Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD Sharp & Dohme GmbH

Modul 4A

Anhang 4-G: Weitere Ergebnisse

Neoadjuvante und anschließend adjuvante Behandlung des resezierbaren NSCLC mit hohem Rezidivrisiko

Stand: 19.04.2024

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Anhang 4-G1: Folgetherapien nach Fortschreiten bzw. Wiederauftreten der Erkrankung

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.1.1 die Ergebnisse der Folgetherapien bei Patient:innen nach Fortschreiten bzw. Wiederauftreten der Erkankung dargestellt.

Tabelle 4G-1: Patient:innen mit mindestens einer Folgetherapie nach lokoregionalem Progress / Rezidiv oder Fernmetastasierung

Study: KEYNOTE 671[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab (N^c = 123) n (%)**	**Placebo + Chemotherapy[b] / Placebo (N^c = 206) n (%)**
1st subsequent treatment	99 (80.5)	180 (87.4)
After LP/LR	39 (39.4)	72 (40.0)
After DM	60 (60.6)	108 (60.0)

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

c: Number of participants: intention-to-treat population, participants with LP/LR or DM

Due to an unknown LP/LR vs. DM assessment, a total of 3 participants with an LP/LR or DM are excluded

DM: Distant Metastasis; LP/LR: Locoregional Progression or Locoregional Recurrence

Tabelle 4G-2: Art der ersten Folgetherapie nach lokoregionalem Progress / Rezidiv

Study: KEYNOTE 671[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab (N^c = 39)**	**Placebo + Chemotherapy[b] / Placebo (N^c = 72)**
Systemic therapy[d]	28 (71.8)	60 (83.3)
ICI	4 (10.3)	22 (30.6)
Non-ICI	24 (61.5)	38 (52.8)
Radiation	9 (23.1)	12 (16.7)
Surgery	2 (5.1)	0 (0.0)

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

c: Number of participants: intention-to-treat population, participants with LP/LR who received subsequent therapy after LP/LR

d: Systemic therapy includes chemoradiation in which chemotherapy and radiotherapy were given concurrently (chemotherapy and radiation therapy received within 7 days, regardless of whether the first was chemotherapy or radiation) or sequentially (chemotherapy received as first therapy and radiation after 7 days but within 120 days).

ICI: Immune Checkpoint Inhibitor; LP/LR: Locoregional Progression or Locoregional Recurrence

Tabelle 4G-3: Art der ersten Folgetherapie nach Fernmetastasierung

Study: KEYNOTE 671[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab (N^c = 60)**	**Placebo + Chemotherapy[b] / Placebo (N^c = 108)**
Systemic therapy[d]	48 (80.0)	84 (77.8)
ICI	12 (20.0)	46 (42.6)
Non-ICI	36 (60.0)	38 (35.2)
Radiation	9 (15.0)	16 (14.8)
Surgery	3 (5.0)	8 (7.4)

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

c: Number of participants: intention-to-treat population, participants with DM who received subsequent treatment after DM

d: Systemic therapy includes chemoradiation in which chemotherapy and radiotherapy were given concurrently (chemotherapy and radiation therapy received within 7 days, regardless of whether the first was chemotherapy or radiation) or sequentially (chemotherapy received as first therapy and radiation after 7 days but within 120 days).

DM: Distant Metastasis; ICI: Immune Checkpoint Inhibitor

Anhang 4-G2: Ereignisfreies Überleben (BICR)

Im Folgenden wird ergänzend zu Abschnitt 4.3.1.3.1.2.1 der Endpunkt Ereignisfreies Überleben (BICR) dargestellt. Die Ereignisse im Rahmen dieses Endpunkts wurden durch das verblindete, unabhängige, zentrale Review-Komitee (BICR) erfasst. Innerhalb dieser Operationalisierung wurden sowohl Progresse (neoadjuvant) als auch Rezidive (adjuvant) als „Progressive Disease“ erfasst.

Tabelle 4G-4: Ergebnisse für den Endpunkt Ereignisfreies Überleben (BICR) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[b] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo	
	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]
Event-Free Survival (BICR Primary Censoring Rule)	397	167 (42.1)	47.6 [32.5; -]	400	234 (58.5)	18.4 [14.8; 22.8]	0.62 [0.51; 0.76]	< 0.001

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

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

e: Based on Cox regression model with treatment as a covariate stratified by Stage (II vs. III), TPS (≥ 50% vs. < 50%), Histology (Squamous vs. Non-squamous) and Region (East Asia vs. non-East Asia), where Region is collapsed for Stage II TPS ≥ 50% Non-squamous and Stage II TPS ≥ 50% Squamous

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

BICR: Blinded Independent Central Review; CI: Confidence Interval; TPS: Tumor Proportion Score

Tabelle 4G-5: Übersicht der Einzelkomponenten zum Endpunkt Ereignisfreies Überleben (BICR) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]	Participants with Event n (%)	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab (N[c] = 397)	Placebo + Chemotherapy[b] / Placebo (N[c] = 400)
Type of First Event in Event-Free Survival Based on BICR Assessment (Primary Censoring Rule), n (%)		
No event	230 (57.9)	166 (41.5)
Event	167 (42.1)	234 (58.5)
Death	62 (15.6)	53 (13.3)
Local Progression Preventing Surgery	1 (0.3)	5 (1.3)
Progressive Disease[d]	99 (24.9)	163 (40.8)
Unresectable	5 (1.3)	13 (3.3)

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Radiographic disease progression per RECIST 1.1

BICR: Blinded Independent Central Review; RECIST: Response Evaluation Criteria In Solid Tumors

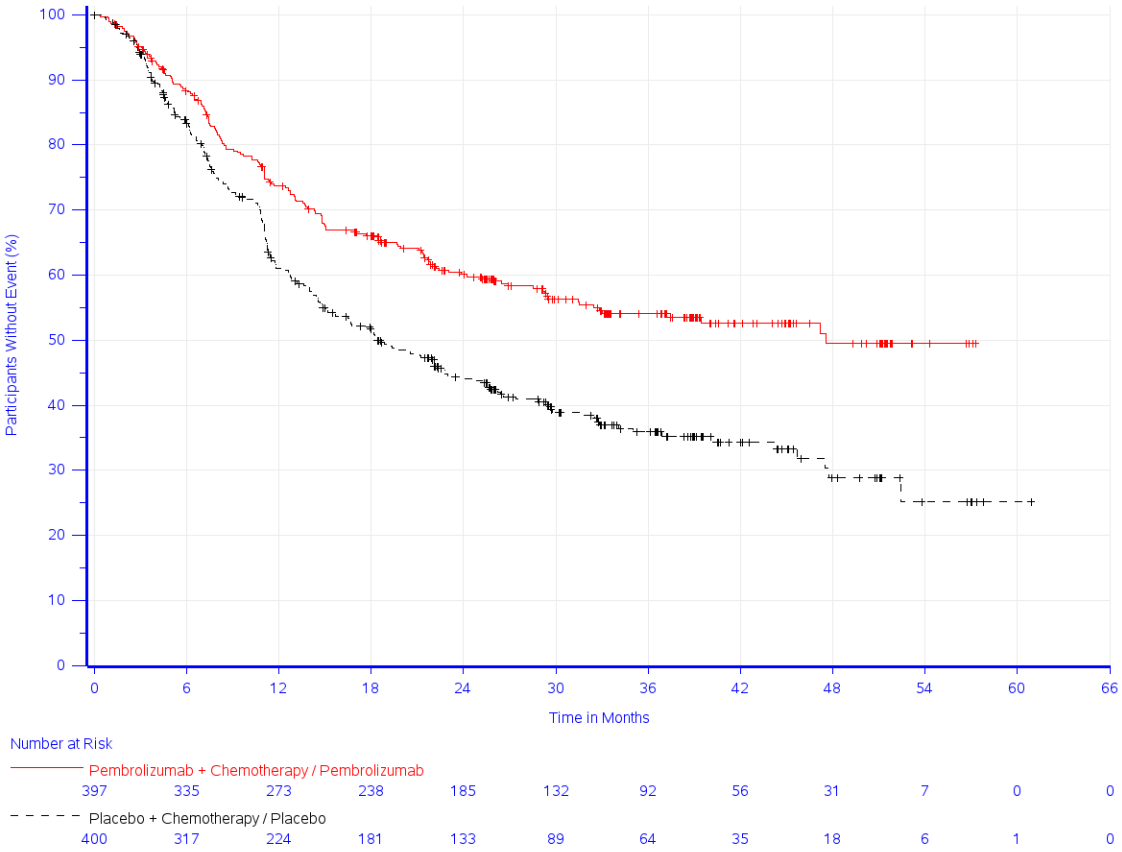

Abbildung 4G-1: Kaplan-Meier-Kurve für den Endpunkt Ereignisfreies Überleben (BICR) der Studie KEYNOTE 671

Anhang 4-G3: Rücklaufquoten des EORTC QLQ-C30, EORTC QLQ-LC13 und EQ-5D VAS

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.2.4. bzw. Abschnitt 4.3.1.3.1.3.1 die Rücklaufquoten des EORTC QLQ-C30, des EORTC QLQ-LC13 und der EQ-5D VAS dargestellt.

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

Tabelle 4G-6: Gründe für das Fehlen von Werten im EORTC QLQ-C30

		Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
Treatment Visit	Category	n	(%)	n	(%)
BASELINE	**Expected to Complete Questionnaires**	**395**	**(100.0)**	**398**	**(100.0)**
	Completed	388	(98.2)	391	(98.2)
	Compliance (% in those expected to complete questionnaires)	388	(98.2)	391	(98.2)
	Not completed	7	(1.8)	7	(1.8)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	2	(0.5)	1	(0.3)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	0	(0.0)
	Other	4	(1.0)	3	(0.8)
	With visit, no record	0	(0.0)	3	(0.8)
	Missing by Design	**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 death	0	(0.0)	0	(0.0)
	Discontinued due to local progression preventing surgery	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
BASELINE	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 protocol violation	0	(0.0)	0	(0.0)
	Discontinued due to relapse/recurrence	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by participant	0	(0.0)	0	(0.0)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Neoadjuvant Week 11	**Expected to Complete Questionnaires**	**386**	**(97.7)**	**392**	**(98.5)**
	Completed	344	(87.1)	354	(88.9)
	Compliance (% in those expected to complete questionnaires)	344	(89.1)	354	(90.3)
	Not completed	42	(10.6)	38	(9.5)
	Participant did not complete due to disease under study	2	(0.5)	0	(0.0)
	Not completed due to site staff error	15	(3.8)	9	(2.3)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	1	(0.3)	0	(0.0)
	Participant lost to follow-up/unable to contact	1	(0.3)	1	(0.3)
	Participant did not complete due to side effects of treatment	2	(0.5)	3	(0.8)
	Participant refused for other reasons	7	(1.8)	6	(1.5)
	Other	10	(2.5)	15	(3.8)
	With visit, no record	4	(1.0)	4	(1.0)
	Missing by Design	**9**	**(2.3)**	**6**	**(1.5)**
	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 death	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Neoadjuvant Week 11	Discontinued due to local progression preventing surgery	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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 protocol violation	0	(0.0)	0	(0.0)
	Discontinued due to relapse/recurrence	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by participant	0	(0.0)	0	(0.0)
	Translation not available in participants language	1	(0.3)	0	(0.0)
	Participant died	7	(1.8)	6	(1.5)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Adjuvant Week 1	**Expected to Complete Questionnaires**	**333**	**(84.3)**	**329**	**(82.7)**
	Completed	304	(77.0)	304	(76.4)
	Compliance (% in those expected to complete questionnaires)	304	(91.3)	304	(92.4)
	Not completed	29	(7.3)	25	(6.3)
	Participant did not complete due to disease under study	0	(0.0)	2	(0.5)
	Not completed due to site staff error	11	(2.8)	6	(1.5)
	Participant in hospital or hospice	0	(0.0)	1	(0.3)
	Participant was physically unable to complete	1	(0.3)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	4	(1.0)	3	(0.8)
	Other	8	(2.0)	6	(1.5)
	With visit, no record	5	(1.3)	7	(1.8)
	Missing by Design	**62**	**(15.7)**	**69**	**(17.3)**
	Discontinued due to adverse event	4	(1.0)	3	(0.8)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 1	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to death	12	(3.0)	8	(2.0)
	Discontinued due to local progression preventing surgery	1	(0.3)	3	(0.8)
	Discontinued due to non-study anti-cancer therapy	1	(0.3)	4	(1.0)
	Discontinued due to physician decision	0	(0.0)	1	(0.3)
	Discontinued due to progressive disease	11	(2.8)	17	(4.3)
	Discontinued due to protocol violation	0	(0.0)	0	(0.0)
	Discontinued due to relapse/recurrence	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by participant	5	(1.3)	6	(1.5)
	Translation not available in participants language	1	(0.3)	0	(0.0)
	Participant died	7	(1.8)	4	(1.0)
	Visit not reached	0	(0.0)	1	(0.3)
	Visit not scheduled	20	(5.1)	22	(5.5)
Adjuvant Week 4	**Expected to Complete Questionnaires**	**289**	**(73.2)**	**277**	**(69.6)**
	Completed	274	(69.4)	249	(62.6)
	Compliance (% in those expected to complete questionnaires)	274	(94.8)	249	(89.9)
	Not completed	15	(3.8)	28	(7.0)
	Participant did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	9	(2.3)	13	(3.3)
	Participant in hospital or hospice	1	(0.3)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	1	(0.3)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	3	(0.8)
	Other	4	(1.0)	8	(2.0)
	With visit, no record	0	(0.0)	2	(0.5)
	Missing by Design	**106**	**(26.8)**	**121**	**(30.4)**

