-; -]	0.43 [0.21; 0.87]	0.019	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Primary tumor site									
Oropharynx/Oral Cavity	243	19 (7.8)	Not reached [-; -]	215	23 (10.7)	Not reached [-; -]	0.57 [0.30; 1.07]	0.078	0.853
Larynx	76	8 (10.5)	Not reached [-; -]	61	8 (13.1)	37.4 [-; -]	0.39 [0.13; 1.14]	0.085	
Hypopharynx	26	5 (19.2)	Not reached [23.7; -]	24	4 (16.7)	Not reached [16.9; -]	0.62 [0.15; 2.62]	0.513	
PD-L1 status									
TPS < 50%	243	24 (9.9)	Not reached [-; -]	203	25 (12.3)	37.4 [-; -]	0.48 [0.26; 0.88]	0.018	0.990
TPS ≥ 50%	102	8 (7.8)	Not reached [-; -]	97	10 (10.3)	Not reached [-; -]	0.63 [0.24; 1.64]	0.342	
SOC: Investigations - PT[g]: Neutrophil count decreased									
Sex									
Male	270	14 (5.2)	Not reached [-; -]	237	33 (13.9)	Not reached [-; -]	0.23 [0.12; 0.46]	< 0.001	0.130
Female	75	4 (5.3)	Not reached [-; -]	63	3 (4.8)	Not reached [-; -]	1.02[h] [0.23; 4.64]	0.975[h]	
Age									
< 65	235	11 (4.7)	Not reached [-; -]	195	20 (10.3)	Not reached [-; -]	0.32 [0.15; 0.69]	0.004	0.857
≥ 65	110	7 (6.4)	Not reached [-; -]	105	16 (15.2)	Not reached [-; -]	0.29 [0.11; 0.77]	0.013	
Tumor Stage									
III	86	5 (5.8)	Not reached [-; -]	79	8 (10.1)	Not reached [-; -]	0.30[h] [0.08; 1.06]	0.062[h]	0.798
IVA	257	13 (5.1)	Not reached [-; -]	221	28 (12.7)	Not reached [-; -]	0.31 [0.15; 0.61]	< 0.001	
Region									
North America	62	2 (3.2)	Not reached [-; -]	40	2 (5.0)	Not reached [-; -]	0.67[h] [0.09; 4.77]	0.691[h]	0.913
European Union	134	6 (4.5)	Not reached [-; -]	127	15 (11.8)	Not reached [-; -]	0.24 [0.09; 0.69]	0.008	
Rest of World	149	10 (6.7)	Not reached [-; -]	133	19 (14.3)	Not reached [-; -]	0.30 [0.13; 0.68]	0.004	
Primary tumor site									
Oropharynx/Oral Cavity	243	8 (3.3)	Not reached [-; -]	215	25 (11.6)	Not reached [-; -]	0.25 [0.11; 0.55]	< 0.001	0.175
Larynx	76	7 (9.2)	Not reached [-; -]	61	5 (8.2)	Not reached [-; -]	0.62[h] [0.18; 2.11]	0.440[h]	
Hypopharynx	26	3 (11.5)	Not reached [-; -]	24	6 (25.0)	Not reached [16.1; -]	0.20 [0.04; 1.11]	0.066	
PD-L1 status									
TPS < 50%	243	11 (4.5)	Not reached [-; -]	203	27 (13.3)	Not reached [-; -]	0.23 [0.11; 0.49]	< 0.001	0.168
TPS ≥ 50%	102	7 (6.9)	Not reached [-; -]	97	9 (9.3)	Not reached [-; -]	0.50 [0.17; 1.44]	0.200	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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: Infections and infestations - PT[g]: Pneumonia									
Age									
< 65	235	5 (2.1)	Not reached [-; -]	195	11 (5.6)	Not reached [22.4; -]	0.12 [0.03; 0.51]	0.004	0.289
≥ 65	110	7 (6.4)	Not reached [-; -]	105	10 (9.5)	Not reached [22.1; -]	0.44 [0.15; 1.29]	0.134	
Tumor Stage									
III	86	3 (3.5)	Not reached [-; -]	79	4 (5.1)	22.1 [20.0; -]	0.31 [0.05; 1.75]	0.183	0.799
IVA	257	9 (3.5)	Not reached [-; -]	221	17 (7.7)	Not reached [23.7; -]	0.22 [0.08; 0.59]	0.003	
Region									
North America	62	3 (4.8)	Not reached [-; -]	40	1 (2.5)	Not reached [-; -]	1.12 [0.10; 12.41]	0.924	0.224
European Union	134	3 (2.2)	Not reached [-; -]	127	12 (9.4)	Not reached [22.4; -]	0.12 [0.03; 0.51]	0.004	
Rest of World	149	6 (4.0)	Not reached [-; -]	133	8 (6.0)	Not reached [22.1; -]	0.30 [0.08; 1.09]	0.068	
Primary tumor site									
Oropharynx/Oral Cavity	243	8 (3.3)	Not reached [-; -]	215	13 (6.0)	Not reached [23.7; -]	0.23 [0.08; 0.70]	0.009	0.696
Larynx	76	3 (3.9)	Not reached [-; -]	61	7 (11.5)	Not reached [22.1; -]	0.18 [0.04; 0.83]	0.028	
Hypopharynx	26	1 (3.8)	Not reached [-; -]	24	1 (4.2)	Not reached [-; -]	0.90[h] [0.06; 14.45]	0.943[h]	
SOC: Gastrointestinal disorders - PT[g]: Stomatitis									
Sex									
Male	270	33 (12.2)	Not reached [-; -]	237	30 (12.7)	Not reached [-; -]	0.58 [0.34; 0.98]	0.043	0.663
Female	75	11 (14.7)	Not reached [-; -]	63	12 (19.0)	Not reached [-; -]	0.36 [0.14; 0.94]	0.037	
Age									
< 65	235	34 (14.5)	Not reached [-; -]	195	25 (12.8)	Not reached [23.0; -]	0.58 [0.33; 1.02]	0.057	0.274
≥ 65	110	10 (9.1)	Not reached [-; -]	105	17 (16.2)	Not reached [-; -]	0.41 [0.18; 0.96]	0.039	
Tumor Stage									
III	86	16 (18.6)	Not reached [-; -]	79	11 (13.9)	Not reached [-; -]	0.76 [0.34; 1.70]	0.502	0.450
IVA	257	28 (10.9)	Not reached [-; -]	221	31 (14.0)	Not reached [-; -]	0.44 [0.25; 0.77]	0.004	
Region									
North America	62	9 (14.5)	Not reached [-; -]	40	8 (20.0)	Not reached [-; -]	0.44 [0.16; 1.22]	0.114	0.591
European Union	134	21 (15.7)	Not reached [-; -]	127	20 (15.7)	Not reached [23.0; -]	0.62 [0.32; 1.21]	0.160	