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 4	Discontinued due to adverse event	7	(1.8)	4	(1.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to death	18	(4.6)	11	(2.8)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	10	(2.5)
	Discontinued due to physician decision	1	(0.3)	2	(0.5)
	Discontinued due to progressive disease	26	(6.6)	41	(10.3)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	0	(0.0)	3	(0.8)
	Discontinued due to withdrawal by participant	10	(2.5)	13	(3.3)
	Translation not available in participants language	1	(0.3)	0	(0.0)
	Participant died	2	(0.5)	1	(0.3)
	Visit not reached	0	(0.0)	2	(0.5)
	Visit not scheduled	37	(9.4)	29	(7.3)
Adjuvant Week 7	**Expected to Complete Questionnaires**	**283**	**(71.6)**	**257**	**(64.6)**
	Completed	266	(67.3)	242	(60.8)
	Compliance (% in those expected to complete questionnaires)	266	(94.0)	242	(94.2)
	Not completed	17	(4.3)	15	(3.8)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	6	(1.5)	3	(0.8)
	Participant in hospital or hospice	1	(0.3)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	1	(0.3)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	0	(0.0)	1	(0.3)
	Other	6	(1.5)	8	(2.0)
	With visit, no record	4	(1.0)	2	(0.5)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 7	**Missing by Design**	**112**	**(28.4)**	**141**	**(35.4)**
	Discontinued due to adverse event	7	(1.8)	5	(1.3)
	Discontinued due to clinical progression	0	(0.0)	1	(0.3)
	Discontinued due to death	18	(4.6)	12	(3.0)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	1	(0.3)	2	(0.5)
	Discontinued due to progressive disease	28	(7.1)	49	(12.3)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	1	(0.3)	3	(0.8)
	Discontinued due to withdrawal by participant	11	(2.8)	16	(4.0)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	2	(0.5)	1	(0.3)
	Visit not reached	0	(0.0)	2	(0.5)
	Visit not scheduled	40	(10.1)	33	(8.3)
Adjuvant Week 10	**Expected to Complete Questionnaires**	**294**	**(74.4)**	**266**	**(66.8)**
	Completed	271	(68.6)	247	(62.1)
	Compliance (% in those expected to complete questionnaires)	271	(92.2)	247	(92.9)
	Not completed	23	(5.8)	19	(4.8)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	7	(1.8)	7	(1.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	1	(0.3)	0	(0.0)
	Participant lost to follow-up/unable to contact	1	(0.3)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	3	(0.8)	3	(0.8)
	Other	8	(2.0)	7	(1.8)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 10	With visit, no record	3	(0.8)	2	(0.5)
	Missing by Design	**101**	**(25.6)**	**132**	**(33.2)**
	Discontinued due to adverse event	7	(1.8)	5	(1.3)
	Discontinued due to clinical progression	0	(0.0)	1	(0.3)
	Discontinued due to death	22	(5.6)	13	(3.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	11	(2.8)
	Discontinued due to physician decision	1	(0.3)	2	(0.5)
	Discontinued due to progressive disease	29	(7.3)	56	(14.1)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	1	(0.3)	4	(1.0)
	Discontinued due to withdrawal by participant	11	(2.8)	19	(4.8)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	2	(0.5)	1	(0.3)
	Visit not reached	1	(0.3)	1	(0.3)
	Visit not scheduled	23	(5.8)	14	(3.5)
Adjuvant Week 19	**Expected to Complete Questionnaires**	**266**	**(67.3)**	**243**	**(61.1)**
	Completed	239	(60.5)	218	(54.8)
	Compliance (% in those expected to complete questionnaires)	239	(89.8)	218	(89.7)
	Not completed	27	(6.8)	25	(6.3)
	Participant did not complete due to disease under study	0	(0.0)	2	(0.5)
	Not completed due to site staff error	8	(2.0)	7	(1.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	1	(0.3)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	3	(0.8)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 19	Other	9	(2.3)	7	(1.8)
	With visit, no record	8	(2.0)	6	(1.5)
	Missing by Design	**129**	**(32.7)**	**155**	**(38.9)**
	Discontinued due to adverse event	9	(2.3)	5	(1.3)
	Discontinued due to clinical progression	0	(0.0)	1	(0.3)
	Discontinued due to death	24	(6.1)	16	(4.0)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	1	(0.3)	2	(0.5)
	Discontinued due to progressive disease	41	(10.4)	70	(17.6)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	3	(0.8)	4	(1.0)
	Discontinued due to withdrawal by participant	11	(2.8)	21	(5.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	2	(0.5)	0	(0.0)
	Visit not reached	5	(1.3)	5	(1.3)
	Visit not scheduled	29	(7.3)	14	(3.5)
Adjuvant Week 28	**Expected to Complete Questionnaires**	**268**	**(67.8)**	**227**	**(57.0)**
	Completed	220	(55.7)	202	(50.8)
	Compliance (% in those expected to complete questionnaires)	220	(82.1)	202	(89.0)
	Not completed	48	(12.2)	25	(6.3)
	Participant did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	14	(3.5)	3	(0.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 28	Participant refused for other reasons	4	(1.0)	3	(0.8)
	Other	16	(4.1)	6	(1.5)
	With visit, no record	14	(3.5)	12	(3.0)
	Missing by Design	**127**	**(32.2)**	**171**	**(43.0)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	26	(6.6)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	3	(0.8)	2	(0.5)
	Discontinued due to progressive disease	54	(13.7)	82	(20.6)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	4	(1.0)	7	(1.8)
	Discontinued due to withdrawal by participant	12	(3.0)	26	(6.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	1	(0.3)	1	(0.3)
	Visit not reached	8	(2.0)	3	(0.8)
	Visit not scheduled	7	(1.8)	7	(1.8)
Adjuvant Week 37	**Expected to Complete Questionnaires**	**256**	**(64.8)**	**214**	**(53.8)**
	Completed	231	(58.5)	200	(50.3)
	Compliance (% in those expected to complete questionnaires)	231	(90.2)	200	(93.5)
	Not completed	25	(6.3)	14	(3.5)
	Participant did not complete due to disease under study	1	(0.3)	0	(0.0)
	Not completed due to site staff error	5	(1.3)	4	(1.0)
	Participant in hospital or hospice	1	(0.3)	1	(0.3)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 37	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	4	(1.0)	1	(0.3)
	Other	8	(2.0)	6	(1.5)
	With visit, no record	6	(1.5)	2	(0.5)
	Missing by Design	**139**	**(35.2)**	**184**	**(46.2)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	27	(6.8)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	2	(0.5)	2	(0.5)
	Discontinued due to progressive disease	63	(15.9)	97	(24.4)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	5	(1.3)	10	(2.5)
	Discontinued due to withdrawal by participant	15	(3.8)	30	(7.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	5	(1.3)	0	(0.0)
	Visit not scheduled	10	(2.5)	2	(0.5)
Adjuvant Week 53	**Expected to Complete Questionnaires**	**232**	**(58.7)**	**170**	**(42.7)**
	Completed	194	(49.1)	147	(36.9)
	Compliance (% in those expected to complete questionnaires)	194	(83.6)	147	(86.5)
	Not completed	38	(9.6)	23	(5.8)
	Participant did not complete due to disease under study	1	(0.3)	0	(0.0)
	Not completed due to site staff error	19	(4.8)	10	(2.5)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 53	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	2	(0.5)	1	(0.3)
	Other	13	(3.3)	10	(2.5)
	With visit, no record	3	(0.8)	2	(0.5)
	Missing by Design	**163**	**(41.3)**	**228**	**(57.3)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	27	(6.8)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	2	(0.5)	3	(0.8)
	Discontinued due to progressive disease	77	(19.5)	112	(28.1)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	8	(2.0)	17	(4.3)
	Discontinued due to withdrawal by participant	17	(4.3)	33	(8.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	6	(1.5)	5	(1.3)
	Visit not scheduled	14	(3.5)	15	(3.8)
Adjuvant Week 69	**Expected to Complete Questionnaires**	**212**	**(53.7)**	**149**	**(37.4)**
	Completed	170	(43.0)	127	(31.9)
	Compliance (% in those expected to complete questionnaires)	170	(80.2)	127	(85.2)
	Not completed	42	(10.6)	22	(5.5)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	13	(3.3)	5	(1.3)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 69	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	4	(1.0)	2	(0.5)
	Other	24	(6.1)	12	(3.0)
	With visit, no record	1	(0.3)	3	(0.8)
	Missing by Design	**183**	**(46.3)**	**249**	**(62.6)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	27	(6.8)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	82	(20.8)	131	(32.9)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	10	(2.5)	18	(4.5)
	Discontinued due to withdrawal by participant	19	(4.8)	33	(8.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	1	(0.3)	0	(0.0)
	Visit not reached	23	(5.8)	19	(4.8)
	Visit not scheduled	5	(1.3)	2	(0.5)
Adjuvant Week 85	**Expected to Complete Questionnaires**	**175**	**(44.3)**	**114**	**(28.6)**
	Completed	151	(38.2)	96	(24.1)
	Compliance (% in those expected to complete questionnaires)	151	(86.3)	96	(84.2)
	Not completed	24	(6.1)	18	(4.5)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	8	(2.0)	7	(1.8)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 85	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	3	(0.8)	2	(0.5)
	Other	13	(3.3)	9	(2.3)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**220**	**(55.7)**	**284**	**(71.4)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	32	(8.1)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	89	(22.5)	146	(36.7)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	12	(3.0)	20	(5.0)
	Discontinued due to withdrawal by participant	23	(5.8)	34	(8.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	44	(11.1)	35	(8.8)
	Visit not scheduled	4	(1.0)	3	(0.8)
Adjuvant Week 101	**Expected to Complete Questionnaires**	**143**	**(36.2)**	**93**	**(23.4)**
	Completed	121	(30.6)	80	(20.1)
	Compliance (% in those expected to complete questionnaires)	121	(84.6)	80	(86.0)
	Not completed	22	(5.6)	13	(3.3)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 101	Not completed due to site staff error	6	(1.5)	4	(1.0)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	0	(0.0)
	Other	12	(3.0)	9	(2.3)
	With visit, no record	3	(0.8)	0	(0.0)
	Missing by Design	**252**	**(63.8)**	**305**	**(76.6)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	33	(8.4)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	91	(23.0)	151	(37.9)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	15	(3.8)	21	(5.3)
	Discontinued due to withdrawal by participant	23	(5.8)	35	(8.8)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	69	(17.5)	50	(12.6)
	Visit not scheduled	4	(1.0)	2	(0.5)
Adjuvant Week 117	**Expected to Complete Questionnaires**	**121**	**(30.6)**	**75**	**(18.8)**
	Completed	110	(27.8)	65	(16.3)
	Compliance (% in those expected to complete questionnaires)	110	(90.9)	65	(86.7)
	Not completed	11	(2.8)	10	(2.5)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 117	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	2	(0.5)	6	(1.5)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	1	(0.3)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	0	(0.0)	0	(0.0)
	Other	8	(2.0)	3	(0.8)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**274**	**(69.4)**	**323**	**(81.2)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	35	(8.9)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	93	(23.5)	153	(38.4)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	15	(3.8)	22	(5.5)
	Discontinued due to withdrawal by participant	23	(5.8)	37	(9.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	89	(22.5)	63	(15.8)
	Visit not scheduled	1	(0.3)	2	(0.5)
Adjuvant Week 133	**Expected to Complete Questionnaires**	**96**	**(24.3)**	**44**	**(11.1)**
	Completed	84	(21.3)	37	(9.3)
	Compliance (% in those expected to complete questionnaires)	84	(87.5)	37	(84.1)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 133	Not completed	12	(3.0)	7	(1.8)
	Participant did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	3	(0.8)	3	(0.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	2	(0.5)	0	(0.0)
	Other	6	(1.5)	3	(0.8)
	With visit, no record	1	(0.3)	0	(0.0)
	Missing by Design	**299**	**(75.7)**	**354**	**(88.9)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	37	(9.4)	18	(4.5)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	98	(24.8)	154	(38.7)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	15	(3.8)	23	(5.8)
	Discontinued due to withdrawal by participant	24	(6.1)	36	(9.0)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	105	(26.6)	91	(22.9)
	Visit not scheduled	2	(0.5)	3	(0.8)
Adjuvant Week 159	**Expected to Complete Questionnaires**	**74**	**(18.7)**	**42**	**(10.6)**
	Completed	70	(17.7)	35	(8.8)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 159	Compliance (% in those expected to complete questionnaires)	70	(94.6)	35	(83.3)
	Not completed	4	(1.0)	7	(1.8)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	3	(0.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	1	(0.3)
	Other	3	(0.8)	2	(0.5)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**321**	**(81.3)**	**356**	**(89.4)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	37	(9.4)	18	(4.5)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	99	(25.1)	158	(39.7)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	15	(3.8)	24	(6.0)
	Discontinued due to withdrawal by participant	25	(6.3)	37	(9.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	126	(31.9)	90	(22.6)
	Visit not scheduled	1	(0.3)	0	(0.0)
Adjuvant Week 185	**Expected to Complete Questionnaires**	**39**	**(9.9)**	**21**	**(5.3)**

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 185	Completed	31	(7.8)	18	(4.5)
	Compliance (% in those expected to complete questionnaires)	31	(79.5)	18	(85.7)
	Not completed	8	(2.0)	3	(0.8)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	2	(0.5)	2	(0.5)
	Participant in hospital or hospice	1	(0.3)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	2	(0.5)	0	(0.0)
	Other	3	(0.8)	1	(0.3)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**356**	**(90.1)**	**377**	**(94.7)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	38	(9.6)	19	(4.8)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	100	(25.3)	160	(40.2)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	16	(4.1)	25	(6.3)
	Discontinued due to withdrawal by participant	27	(6.8)	38	(9.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	155	(39.2)	106	(26.6)
	Visit not scheduled	2	(0.5)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 211	**Expected to Complete Questionnaires**	**24**	**(6.1)**	**11**	**(2.8)**
	Completed	23	(5.8)	10	(2.5)
	Compliance (% in those expected to complete questionnaires)	23	(95.8)	10	(90.9)
	Not completed	1	(0.3)	1	(0.3)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	1	(0.3)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**371**	**(93.9)**	**387**	**(97.2)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	38	(9.6)	19	(4.8)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	100	(25.3)	161	(40.5)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	16	(4.1)	25	(6.3)
	Discontinued due to withdrawal by participant	28	(7.1)	38	(9.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	171	(43.3)	115	(28.9)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 211	Visit not scheduled	0	(0.0)	0	(0.0)
Adjuvant Week 237	**Expected to Complete Questionnaires**	**5**	**(1.3)**	**5**	**(1.3)**
	Completed	3	(0.8)	5	(1.3)
	Compliance (% in those expected to complete questionnaires)	3	(60.0)	5	(100.0)
	Not completed	2	(0.5)	0	(0.0)
	Participant 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)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant 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	**390**	**(98.7)**	**393**	**(98.7)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	38	(9.6)	19	(4.8)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	101	(25.6)	161	(40.5)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	16	(4.1)	25	(6.3)
	Discontinued due to withdrawal by participant	28	(7.1)	38	(9.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 237	Visit not reached	189	(47.8)	121	(30.4)
	Visit not scheduled	0	(0.0)	0	(0.0)

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

Compliance is the proportion of patients 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 patients in the analysis population (N).

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

Database Cutoff Date: 10JUL2023

Anhang 4-G3.2: Rücklaufquoten des EORTC QLQ-LC13

Tabelle 4G-7: Gründe für das Fehlen von Werten im EORTC QLQ-LC13

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
BASELINE	**Expected to Complete Questionnaires**	**395**	**(100.0)**	**398**	**(100.0)**
	Completed	386	(97.7)	388	(97.5)
	Compliance (% in those expected to complete questionnaires)	386	(97.7)	388	(97.5)
	Not completed	9	(2.3)	10	(2.5)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	3	(0.8)	1	(0.3)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	1	(0.3)
	Other	5	(1.3)	5	(1.3)
	With visit, no record	0	(0.0)	3	(0.8)
	Missing by Design	**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 death	0	(0.0)	0	(0.0)
	Discontinued due to local progression preventing surgery	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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 protocol violation	0	(0.0)	0	(0.0)
	Discontinued due to relapse/recurrence	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by participant	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
BASELINE	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Neoadjuvant Week 11	**Expected to Complete Questionnaires**	**386**	**(97.7)**	**392**	**(98.5)**
	Completed	343	(86.8)	352	(88.4)
	Compliance (% in those expected to complete questionnaires)	343	(88.9)	352	(89.8)
	Not completed	43	(10.9)	40	(10.1)
	Participant did not complete due to disease under study	2	(0.5)	0	(0.0)
	Not completed due to site staff error	15	(3.8)	9	(2.3)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	1	(0.3)	0	(0.0)
	Participant lost to follow-up/unable to contact	1	(0.3)	1	(0.3)
	Participant did not complete due to side effects of treatment	2	(0.5)	4	(1.0)
	Participant refused for other reasons	8	(2.0)	6	(1.5)
	Other	10	(2.5)	16	(4.0)
	With visit, no record	4	(1.0)	4	(1.0)
	Missing by Design	**9**	**(2.3)**	**6**	**(1.5)**
	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 death	0	(0.0)	0	(0.0)
	Discontinued due to local progression preventing surgery	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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 protocol violation	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Neoadjuvant Week 11	Discontinued due to relapse/recurrence	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by participant	0	(0.0)	0	(0.0)
	Translation not available in participants language	1	(0.3)	0	(0.0)
	Participant died	7	(1.8)	6	(1.5)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Adjuvant Week 1	**Expected to Complete Questionnaires**	**333**	**(84.3)**	**329**	**(82.7)**
	Completed	304	(77.0)	304	(76.4)
	Compliance (% in those expected to complete questionnaires)	304	(91.3)	304	(92.4)
	Not completed	29	(7.3)	25	(6.3)
	Participant did not complete due to disease under study	0	(0.0)	2	(0.5)
	Not completed due to site staff error	11	(2.8)	6	(1.5)
	Participant in hospital or hospice	0	(0.0)	1	(0.3)
	Participant was physically unable to complete	1	(0.3)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	4	(1.0)	3	(0.8)
	Other	8	(2.0)	6	(1.5)
	With visit, no record	5	(1.3)	7	(1.8)
	Missing by Design	**62**	**(15.7)**	**69**	**(17.3)**
	Discontinued due to adverse event	4	(1.0)	3	(0.8)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to death	12	(3.0)	8	(2.0)
	Discontinued due to local progression preventing surgery	1	(0.3)	3	(0.8)
	Discontinued due to non-study anti-cancer therapy	1	(0.3)	4	(1.0)
	Discontinued due to physician decision	0	(0.0)	1	(0.3)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 1	Discontinued due to progressive disease	11	(2.8)	17	(4.3)
	Discontinued due to protocol violation	0	(0.0)	0	(0.0)
	Discontinued due to relapse/recurrence	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by participant	5	(1.3)	6	(1.5)
	Translation not available in participants language	1	(0.3)	0	(0.0)
	Participant died	7	(1.8)	4	(1.0)
	Visit not reached	0	(0.0)	1	(0.3)
	Visit not scheduled	20	(5.1)	22	(5.5)
Adjuvant Week 4	**Expected to Complete Questionnaires**	**289**	**(73.2)**	**277**	**(69.6)**
	Completed	272	(68.9)	249	(62.6)
	Compliance (% in those expected to complete questionnaires)	272	(94.1)	249	(89.9)
	Not completed	17	(4.3)	28	(7.0)
	Participant did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	9	(2.3)	13	(3.3)
	Participant in hospital or hospice	1	(0.3)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	1	(0.3)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	3	(0.8)
	Other	6	(1.5)	8	(2.0)
	With visit, no record	0	(0.0)	2	(0.5)
	Missing by Design	**106**	**(26.8)**	**121**	**(30.4)**
	Discontinued due to adverse event	7	(1.8)	4	(1.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to death	18	(4.6)	11	(2.8)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	10	(2.5)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 4	Discontinued due to physician decision	1	(0.3)	2	(0.5)
	Discontinued due to progressive disease	26	(6.6)	41	(10.3)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	0	(0.0)	3	(0.8)
	Discontinued due to withdrawal by participant	10	(2.5)	13	(3.3)
	Translation not available in participants language	1	(0.3)	0	(0.0)
	Participant died	2	(0.5)	1	(0.3)
	Visit not reached	0	(0.0)	2	(0.5)
	Visit not scheduled	37	(9.4)	29	(7.3)
Adjuvant Week 7	**Expected to Complete Questionnaires**	**283**	**(71.6)**	**257**	**(64.6)**
	Completed	265	(67.1)	242	(60.8)
	Compliance (% in those expected to complete questionnaires)	265	(93.6)	242	(94.2)
	Not completed	18	(4.6)	15	(3.8)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	6	(1.5)	3	(0.8)
	Participant in hospital or hospice	1	(0.3)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	1	(0.3)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	0	(0.0)	1	(0.3)
	Other	7	(1.8)	8	(2.0)
	With visit, no record	4	(1.0)	2	(0.5)
	Missing by Design	**112**	**(28.4)**	**141**	**(35.4)**
	Discontinued due to adverse event	7	(1.8)	5	(1.3)
	Discontinued due to clinical progression	0	(0.0)	1	(0.3)
	Discontinued due to death	18	(4.6)	12	(3.0)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 7	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	1	(0.3)	2	(0.5)
	Discontinued due to progressive disease	28	(7.1)	49	(12.3)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	1	(0.3)	3	(0.8)
	Discontinued due to withdrawal by participant	11	(2.8)	16	(4.0)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	2	(0.5)	1	(0.3)
	Visit not reached	0	(0.0)	2	(0.5)
	Visit not scheduled	40	(10.1)	33	(8.3)
Adjuvant Week 10	**Expected to Complete Questionnaires**	**294**	**(74.4)**	**266**	**(66.8)**
	Completed	270	(68.4)	247	(62.1)
	Compliance (% in those expected to complete questionnaires)	270	(91.8)	247	(92.9)
	Not completed	24	(6.1)	19	(4.8)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	7	(1.8)	7	(1.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	1	(0.3)	0	(0.0)
	Participant lost to follow-up/unable to contact	1	(0.3)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	3	(0.8)	3	(0.8)
	Other	9	(2.3)	7	(1.8)
	With visit, no record	3	(0.8)	2	(0.5)
	Missing by Design	**101**	**(25.6)**	**132**	**(33.2)**
	Discontinued due to adverse event	7	(1.8)	5	(1.3)
	Discontinued due to clinical progression	0	(0.0)	1	(0.3)
	Discontinued due to death	22	(5.6)	13	(3.3)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 10	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	11	(2.8)
	Discontinued due to physician decision	1	(0.3)	2	(0.5)
	Discontinued due to progressive disease	29	(7.3)	56	(14.1)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	1	(0.3)	4	(1.0)
	Discontinued due to withdrawal by participant	11	(2.8)	19	(4.8)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	2	(0.5)	1	(0.3)
	Visit not reached	1	(0.3)	1	(0.3)
	Visit not scheduled	23	(5.8)	14	(3.5)
Adjuvant Week 19	**Expected to Complete Questionnaires**	**266**	**(67.3)**	**243**	**(61.1)**
	Completed	239	(60.5)	218	(54.8)
	Compliance (% in those expected to complete questionnaires)	239	(89.8)	218	(89.7)
	Not completed	27	(6.8)	25	(6.3)
	Participant did not complete due to disease under study	0	(0.0)	2	(0.5)
	Not completed due to site staff error	8	(2.0)	7	(1.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	1	(0.3)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	2	(0.5)
	Other	9	(2.3)	8	(2.0)
	With visit, no record	8	(2.0)	6	(1.5)
	Missing by Design	**129**	**(32.7)**	**155**	**(38.9)**
	Discontinued due to adverse event	9	(2.3)	5	(1.3)
	Discontinued due to clinical progression	0	(0.0)	1	(0.3)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 19	Discontinued due to death	24	(6.1)	16	(4.0)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	1	(0.3)	2	(0.5)
	Discontinued due to progressive disease	41	(10.4)	70	(17.6)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	3	(0.8)	4	(1.0)
	Discontinued due to withdrawal by participant	11	(2.8)	21	(5.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	2	(0.5)	0	(0.0)
	Visit not reached	5	(1.3)	5	(1.3)
	Visit not scheduled	29	(7.3)	14	(3.5)
Adjuvant Week 28	**Expected to Complete Questionnaires**	**268**	**(67.8)**	**227**	**(57.0)**
	Completed	219	(55.4)	202	(50.8)
	Compliance (% in those expected to complete questionnaires)	219	(81.7)	202	(89.0)
	Not completed	49	(12.4)	25	(6.3)
	Participant did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	14	(3.5)	3	(0.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	4	(1.0)	3	(0.8)
	Other	17	(4.3)	6	(1.5)
	With visit, no record	14	(3.5)	12	(3.0)
	Missing by Design	**127**	**(32.2)**	**171**	**(43.0)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 28	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	26	(6.6)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	3	(0.8)	2	(0.5)
	Discontinued due to progressive disease	54	(13.7)	82	(20.6)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	4	(1.0)	7	(1.8)
	Discontinued due to withdrawal by participant	12	(3.0)	26	(6.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	1	(0.3)	1	(0.3)
	Visit not reached	8	(2.0)	3	(0.8)
	Visit not scheduled	7	(1.8)	7	(1.8)
Adjuvant Week 37	**Expected to Complete Questionnaires**	**256**	**(64.8)**	**214**	**(53.8)**
	Completed	231	(58.5)	200	(50.3)
	Compliance (% in those expected to complete questionnaires)	231	(90.2)	200	(93.5)
	Not completed	25	(6.3)	14	(3.5)
	Participant did not complete due to disease under study	1	(0.3)	0	(0.0)
	Not completed due to site staff error	5	(1.3)	4	(1.0)
	Participant in hospital or hospice	1	(0.3)	1	(0.3)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	4	(1.0)	1	(0.3)
	Other	8	(2.0)	6	(1.5)
	With visit, no record	6	(1.5)	2	(0.5)
	Missing by Design	**139**	**(35.2)**	**184**	**(46.2)**