Rest of World	149	14 (9.4)	Not reached [-; -]	133	14 (10.5)	Not reached [-; -]	0.44 [0.20; 1.00]	0.050[i]	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Primary tumor site									
Oropharynx/Oral Cavity	243	42 (17.3)	Not reached [-; -]	215	40 (18.6)	Not reached [23.0; -]	0.55 [0.34; 0.87]	0.012	0.378
Larynx	76	0 (0.0)	Not reached [-; -]	61	1 (1.6)	Not reached [-; -]	0.27[h] [0.00; 24.31]	0.566[h]	
Hypopharynx	26	2 (7.7)	Not reached [-; -]	24	1 (4.2)	Not reached [-; -]	0.32[h] [0.01; 8.44]	0.492[h]	
PD-L1 status									
TPS < 50%	243	25 (10.3)	Not reached [-; -]	203	25 (12.3)	Not reached [-; -]	0.49 [0.27; 0.88]	0.018	0.469
TPS ≥ 50%	102	19 (18.6)	Not reached [-; -]	97	17 (17.5)	Not reached [23.0; -]	0.62 [0.30; 1.26]	0.182	
SOC: Investigations - PT[g]: Weight decreased									
Sex									
Male	270	35 (13.0)	Not reached [-; -]	237	23 (9.7)	Not reached [28.0; -]	0.38 [0.20; 0.75]	0.005	0.275
Female	75	14 (18.7)	88.1 [61.3; -]	63	5 (7.9)	27.6 [27.6; -]	0.27 [0.07; 1.06]	0.060	
Age									
< 65	235	39 (16.6)	88.1 [-; -]	195	20 (10.3)	30.4 [27.6; -]	0.36 [0.18; 0.73]	0.005	0.973
≥ 65	110	10 (9.1)	Not reached [-; -]	105	8 (7.6)	Not reached [28.0; -]	0.31 [0.09; 1.04]	0.057	
Tumor Stage									
III	86	16 (18.6)	Not reached [-; -]	79	8 (10.1)	28.0 [27.6; -]	0.55 [0.20; 1.55]	0.257	0.822
IVA	257	33 (12.8)	88.1 [-; -]	221	20 (9.0)	Not reached [-; -]	0.29 [0.14; 0.62]	0.001	
Region									
North America	62	11 (17.7)	88.1 [-; -]	40	4 (10.0)	28.0 [-; -]	0.29 [0.06; 1.32]	0.111	0.134
European Union	134	24 (17.9)	Not reached [-; -]	127	11 (8.7)	30.4 [27.6; -]	0.46 [0.18; 1.22]	0.118	
Rest of World	149	14 (9.4)	Not reached [-; -]	133	13 (9.8)	Not reached [21.1; -]	0.28 [0.11; 0.72]	0.008	
Primary tumor site									
Oropharynx/Oral Cavity	243	42 (17.3)	88.1 [-; -]	215	25 (11.6)	28.0 [27.6; -]	0.32 [0.16; 0.63]	< 0.001	0.201
Larynx	76	4 (5.3)	Not reached [-; -]	61	3 (4.9)	Not reached [-; -]	0.57 [0.11; 3.05]	0.515	
Hypopharynx	26	3 (11.5)	Not reached [-; -]	24	0 (0.0)	Not reached [-; -]	0.15[h] [0.00; 13.68]	0.405[h]	
PD-L1 status									
TPS < 50%	243	35 (14.4)	Not reached [-; -]	203	20 (9.9)	28.0 [27.6; -]	0.43 [0.21; 0.86]	0.017	0.909
TPS ≥ 50%	102	14 (13.7)	88.1 [-; -]	97	8 (8.2)	30.4 [-; -]	0.19 [0.06; 0.69]	0.011	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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: Investigations - PT[g]: White blood cell count decreased									
Sex									
Male	270	14 (5.2)	Not reached [-; -]	237	23 (9.7)	Not reached [-; -]	0.37 [0.19; 0.75]	0.006	0.977
Female	75	3 (4.0)	Not reached [-; -]	63	5 (7.9)	Not reached [-; -]	0.37 [0.08; 1.67]	0.196	
Age									
< 65	235	11 (4.7)	Not reached [-; -]	195	19 (9.7)	Not reached [-; -]	0.32 [0.15; 0.70]	0.004	0.444
≥ 65	110	6 (5.5)	Not reached [-; -]	105	9 (8.6)	Not reached [-; -]	0.53 [0.18; 1.57]	0.251	
Tumor Stage									
III	86	5 (5.8)	Not reached [-; -]	79	8 (10.1)	Not reached [-; -]	0.28 [0.08; 1.04]	0.057	0.867
IVA	257	12 (4.7)	Not reached [-; -]	221	20 (9.0)	Not reached [-; -]	0.42 [0.20; 0.88]	0.021	
Region									
North America	62	1 (1.6)	Not reached [-; -]	40	1 (2.5)	Not reached [-; -]	0.45[h] [0.03; 7.47]	0.575[h]	0.137
European Union	134	9 (6.7)	Not reached [-; -]	127	9 (7.1)	Not reached [-; -]	0.73 [0.28; 1.94]	0.532	
Rest of World	149	7 (4.7)	Not reached [-; -]	133	18 (13.5)	Not reached [-; -]	0.23 [0.09; 0.58]	0.002	
Primary tumor site									
Oropharynx/Oral Cavity	243	10 (4.1)	Not reached [-; -]	215	16 (7.4)	Not reached [-; -]	0.42 [0.18; 0.96]	0.040	0.135
Larynx	76	6 (7.9)	Not reached [-; -]	61	5 (8.2)	Not reached [-; -]	0.63 [0.18; 2.16]	0.464	
Hypopharynx	26	1 (3.8)	Not reached [-; -]	24	7 (29.2)	Not reached [16.1; -]	0.10[h] [0.01; 0.77]	0.027[h]	
PD-L1 status									
TPS < 50%	243	11 (4.5)	Not reached [-; -]	203	21 (10.3)	Not reached [-; -]	0.32 [0.15; 0.68]	0.003	0.293
TPS ≥ 50%	102	6 (5.9)	Not reached [-; -]	97	7 (7.2)	Not reached [-; -]	0.57[h] [0.18; 1.83]	0.349[h]	
SOC: Injury, poisoning and procedural complications - PT[g]: Radiation skin injury									
Sex									
Male	270	10 (3.7)	Not reached [-; -]	237	12 (5.1)	Not reached [-; -]	0.39 [0.16; 0.98]	0.046	0.781
Female	75	5 (6.7)	Not reached [-; -]	63	5 (7.9)	Not reached [-; -]	0.58[h] [0.15; 2.21]	0.425[h]	
Age									
< 65	235	11 (4.7)	Not reached [-; -]	195	8 (4.1)	Not reached [-; -]	0.56 [0.21; 1.52]	0.257	0.275
≥ 65	110	4 (3.6)	Not reached [-; -]	105	9 (8.6)	Not reached [-; -]	0.33 [0.09; 1.15]	0.082	