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 37	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	27	(6.8)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	2	(0.5)	2	(0.5)
	Discontinued due to progressive disease	63	(15.9)	97	(24.4)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	5	(1.3)	10	(2.5)
	Discontinued due to withdrawal by participant	15	(3.8)	30	(7.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	5	(1.3)	0	(0.0)
	Visit not scheduled	10	(2.5)	2	(0.5)
Adjuvant Week 53	**Expected to Complete Questionnaires**	**232**	**(58.7)**	**170**	**(42.7)**
	Completed	193	(48.9)	147	(36.9)
	Compliance (% in those expected to complete questionnaires)	193	(83.2)	147	(86.5)
	Not completed	39	(9.9)	23	(5.8)
	Participant did not complete due to disease under study	1	(0.3)	0	(0.0)
	Not completed due to site staff error	19	(4.8)	10	(2.5)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	2	(0.5)	1	(0.3)
	Other	14	(3.5)	10	(2.5)
	With visit, no record	3	(0.8)	2	(0.5)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 53	**Missing by Design**	**163**	**(41.3)**	**228**	**(57.3)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	27	(6.8)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	2	(0.5)	3	(0.8)
	Discontinued due to progressive disease	77	(19.5)	112	(28.1)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	8	(2.0)	17	(4.3)
	Discontinued due to withdrawal by participant	17	(4.3)	33	(8.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	6	(1.5)	5	(1.3)
	Visit not scheduled	14	(3.5)	15	(3.8)
Adjuvant Week 69	**Expected to Complete Questionnaires**	**212**	**(53.7)**	**149**	**(37.4)**
	Completed	170	(43.0)	126	(31.7)
	Compliance (% in those expected to complete questionnaires)	170	(80.2)	126	(84.6)
	Not completed	42	(10.6)	23	(5.8)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	13	(3.3)	5	(1.3)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	4	(1.0)	2	(0.5)
	Other	24	(6.1)	13	(3.3)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 69	With visit, no record	1	(0.3)	3	(0.8)
	Missing by Design	**183**	**(46.3)**	**249**	**(62.6)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	27	(6.8)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	82	(20.8)	131	(32.9)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	10	(2.5)	18	(4.5)
	Discontinued due to withdrawal by participant	19	(4.8)	33	(8.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	1	(0.3)	0	(0.0)
	Visit not reached	23	(5.8)	19	(4.8)
	Visit not scheduled	5	(1.3)	2	(0.5)
Adjuvant Week 85	**Expected to Complete Questionnaires**	**175**	**(44.3)**	**114**	**(28.6)**
	Completed	151	(38.2)	96	(24.1)
	Compliance (% in those expected to complete questionnaires)	151	(86.3)	96	(84.2)
	Not completed	24	(6.1)	18	(4.5)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	8	(2.0)	7	(1.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	3	(0.8)	2	(0.5)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 85	Other	13	(3.3)	9	(2.3)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**220**	**(55.7)**	**284**	**(71.4)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	32	(8.1)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	89	(22.5)	146	(36.7)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	12	(3.0)	20	(5.0)
	Discontinued due to withdrawal by participant	23	(5.8)	34	(8.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	44	(11.1)	35	(8.8)
	Visit not scheduled	4	(1.0)	3	(0.8)
Adjuvant Week 101	**Expected to Complete Questionnaires**	**143**	**(36.2)**	**93**	**(23.4)**
	Completed	121	(30.6)	80	(20.1)
	Compliance (% in those expected to complete questionnaires)	121	(84.6)	80	(86.0)
	Not completed	22	(5.6)	13	(3.3)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	6	(1.5)	4	(1.0)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 101	Participant refused for other reasons	1	(0.3)	0	(0.0)
	Other	12	(3.0)	9	(2.3)
	With visit, no record	3	(0.8)	0	(0.0)
	Missing by Design	**252**	**(63.8)**	**305**	**(76.6)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	33	(8.4)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	91	(23.0)	151	(37.9)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	15	(3.8)	21	(5.3)
	Discontinued due to withdrawal by participant	23	(5.8)	35	(8.8)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	69	(17.5)	50	(12.6)
	Visit not scheduled	4	(1.0)	2	(0.5)
Adjuvant Week 117	**Expected to Complete Questionnaires**	**121**	**(30.6)**	**75**	**(18.8)**
	Completed	108	(27.3)	65	(16.3)
	Compliance (% in those expected to complete questionnaires)	108	(89.3)	65	(86.7)
	Not completed	13	(3.3)	10	(2.5)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	2	(0.5)	6	(1.5)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	1	(0.3)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	1	(0.3)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 117	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	0	(0.0)
	Other	9	(2.3)	3	(0.8)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**274**	**(69.4)**	**323**	**(81.2)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	35	(8.9)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	93	(23.5)	153	(38.4)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	15	(3.8)	22	(5.5)
	Discontinued due to withdrawal by participant	23	(5.8)	37	(9.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	89	(22.5)	63	(15.8)
	Visit not scheduled	1	(0.3)	2	(0.5)
Adjuvant Week 133	**Expected to Complete Questionnaires**	**96**	**(24.3)**	**44**	**(11.1)**
	Completed	84	(21.3)	37	(9.3)
	Compliance (% in those expected to complete questionnaires)	84	(87.5)	37	(84.1)
	Not completed	12	(3.0)	7	(1.8)
	Participant did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	3	(0.8)	3	(0.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 133	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	2	(0.5)	0	(0.0)
	Other	6	(1.5)	3	(0.8)
	With visit, no record	1	(0.3)	0	(0.0)
	Missing by Design	**299**	**(75.7)**	**354**	**(88.9)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	37	(9.4)	18	(4.5)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	98	(24.8)	154	(38.7)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	15	(3.8)	23	(5.8)
	Discontinued due to withdrawal by participant	24	(6.1)	36	(9.0)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	105	(26.6)	91	(22.9)
	Visit not scheduled	2	(0.5)	3	(0.8)
Adjuvant Week 159	**Expected to Complete Questionnaires**	**74**	**(18.7)**	**42**	**(10.6)**
	Completed	70	(17.7)	35	(8.8)
	Compliance (% in those expected to complete questionnaires)	70	(94.6)	35	(83.3)
	Not completed	4	(1.0)	7	(1.8)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	3	(0.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 159	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	1	(0.3)
	Other	3	(0.8)	2	(0.5)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**321**	**(81.3)**	**356**	**(89.4)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	37	(9.4)	18	(4.5)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	99	(25.1)	158	(39.7)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	15	(3.8)	24	(6.0)
	Discontinued due to withdrawal by participant	25	(6.3)	37	(9.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	126	(31.9)	90	(22.6)
	Visit not scheduled	1	(0.3)	0	(0.0)
Adjuvant Week 185	**Expected to Complete Questionnaires**	**39**	**(9.9)**	**21**	**(5.3)**
	Completed	31	(7.8)	18	(4.5)
	Compliance (% in those expected to complete questionnaires)	31	(79.5)	18	(85.7)
	Not completed	8	(2.0)	3	(0.8)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	2	(0.5)	2	(0.5)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 185	Participant in hospital or hospice	1	(0.3)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	2	(0.5)	0	(0.0)
	Other	3	(0.8)	1	(0.3)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**356**	**(90.1)**	**377**	**(94.7)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	38	(9.6)	19	(4.8)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	100	(25.3)	160	(40.2)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	16	(4.1)	25	(6.3)
	Discontinued due to withdrawal by participant	27	(6.8)	38	(9.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	155	(39.2)	106	(26.6)
	Visit not scheduled	2	(0.5)	0	(0.0)
Adjuvant Week 211	**Expected to Complete Questionnaires**	**24**	**(6.1)**	**11**	**(2.8)**
	Completed	23	(5.8)	10	(2.5)
	Compliance (% in those expected to complete questionnaires)	23	(95.8)	10	(90.9)
	Not completed	1	(0.3)	1	(0.3)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 211	Not completed due to site staff error	0	(0.0)	1	(0.3)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**371**	**(93.9)**	**387**	**(97.2)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	38	(9.6)	19	(4.8)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	100	(25.3)	161	(40.5)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	16	(4.1)	25	(6.3)
	Discontinued due to withdrawal by participant	28	(7.1)	38	(9.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	171	(43.3)	115	(28.9)
	Visit not scheduled	0	(0.0)	0	(0.0)
Adjuvant Week 237	**Expected to Complete Questionnaires**	**5**	**(1.3)**	**5**	**(1.3)**
	Completed	3	(0.8)	5	(1.3)
	Compliance (% in those expected to complete questionnaires)	3	(60.0)	5	(100.0)
	Not completed	2	(0.5)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Adjuvant Week 237	Participant 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)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant 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	**390**	**(98.7)**	**393**	**(98.7)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	38	(9.6)	19	(4.8)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	101	(25.6)	161	(40.5)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	16	(4.1)	25	(6.3)
	Discontinued due to withdrawal by participant	28	(7.1)	38	(9.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	189	(47.8)	121	(30.4)
	Visit not scheduled	0	(0.0)	0	(0.0)

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

Compliance is the proportion of patients 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 patients in the analysis population (N).

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=398	
		n	(%)	n	(%)
Missing by design includes: adverse event, death, discontinuation, translations not available, and no visit scheduled. Database Cutoff Date: 10JUL2023					

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

Tabelle 4G-8: Gründe für das Fehlen von Werten in der EQ-5D VAS

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
BASELINE	**Expected to Complete Questionnaires**	**395**	**(100.0)**	**399**	**(100.0)**
	Completed	389	(98.5)	392	(98.2)
	Compliance (% in those expected to complete questionnaires)	389	(98.5)	392	(98.2)
	Not completed	6	(1.5)	7	(1.8)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	2	(0.5)	2	(0.5)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	0	(0.0)
	Other	3	(0.8)	2	(0.5)
	With visit, no record	0	(0.0)	3	(0.8)
	Missing by Design	**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 death	0	(0.0)	0	(0.0)
	Discontinued due to local progression preventing surgery	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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 protocol violation	0	(0.0)	0	(0.0)
	Discontinued due to relapse/recurrence	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by participant	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
BASELINE	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Neoadjuvant Week 11	**Expected to Complete Questionnaires**	**386**	**(97.7)**	**393**	**(98.5)**
	Completed	345	(87.3)	356	(89.2)
	Compliance (% in those expected to complete questionnaires)	345	(89.4)	356	(90.6)
	Not completed	41	(10.4)	37	(9.3)
	Participant did not complete due to disease under study	2	(0.5)	0	(0.0)
	Not completed due to site staff error	15	(3.8)	8	(2.0)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	1	(0.3)	0	(0.0)
	Participant lost to follow-up/unable to contact	1	(0.3)	1	(0.3)
	Participant did not complete due to side effects of treatment	2	(0.5)	3	(0.8)
	Participant refused for other reasons	6	(1.5)	6	(1.5)
	Other	10	(2.5)	15	(3.8)
	With visit, no record	4	(1.0)	4	(1.0)
	Missing by Design	**9**	**(2.3)**	**6**	**(1.5)**
	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 death	0	(0.0)	0	(0.0)
	Discontinued due to local progression preventing surgery	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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 protocol violation	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Neoadjuvant Week 11	Discontinued due to relapse/recurrence	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by participant	0	(0.0)	0	(0.0)
	Translation not available in participants language	1	(0.3)	0	(0.0)
	Participant died	7	(1.8)	6	(1.5)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
Adjuvant Week 1	**Expected to Complete Questionnaires**	**333**	**(84.3)**	**329**	**(82.5)**
	Completed	305	(77.2)	307	(76.9)
	Compliance (% in those expected to complete questionnaires)	305	(91.6)	307	(93.3)
	Not completed	28	(7.1)	22	(5.5)
	Participant did not complete due to disease under study	0	(0.0)	2	(0.5)
	Not completed due to site staff error	11	(2.8)	6	(1.5)
	Participant in hospital or hospice	0	(0.0)	1	(0.3)
	Participant was physically unable to complete	1	(0.3)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	4	(1.0)	2	(0.5)
	Other	7	(1.8)	4	(1.0)
	With visit, no record	5	(1.3)	7	(1.8)
	Missing by Design	**62**	**(15.7)**	**70**	**(17.5)**
	Discontinued due to adverse event	4	(1.0)	3	(0.8)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to death	12	(3.0)	8	(2.0)
	Discontinued due to local progression preventing surgery	1	(0.3)	3	(0.8)
	Discontinued due to non-study anti-cancer therapy	1	(0.3)	4	(1.0)
	Discontinued due to physician decision	0	(0.0)	1	(0.3)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 1	Discontinued due to progressive disease	11	(2.8)	18	(4.5)
	Discontinued due to protocol violation	0	(0.0)	0	(0.0)
	Discontinued due to relapse/recurrence	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by participant	5	(1.3)	6	(1.5)
	Translation not available in participants language	1	(0.3)	0	(0.0)
	Participant died	7	(1.8)	4	(1.0)
	Visit not reached	0	(0.0)	1	(0.3)
	Visit not scheduled	20	(5.1)	22	(5.5)
Adjuvant Week 4	**Expected to Complete Questionnaires**	**289**	**(73.2)**	**277**	**(69.4)**
	Completed	274	(69.4)	249	(62.4)
	Compliance (% in those expected to complete questionnaires)	274	(94.8)	249	(89.9)
	Not completed	15	(3.8)	28	(7.0)
	Participant did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	9	(2.3)	13	(3.3)
	Participant in hospital or hospice	1	(0.3)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	1	(0.3)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	3	(0.8)
	Other	4	(1.0)	8	(2.0)
	With visit, no record	0	(0.0)	2	(0.5)
	Missing by Design	**106**	**(26.8)**	**122**	**(30.6)**
	Discontinued due to adverse event	7	(1.8)	4	(1.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to death	18	(4.6)	11	(2.8)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	10	(2.5)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 4	Discontinued due to physician decision	1	(0.3)	2	(0.5)
	Discontinued due to progressive disease	26	(6.6)	42	(10.5)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	0	(0.0)	3	(0.8)
	Discontinued due to withdrawal by participant	10	(2.5)	13	(3.3)
	Translation not available in participants language	1	(0.3)	0	(0.0)
	Participant died	2	(0.5)	1	(0.3)
	Visit not reached	0	(0.0)	2	(0.5)
	Visit not scheduled	37	(9.4)	29	(7.3)
Adjuvant Week 7	**Expected to Complete Questionnaires**	**283**	**(71.6)**	**257**	**(64.4)**
	Completed	266	(67.3)	243	(60.9)
	Compliance (% in those expected to complete questionnaires)	266	(94.0)	243	(94.6)
	Not completed	17	(4.3)	14	(3.5)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	6	(1.5)	3	(0.8)
	Participant in hospital or hospice	1	(0.3)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	0	(0.0)	1	(0.3)
	Other	6	(1.5)	8	(2.0)
	With visit, no record	4	(1.0)	2	(0.5)
	Missing by Design	**112**	**(28.4)**	**142**	**(35.6)**
	Discontinued due to adverse event	7	(1.8)	5	(1.3)
	Discontinued due to clinical progression	0	(0.0)	1	(0.3)
	Discontinued due to death	18	(4.6)	12	(3.0)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 7	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	1	(0.3)	2	(0.5)
	Discontinued due to progressive disease	28	(7.1)	50	(12.5)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	1	(0.3)	3	(0.8)
	Discontinued due to withdrawal by participant	11	(2.8)	16	(4.0)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	2	(0.5)	1	(0.3)
	Visit not reached	0	(0.0)	2	(0.5)
	Visit not scheduled	40	(10.1)	33	(8.3)
Adjuvant Week 10	**Expected to Complete Questionnaires**	**294**	**(74.4)**	**266**	**(66.7)**
	Completed	271	(68.6)	247	(61.9)
	Compliance (% in those expected to complete questionnaires)	271	(92.2)	247	(92.9)
	Not completed	23	(5.8)	19	(4.8)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	7	(1.8)	7	(1.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	1	(0.3)	0	(0.0)
	Participant lost to follow-up/unable to contact	1	(0.3)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	3	(0.8)	3	(0.8)
	Other	8	(2.0)	7	(1.8)
	With visit, no record	3	(0.8)	2	(0.5)
	Missing by Design	**101**	**(25.6)**	**133**	**(33.3)**
	Discontinued due to adverse event	7	(1.8)	5	(1.3)
	Discontinued due to clinical progression	0	(0.0)	1	(0.3)
	Discontinued due to death	22	(5.6)	13	(3.3)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 10	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	11	(2.8)
	Discontinued due to physician decision	1	(0.3)	2	(0.5)
	Discontinued due to progressive disease	29	(7.3)	57	(14.3)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	1	(0.3)	4	(1.0)
	Discontinued due to withdrawal by participant	11	(2.8)	19	(4.8)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	2	(0.5)	1	(0.3)
	Visit not reached	1	(0.3)	1	(0.3)
	Visit not scheduled	23	(5.8)	14	(3.5)
Adjuvant Week 19	**Expected to Complete Questionnaires**	**266**	**(67.3)**	**243**	**(60.9)**
	Completed	239	(60.5)	218	(54.6)
	Compliance (% in those expected to complete questionnaires)	239	(89.8)	218	(89.7)
	Not completed	27	(6.8)	25	(6.3)
	Participant did not complete due to disease under study	0	(0.0)	2	(0.5)
	Not completed due to site staff error	8	(2.0)	7	(1.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	1	(0.3)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	3	(0.8)
	Other	9	(2.3)	7	(1.8)
	With visit, no record	8	(2.0)	6	(1.5)
	Missing by Design	**129**	**(32.7)**	**156**	**(39.1)**
	Discontinued due to adverse event	9	(2.3)	5	(1.3)
	Discontinued due to clinical progression	0	(0.0)	1	(0.3)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 19	Discontinued due to death	24	(6.1)	16	(4.0)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	1	(0.3)	2	(0.5)
	Discontinued due to progressive disease	41	(10.4)	71	(17.8)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	3	(0.8)	4	(1.0)
	Discontinued due to withdrawal by participant	11	(2.8)	21	(5.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	2	(0.5)	0	(0.0)
	Visit not reached	5	(1.3)	5	(1.3)
	Visit not scheduled	29	(7.3)	14	(3.5)
Adjuvant Week 28	**Expected to Complete Questionnaires**	**268**	**(67.8)**	**227**	**(56.9)**
	Completed	220	(55.7)	202	(50.6)
	Compliance (% in those expected to complete questionnaires)	220	(82.1)	202	(89.0)
	Not completed	48	(12.2)	25	(6.3)
	Participant did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	14	(3.5)	3	(0.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	4	(1.0)	3	(0.8)
	Other	16	(4.1)	6	(1.5)
	With visit, no record	14	(3.5)	12	(3.0)
	Missing by Design	**127**	**(32.2)**	**172**	**(43.1)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 28	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	26	(6.6)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	3	(0.8)	2	(0.5)
	Discontinued due to progressive disease	54	(13.7)	83	(20.8)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	4	(1.0)	7	(1.8)
	Discontinued due to withdrawal by participant	12	(3.0)	26	(6.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	1	(0.3)	1	(0.3)
	Visit not reached	8	(2.0)	3	(0.8)
	Visit not scheduled	7	(1.8)	7	(1.8)
Adjuvant Week 37	**Expected to Complete Questionnaires**	**256**	**(64.8)**	**214**	**(53.6)**
	Completed	231	(58.5)	200	(50.1)
	Compliance (% in those expected to complete questionnaires)	231	(90.2)	200	(93.5)
	Not completed	25	(6.3)	14	(3.5)
	Participant did not complete due to disease under study	1	(0.3)	0	(0.0)
	Not completed due to site staff error	5	(1.3)	4	(1.0)
	Participant in hospital or hospice	1	(0.3)	1	(0.3)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	4	(1.0)	1	(0.3)
	Other	8	(2.0)	6	(1.5)
	With visit, no record	6	(1.5)	2	(0.5)
	Missing by Design	**139**	**(35.2)**	**185**	**(46.4)**

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 37	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	27	(6.8)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	2	(0.5)	2	(0.5)
	Discontinued due to progressive disease	63	(15.9)	98	(24.6)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	5	(1.3)	10	(2.5)
	Discontinued due to withdrawal by participant	15	(3.8)	30	(7.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	5	(1.3)	0	(0.0)
	Visit not scheduled	10	(2.5)	2	(0.5)
Adjuvant Week 53	**Expected to Complete Questionnaires**	**232**	**(58.7)**	**170**	**(42.6)**
	Completed	194	(49.1)	147	(36.8)
	Compliance (% in those expected to complete questionnaires)	194	(83.6)	147	(86.5)
	Not completed	38	(9.6)	23	(5.8)
	Participant did not complete due to disease under study	1	(0.3)	0	(0.0)
	Not completed due to site staff error	19	(4.8)	10	(2.5)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	2	(0.5)	1	(0.3)
	Other	13	(3.3)	10	(2.5)
	With visit, no record	3	(0.8)	2	(0.5)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 53	**Missing by Design**	**163**	**(41.3)**	**229**	**(57.4)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	27	(6.8)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	2	(0.5)	3	(0.8)
	Discontinued due to progressive disease	77	(19.5)	113	(28.3)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	8	(2.0)	17	(4.3)
	Discontinued due to withdrawal by participant	17	(4.3)	33	(8.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	6	(1.5)	5	(1.3)
	Visit not scheduled	14	(3.5)	15	(3.8)
Adjuvant Week 69	**Expected to Complete Questionnaires**	**213**	**(53.9)**	**149**	**(37.3)**
	Completed	171	(43.3)	127	(31.8)
	Compliance (% in those expected to complete questionnaires)	171	(80.3)	127	(85.2)
	Not completed	42	(10.6)	22	(5.5)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	13	(3.3)	5	(1.3)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	4	(1.0)	2	(0.5)
	Other	24	(6.1)	12	(3.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 69	With visit, no record	1	(0.3)	3	(0.8)
	Missing by Design	**182**	**(46.1)**	**250**	**(62.7)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	27	(6.8)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	82	(20.8)	132	(33.1)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	10	(2.5)	18	(4.5)
	Discontinued due to withdrawal by participant	19	(4.8)	33	(8.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	1	(0.3)	0	(0.0)
	Visit not reached	22	(5.6)	19	(4.8)
	Visit not scheduled	5	(1.3)	2	(0.5)
Adjuvant Week 85	**Expected to Complete Questionnaires**	**175**	**(44.3)**	**114**	**(28.6)**
	Completed	151	(38.2)	96	(24.1)
	Compliance (% in those expected to complete questionnaires)	151	(86.3)	96	(84.2)
	Not completed	24	(6.1)	18	(4.5)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	8	(2.0)	7	(1.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	3	(0.8)	2	(0.5)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 85	Other	13	(3.3)	9	(2.3)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**220**	**(55.7)**	**285**	**(71.4)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	0	(0.0)	2	(0.5)
	Discontinued due to death	32	(8.1)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	89	(22.5)	147	(36.8)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	12	(3.0)	20	(5.0)
	Discontinued due to withdrawal by participant	23	(5.8)	34	(8.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	44	(11.1)	35	(8.8)
	Visit not scheduled	4	(1.0)	3	(0.8)
Adjuvant Week 101	**Expected to Complete Questionnaires**	**143**	**(36.2)**	**93**	**(23.3)**
	Completed	121	(30.6)	80	(20.1)
	Compliance (% in those expected to complete questionnaires)	121	(84.6)	80	(86.0)
	Not completed	22	(5.6)	13	(3.3)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	6	(1.5)	4	(1.0)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 101	Participant refused for other reasons	1	(0.3)	0	(0.0)
	Other	12	(3.0)	9	(2.3)
	With visit, no record	3	(0.8)	0	(0.0)
	Missing by Design	**252**	**(63.8)**	**306**	**(76.7)**
	Discontinued due to adverse event	8	(2.0)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	33	(8.4)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	91	(23.0)	152	(38.1)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	15	(3.8)	21	(5.3)
	Discontinued due to withdrawal by participant	23	(5.8)	35	(8.8)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	69	(17.5)	50	(12.5)
	Visit not scheduled	4	(1.0)	2	(0.5)
Adjuvant Week 117	**Expected to Complete Questionnaires**	**121**	**(30.6)**	**75**	**(18.8)**
	Completed	110	(27.8)	65	(16.3)
	Compliance (% in those expected to complete questionnaires)	110	(90.9)	65	(86.7)
	Not completed	11	(2.8)	10	(2.5)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	2	(0.5)	6	(1.5)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	1	(0.3)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	1	(0.3)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 117	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	0	(0.0)	0	(0.0)
	Other	8	(2.0)	3	(0.8)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**274**	**(69.4)**	**324**	**(81.2)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	35	(8.9)	17	(4.3)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	93	(23.5)	154	(38.6)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	15	(3.8)	22	(5.5)
	Discontinued due to withdrawal by participant	23	(5.8)	37	(9.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	89	(22.5)	63	(15.8)
	Visit not scheduled	1	(0.3)	2	(0.5)
Adjuvant Week 133	**Expected to Complete Questionnaires**	**96**	**(24.3)**	**44**	**(11.0)**
	Completed	84	(21.3)	37	(9.3)
	Compliance (% in those expected to complete questionnaires)	84	(87.5)	37	(84.1)
	Not completed	12	(3.0)	7	(1.8)
	Participant did not complete due to disease under study	0	(0.0)	1	(0.3)
	Not completed due to site staff error	3	(0.8)	3	(0.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 133	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	2	(0.5)	0	(0.0)
	Other	6	(1.5)	3	(0.8)
	With visit, no record	1	(0.3)	0	(0.0)
	Missing by Design	**299**	**(75.7)**	**355**	**(89.0)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	37	(9.4)	18	(4.5)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	98	(24.8)	155	(38.8)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	15	(3.8)	23	(5.8)
	Discontinued due to withdrawal by participant	24	(6.1)	36	(9.0)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	105	(26.6)	91	(22.8)
	Visit not scheduled	2	(0.5)	3	(0.8)
Adjuvant Week 159	**Expected to Complete Questionnaires**	**74**	**(18.7)**	**42**	**(10.5)**
	Completed	70	(17.7)	35	(8.8)
	Compliance (% in those expected to complete questionnaires)	70	(94.6)	35	(83.3)
	Not completed	4	(1.0)	7	(1.8)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	3	(0.8)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 159	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	1	(0.3)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	1	(0.3)
	Other	3	(0.8)	2	(0.5)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**321**	**(81.3)**	**357**	**(89.5)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	37	(9.4)	18	(4.5)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	99	(25.1)	159	(39.8)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	15	(3.8)	24	(6.0)
	Discontinued due to withdrawal by participant	25	(6.3)	37	(9.3)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	126	(31.9)	90	(22.6)
	Visit not scheduled	1	(0.3)	0	(0.0)
Adjuvant Week 185	**Expected to Complete Questionnaires**	**39**	**(9.9)**	**21**	**(5.3)**
	Completed	32	(8.1)	18	(4.5)
	Compliance (% in those expected to complete questionnaires)	32	(82.1)	18	(85.7)
	Not completed	7	(1.8)	3	(0.8)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	2	(0.5)	2	(0.5)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 185	Participant in hospital or hospice	1	(0.3)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	0	(0.0)
	Other	3	(0.8)	1	(0.3)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**356**	**(90.1)**	**378**	**(94.7)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	38	(9.6)	19	(4.8)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	100	(25.3)	161	(40.4)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	16	(4.1)	25	(6.3)
	Discontinued due to withdrawal by participant	27	(6.8)	38	(9.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	155	(39.2)	106	(26.6)
	Visit not scheduled	2	(0.5)	0	(0.0)
Adjuvant Week 211	**Expected to Complete Questionnaires**	**24**	**(6.1)**	**11**	**(2.8)**
	Completed	23	(5.8)	10	(2.5)
	Compliance (% in those expected to complete questionnaires)	23	(95.8)	10	(90.9)
	Not completed	1	(0.3)	1	(0.3)
	Participant did not complete due to disease under study	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 211	Not completed due to site staff error	0	(0.0)	1	(0.3)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant refused for other reasons	1	(0.3)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**371**	**(93.9)**	**388**	**(97.2)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	38	(9.6)	19	(4.8)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	100	(25.3)	162	(40.6)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	16	(4.1)	25	(6.3)
	Discontinued due to withdrawal by participant	28	(7.1)	38	(9.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	171	(43.3)	115	(28.8)
	Visit not scheduled	0	(0.0)	0	(0.0)
Adjuvant Week 237	**Expected to Complete Questionnaires**	**5**	**(1.3)**	**5**	**(1.3)**
	Completed	3	(0.8)	5	(1.3)
	Compliance (% in those expected to complete questionnaires)	3	(60.0)	5	(100.0)
	Not completed	2	(0.5)	0	(0.0)

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Adjuvant Week 237	Participant 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)
	Participant in hospital or hospice	0	(0.0)	0	(0.0)
	Participant was physically unable to complete	0	(0.0)	0	(0.0)
	Participant lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Participant did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Participant 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	**390**	**(98.7)**	**394**	**(98.7)**
	Discontinued due to adverse event	9	(2.3)	7	(1.8)
	Discontinued due to clinical progression	1	(0.3)	2	(0.5)
	Discontinued due to death	38	(9.6)	19	(4.8)
	Discontinued due to local progression preventing surgery	1	(0.3)	5	(1.3)
	Discontinued due to non-study anti-cancer therapy	2	(0.5)	12	(3.0)
	Discontinued due to physician decision	4	(1.0)	3	(0.8)
	Discontinued due to progressive disease	101	(25.6)	162	(40.6)
	Discontinued due to protocol violation	1	(0.3)	0	(0.0)
	Discontinued due to relapse/recurrence	16	(4.1)	25	(6.3)
	Discontinued due to withdrawal by participant	28	(7.1)	38	(9.5)
	Translation not available in participants language	0	(0.0)	0	(0.0)
	Participant died	0	(0.0)	0	(0.0)
	Visit not reached	189	(47.8)	121	(30.3)
	Visit not scheduled	0	(0.0)	0	(0.0)

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

Compliance is the proportion of patients 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 patients in the analysis population (N).

Treatment Visit	Category	Pembro + Chemo/Pembro N=395		Placebo + Chemo/Placebo N=399	
		n	(%)	n	(%)
Missing by design includes: adverse event, death, discontinuation, translations not available, and no visit scheduled. Database Cutoff Date: 10JUL2023					

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

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

Anhang 4-G4.1: Mortalität

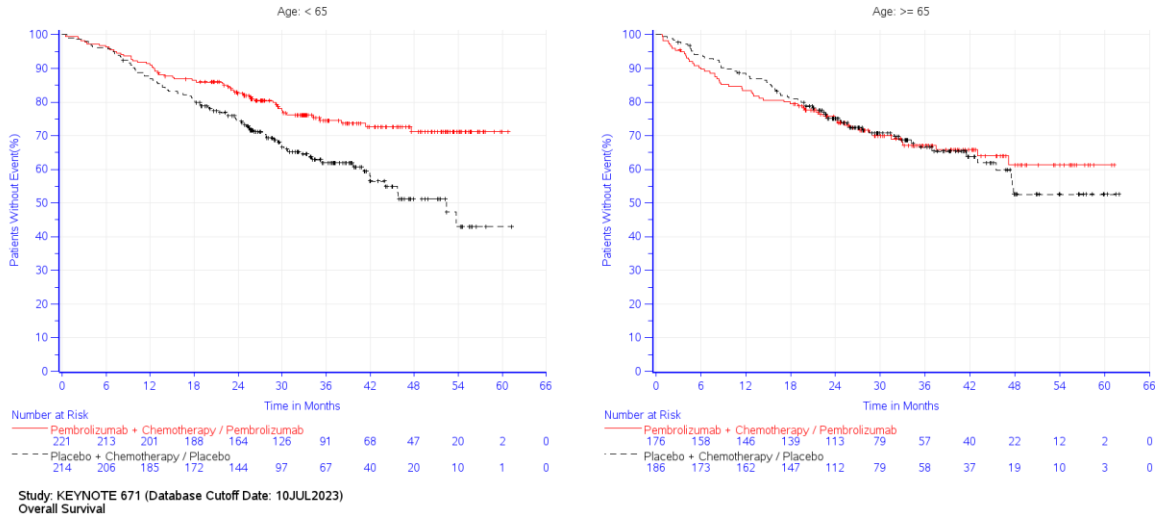

Abbildung 4G-2: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für den Endpunkt Gesamtüberleben der Studie KEYNOTE 671

Anhang 4-G4.2: Morbidität

Zeit bis zur ersten Folgeoperation

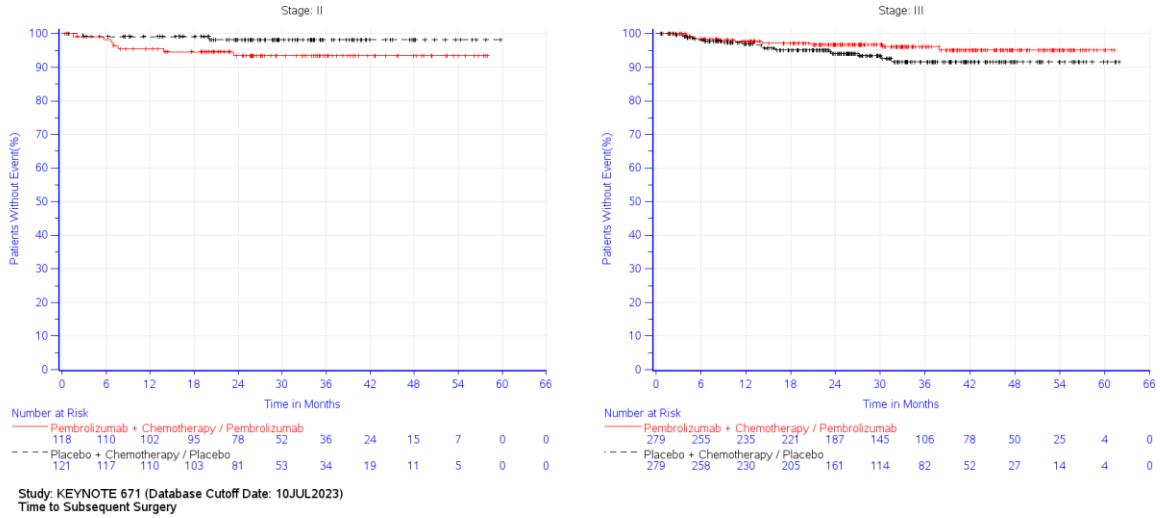

Abbildung 4G-3: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Tumorstadium für den Endpunkt Zeit bis zur ersten Folgeoperation der Studie KEYNOTE 671

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

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

Anhang 4-G5.1: Mortalität

Tabelle 4G-9: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**			**Placebo + Chemotherapy[b] / Placebo**			**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
Overall Survival	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Sex									
Male	279	89 (31.9)	Not reached [-; -]	284	114 (40.1)	45.8 [41.1; -]	0.73 [0.55; 0.96]	0.023	0.852
Female	118	21 (17.8)	Not reached [-; -]	116	30 (25.9)	Not reached [47.6; -]	0.69 [0.39; 1.20]	0.189	
ECOG Performance Status									
0	253	62 (24.5)	Not reached [-; -]	246	77 (31.3)	Not reached [47.5; -]	0.74 [0.53; 1.03]	0.075	0.964
1	144	48 (33.3)	Not reached [47.2; -]	154	67 (43.5)	44.1 [34.1; -]	0.72 [0.50; 1.04]	0.079	
Region									
WHO Stratum A	204	51 (25.0)	Not reached [-; -]	217	66 (30.4)	Not reached [47.6; -]	0.78 [0.54; 1.13]	0.194	0.467
Rest of World	193	59 (30.6)	Not reached [-; -]	183	78 (42.6)	42.0 [34.1; -]	0.66 [0.47; 0.93]	0.018	
Stage									
II	118	26 (22.0)	Not reached [-; -]	121	39 (32.2)	53.7 [42.0; -]	0.67 [0.41; 1.10]	0.116	0.785
III	279	84 (30.1)	Not reached [-; -]	279	105 (37.6)	52.4 [44.1; -]	0.74 [0.55; 0.98]	0.036	
PD-L1 Status									
TPS ≥ 50%	132	23 (17.4)	Not reached [-; -]	134	39 (29.1)	Not reached [-; -]	0.55 [0.33; 0.92]	0.023	0.178
TPS < 50%	265	87 (32.8)	Not reached [-; -]	266	105 (39.5)	47.5 [42.0; -]	0.79 [0.60; 1.06]	0.112	
Histology									
Squamous	171	61 (35.7)	Not reached [47.2; -]	173	80 (46.2)	42.0 [30.7; 47.8]	0.71 [0.51; 0.99]	0.044	0.881
Non-Squamous	226	49 (21.7)	Not reached [-; -]	227	64 (28.2)	Not reached [52.4; -]	0.73 [0.50; 1.06]	0.098	
ALK Translocation Status									
Yes	12	1 (8.3)	Not reached [47.6; -]	9	1 (11.1)	Not reached [9.6; -]	n.a. [n.a.; n.a.]	0.997	0.993
No	104	22 (21.2)	Not reached [-; -]	132	38 (28.8)	Not reached [52.4; -]	0.70 [0.41; 1.18]	0.181	