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC		
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]
Tumor Stage									
III	86	4 (4.7)	Not reached [-; -]	79	3 (3.8)	Not reached [-; -]	0.62[h] [0.12; 3.14]	0.567[h]	0.663
IVA	257	11 (4.3)	Not reached [-; -]	221	14 (6.3)	Not reached [-; -]	0.41 [0.17; 0.96]	0.040	
Region									
North America	62	1 (1.6)	Not reached [-; -]	40	2 (5.0)	Not reached [18.3; -]	0.20 [0.02; 2.53]	0.215	0.074
European Union	134	8 (6.0)	Not reached [-; -]	127	4 (3.1)	Not reached [-; -]	1.08[h] [0.30; 3.94]	0.905[h]	
Rest of World	149	6 (4.0)	Not reached [-; -]	133	11 (8.3)	Not reached [-; -]	0.29[h] [0.10; 0.82]	0.021[h]	
Primary tumor site									
Oropharynx/Oral Cavity	243	12 (4.9)	Not reached [-; -]	215	12 (5.6)	Not reached [-; -]	0.47 [0.20; 1.15]	0.098	0.612
Larynx	76	2 (2.6)	Not reached [-; -]	61	4 (6.6)	Not reached [-; -]	0.36[h] [0.07; 1.93]	0.232[h]	
Hypopharynx	26	1 (3.8)	Not reached [-; -]	24	1 (4.2)	Not reached [-; -]	0.50[h] [0.03; 9.68]	0.646[h]	
PD-L1 status									
TPS < 50%	243	11 (4.5)	Not reached [-; -]	203	8 (3.9)	Not reached [-; -]	0.60 [0.22; 1.63]	0.321	0.196
TPS ≥ 50%	102	4 (3.9)	Not reached [-; -]	97	9 (9.3)	Not reached [-; -]	0.31[h] [0.09; 1.07]	0.063[h]	