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[b] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
Overall Survival	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Unknown/Missing	281	87 (31.0)	Not reached [-; -]	259	105 (40.5)	45.8 [41.5; -]	0.72 [0.54; 0.96]	0.023	
Known EGFR Activating Mutation Status									
Yes	14	1 (7.1)	Not reached [-; -]	19	5 (26.3)	Not reached [27.3; -]	0.24 [0.03; 2.03]	0.189	0.463
No	111	20 (18.0)	Not reached [-; -]	124	33 (26.6)	Not reached [52.4; -]	0.64 [0.37; 1.11]	0.115	
Unknown/Missing	272	89 (32.7)	Not reached [-; -]	257	106 (41.2)	45.8 [41.1; -]	0.75 [0.56; 0.99]	0.044	
Smoking Status									
Never Smoker	54	10 (18.5)	Not reached [-; -]	47	9 (19.1)	Not reached [47.5; -]	1.00 [0.41; 2.46]	0.999	0.473
Former Smoker	247	69 (27.9)	Not reached [-; -]	250	87 (34.8)	53.7 [43.0; -]	0.76 [0.56; 1.05]	0.095	
Current Smoker	96	31 (32.3)	Not reached [-; -]	103	48 (46.6)	42.0 [26.1; -]	0.59 [0.38; 0.93]	0.023	
Race									
White	250	73 (29.2)	Not reached [-; -]	239	97 (40.6)	47.5 [41.5; -]	0.66 [0.49; 0.90]	0.008	0.235
All Others	134	34 (25.4)	Not reached [-; -]	145	39 (26.9)	Not reached [45.5; -]	0.93 [0.59; 1.48]	0.764	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

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

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

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

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

ALK: Anaplastic Lymphoma Kinase; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal Growth Factor Receptor; n.a.: not applicable (when estimation not possible); PD-L1: Programmed Death-Ligand 1; TPS: Tumor Proportion Score; WHO: World Health Organization

Anhang 4-G5.2: Morbidität

Ereignisfreies Überleben

Tabelle 4G-10: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Ereignisfreies Überleben aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**			**Placebo + Chemotherapy[b] / Placebo**			**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
Event-Free Survival Based on Investigator Assessment	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Sex									
Male	279	127 (45.5)	47.2 [28.6; -]	284	178 (62.7)	18.3 [14.6; 22.4]	0.62 [0.49; 0.78]	< 0.001	0.442
Female	118	47 (39.8)	51.1 [31.7; -]	116	70 (60.3)	19.0 [11.7; 26.3]	0.52 [0.36; 0.75]	< 0.001	
Age									
< 65	221	88 (39.8)	Not reached [40.1; -]	214	136 (63.6)	17.9 [14.2; 22.1]	0.51 [0.39; 0.67]	< 0.001	0.105
≥ 65	176	86 (48.9)	31.7 [25.2; -]	186	112 (60.2)	21.1 [14.5; 25.6]	0.70 [0.52; 0.92]	0.011	
ECOG Performance Status									
0	253	105 (41.5)	Not reached [34.1; -]	246	150 (61.0)	20.6 [14.1; 23.3]	0.57 [0.45; 0.74]	< 0.001	0.647
1	144	69 (47.9)	37.5 [25.1; -]	154	98 (63.6)	16.6 [14.3; 22.1]	0.62 [0.46; 0.84]	0.002	
Region									
WHO Stratum A	204	84 (41.2)	47.6 [38.0; -]	217	127 (58.5)	19.6 [14.6; 25.6]	0.60 [0.46; 0.80]	< 0.001	0.844
Rest of World	193	90 (46.6)	34.1 [26.0; -]	183	121 (66.1)	16.6 [13.2; 22.1]	0.57 [0.44; 0.75]	< 0.001	
Stage									
II	118	40 (33.9)	Not reached [37.5; -]	121	62 (51.2)	22.9 [21.2; -]	0.59 [0.40; 0.88]	0.010	0.842
III	279	134 (48.0)	38.0 [25.2; -]	279	186 (66.7)	14.3 [11.8; 18.1]	0.58 [0.46; 0.72]	< 0.001	
PD-L1 Status									
TPS ≥ 50%	132	41 (31.1)	Not reached [47.2; -]	134	70 (52.2)	26.3 [14.6; -]	0.48 [0.33; 0.71]	< 0.001	0.184
TPS < 50%	265	133 (50.2)	31.5 [22.6; 51.1]	266	178 (66.9)	16.6 [14.0; 21.2]	0.63 [0.51; 0.79]	< 0.001	
Histology									
Squamous	171	72 (42.1)	51.1 [37.5; -]	173	117 (67.6)	15.2 [12.8; 22.0]	0.51 [0.38; 0.69]	< 0.001	0.191
Non-Squamous	226	102 (45.1)	39.2 [27.7; -]	227	131 (57.7)	21.2 [14.8; 26.3]	0.66 [0.51; 0.86]	0.002	
ALK Translocation Status									
Yes	12	6 (50.0)	47.6 [4.5; -]	9	3 (33.3)	Not reached [0.4; -]	1.29 [0.31; 5.43]	0.725	0.254
No	104	42 (40.4)	Not reached [24.2; -]	132	85 (64.4)	14.5 [11.4; 21.1]	0.50 [0.35; 0.73]	< 0.001	
Unknown/Missing	281	126 (44.8)	40.1 [32.5; -]	259	160 (61.8)	21.1 [15.1; 22.9]	0.62 [0.49; 0.78]	< 0.001	

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[b] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
Event-Free Survival Based on Investigator Assessment	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Known EGFR Activating Mutation Status									
Yes	14	5 (35.7)	Not reached [16.4; -]	19	13 (68.4)	11.7 [5.8; 23.8]	0.32 [0.11; 0.91]	0.032	0.435
No	111	42 (37.8)	Not reached [29.4; -]	124	72 (58.1)	19.6 [13.8; 25.9]	0.55 [0.38; 0.81]	0.002	
Unknown/Missing	272	127 (46.7)	39.2 [29.3; -]	257	163 (63.4)	18.5 [14.6; 22.6]	0.62 [0.49; 0.79]	< 0.001	
Smoking Status									
Never Smoker	54	25 (46.3)	39.2 [22.1; -]	47	25 (53.2)	21.4 [9.4; -]	0.77 [0.44; 1.35]	0.368	0.596
Former Smoker	247	105 (42.5)	47.6 [31.7; -]	250	155 (62.0)	21.1 [14.7; 22.8]	0.59 [0.46; 0.75]	< 0.001	
Current Smoker	96	44 (45.8)	51.1 [26.3; -]	103	68 (66.0)	14.8 [11.4; 22.0]	0.53 [0.36; 0.77]	0.001	
Race									
White	250	109 (43.6)	47.6 [31.7; -]	239	151 (63.2)	18.1 [14.2; 22.1]	0.56 [0.44; 0.72]	< 0.001	0.570
All Others	134	57 (42.5)	39.4 [25.8; -]	145	85 (58.6)	21.7 [14.9; 29.5]	0.63 [0.45; 0.88]	0.007	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

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

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

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

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

ALK: Anaplastic Lymphoma Kinase; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal Growth Factor Receptor; PD-L1: Programmed Death-Ligand 1; TPS: Tumor Proportion Score; WHO: World Health Organization

Pathologische Komplettremission

Tabelle 4G-11: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Ereignisfreies Überleben aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab		Placebo + Chemotherapy[b] / Placebo		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
BIPR Pathologic Complete Response Indicator	N[c]	Participants with Event n (%)	N[c]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	p-Value for Interaction[f] Test
Sex							
Male	279	46 (16.5)	284	10 (3.5)	4.68 [2.41; 9.09]	< 0.001	0.864
Female	118	26 (22.0)	116	6 (5.2)	4.26 [1.82; 9.97]	< 0.001	
Age							
< 65	221	45 (20.4)	214	9 (4.2)	4.84 [2.43; 9.66]	< 0.001	0.751
≥ 65	176	27 (15.3)	186	7 (3.8)	4.08 [1.82; 9.12]	< 0.001	
ECOG Performance Status							
0	253	54 (21.3)	246	11 (4.5)	4.77 [2.56; 8.91]	< 0.001	0.716

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab		Placebo + Chemotherapy[b] / Placebo		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
BIPR Pathologic Complete Response Indicator	**Participants with Event**		**Participants with Event**		**Risk Ratio/ Peto-Odds Ratio[d]**		**p-Value for Interaction[f] Test**
	N[c]	**n (%)**	**N[c]**	**n (%)**	**[95 %-CI]**	**p-Value[e]**	
1	144	18 (12.5)	154	5 (3.2)	3.85 [1.47; 10.10]	0.006	
Region							
WHO Stratum A	204	37 (18.1)	217	9 (4.1)	4.37 [2.17; 8.83]	< 0.001	0.881
Rest of World	193	35 (18.1)	183	7 (3.8)	4.74 [2.16; 10.40]	< 0.001	
Stage							
II	118	29 (24.6)	121	4 (3.3)	7.43 [2.70; 20.50]	< 0.001	0.209
III	279	43 (15.4)	279	12 (4.3)	3.58 [1.93; 6.65]	< 0.001	
PD-L1 Status							
TPS ≥ 50%	132	36 (27.3)	134	8 (6.0)	4.57 [2.21; 9.45]	< 0.001	0.983
TPS < 50%	265	36 (13.6)	266	8 (3.0)	4.52 [2.14; 9.53]	< 0.001	
Histology							
Squamous	171	20 (11.7)	173	8 (4.6)	2.53 [1.15; 5.59]	0.022	0.085
Non-Squamous	226	52 (23.0)	227	8 (3.5)	6.53 [3.17; 13.43]	< 0.001	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Peto-Odds Ratio instead of Relative Risk if incidence is ≤ 1 % or ≥ 99 % in at least one cell

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

f: Based on generalized linear model with subgroup, treatment as covariates as well as treatment by subgroup interaction, considering a binomial distribution with log link function (p-value of likelihood ratio test for interaction term)

Responses are based on BIPR assessments

BIPR: Blinded Independent Pathologist Review; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Death-Ligand 1; TPS: Tumor Proportion Score; WHO: World Health Organization

Zeit bis zur ersten Folgetherapie

Tabelle 4G-12: 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 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[b] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
Time to Subsequent Oncologic Therapy	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Sex									
Male	279	77 (27.6)	Not reached [-; -]	284	136 (47.9)	27.2 [22.7; 44.9]	0.50 [0.37; 0.66]	< 0.001	0.296
Female	118	33 (28.0)	Not reached [47.8; -]	116	65 (56.0)	21.0 [11.3; 33.6]	0.38 [0.25; 0.58]	< 0.001	
Age									
< 65	221	65 (29.4)	Not reached [-; -]	214	122 (57.0)	19.7 [15.4; 23.9]	0.41 [0.30; 0.56]	< 0.001	0.291
≥ 65	176	45 (25.6)	Not reached [-; -]	186	79 (42.5)	41.1 [25.3; -]	0.52 [0.36; 0.76]	< 0.001	
ECOG Performance Status									

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[b] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
Time to Subsequent Oncologic Therapy	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
0	253	65 (25.7)	Not reached [-; -]	246	121 (49.2)	26.2 [19.7; -]	0.44 [0.32; 0.59]	< 0.001	0.725
1	144	45 (31.3)	Not reached [52.0; -]	154	80 (51.9)	23.8 [15.6; 44.9]	0.49 [0.34; 0.71]	< 0.001	
Region									
WHO Stratum A	204	65 (31.9)	Not reached [-; -]	217	113 (52.1)	23.4 [16.1; 44.9]	0.51 [0.37; 0.69]	< 0.001	0.384
Rest of World	193	45 (23.3)	Not reached [-; -]	183	88 (48.1)	27.7 [19.7; -]	0.40 [0.28; 0.57]	< 0.001	
Stage									
II	118	24 (20.3)	Not reached [-; -]	121	52 (43.0)	Not reached [23.9; -]	0.42 [0.26; 0.68]	< 0.001	0.819
III	279	86 (30.8)	Not reached [-; -]	279	149 (53.4)	21.0 [15.3; 26.8]	0.46 [0.35; 0.60]	< 0.001	
PD-L1 Status									
TPS ≥ 50%	132	26 (19.7)	Not reached [-; -]	134	53 (39.6)	Not reached [23.9; -]	0.41 [0.26; 0.65]	< 0.001	0.529
TPS < 50%	265	84 (31.7)	Not reached [-; -]	266	148 (55.6)	23.0 [16.2; 26.2]	0.47 [0.36; 0.62]	< 0.001	
Histology									
Squamous	171	38 (22.2)	Not reached [-; -]	173	86 (49.7)	26.8 [18.1; 39.9]	0.38 [0.26; 0.56]	< 0.001	0.207
Non-Squamous	226	72 (31.9)	Not reached [-; -]	227	115 (50.7)	23.5 [19.3; 44.9]	0.51 [0.38; 0.68]	< 0.001	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Death-Ligand 1; TPS: Tumor Proportion Score; WHO: World Health Organization

Zeit bis zur ersten Folgeoperation

Tabelle 4G-13: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Zeit bis zur ersten Folgeoperation aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**			**Placebo + Chemotherapy[b] / Placebo**			**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
Time to Subsequent Surgery	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Sex									
Male	279	14 (5.0)	Not reached [-; -]	284	11 (3.9)	Not reached [-; -]	1.24 [0.56; 2.73]	0.594	0.109
Female	118	3 (2.5)	Not reached [-; -]	116	8 (6.9)	Not reached [-; -]	0.36 [0.10; 1.38]	0.137	
Age									
< 65	221	10 (4.5)	Not reached [-; -]	214	10 (4.7)	Not reached [-; -]	0.90 [0.37; 2.15]	0.805	0.911
≥ 65	176	7 (4.0)	Not reached [-; -]	186	9 (4.8)	Not reached [-; -]	0.84 [0.31; 2.26]	0.734	
ECOG Performance Status									
0	253	13 (5.1)	Not reached [-; -]	246	10 (4.1)	Not reached [-; -]	1.26 [0.55; 2.88]	0.582	0.142
1	144	4 (2.8)	Not reached [-; -]	154	9 (5.8)	Not reached [-; -]	0.43 [0.13; 1.41]	0.165	
Region									
WHO Stratum A	204	13 (6.4)	Not reached [-; -]	217	14 (6.5)	Not reached [-; -]	0.97 [0.46; 2.07]	0.938	0.720
Rest of World	193	4 (2.1)	Not reached [-; -]	183	5 (2.7)	Not reached [-; -]	0.71 [0.19; 2.67]	0.617	
PD-L1 Status									
TPS ≥ 50%	132	2 (1.5)	Not reached [-; -]	134	6 (4.5)	Not reached [-; -]	0.31 [0.06; 1.54]	0.153	0.116
TPS < 50%	265	15 (5.7)	Not reached [-; -]	266	13 (4.9)	Not reached [-; -]	1.16 [0.55; 2.44]	0.693	
Histology									
Squamous	171	7 (4.1)	Not reached [-; -]	173	6 (3.5)	Not reached [-; -]	1.14 [0.38; 3.40]	0.813	0.548
Non-Squamous	226	10 (4.4)	Not reached [-; -]	227	13 (5.7)	Not reached [-; -]	0.76 [0.33; 1.72]	0.506	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Death-Ligand 1; TPS: Tumor Proportion Score; WHO: World Health Organization

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30: Symptomskala Erschöpfung

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

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-C30 Fatigue	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	262	20.48 (20.39)	5.52 (0.89)	-2.60	-0.14	0.570
Placebo + Chemotherapy[b] / Placebo	282	265	18.99 (18.46)	8.11 (0.91)	[-5.11; -0.09]	[-0.27; -0.00]	
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	109	19.78 (19.38)	10.13 (1.71)	-0.87	-	
Placebo + Chemotherapy[b] / Placebo	116	111	21.02 (23.94)	11.00 (1.77)	[-5.72; 3.99]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	233	17.36 (17.34)	7.77 (0.99)	-1.61	-	0.556
Placebo + Chemotherapy[b] / Placebo	245	233	16.02 (16.79)	9.38 (1.02)	[-4.40; 1.18]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	25.20 (23.23)	4.98 (1.37)	-3.27	-	
Placebo + Chemotherapy[b] / Placebo	153	143	25.41 (23.76)	8.25 (1.40)	[-7.13; 0.58]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	193	23.66 (21.75)	8.50 (1.15)	-0.92	-	0.499
Placebo + Chemotherapy[b] / Placebo	215	203	22.93 (23.11)	9.42 (1.15)	[-4.12; 2.28]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	178	16.60 (17.41)	5.28 (1.10)	-2.97	-	
Placebo + Chemotherapy[b] / Placebo	183	173	15.67 (15.34)	8.25 (1.16)	[-6.13; 0.18]		

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Fatigue	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	20.15 (19.97)	5.91 (1.49)	-3.37	-	0.607
Placebo + Chemotherapy[b] / Placebo	121	117	16.33 (16.92)	9.28 (1.46)	[-7.49; 0.75]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	264	20.33 (20.15)	7.22 (0.97)	-1.68	-	
Placebo + Chemotherapy[b] / Placebo	277	259	21.06 (21.41)	8.90 (1.01)	[-4.43; 1.07]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	123	20.51 (18.98)	5.62 (1.42)	-3.89	-	0.252
Placebo + Chemotherapy[b] / Placebo	132	126	19.14 (20.69)	9.51 (1.44)	[-7.89; 0.11]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	20.16 (20.63)	7.56 (0.99)	-1.09	-	
Placebo + Chemotherapy[b] / Placebo	266	250	19.82 (20.02)	8.65 (1.02)	[-3.88; 1.70]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	23.33 (21.52)	6.58 (1.18)	-2.31	-	0.868
Placebo + Chemotherapy[b] / Placebo	171	158	19.20 (19.29)	8.90 (1.23)	[-5.67; 1.04]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	210	17.94 (18.60)	6.96 (1.11)	-2.23	-	
Placebo + Chemotherapy[b] / Placebo	227	218	19.88 (20.91)	9.19 (1.13)	[-5.36; 0.89]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

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

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

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

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Fatigue	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
h: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed							
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization							