a: Database Cutoff Date: 25JUL2024

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

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

d: Based on Cox regression model with treatment as a covariate. Ties are handled using Efron's method

e: Two-sided p-value using Wald test

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 specific adverse event appears on this report only if its incidence ≥ 5% or (incidence ≥ 1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05, and the interaction p-value is greater than or equal to 0.05 or not calculated

h: Obtained via the Firth penalized likelihood approach to Cox regression model with treatment as a covariate. Ties are handled using Breslow's method

i: Unrounded p-value < 0.050

CI: Confidence Interval; CPS: Combined Positive Score; CTCAE: Common Terminology Criteria for Adverse Events; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup category and at least 10 participants with events in one of the subgroup categories necessary); PD-L1: Programmed Cell Death - Ligand 1; PT: Preferred Term; SOC: System Organ Class; SoC: Standard of Care; TPS: Tumor Proportion Score

Anhang 4-G6: Ergebnisse der ergänzenden Morbiditätsendpunkte Fernmetastasenfreies Überleben, Major Pathological Response gemäß BIPR und Pathologische Komplettremission

Im Folgenden werden ergänzend die Ergebnisse der Morbiditätsendpunkte Fernmetastasenfreies Überleben, Major Pathological Response (mPR) gemäß BIPR und Pathologische Komplettremission dargestellt. Da die Ergebnisse für die vorliegende Nutzenbewertung nicht zur Ableitung des Zusatznutzens herangezogen werden, werden keine Subgruppenanalysen dargestellt.

Alle Ergebnisse beziehen sich auf das zulassungsbegründende Database Cutoff Date (25. Juli 2024).

Fernmetastasenfreies Überleben

Tabelle 4G-51: Ergebnisse für den Endpunkt Fernmetastasenfreies Überleben aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	Pembrolizumab			SoC			Pembrolizumab vs. SoC	
	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]
Distant Metastases Free Survival (IRC Primary Censoring Rule)	347	119 (34.3)	59.7 [40.5; -]	335	145 (43.3)	32.7 [22.1; 50.1]	0.68 [0.53; 0.87]	0.002

a: Database Cutoff Date: 25JUL2024

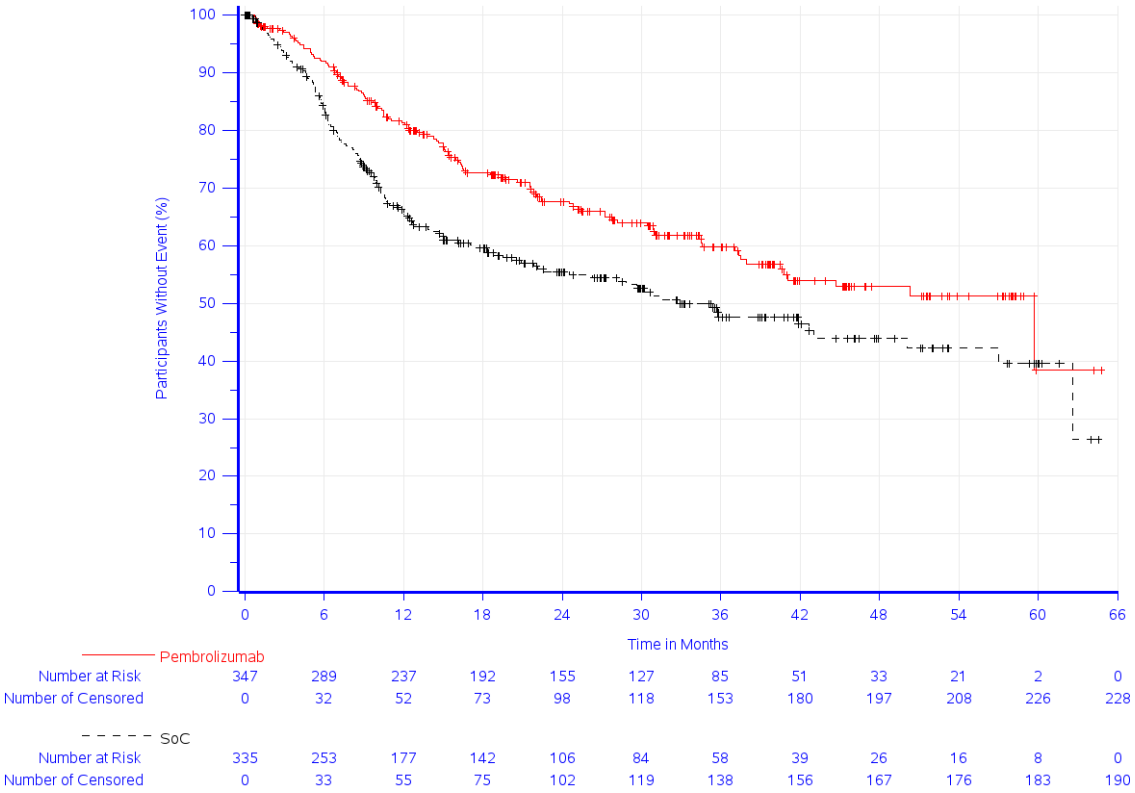
b: Number of participants: intention-to-treat population with CPS ≥ 1

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

d: Based on Cox regression model with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx) and tumor stage (III vs. IVA). Ties are handled using Efron's method

e: Two-sided p-value using Wald test

CI: Confidence Interval; CPS: Combined Positive Score; IRC: Independent Review Committee; SoC: Standard of Care



Study: KEYNOTE 689 (Database Cutoff Date: 25JUL2024)
Distant Metastases Free Survival (IRC Primary Censoring Rule)

Abbildung 4G-19: Kaplan-Meier-Kurve für den Endpunkt Fernmetastasenfreies Überleben gemäß BICR der Studie KEYNOTE 689

Major Pathological Response

Tabelle 4G-52: Ergebnisse für den Endpunkt Major Pathological Response aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	Pembrolizumab		SoC		Pembrolizumab vs. SoC		
	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Difference in %[e] [95 %-CI]
BIPR Major Pathological Response Indicator	347	34 (9.8)	335	0 (0.0)	7.83 [3.93; 15.61]	< 0.001	9.75 [7.00; 13.34]

a: Database Cutoff Date: 25JUL2024
b: Number of participants: intention-to-treat population with CPS ≥ 1
c: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is ≤ 1 % or ≥ 99 % in at least one cell of the stratum defined by stratification factors primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx) and tumor stage (III vs. IVA)
d: Two-sided p-value based on Wald test
e: Miettinen and Nurminen method stratified by primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx) and tumor stage (III vs. IVA)
BIPR: Blinded Independent Pathologist Review; CI: Confidence Interval; CPS: Combined Positive Score; SoC: Standard of Care

Pathologische Komplettremission

Tabelle 4G-53: Ergebnisse für den Endpunkt Pathologische Komplettremission aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	Pembrolizumab		SoC		Pembrolizumab vs. SoC		
	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Risk Ratio/Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Difference in %[e] [95 %-CI]
BIPR Pathologic Complete Response Indicator	347	11 (3.2)	335	0 (0.0)	7.16 [2.18; 23.55]	0.001	3.14 [1.59; 5.55]

a: Database Cutoff Date: 25JUL2024

b: Number of participants: intention-to-treat population with CPS ≥ 1

c: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is ≤ 1 % or ≥ 99 % in at least one cell of the stratum defined by stratification factors primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx) and tumor stage (III vs. IVA)

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

e: Miettinen and Nurminen method stratified by primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx) and tumor stage (III vs. IVA)

BIPR: Blinded Independent Pathologist Review; CI: Confidence Interval; CPS: Combined Positive Score; SoC: Standard of Care

Anhang 4-G7: Ergebnisse zur post-adjuvanten CRT/RT Woche 25 für EORTC QLQ-C30, EORTC QLQ-H&N35 und EQ-5D VAS

Im Folgenden werden ergänzend die Ergebnisse zur post-adjuvanten CRT/RT Woche 25 für den EORTC QLQ-C30, EORTC QLQ-H&N35 und EQ-5D VAS dargestellt. Da die Ergebnisse für die vorliegende Nutzenbewertung nicht zur Ableitung des Zusatznutzens herangezogen werden, werden keine Subgruppenanalysen dargestellt.

Alle Ergebnisse beziehen sich auf das zulassungsbegründende Database Cutoff Date (25. Juli 2024).