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-15: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Übelkeit und Erbrechen des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-C30 Nausea and Vomiting	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	210	2.70 (9.95)	3.54 (0.59)	-1.15	-	0.232
Placebo + Chemotherapy[b] / Placebo	213	204	3.92 (12.20)	4.68 (0.64)	[-2.87; 0.58]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	1.86 (7.90)	4.23 (0.52)	0.25	-	
Placebo + Chemotherapy[b] / Placebo	185	172	1.94 (6.94)	3.99 (0.53)	[-1.21; 1.71]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	233	1.93 (8.32)	4.25 (0.50)	-0.40	-	0.686
Placebo + Chemotherapy[b] / Placebo	245	233	1.93 (7.73)	4.65 (0.52)	[-1.83; 1.02]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	3.02 (10.31)	3.13 (0.68)	-0.77	-	
Placebo + Chemotherapy[b] / Placebo	153	143	4.78 (13.06)	3.91 (0.72)	[-2.73; 1.19]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	193	2.68 (8.84)	2.86 (0.61)	-0.96	-	0.528
Placebo + Chemotherapy[b] / Placebo	215	203	4.27 (12.56)	3.82 (0.62)	[-2.67; 0.75]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	178	1.97 (9.42)	5.10 (0.54)	-0.19	-	
Placebo + Chemotherapy[b] / Placebo	183	173	1.54 (6.03)	5.29 (0.60)	[-1.79; 1.40]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	2.96 (9.10)	4.19 (0.70)	0.14	-	0.425

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Nausea and Vomiting	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	121	117	1.28 (5.43)	4.05 (0.70)	[-1.83; 2.11]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	264	2.08 (9.13)	3.69 (0.49)	-0.84	-	
Placebo + Chemotherapy[b] / Placebo	277	259	3.80 (11.63)	4.53 (0.53)	[-2.26; 0.58]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	123	2.71 (11.57)	4.19 (0.75)	-0.51	-	0.895
Placebo + Chemotherapy[b] / Placebo	132	126	3.04 (11.81)	4.70 (0.78)	[-2.65; 1.63]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	2.15 (7.64)	3.65 (0.47)	-0.59	-	
Placebo + Chemotherapy[b] / Placebo	266	250	3.00 (9.26)	4.24 (0.50)	[-1.94; 0.77]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	3.42 (10.39)	3.05 (0.52)	-0.37	-	0.671
Placebo + Chemotherapy[b] / Placebo	171	158	2.74 (9.93)	3.42 (0.56)	[-1.88; 1.14]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	210	1.51 (7.93)	4.39 (0.58)	-0.73	-	
Placebo + Chemotherapy[b] / Placebo	227	218	3.21 (10.36)	5.12 (0.61)	[-2.39; 0.93]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

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

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

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

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

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Schmerzen

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

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-C30 Pain	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	262	13.04 (21.70)	4.78 (0.87)	-2.60	-0.14	0.374
Placebo + Chemotherapy[b] / Placebo	282	265	11.89 (19.58)	7.38 (0.89)	[-5.05; -0.15]	[-0.27; -0.01]	
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	109	16.21 (21.69)	3.89 (1.56)	-4.77	-0.22	
Placebo + Chemotherapy[b] / Placebo	116	111	18.77 (26.03)	8.66 (1.62)	[-9.20; -0.35]	[-0.42; -0.02]	
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	233	11.02 (17.92)	5.34 (0.93)	-1.87	-	0.145
Placebo + Chemotherapy[b] / Placebo	245	233	10.94 (18.84)	7.22 (0.96)	[-4.50; 0.75]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	18.96 (26.27)	3.08 (1.33)	-5.39	-0.26	
Placebo + Chemotherapy[b] / Placebo	153	143	18.76 (25.40)	8.47 (1.35)	[-9.13; -1.66]	[-0.43; -0.08]	
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	193	16.84 (24.41)	5.29 (1.12)	-2.21	-	0.454
Placebo + Chemotherapy[b] / Placebo	215	203	16.34 (24.48)	7.50 (1.12)	[-5.32; 0.89]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	178	10.86 (17.91)	3.82 (1.04)	-4.08	-0.22	
Placebo + Chemotherapy[b] / Placebo	183	173	11.08 (18.00)	7.90 (1.09)	[-7.04; -1.12]	[-0.38; -0.06]	
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	11.21 (20.19)	4.88 (1.49)	-3.66	-	0.678

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Pain	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	121	117	7.55 (12.85)	8.54 (1.46)	[-7.78; 0.46]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	264	15.09 (22.25)	4.31 (0.89)	-2.88	-0.15	
Placebo + Chemotherapy[b] / Placebo	277	259	16.80 (24.38)	7.18 (0.94)	[-5.41; -0.34]	[-0.27; -0.02]	
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	123	12.60 (20.51)	4.99 (1.24)	-2.71	-	0.825
Placebo + Chemotherapy[b] / Placebo	132	126	13.49 (20.52)	7.70 (1.26)	[-6.20; 0.78]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	14.65 (22.30)	4.36 (0.98)	-3.31	-0.16	
Placebo + Chemotherapy[b] / Placebo	266	250	14.13 (22.56)	7.67 (1.01)	[-6.06; -0.56]	[-0.30; -0.03]	
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	12.42 (21.67)	6.08 (1.11)	-1.96	-	0.291
Placebo + Chemotherapy[b] / Placebo	171	158	12.24 (19.59)	8.05 (1.16)	[-5.11; 1.18]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	210	15.16 (21.73)	3.40 (1.06)	-4.13	-0.20	
Placebo + Chemotherapy[b] / Placebo	227	218	15.14 (23.36)	7.53 (1.08)	[-7.10; -1.15]	[-0.34; -0.06]	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

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

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

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

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

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Atemnot (Dyspnoe)

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

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-C30 Dyspnoea	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	262	21.76 (24.88)	5.17 (1.03)	-4.18	-0.19	0.714
Placebo + Chemotherapy[b] / Placebo	282	265	21.64 (24.13)	9.35 (1.06)	[-7.08; -1.27]	[-0.31; -0.06]	
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	109	21.41 (22.92)	6.71 (1.77)	-2.98	-	
Placebo + Chemotherapy[b] / Placebo	116	111	18.92 (25.67)	9.69 (1.82)	[-7.99; 2.04]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	193	25.39 (27.11)	5.28 (1.27)	-4.24	-0.18	0.678
Placebo + Chemotherapy[b] / Placebo	215	203	24.63 (27.87)	9.53 (1.28)	[-7.79; -0.70]	[-0.32; -0.03]	
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	178	17.60 (20.10)	6.23 (1.25)	-2.91	-	
Placebo + Chemotherapy[b] / Placebo	183	173	16.38 (19.23)	9.14 (1.31)	[-6.48; 0.65]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	22.74 (23.61)	4.70 (1.75)	-5.12	-0.22	0.527
Placebo + Chemotherapy[b] / Placebo	121	117	19.66 (21.51)	9.82 (1.71)	[-9.95; -0.30]	[-0.42; -0.01]	
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	264	21.21 (24.59)	6.01 (1.04)	-3.29	-0.14	
Placebo + Chemotherapy[b] / Placebo	277	259	21.36 (25.89)	9.30 (1.09)	[-6.26; -0.33]	[-0.27; -0.01]	
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	123	20.60 (23.96)	5.61 (1.54)	-3.65	-	0.876

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Dyspnoea	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	132	126	18.52 (23.31)	9.27 (1.56)	[-7.98; 0.67]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	22.18 (24.48)	5.59 (1.11)	-3.92	-0.17	
Placebo + Chemotherapy[b] / Placebo	266	250	22.00 (25.18)	9.51 (1.14)	[-7.05; -0.80]	[-0.31; -0.03]	
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	26.50 (26.90)	3.46 (1.45)	-5.24	-0.22	0.313
Placebo + Chemotherapy[b] / Placebo	171	158	23.84 (25.82)	8.70 (1.51)	[-9.38; -1.11]	[-0.39; -0.05]	
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	210	17.94 (21.41)	7.20 (1.13)	-2.70	-	
Placebo + Chemotherapy[b] / Placebo	227	218	18.65 (23.49)	9.90 (1.15)	[-5.87; 0.47]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

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

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

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

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

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

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

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-C30 Insomnia	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	262	20.74 (27.18)	-0.36 (1.03)	-1.92	-	0.525
Placebo + Chemotherapy[b] / Placebo	282	265	16.35 (23.94)	1.56 (1.05)	[-4.81; 0.98]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	109	28.44 (31.37)	-2.43 (1.84)	-3.59	-	
Placebo + Chemotherapy[b] / Placebo	116	111	26.13 (32.23)	1.17 (1.90)	[-8.81; 1.62]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	210	24.29 (29.49)	-1.85 (1.21)	-3.18	-	0.514
Placebo + Chemotherapy[b] / Placebo	213	204	20.42 (29.07)	1.34 (1.27)	[-6.64; 0.27]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	21.33 (27.53)	0.14 (1.38)	-1.54	-	
Placebo + Chemotherapy[b] / Placebo	185	172	17.83 (24.29)	1.68 (1.38)	[-5.37; 2.30]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	233	22.03 (27.35)	-1.04 (1.11)	-2.58	-	0.833
Placebo + Chemotherapy[b] / Placebo	245	233	18.88 (26.19)	1.54 (1.14)	[-5.71; 0.55]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	24.64 (30.75)	-0.88 (1.56)	-2.02	-	
Placebo + Chemotherapy[b] / Placebo	153	143	19.81 (28.32)	1.14 (1.60)	[-6.43; 2.39]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	193	29.88 (30.23)	-4.83 (1.32)	-3.36	-	0.348

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Insomnia	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	215	203	25.62 (30.95)	-1.47 (1.33)	[-7.05; 0.33]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	178	15.54 (24.84)	3.36 (1.23)	-1.27	-	
Placebo + Chemotherapy[b] / Placebo	183	173	11.75 (18.93)	4.63 (1.30)	[-4.79; 2.25]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	20.25 (26.99)	-0.26 (1.56)	-0.89	-	0.469
Placebo + Chemotherapy[b] / Placebo	121	117	15.67 (25.36)	0.63 (1.54)	[-5.22; 3.44]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	264	24.12 (29.27)	-1.35 (1.11)	-3.13	-	
Placebo + Chemotherapy[b] / Placebo	277	259	20.85 (27.58)	1.78 (1.16)	[-6.29; 0.03]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	123	22.49 (28.47)	-4.78 (1.57)	-5.50	-0.23	0.114
Placebo + Chemotherapy[b] / Placebo	132	126	23.54 (31.57)	0.71 (1.60)	[-9.91; -1.09]	[-0.41; -0.05]	
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	23.25 (28.79)	0.89 (1.11)	-1.05	-	
Placebo + Chemotherapy[b] / Placebo	266	250	17.07 (24.13)	1.94 (1.14)	[-4.19; 2.09]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	22.77 (30.14)	0.24 (1.34)	-2.06	-	0.610
Placebo + Chemotherapy[b] / Placebo	171	158	16.24 (24.88)	2.29 (1.40)	[-5.88; 1.77]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	210	23.17 (27.52)	-1.92 (1.24)	-2.82	-	
Placebo + Chemotherapy[b] / Placebo	227	218	21.41 (28.27)	0.90 (1.25)	[-6.28; 0.63]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Insomnia	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**

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

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

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

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

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Appetitverlust

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

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-C30 Appetite Loss	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	262	10.43 (22.06)	4.65 (0.83)	-0.96	-	0.633
Placebo + Chemotherapy[b] / Placebo	282	265	7.17 (16.25)	5.61 (0.86)	[-3.32; 1.39]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	109	12.23 (21.11)	2.73 (1.57)	-1.89	-	
Placebo + Chemotherapy[b] / Placebo	116	111	12.91 (25.49)	4.62 (1.65)	[-6.39; 2.62]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	210	10.32 (21.74)	1.79 (0.98)	-2.23	-	0.313
Placebo + Chemotherapy[b] / Placebo	213	204	9.64 (20.39)	4.02 (1.04)	[-5.04; 0.58]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	11.80 (21.86)	7.08 (1.15)	0.11	-	
Placebo + Chemotherapy[b] / Placebo	185	172	7.95 (18.60)	6.97 (1.17)	[-3.12; 3.34]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	233	8.15 (19.94)	5.80 (0.86)	-1.08	-	0.765
Placebo + Chemotherapy[b] / Placebo	245	233	6.87 (16.39)	6.88 (0.90)	[-3.53; 1.37]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	15.70 (23.89)	1.04 (1.39)	-1.21	-	
Placebo + Chemotherapy[b] / Placebo	153	143	12.12 (23.59)	2.25 (1.43)	[-5.14; 2.71]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	193	13.99 (24.18)	3.13 (1.08)	-0.26	-	0.459

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Appetite Loss	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	215	203	10.34 (21.42)	3.39 (1.09)	[-3.28; 2.76]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	178	7.68 (18.34)	5.30 (1.05)	-2.21	-	
Placebo + Chemotherapy[b] / Placebo	183	173	7.13 (17.07)	7.50 (1.12)	[-5.24; 0.82]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	6.85 (14.29)	5.17 (1.30)	-1.32	-	0.913
Placebo + Chemotherapy[b] / Placebo	121	117	6.27 (15.74)	6.49 (1.29)	[-4.94; 2.30]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	264	12.63 (23.98)	3.56 (0.91)	-1.13	-	
Placebo + Chemotherapy[b] / Placebo	277	259	10.04 (21.01)	4.69 (0.97)	[-3.74; 1.48]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	123	12.74 (24.71)	3.36 (1.23)	-2.09	-	0.506
Placebo + Chemotherapy[b] / Placebo	132	126	8.99 (20.83)	5.45 (1.27)	[-5.58; 1.40]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	10.08 (20.16)	4.61 (0.95)	-0.63	-	
Placebo + Chemotherapy[b] / Placebo	266	250	8.80 (18.96)	5.24 (0.99)	[-3.32; 2.07]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	12.42 (22.30)	2.50 (1.13)	-1.89	-	0.734
Placebo + Chemotherapy[b] / Placebo	171	158	8.44 (18.02)	4.40 (1.20)	[-5.16; 1.37]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	210	9.84 (21.34)	5.26 (1.01)	-0.73	-	
Placebo + Chemotherapy[b] / Placebo	227	218	9.17 (20.68)	5.99 (1.03)	[-3.57; 2.11]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Appetite Loss	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**

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

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

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

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

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Verstopfung

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

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-C30 Constipation	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	262	8.65 (19.39)	2.07 (0.84)	-1.00	-	0.353
Placebo + Chemotherapy[b] / Placebo	282	265	7.42 (17.39)	3.06 (0.87)	[-3.37; 1.38]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	109	11.62 (21.93)	3.25 (1.58)	1.46	-	
Placebo + Chemotherapy[b] / Placebo	116	111	15.32 (27.99)	1.79 (1.65)	[-3.06; 5.98]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	210	8.41 (19.51)	2.36 (0.99)	-0.28	-	0.886
Placebo + Chemotherapy[b] / Placebo	213	204	9.64 (22.43)	2.64 (1.04)	[-3.10; 2.54]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	10.97 (21.01)	2.41 (1.19)	-0.40	-	
Placebo + Chemotherapy[b] / Placebo	185	172	9.88 (20.05)	2.81 (1.20)	[-3.72; 2.92]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	233	8.44 (18.83)	3.44 (0.94)	-1.30	-	0.194
Placebo + Chemotherapy[b] / Placebo	245	233	8.73 (17.65)	4.74 (0.97)	[-3.95; 1.36]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	11.35 (22.24)	0.58 (1.28)	1.43	-	
Placebo + Chemotherapy[b] / Placebo	153	143	11.42 (26.27)	-0.84 (1.31)	[-2.19; 5.04]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	193	12.26 (22.42)	0.29 (1.08)	0.09	-	0.758

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Constipation	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	215	203	14.29 (25.66)	0.20 (1.09)	[-2.93; 3.12]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	178	6.55 (17.01)	4.72 (1.07)	-0.83	-	
Placebo + Chemotherapy[b] / Placebo	183	173	4.43 (12.95)	5.55 (1.13)	[-3.88; 2.22]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	11.21 (22.87)	2.16 (1.34)	1.00	-	0.477
Placebo + Chemotherapy[b] / Placebo	121	117	7.41 (16.44)	1.16 (1.32)	[-2.71; 4.71]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	264	8.84 (19.00)	2.58 (0.92)	-0.82	-	
Placebo + Chemotherapy[b] / Placebo	277	259	10.81 (23.18)	3.41 (0.98)	[-3.47; 1.82]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	123	11.38 (22.11)	1.99 (1.35)	-0.98	-	0.649
Placebo + Chemotherapy[b] / Placebo	132	126	11.90 (24.02)	2.97 (1.38)	[-4.79; 2.83]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	8.60 (19.15)	2.67 (0.92)	0.15	-	
Placebo + Chemotherapy[b] / Placebo	266	250	8.67 (19.83)	2.53 (0.95)	[-2.45; 2.75]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	10.56 (22.18)	1.51 (1.04)	-0.74	-	0.828
Placebo + Chemotherapy[b] / Placebo	171	158	6.54 (17.02)	2.26 (1.09)	[-3.72; 2.23]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	210	8.73 (18.53)	3.04 (1.08)	-0.12	-	
Placebo + Chemotherapy[b] / Placebo	227	218	12.08 (23.77)	3.16 (1.10)	[-3.14; 2.91]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Constipation	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**

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

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

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

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

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Diarrhoe

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

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-C30 Diarrhea	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	262	3.05 (12.69)	1.19 (0.54)	0.23	-	0.518
Placebo + Chemotherapy[b] / Placebo	282	265	5.03 (14.50)	0.96 (0.56)	[-1.30; 1.77]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	109	7.03 (18.74)	2.16 (0.92)	1.13	-	
Placebo + Chemotherapy[b] / Placebo	116	111	3.00 (10.59)	1.02 (0.97)	[-1.52; 3.79]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	210	4.76 (15.24)	0.57 (0.61)	0.58	-	0.949
Placebo + Chemotherapy[b] / Placebo	213	204	5.39 (15.10)	-0.01 (0.64)	[-1.16; 2.32]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	3.52 (14.24)	2.79 (0.74)	0.69	-	
Placebo + Chemotherapy[b] / Placebo	185	172	3.29 (11.20)	2.10 (0.75)	[-1.38; 2.76]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	233	3.58 (12.05)	1.73 (0.56)	0.79	-	0.800
Placebo + Chemotherapy[b] / Placebo	245	233	4.72 (13.90)	0.94 (0.59)	[-0.81; 2.38]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	5.31 (18.56)	1.39 (0.85)	0.43	-	
Placebo + Chemotherapy[b] / Placebo	153	143	3.96 (12.81)	0.96 (0.87)	[-1.97; 2.83]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	3.12 (11.70)	2.22 (0.71)	2.16	0.18	0.107

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Diarrhea	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	121	117	2.85 (10.33)	0.05 (0.70)	[0.20; 4.13]	[0.02; 0.34]	
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	264	4.67 (15.90)	1.25 (0.61)	-0.19	-	
Placebo + Chemotherapy[b] / Placebo	277	259	5.15 (14.65)	1.44 (0.64)	[-1.93; 1.55]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	123	4.61 (14.98)	0.25 (0.72)	0.76	-	0.707
Placebo + Chemotherapy[b] / Placebo	132	126	5.82 (15.25)	-0.51 (0.74)	[-1.28; 2.79]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	4.03 (14.75)	2.19 (0.61)	0.36	-	
Placebo + Chemotherapy[b] / Placebo	266	250	3.73 (12.47)	1.83 (0.63)	[-1.36; 2.08]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	3.93 (14.61)	1.56 (0.75)	0.86	-	0.634
Placebo + Chemotherapy[b] / Placebo	171	158	4.43 (13.09)	0.70 (0.79)	[-1.28; 3.00]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	210	4.44 (14.99)	1.58 (0.62)	0.39	-	
Placebo + Chemotherapy[b] / Placebo	227	218	4.43 (13.79)	1.20 (0.63)	[-1.35; 2.13]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score