EORTC QLQ-C30 Globaler Gesundheitsstatus und Funktionsskalen

Tabelle 4G-54: Ergebnisse für den Endpunkt Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30) zur post-adjuvanten CRT/RT Woche 25 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	Baseline		Post-Adjuvant CRT/RT Week 25		Change from Baseline to Post-Adjuvant CRT/RT Week 25		Pembrolizumab vs. SoC		
							Mean Difference at Post-Adjuvant CRT/RT Week 25		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 25
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]
EORTC QLQ-C30 Global Health Status/QoL									
Global Health Status/QoL									
Pembrolizumab	324	63.73 (20.36)	170	68.97 (18.42)	340	3.62 [0.90; 6.34]	-1.41	0.437	-
SoC	265	62.52 (21.69)	162	70.32 (18.81)	291	5.03 [2.23; 7.83]	[-4.96; 2.15]		-
EORTC QLQ-C30 Functional Scales									
Emotional functioning									
Pembrolizumab	324	74.13 (21.51)	170	79.61 (20.87)	340	3.54 [0.66; 6.41]	2.80	0.162	-
SoC	265	71.35 (22.27)	162	75.00 (22.12)	291	0.74 [-2.23; 3.70]	[-1.13; 6.73]		-
Cognitive functioning									
Pembrolizumab	324	87.91 (19.38)	170	86.57 (16.65)	340	-2.49 [-4.92; -0.05]	1.19	0.483	-
SoC	265	87.30 (18.24)	162	85.49 (18.59)	291	-3.68 [-6.21; -1.14]	[-2.15; 4.53]		-
Physical Functioning									
Pembrolizumab	324	86.38 (17.24)	170	83.14 (16.20)	340	-7.42 [-9.71; -5.13]	0.65	0.688	-
SoC	265	86.42 (17.67)	162	81.65 (17.55)	291	-8.07 [-10.46; -5.68]	[-2.54; 3.84]		-

Study: KEYNOTE 689[a]	Baseline		Post-Adjuvant CRT/RT Week 25		Change from Baseline to Post-Adjuvant CRT/RT Week 25		Pembrolizumab vs. SoC		
							Mean Difference at Post-Adjuvant CRT/RT Week 25		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 25
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]
Role functioning									
Pembrolizumab	324	80.56 (25.41)	170	76.76 (23.80)	340	-7.47 [-11.03; -3.92]	0.17	0.944	-
SoC	265	82.52 (25.34)	162	76.75 (24.46)	291	-7.64 [-11.30; -3.99]	[-4.59; 4.93]		-
Social functioning									
Pembrolizumab	324	80.81 (24.35)	170	79.22 (23.97)	340	-5.96 [-9.44; -2.48]	-1.88	0.434	-
SoC	265	79.62 (25.04)	162	78.19 (24.10)	291	-4.08 [-7.68; -0.48]	[-6.59; 2.84]		-

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction, and stratification factors by primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumor Stage: III vs. IVA and PD-L1 status (TPS ≥ 50% vs. TPS<50%)

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

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; QoL: Quality of Life; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score

EORTC QLQ-C30 Symptomskalen, EORTC QLQ-H&N35 und EQ-5D VAS

Tabelle 4G-55: Ergebnisse für die Endpunkte Krankheitssymptomatik (EORTC QLQ-C30 und EORTC QLQ-H&N35) und Gesundheitszustand (EQ-5D VAS) zur post-adjuvanten CRT/RT Woche 25 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 689[a]	Baseline		Post-Adjuvant CRT/RT Week 25		Change from Baseline to Post-Adjuvant CRT/RT Week 25		Pembrolizumab vs. SoC		
							Mean Difference at Post-Adjuvant CRT/RT Week 25		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 25
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]
EORTC QLQ-C30 Symptom Scales									
Fatigue									
Pembrolizumab	324	25.93 (22.48)	170	27.12 (19.68)	340	4.22 [1.15; 7.29]	-0.38	0.854	-
SoC	265	27.71 (25.97)	162	29.42 (23.28)	291	4.61 [1.41; 7.81]	[-4.49; 3.72]		-