EORTC QLQ-LC13: Symptomskala Dyspnoe

Tabelle 4G-22: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Dyspnoe des EORTC QLQ-LC13 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-LC13 Dyspnoea	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	261	16.18 (17.85)	5.77 (0.82)	-2.64	-0.15	0.098
Placebo + Chemotherapy[b] / Placebo	282	264	15.40 (16.54)	8.42 (0.83)	[-4.94; -0.35]	[-0.29; -0.02]	
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	108	15.95 (15.81)	7.89 (1.33)	1.37	-	
Placebo + Chemotherapy[b] / Placebo	116	109	17.43 (20.19)	6.52 (1.37)	[-2.39; 5.13]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	231	14.00 (16.13)	6.96 (0.86)	0.07	-	0.057
Placebo + Chemotherapy[b] / Placebo	245	232	13.51 (16.00)	6.89 (0.88)	[-2.35; 2.48]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	19.65 (18.52)	5.36 (1.18)	-4.35	-0.24	
Placebo + Chemotherapy[b] / Placebo	153	141	20.09 (19.51)	9.70 (1.20)	[-7.66; -1.04]	[-0.42; -0.06]	
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	192	17.94 (19.08)	6.70 (0.98)	-1.14	-	0.710
Placebo + Chemotherapy[b] / Placebo	215	200	17.67 (19.90)	7.84 (0.99)	[-3.88; 1.60]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	177	14.12 (14.82)	6.09 (1.00)	-1.89	-	
Placebo + Chemotherapy[b] / Placebo	183	173	14.07 (14.52)	7.98 (1.04)	[-4.72; 0.95]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	15.58 (16.99)	5.05 (1.37)	-3.50	-	0.210

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Dyspnoea	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	121	117	14.43 (16.65)	8.55 (1.34)	[-7.29; 0.29]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	262	16.33 (17.39)	6.90 (0.80)	-0.72	-	
Placebo + Chemotherapy[b] / Placebo	277	256	16.71 (18.12)	7.62 (0.84)	[-3.01; 1.57]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	121	16.35 (16.49)	5.11 (1.22)	-3.02	-	0.310
Placebo + Chemotherapy[b] / Placebo	132	125	15.02 (17.30)	8.13 (1.23)	[-6.43; 0.39]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	15.99 (17.65)	7.00 (0.86)	-0.79	-	
Placebo + Chemotherapy[b] / Placebo	266	248	16.49 (17.88)	7.80 (0.89)	[-3.21; 1.63]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	19.46 (19.52)	5.87 (1.14)	-1.46	-	0.886
Placebo + Chemotherapy[b] / Placebo	171	157	17.55 (18.92)	7.33 (1.19)	[-4.70; 1.79]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	208	13.51 (14.80)	6.71 (0.88)	-1.60	-	
Placebo + Chemotherapy[b] / Placebo	227	216	14.87 (16.68)	8.31 (0.89)	[-4.05; 0.85]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-LC13: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer Module 13; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Dyspnoea	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Health Organization							

EORTC QLQ-LC13: Symptomskala Husten

Tabelle 4G-23: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Husten des EORTC QLQ-LC13 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-LC13 Coughing	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	261	31.29 (25.07)	-9.55 (0.95)	-2.30	-	0.361
Placebo + Chemotherapy[b] / Placebo	282	264	34.09 (25.50)	-7.25 (0.98)	[-4.99; 0.39]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	108	30.25 (26.39)	-5.38 (1.52)	0.32	-	
Placebo + Chemotherapy[b] / Placebo	116	109	33.94 (26.44)	-5.71 (1.61)	[-4.04; 4.69]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	208	30.29 (25.72)	-7.60 (1.08)	-2.12	-	0.533
Placebo + Chemotherapy[b] / Placebo	213	201	32.67 (25.81)	-5.49 (1.14)	[-5.20; 0.96]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	31.88 (25.10)	-9.21 (1.25)	-0.74	-	
Placebo + Chemotherapy[b] / Placebo	185	172	35.66 (25.64)	-8.47 (1.26)	[-4.23; 2.75]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	231	29.00 (24.88)	-5.87 (1.02)	-0.32	-	0.244
Placebo + Chemotherapy[b] / Placebo	245	232	31.47 (25.60)	-5.55 (1.06)	[-3.22; 2.58]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	34.30 (26.08)	-12.63 (1.34)	-3.55	-	
Placebo + Chemotherapy[b] / Placebo	153	141	38.30 (25.49)	-9.08 (1.38)	[-7.35; 0.24]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	192	32.64 (26.41)	-8.16 (1.19)	-1.41	-	0.902

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Coughing	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	215	200	35.00 (27.10)	-6.75 (1.20)	[-4.72; 1.90]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	177	29.19 (24.27)	-8.46 (1.09)	-1.51	-	
Placebo + Chemotherapy[b] / Placebo	183	173	32.95 (24.11)	-6.96 (1.16)	[-4.65; 1.64]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	28.04 (25.55)	-7.66 (1.46)	-0.38	-	0.448
Placebo + Chemotherapy[b] / Placebo	121	117	31.05 (24.26)	-7.28 (1.44)	[-4.43; 3.67]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	262	32.19 (25.33)	-8.75 (0.97)	-2.16	-	
Placebo + Chemotherapy[b] / Placebo	277	256	35.42 (26.32)	-6.59 (1.03)	[-4.95; 0.62]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	121	30.85 (23.64)	-8.26 (1.41)	-1.43	-	0.957
Placebo + Chemotherapy[b] / Placebo	132	125	33.87 (23.94)	-6.83 (1.44)	[-5.40; 2.54]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	31.05 (26.31)	-8.35 (0.99)	-1.53	-	
Placebo + Chemotherapy[b] / Placebo	266	248	34.14 (26.65)	-6.82 (1.04)	[-4.36; 1.29]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	36.44 (24.66)	-12.45 (1.21)	-2.13	-	0.691
Placebo + Chemotherapy[b] / Placebo	171	157	36.52 (24.40)	-10.33 (1.27)	[-5.58; 1.32]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	208	26.76 (25.26)	-5.34 (1.10)	-0.99	-	
Placebo + Chemotherapy[b] / Placebo	227	216	32.25 (26.59)	-4.34 (1.12)	[-4.09; 2.11]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Coughing	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-LC13: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer Module 13; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-LC13: Symptomskala Hämoptoe

Tabelle 4G-24: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Hämoptoe des EORTC QLQ-LC13 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-LC13 Haemoptysis	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	261	5.24 (14.70)	-5.31 (0.31)	-0.56	-	0.366
Placebo + Chemotherapy[b] / Placebo	282	264	8.21 (18.27)	-4.75 (0.32)	[-1.44; 0.31]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	108	4.63 (14.74)	-4.76 (0.25)	0.01	-	
Placebo + Chemotherapy[b] / Placebo	116	109	5.20 (13.74)	-4.77 (0.28)	[-0.74; 0.75]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	208	5.77 (15.67)	-5.18 (0.38)	-0.76	-	0.248
Placebo + Chemotherapy[b] / Placebo	213	201	6.97 (16.87)	-4.42 (0.40)	[-1.85; 0.33]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	4.14 (13.31)	-5.25 (0.19)	-0.14	-	
Placebo + Chemotherapy[b] / Placebo	185	172	7.75 (17.42)	-5.11 (0.19)	[-0.68; 0.39]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	231	5.34 (14.43)	-4.76 (0.35)	-0.18	-	0.282
Placebo + Chemotherapy[b] / Placebo	245	232	7.47 (17.86)	-4.58 (0.36)	[-1.17; 0.81]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	4.59 (15.17)	-5.89 (0.31)	-0.87	-	
Placebo + Chemotherapy[b] / Placebo	153	141	7.09 (15.84)	-5.02 (0.33)	[-1.77; 0.02]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	192	5.73 (16.24)	-6.03 (0.23)	-0.06	-	0.264

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Haemoptysis	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	215	200	7.17 (16.33)	-5.97 (0.24)	[-0.71; 0.59]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	177	4.33 (12.81)	-4.25 (0.38)	-0.77	-	
Placebo + Chemotherapy[b] / Placebo	183	173	7.51 (18.01)	-3.48 (0.40)	[-1.86; 0.32]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	5.30 (13.85)	-5.36 (0.26)	-0.06	-	0.448
Placebo + Chemotherapy[b] / Placebo	121	117	8.26 (17.46)	-5.30 (0.27)	[-0.81; 0.69]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	262	4.96 (15.05)	-5.13 (0.26)	-0.54	-	
Placebo + Chemotherapy[b] / Placebo	277	256	6.90 (16.96)	-4.59 (0.28)	[-1.29; 0.22]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	121	7.99 (18.77)	-6.57 (0.71)	-1.41	-	0.335
Placebo + Chemotherapy[b] / Placebo	132	125	7.73 (18.03)	-5.15 (0.71)	[-3.40; 0.57]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	3.63 (12.01)	-4.43 (0.19)	-0.28	-	
Placebo + Chemotherapy[b] / Placebo	266	248	7.12 (16.66)	-4.15 (0.21)	[-0.83; 0.28]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	4.76 (14.36)	-5.41 (0.28)	-0.20	-	0.315
Placebo + Chemotherapy[b] / Placebo	171	157	7.43 (17.54)	-5.21 (0.30)	[-1.00; 0.60]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	208	5.29 (14.97)	-5.08 (0.33)	-0.67	-	
Placebo + Chemotherapy[b] / Placebo	227	216	7.25 (16.82)	-4.41 (0.33)	[-1.60; 0.25]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Haemoptysis	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-LC13: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer Module 13; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-LC13: Symptomskala Mundschmerzen

Tabelle 4G-25: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Mundschmerzen des EORTC QLQ-LC13 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-LC13 Sore Mouth	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	261	1.79 (7.52)	2.41 (0.53)	0.31	-	0.418
Placebo + Chemotherapy[b] / Placebo	282	264	1.89 (8.26)	2.10 (0.54)	[-1.17; 1.80]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	108	2.78 (9.26)	5.22 (1.10)	1.66	-	
Placebo + Chemotherapy[b] / Placebo	116	109	2.75 (12.11)	3.56 (1.16)	[-1.48; 4.81]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	208	1.60 (7.15)	3.06 (0.65)	0.44	-	0.656
Placebo + Chemotherapy[b] / Placebo	213	201	2.32 (9.73)	2.62 (0.69)	[-1.42; 2.31]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	2.69 (9.11)	3.56 (0.78)	1.17	-	
Placebo + Chemotherapy[b] / Placebo	185	172	1.94 (9.34)	2.38 (0.78)	[-1.00; 3.34]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	231	2.31 (8.48)	3.84 (0.67)	0.82	-	0.903
Placebo + Chemotherapy[b] / Placebo	245	232	2.16 (9.31)	3.03 (0.69)	[-1.08; 2.71]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	1.69 (7.34)	2.08 (0.69)	0.38	-	
Placebo + Chemotherapy[b] / Placebo	153	141	2.13 (9.93)	1.70 (0.72)	[-1.58; 2.34]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	192	1.74 (7.43)	5.37 (0.75)	1.85	-	0.157

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Sore Mouth	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	215	200	2.33 (9.75)	3.51 (0.76)	[-0.24; 3.95]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	177	2.45 (8.72)	1.05 (0.60)	-0.21	-	
Placebo + Chemotherapy[b] / Placebo	183	173	1.93 (9.31)	1.26 (0.63)	[-1.92; 1.50]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	2.18 (8.28)	3.55 (0.91)	2.45	-	0.116
Placebo + Chemotherapy[b] / Placebo	121	117	2.28 (8.45)	1.10 (0.90)	[-0.07; 4.98]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	262	2.04 (8.00)	3.12 (0.59)	-0.10	-	
Placebo + Chemotherapy[b] / Placebo	277	256	2.08 (10.01)	3.22 (0.62)	[-1.78; 1.59]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	121	2.20 (8.32)	4.17 (0.87)	1.70	-	0.288
Placebo + Chemotherapy[b] / Placebo	132	125	1.87 (8.78)	2.48 (0.89)	[-0.76; 4.15]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	2.02 (7.96)	2.76 (0.59)	0.19	-	
Placebo + Chemotherapy[b] / Placebo	266	248	2.28 (9.91)	2.57 (0.62)	[-1.49; 1.87]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	1.86 (7.68)	2.68 (0.70)	0.57	-	0.923
Placebo + Chemotherapy[b] / Placebo	171	157	2.55 (10.36)	2.11 (0.74)	[-1.43; 2.58]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	208	2.24 (8.37)	3.70 (0.69)	0.85	-	
Placebo + Chemotherapy[b] / Placebo	227	216	1.85 (8.90)	2.85 (0.71)	[-1.10; 2.80]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Sore Mouth	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-LC13: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer Module 13; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-LC13: Symptomskala Dysphagie

Tabelle 4G-26: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Dysphagie des EORTC QLQ-LC13 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-LC13 Dysphagia	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	261	2.43 (9.61)	2.06 (0.56)	-1.41	-	0.183
Placebo + Chemotherapy[b] / Placebo	282	264	2.27 (9.37)	3.47 (0.57)	[-2.99; 0.17]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	108	3.09 (9.71)	2.33 (1.20)	1.16	-	
Placebo + Chemotherapy[b] / Placebo	116	109	3.98 (12.61)	1.17 (1.24)	[-2.24; 4.56]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	208	2.08 (8.73)	1.10 (0.65)	-1.49	-	0.206
Placebo + Chemotherapy[b] / Placebo	213	201	2.99 (11.15)	2.59 (0.68)	[-3.33; 0.35]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	3.31 (10.68)	3.45 (0.89)	0.30	-	
Placebo + Chemotherapy[b] / Placebo	185	172	2.52 (9.54)	3.15 (0.90)	[-2.19; 2.79]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	231	2.45 (8.72)	2.60 (0.67)	-0.57	-	0.840
Placebo + Chemotherapy[b] / Placebo	245	232	2.30 (9.02)	3.17 (0.69)	[-2.47; 1.32]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	2.90 (11.01)	1.26 (0.88)	-0.96	-	
Placebo + Chemotherapy[b] / Placebo	153	141	3.55 (12.41)	2.21 (0.91)	[-3.45; 1.53]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	2.80 (9.30)	1.96 (1.06)	0.98	-	0.134

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Dysphagia	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	121	117	3.13 (11.57)	0.97 (1.04)	[-1.94; 3.91]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	262	2.54 (9.78)	2.22 (0.61)	-1.47	-	
Placebo + Chemotherapy[b] / Placebo	277	256	2.60 (9.89)	3.69 (0.64)	[-3.20; 0.26]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	121	1.38 (7.93)	3.41 (1.09)	0.96	-	0.187
Placebo + Chemotherapy[b] / Placebo	132	125	3.47 (12.58)	2.45 (1.09)	[-2.08; 4.01]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	3.23 (10.32)	1.63 (0.60)	-1.38	-	
Placebo + Chemotherapy[b] / Placebo	266	248	2.42 (9.17)	3.02 (0.62)	[-3.07; 0.31]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	2.69 (9.11)	2.07 (0.75)	-0.16	-	0.567
Placebo + Chemotherapy[b] / Placebo	171	157	2.97 (10.92)	2.23 (0.79)	[-2.31; 1.99]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	208	2.56 (10.04)	2.24 (0.76)	-1.01	-	
Placebo + Chemotherapy[b] / Placebo	227	216	2.62 (10.08)	3.24 (0.76)	[-3.12; 1.11]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-LC13: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer Module 13; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score

EORTC QLQ-LC13: Periphere Neuropathie

Tabelle 4G-27: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Periphere Neuropathie des EORTC QLQ-LC13 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-LC13 Peripheral Neuropathy	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	261	6.26 (15.44)	5.38 (0.99)	-0.80	-	0.290
Placebo + Chemotherapy[b] / Placebo	282	264	7.07 (18.40)	6.18 (1.01)	[-3.57; 1.97]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	108	6.79 (14.95)	8.59 (1.77)	2.10	-	
Placebo + Chemotherapy[b] / Placebo	116	109	7.95 (17.51)	6.49 (1.83)	[-2.91; 7.12]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	208	6.41 (14.34)	7.65 (1.23)	-0.35	-	0.690
Placebo + Chemotherapy[b] / Placebo	213	201	6.14 (15.67)	8.00 (1.29)	[-3.85; 3.15]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	6.42 (16.46)	4.57 (1.20)	0.42	-	
Placebo + Chemotherapy[b] / Placebo	185	172	8.72 (20.59)	4.16 (1.20)	[-2.93; 3.77]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	231	5.63 (13.97)	5.96 (1.07)	-0.40	-	0.578
Placebo + Chemotherapy[b] / Placebo	245	232	6.47 (17.03)	6.36 (1.10)	[-3.42; 2.62]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	7.73 (17.22)	6.92 (1.50)	0.88	-	
Placebo + Chemotherapy[b] / Placebo	153	141	8.75 (19.78)	6.04 (1.53)	[-3.34; 5.09]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	192	7.12 (16.75)	8.34 (1.29)	0.74	-	0.643

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Peripheral Neuropathy	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	215	200	7.00 (18.18)	7.60 (1.29)	[-2.84; 4.32]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	177	5.65 (13.51)	4.21 (1.16)	-0.40	-	
Placebo + Chemotherapy[b] / Placebo	183	173	7.71 (18.11)	4.62 (1.21)	[-3.71; 2.90]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	5.92 (14.34)	4.98 (1.56)	-1.78	-	0.349
Placebo + Chemotherapy[b] / Placebo	121	117	5.13 (12.85)	6.76 (1.52)	[-6.08; 2.51]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	262	6.62 (15.67)	6.77 (1.05)	0.77	-	
Placebo + Chemotherapy[b] / Placebo	277	256	8.33 (20.02)	6.00 (1.10)	[-2.23; 3.77]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	121	7.71 (16.53)	5.65 (1.41)	-1.35	-	0.410
Placebo + Chemotherapy[b] / Placebo	132	125	6.40 (16.23)	7.00 (1.43)	[-5.31; 2.61]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	5.78 (14.62)	6.61 (1.11)	0.77	-	
Placebo + Chemotherapy[b] / Placebo	266	248	7.80 (19.02)	5.84 (1.14)	[-2.35; 3.89]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	6.21 (14.53)	6.63 (1.31)	0.89	-	0.531
Placebo + Chemotherapy[b] / Placebo	171	157	7.86 (20.02)	5.74 (1.37)	[-2.84; 4.61]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	208	6.57 (15.87)	6.10 (1.17)	-0.55	-	
Placebo + Chemotherapy[b] / Placebo	227	216	6.94 (16.65)	6.65 (1.18)	[-3.83; 2.73]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Peripheral Neuropathy	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
e: Mean and SD at baseline are calculated based on number of participants with data available for analysis							
f: MMRM of change from baseline with treatment, time and baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed							
g: Standardized mean difference (Hedges'g) is only calculated if confidence interval for mean difference does not include zero							
h: MMRM of change from baseline with treatment, subgroup, time and baseline endpoint score as covariates and treatment-by-subgroup interaction. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed							
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-LC13: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer Module 13; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization							