Study: KEYNOTE 689[a]	Baseline		Post-Adjuvant CRT/RT Week 25		Change from Baseline to Post-Adjuvant CRT/RT Week 25		Pembrolizumab vs. SoC		
							Mean Difference at Post-Adjuvant CRT/RT Week 25		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 25
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][c]
Nausea and vomiting									
Pembrolizumab	324	4.68 (12.42)	170	5.49 (13.17)	340	2.48 [0.54; 4.42]	2.24	0.091	-
SoC	265	4.72 (11.78)	162	4.42 (12.29)	291	0.23 [-1.79; 2.25]	[-0.36; 4.85]		-
Pain									
Pembrolizumab	324	32.46 (29.15)	170	19.61 (21.63)	340	-10.63 [-14.08; -7.18]	-1.72	0.445	-
SoC	265	33.71 (28.20)	162	20.78 (22.14)	291	-8.91 [-12.45; -5.36]	[-6.15; 2.70]		-
Dyspnea									
Pembrolizumab	324	14.61 (23.44)	170	13.73 (18.34)	340	0.81 [-2.36; 3.99]	-2.98	0.161	-
SoC	265	13.46 (24.08)	162	17.08 (24.15)	291	3.79 [0.53; 7.06]	[-7.16; 1.20]		-
Insomnia									
Pembrolizumab	324	33.44 (31.64)	170	23.92 (28.37)	340	-7.46 [-11.80; -3.11]	-2.26	0.433	-
SoC	265	34.21 (32.10)	162	27.16 (29.54)	291	-5.20 [-9.68; -0.71]	[-7.92; 3.40]		-
Appetite loss									
Pembrolizumab	324	19.96 (26.87)	170	18.82 (23.75)	340	0.17 [-3.77; 4.12]	2.22	0.388	-
SoC	265	25.28 (32.08)	162	19.34 (25.40)	291	-2.04 [-6.07; 1.99]	[-2.83; 7.26]		-
Constipation									
Pembrolizumab	324	15.53 (26.53)	170	10.98 (19.11)	340	-2.19 [-5.63; 1.25]	-0.12	0.956	-
SoC	265	15.85 (24.28)	162	12.76 (23.24)	291	-2.07 [-5.63; 1.49]	[-4.51; 4.27]		-
Diarrhea									
Pembrolizumab	324	7.20 (16.88)	170	6.27 (15.38)	340	0.96 [-1.39; 3.32]	1.46	0.348	-
SoC	265	5.16 (14.89)	162	5.35 (13.86)	291	-0.50 [-2.91; 1.92]	[-1.59; 4.51]		-
EORTC QLQ-H&N35 Symptom Scales									
Pain									
Pembrolizumab	324	32.74 (26.26)	169	19.43 (19.35)	340	-11.79 [-14.91; -8.67]	-2.22	0.281	-
SoC	265	35.31 (26.50)	161	22.00 (22.37)	291	-9.57 [-12.80; -6.35]	[-6.25; 1.82]		-
Swallowing									
Pembrolizumab	324	25.33 (27.85)	169	25.25 (24.20)	340	4.20 [0.59; 7.82]	-2.52	0.310	-
SoC	265	26.26 (27.15)	161	28.88 (27.24)	291	6.72 [3.00; 10.45]	[-7.39; 2.35]		-

Study: KEYNOTE 689[a]	Baseline		Post-Adjuvant CRT/RT Week 25		Change from Baseline to Post-Adjuvant CRT/RT Week 25		Pembrolizumab vs. SoC		
							Mean Difference at Post-Adjuvant CRT/RT Week 25		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 25
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]
Senses Problems									
Pembrolizumab	324	10.24 (18.75)	169	26.63 (28.07)	340	18.32 [14.51; 22.13]	1.52	0.571	-
SoC	265	9.31 (17.51)	161	23.71 (25.04)	291	16.80 [12.91; 20.69]	[-3.75; 6.80]		-
Speech Problems									
Pembrolizumab	324	25.62 (27.85)	169	30.90 (25.18)	340	10.01 [6.64; 13.39]	0.74	0.752	-
SoC	265	25.20 (27.27)	161	32.09 (28.16)	291	9.27 [5.74; 12.80]	[-3.88; 5.37]		-
Trouble with Social Eating									
Pembrolizumab	324	28.25 (30.36)	169	31.25 (27.95)	340	7.13 [3.14; 11.12]	-2.94	0.283	-
SoC	265	26.59 (27.96)	161	34.73 (29.13)	291	10.07 [5.96; 14.18]	[-8.31; 2.44]		-
Trouble with Social Contact									
Pembrolizumab	324	14.69 (21.95)	169	19.41 (24.34)	340	8.52 [5.48; 11.56]	0.42	0.847	-
SoC	265	15.09 (21.69)	161	20.04 (22.94)	291	8.10 [4.97; 11.24]	[-3.85; 4.69]		-
Less Sexuality									
Pembrolizumab	321	23.36 (33.14)	167	27.25 (33.05)	340	8.10 [3.72; 12.48]	4.47	0.141	-
SoC	264	25.63 (34.02)	159	25.37 (31.09)	290	3.63 [-0.88; 8.13]	[-1.48; 10.42]		-
Teeth									
Pembrolizumab	324	27.06 (36.04)	169	23.08 (30.43)	340	-3.02 [-8.12; 2.08]	-2.82	0.397	-
SoC	265	24.28 (32.72)	161	24.22 (32.91)	291	-0.20 [-5.41; 5.01]	[-9.37; 3.73]		-
Opening Mouth									
Pembrolizumab	324	24.18 (32.68)	169	29.39 (34.08)	340	8.03 [3.41; 12.65]	-2.88	0.362	-
SoC	265	27.04 (33.87)	161	33.13 (30.62)	291	10.90 [6.16; 15.65]	[-9.07; 3.31]		-
Dry Mouth									
Pembrolizumab	324	23.87 (28.73)	169	43.00 (34.00)	340	20.27 [15.24; 25.31]	-0.74	0.827	-
SoC	265	21.51 (29.35)	161	42.44 (33.12)	291	21.01 [15.88; 26.15]	[-7.38; 5.90]		-

Study: KEYNOTE 689[a]	Baseline		Post-Adjuvant CRT/RT Week 25		Change from Baseline to Post-Adjuvant CRT/RT Week 25		Pembrolizumab vs. SoC		
							Mean Difference at Post-Adjuvant CRT/RT Week 25		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 25
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][c]
Sticky Saliva									
Pembrolizumab	324	28.81 (34.00)	169	36.69 (31.84)	340	10.86 [5.92; 15.81]	0.93	0.773	-
SoC	265	27.80 (33.50)	161	36.65 (29.86)	291	9.93 [4.89; 14.98]	[-5.38; 7.24]		-
Coughing									
Pembrolizumab	324	21.50 (25.03)	169	23.67 (25.30)	340	2.75 [-1.04; 6.54]	1.45	0.567	-
SoC	265	24.65 (27.45)	161	22.77 (22.49)	291	1.30 [-2.60; 5.20]	[-3.52; 6.42]		-
Felt Ill									
Pembrolizumab	324	22.63 (28.41)	169	20.12 (23.07)	340	-1.72 [-5.28; 1.83]	2.15	0.352	-
SoC	265	26.92 (31.60)	161	18.63 (22.31)	291	-3.87 [-7.51; -0.23]	[-2.38; 6.67]		-
Pain Killers									
Pembrolizumab	324	22.33 (15.70)	169	10.85 (15.66)	340	-10.08 [-12.58; -7.58]	0.61	0.716	-
SoC	265	23.14 (15.39)	161	10.97 (15.71)	291	-10.69 [-13.25; -8.14]	[-2.70; 3.92]		-
Nutritional Supplements									
Pembrolizumab	324	8.44 (14.52)	169	9.27 (14.98)	340	1.62 [-0.68; 3.93]	-0.07	0.963	-
SoC	265	9.31 (14.98)	161	9.94 (15.30)	291	1.69 [-0.67; 4.06]	[-3.14; 2.99]		-
Feeding Tube									
Pembrolizumab	324	2.47 (8.74)	169	7.10 (13.69)	340	7.15 [5.15; 9.16]	1.22	0.390	-
SoC	265	2.26 (8.40)	161	7.25 (13.79)	291	5.94 [3.87; 8.00]	[-1.56; 4.00]		-
Weight Loss									
Pembrolizumab	324	15.43 (16.65)	169	8.88 (14.78)	340	-5.83 [-8.33; -3.33]	2.01	0.196	-
SoC	265	15.47 (16.66)	161	7.45 (13.93)	291	-7.84 [-10.40; -5.28]	[-1.04; 5.06]		-
Weight Gain									
Pembrolizumab	324	4.22 (11.10)	169	12.82 (16.27)	340	8.32 [5.75; 10.89]	0.28	0.875	-
SoC	265	4.53 (11.44)	161	12.42 (16.17)	291	8.04 [5.42; 10.66]	[-3.19; 3.75]		-
EQ-5D VAS									
EQ5D02-EQ VAS Score									
Pembrolizumab	325	71.78 (19.94)	170	75.12 (16.54)	340	0.65 [-1.72; 3.03]	-0.79	0.613	-
SoC	265	70.10 (20.06)	164	73.99 (16.25)	290	1.44 [-1.02; 3.91]	[-3.86; 2.28]		-

Study: KEYNOTE 689[a]	Baseline		Post-Adjuvant CRT/RT Week 25		Change from Baseline to Post-Adjuvant CRT/RT Week 25		Pembrolizumab vs. SoC		
							Mean Difference at Post-Adjuvant CRT/RT Week 25		Standardized Mean Difference at Post-Adjuvant CRT/RT Week 25
	N[b]	Mean (SD)	N[b]	Mean (SD)	N[c]	Mean [95 %-CI][d]	[95 %-CI][d]	p-Value	[95 %-CI][e]

a: Database Cutoff Date: 25JUL2024

b: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available at respective timepoint

c: Number of participants in PRO full-analysis-set population with CPS ≥ 1 with data available for analysis

d: Based on constrained longitudinal data analysis model with the PRO scores as the response variable with covariates for treatment by study visit interaction, and stratification factors by primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumor Stage: III vs. IVA and PD-L1 status (TPS ≥ 50% vs. TPS<50%)

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

CI: Confidence Interval; CPS: Combined Positive Score; CRT: Chemoradiotherapy; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Head and Neck Cancer Module) - Core 35 items; EQ-5D: European Quality of Life 5 Dimensions; PD-L1: Programmed Cell Death - Ligand 1; PRO: Patient Reported Outcome; RT: Radiotherapy; SD: Standard Deviation; SoC: Standard of Care; TPS: Tumor Proportion Score; VAS: Visual Analog Scale