EORTC QLQ-LC13: Alopezie

Tabelle 4G-28: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Alopezie des EORTC QLQ-LC13 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-LC13 Alopecia	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	261	2.17 (10.10)	4.44 (0.63)	-1.82	-0.12	0.593
Placebo + Chemotherapy[b] / Placebo	282	264	1.52 (6.96)	6.27 (0.65)	[-3.61; -0.03]	[-0.23; -0.00]	
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	108	5.25 (17.15)	11.63 (1.49)	-0.24	-	
Placebo + Chemotherapy[b] / Placebo	116	109	4.59 (12.40)	11.87 (1.58)	[-4.52; 4.04]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	208	3.04 (12.53)	6.48 (0.90)	-1.52	-	0.842
Placebo + Chemotherapy[b] / Placebo	213	201	2.16 (8.87)	7.99 (0.95)	[-4.09; 1.05]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	3.11 (12.80)	6.71 (0.96)	-1.05	-	
Placebo + Chemotherapy[b] / Placebo	185	172	2.71 (9.14)	7.76 (0.97)	[-3.74; 1.64]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	231	3.03 (13.02)	6.66 (0.82)	-1.50	-	0.863
Placebo + Chemotherapy[b] / Placebo	245	232	2.44 (8.71)	8.16 (0.86)	[-3.84; 0.84]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	3.14 (12.01)	6.47 (1.11)	-1.09	-	
Placebo + Chemotherapy[b] / Placebo	153	141	2.36 (9.47)	7.56 (1.15)	[-4.23; 2.05]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	192	2.95 (12.65)	8.21 (0.98)	-2.27	-	0.212

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Alopecia	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	215	200	1.33 (6.55)	10.48 (0.99)	[-5.01; 0.47]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	177	3.20 (12.65)	4.79 (0.84)	-0.19	-	
Placebo + Chemotherapy[b] / Placebo	183	173	3.66 (11.05)	4.98 (0.89)	[-2.60; 2.23]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	4.05 (14.98)	5.28 (1.21)	-1.92	-	0.727
Placebo + Chemotherapy[b] / Placebo	121	117	2.28 (8.45)	7.19 (1.20)	[-5.27; 1.44]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	262	2.67 (11.55)	7.21 (0.78)	-1.14	-	
Placebo + Chemotherapy[b] / Placebo	277	256	2.47 (9.24)	8.35 (0.84)	[-3.39; 1.12]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	121	3.86 (13.05)	5.59 (1.14)	-3.44	-0.18	0.079
Placebo + Chemotherapy[b] / Placebo	132	125	2.40 (9.63)	9.03 (1.17)	[-6.66; -0.22]	[-0.34; -0.01]	
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	2.69 (12.44)	7.14 (0.80)	-0.12	-	
Placebo + Chemotherapy[b] / Placebo	266	248	2.42 (8.67)	7.27 (0.84)	[-2.41; 2.16]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	2.28 (10.62)	7.88 (0.99)	0.53	-	0.157
Placebo + Chemotherapy[b] / Placebo	171	157	2.34 (8.54)	7.35 (1.05)	[-2.31; 3.38]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	208	3.69 (13.99)	5.64 (0.87)	-2.68	-0.15	
Placebo + Chemotherapy[b] / Placebo	227	216	2.47 (9.32)	8.32 (0.89)	[-5.13; -0.24]	[-0.28; -0.01]	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Alopecia	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-LC13: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer Module 13; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-LC13: Schmerzen (Brust)

Tabelle 4G-29: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schmerzen (Brust) des EORTC QLQ-LC13 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-LC13 Pain in Chest	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	261	11.62 (20.80)	2.35 (0.92)	-2.81	-0.14	0.217
Placebo + Chemotherapy[b] / Placebo	282	264	11.36 (19.86)	5.17 (0.94)	[-5.39; -0.24]	[-0.27; -0.01]	
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	108	9.57 (18.26)	2.17 (1.18)	-0.21	-	
Placebo + Chemotherapy[b] / Placebo	116	109	11.31 (20.90)	2.39 (1.25)	[-3.60; 3.17]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	208	12.50 (21.33)	1.64 (0.97)	-3.32	-0.17	0.183
Placebo + Chemotherapy[b] / Placebo	213	201	12.11 (19.51)	4.97 (1.02)	[-6.08; -0.56]	[-0.30; -0.03]	
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	9.11 (18.25)	3.17 (1.12)	-0.48	-	
Placebo + Chemotherapy[b] / Placebo	185	172	10.47 (20.87)	3.66 (1.13)	[-3.61; 2.64]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	231	9.24 (18.68)	2.42 (0.86)	-0.44	-	0.061
Placebo + Chemotherapy[b] / Placebo	245	232	11.64 (20.66)	2.85 (0.89)	[-2.88; 2.00]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	14.01 (21.99)	2.05 (1.31)	-4.88	-0.23	
Placebo + Chemotherapy[b] / Placebo	153	141	10.87 (19.31)	6.94 (1.34)	[-8.57; -1.20]	[-0.40; -0.06]	
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	192	11.28 (20.89)	2.39 (1.01)	-2.18	-	0.801

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Pain in Chest	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	215	200	11.17 (20.67)	4.57 (1.02)	[-5.00; 0.63]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	177	10.73 (19.24)	2.28 (1.08)	-1.85	-	
Placebo + Chemotherapy[b] / Placebo	183	173	11.56 (19.55)	4.13 (1.14)	[-4.95; 1.25]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	8.10 (15.08)	2.76 (1.31)	-1.25	-	0.569
Placebo + Chemotherapy[b] / Placebo	121	117	7.69 (16.01)	4.01 (1.29)	[-4.87; 2.37]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	262	12.21 (21.72)	2.02 (0.89)	-2.44	-	
Placebo + Chemotherapy[b] / Placebo	277	256	13.02 (21.59)	4.46 (0.93)	[-4.97; 0.09]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	121	9.37 (18.87)	2.98 (1.22)	-1.71	-	0.824
Placebo + Chemotherapy[b] / Placebo	132	125	11.47 (20.78)	4.69 (1.24)	[-5.15; 1.72]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	11.83 (20.65)	2.00 (0.92)	-2.16	-	
Placebo + Chemotherapy[b] / Placebo	266	248	11.29 (19.85)	4.15 (0.95)	[-4.76; 0.45]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	9.52 (19.87)	3.57 (1.10)	-1.50	-	0.577
Placebo + Chemotherapy[b] / Placebo	171	157	12.74 (22.18)	5.07 (1.16)	[-4.66; 1.65]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	208	12.18 (20.23)	1.38 (0.99)	-2.45	-	
Placebo + Chemotherapy[b] / Placebo	227	216	10.34 (18.50)	3.83 (1.00)	[-5.21; 0.32]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Pain in Chest	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-LC13: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer Module 13; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-LC13: Schmerzen (Arm/Schulter)

Tabelle 4G-30: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schmerzen (Arm/Schulter) des EORTC QLQ-LC13 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-LC13 Pain in Arm or Shoulder	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	261	9.71 (20.24)	0.70 (0.90)	-2.49	-	0.755
Placebo + Chemotherapy[b] / Placebo	282	264	10.35 (20.19)	3.20 (0.92)	[-5.02; 0.04]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	108	11.73 (22.47)	3.08 (1.54)	-1.68	-	
Placebo + Chemotherapy[b] / Placebo	116	109	13.46 (23.18)	4.75 (1.63)	[-6.09; 2.74]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	231	10.39 (20.09)	0.53 (0.97)	-2.75	-0.13	0.420
Placebo + Chemotherapy[b] / Placebo	245	232	12.07 (21.67)	3.28 (1.00)	[-5.50; -0.00]	[-0.27; -0.00]	
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	10.14 (22.28)	3.00 (1.33)	-1.29	-	
Placebo + Chemotherapy[b] / Placebo	153	141	9.93 (20.21)	4.29 (1.37)	[-5.04; 2.45]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	192	11.11 (21.66)	1.89 (1.10)	-1.68	-	0.577
Placebo + Chemotherapy[b] / Placebo	215	200	12.00 (21.92)	3.56 (1.11)	[-4.75; 1.40]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	177	9.42 (20.08)	1.02 (1.11)	-2.64	-	
Placebo + Chemotherapy[b] / Placebo	183	173	10.40 (20.20)	3.67 (1.17)	[-5.82; 0.54]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	10.90 (21.37)	0.49 (1.51)	-3.72	-	0.263

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Pain in Arm or Shoulder	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	121	117	8.26 (17.46)	4.21 (1.48)	[-7.89; 0.45]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	262	10.05 (20.75)	1.87 (0.91)	-1.25	-	
Placebo + Chemotherapy[b] / Placebo	277	256	12.63 (22.51)	3.13 (0.96)	[-3.86; 1.35]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	121	9.37 (20.74)	2.42 (1.31)	-1.85	-	0.741
Placebo + Chemotherapy[b] / Placebo	132	125	11.47 (22.44)	4.26 (1.34)	[-5.54; 1.85]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	10.75 (21.02)	0.89 (0.98)	-2.40	-	
Placebo + Chemotherapy[b] / Placebo	266	248	11.16 (20.48)	3.29 (1.01)	[-5.16; 0.36]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	10.35 (23.34)	1.11 (1.21)	-2.27	-	0.997
Placebo + Chemotherapy[b] / Placebo	171	157	11.46 (22.24)	3.38 (1.26)	[-5.70; 1.17]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	208	10.26 (18.87)	1.67 (1.04)	-2.24	-	
Placebo + Chemotherapy[b] / Placebo	227	216	11.11 (20.33)	3.90 (1.06)	[-5.15; 0.68]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-LC13: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer Module 13; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Pain in Arm or Shoulder	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Health Organization							

EORTC QLQ-LC13: Schmerzen (andere)

Tabelle 4G-31: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schmerzen (andere) des EORTC QLQ-LC13 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-LC13 Pain in Other Parts	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	261	11.37 (21.15)	2.58 (0.85)	-0.53	-	0.471
Placebo + Chemotherapy[b] / Placebo	282	264	11.24 (20.66)	3.11 (0.88)	[-2.93; 1.87]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	108	12.35 (21.18)	4.35 (1.66)	-2.12	-	
Placebo + Chemotherapy[b] / Placebo	116	109	18.65 (24.61)	6.47 (1.75)	[-6.90; 2.66]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	231	10.39 (19.85)	3.62 (0.94)	-0.62	-	0.782
Placebo + Chemotherapy[b] / Placebo	245	232	10.92 (18.75)	4.24 (0.98)	[-3.29; 2.04]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	13.77 (23.04)	2.34 (1.39)	-1.39	-	
Placebo + Chemotherapy[b] / Placebo	153	141	17.49 (26.30)	3.73 (1.43)	[-5.33; 2.56]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	192	14.24 (24.24)	4.37 (1.15)	0.07	-	0.378
Placebo + Chemotherapy[b] / Placebo	215	200	15.33 (23.83)	4.30 (1.16)	[-3.14; 3.28]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	177	8.85 (16.76)	1.83 (1.04)	-1.95	-	
Placebo + Chemotherapy[b] / Placebo	183	173	11.18 (19.78)	3.77 (1.10)	[-4.92; 1.02]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	11.84 (22.08)	2.57 (1.40)	-0.90	-	0.928

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Pain in Other Parts	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	121	117	7.12 (15.05)	3.47 (1.39)	[-4.80; 2.99]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	262	11.58 (20.78)	3.29 (0.95)	-1.12	-	
Placebo + Chemotherapy[b] / Placebo	277	256	16.28 (24.16)	4.41 (1.01)	[-3.84; 1.60]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	121	13.22 (21.72)	1.98 (1.34)	-0.54	-	0.694
Placebo + Chemotherapy[b] / Placebo	132	125	15.47 (24.15)	2.52 (1.37)	[-4.32; 3.24]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	10.89 (20.84)	3.78 (0.97)	-1.17	-	
Placebo + Chemotherapy[b] / Placebo	266	248	12.37 (20.98)	4.95 (1.01)	[-3.91; 1.58]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	10.35 (20.15)	3.62 (1.12)	0.53	-	0.243
Placebo + Chemotherapy[b] / Placebo	171	157	12.31 (21.78)	3.09 (1.18)	[-2.68; 3.73]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	208	12.66 (21.86)	2.82 (1.08)	-2.01	-	
Placebo + Chemotherapy[b] / Placebo	227	216	14.20 (22.37)	4.83 (1.11)	[-5.06; 1.03]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-LC13: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer Module 13; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-LC13 Pain in Other Parts	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Health Organization							

EQ-5D VAS

Tabelle 4G-32: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EQ-5D VAS	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	262	81.04 (14.63)	-3.38 (0.69)	0.80	-	0.184
Placebo + Chemotherapy[b] / Placebo	283	267	79.91 (14.43)	-4.18 (0.70)	[-1.12; 2.73]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	110	79.75 (15.87)	-2.51 (1.24)	2.98	-	
Placebo + Chemotherapy[b] / Placebo	116	111	79.79 (16.97)	-5.49 (1.26)	[-0.49; 6.46]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	211	81.66 (14.12)	-2.58 (0.83)	2.29	-	0.280
Placebo + Chemotherapy[b] / Placebo	214	206	80.01 (15.81)	-4.87 (0.86)	[-0.06; 4.64]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	79.35 (16.03)	-3.78 (0.91)	0.59	-	
Placebo + Chemotherapy[b] / Placebo	185	172	79.70 (14.47)	-4.37 (0.91)	[-1.93; 3.11]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	234	82.30 (13.76)	-4.00 (0.73)	0.77	-	0.262
Placebo + Chemotherapy[b] / Placebo	245	235	82.11 (13.66)	-4.76 (0.75)	[-1.29; 2.83]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	77.88 (16.58)	-1.23 (1.06)	3.09	0.19	
Placebo + Chemotherapy[b] / Placebo	154	143	76.19 (16.84)	-4.32 (1.06)	[0.13; 6.05]	[0.01; 0.38]	
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	194	79.38 (16.04)	-3.90 (0.92)	0.79	-	0.487

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EQ-5D VAS	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	216	205	78.84 (16.60)	-4.69 (0.92)	[-1.76; 3.34]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	178	82.06 (13.69)	-2.17 (0.77)	2.46	0.18	
Placebo + Chemotherapy[b] / Placebo	183	173	81.10 (13.29)	-4.63 (0.81)	[0.26; 4.65]	[0.02; 0.34]	
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	83.57 (14.10)	-3.51 (1.09)	0.49	-	0.306
Placebo + Chemotherapy[b] / Placebo	121	117	80.58 (14.99)	-4.00 (1.07)	[-2.52; 3.50]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	265	79.48 (15.22)	-2.76 (0.73)	2.21	0.15	
Placebo + Chemotherapy[b] / Placebo	278	261	79.56 (15.31)	-4.97 (0.76)	[0.15; 4.28]	[0.01; 0.28]	
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	123	80.51 (15.93)	-3.27 (1.13)	2.74	-	0.402
Placebo + Chemotherapy[b] / Placebo	133	126	81.92 (12.75)	-6.01 (1.14)	[-0.42; 5.91]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	249	80.73 (14.55)	-2.78 (0.72)	1.08	-	
Placebo + Chemotherapy[b] / Placebo	266	252	78.85 (16.21)	-3.86 (0.73)	[-0.93; 3.09]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	80.16 (15.00)	-3.06 (0.88)	1.05	-	0.597
Placebo + Chemotherapy[b] / Placebo	172	159	78.35 (14.97)	-4.11 (0.91)	[-1.43; 3.52]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	211	81.04 (15.02)	-3.08 (0.85)	1.95	-	
Placebo + Chemotherapy[b] / Placebo	227	219	80.98 (15.29)	-5.03 (0.85)	[-0.41; 4.31]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EQ-5D VAS	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EQ-5D: European Quality of Life 5 Dimensions; MMRM: Mixed Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; VAS: Visual Analog Scale; WHO: World Health Organization

Anhang 4-G5.3: Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-33: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Globalen Gesundheitsstatus des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-C30 Global Health Status/QoL	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	262	73.79 (18.90)	-3.51 (0.74)	1.07	-	0.505
Placebo + Chemotherapy[b] / Placebo	282	265	72.80 (18.66)	-4.59 (0.76)	[-1.02; 3.17]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	109	74.08 (18.54)	-4.55 (1.30)	2.19	-	
Placebo + Chemotherapy[b] / Placebo	116	111	72.82 (22.69)	-6.73 (1.36)	[-1.53; 5.90]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	210	74.29 (18.23)	-2.64 (0.86)	2.13	-	0.370
Placebo + Chemotherapy[b] / Placebo	213	204	71.90 (20.54)	-4.78 (0.90)	[-0.32; 4.59]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	73.34 (19.49)	-5.28 (0.99)	0.57	-	
Placebo + Chemotherapy[b] / Placebo	185	172	73.89 (19.12)	-5.85 (1.00)	[-2.19; 3.33]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	233	75.89 (17.30)	-5.51 (0.79)	0.28	-	0.104
Placebo + Chemotherapy[b] / Placebo	245	233	77.22 (17.59)	-5.79 (0.82)	[-1.96; 2.51]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	70.47 (20.64)	-0.56 (1.12)	3.62	0.20	
Placebo + Chemotherapy[b] / Placebo	153	143	65.62 (21.37)	-4.18 (1.14)	[0.47; 6.77]	[0.03; 0.37]	
Stage							

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Global Health Status/QoL	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	75.47 (17.35)	-4.72 (1.21)	-0.20	-	0.247
Placebo + Chemotherapy[b] / Placebo	121	117	73.43 (20.03)	-4.52 (1.19)	[-3.56; 3.15]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	264	73.23 (19.31)	-3.41 (0.77)	2.20	-	
Placebo + Chemotherapy[b] / Placebo	277	259	72.52 (19.88)	-5.61 (0.81)	[-0.00; 4.40]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	123	73.44 (20.42)	-4.11 (1.15)	1.63	-	0.816
Placebo + Chemotherapy[b] / Placebo	132	126	74.80 (20.34)	-5.74 (1.17)	[-1.61; 4.87]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	74.09 (17.93)	-3.66 (0.79)	1.28	-	
Placebo + Chemotherapy[b] / Placebo	266	250	71.80 (19.64)	-4.94 (0.82)	[-0.97; 3.53]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	73.14 (18.93)	-3.71 (0.93)	1.11	-	0.729
Placebo + Chemotherapy[b] / Placebo	171	158	70.46 (20.51)	-4.82 (0.98)	[-1.56; 3.78]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	210	74.44 (18.67)	-3.85 (0.90)	1.71	-	
Placebo + Chemotherapy[b] / Placebo	227	218	74.50 (19.32)	-5.57 (0.92)	[-0.82; 4.25]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

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

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

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

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

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Global Health Status/QoL	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM: Mixed Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; QoL: Quality of Life; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score							

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-34: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-C30 Physical Functioning	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	262	88.47 (14.65)	-5.39 (0.72)	1.59	-	0.292
Placebo + Chemotherapy[b] / Placebo	282	265	89.08 (13.59)	-6.98 (0.73)	[-0.43; 3.61]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	109	87.22 (14.94)	-7.91 (1.37)	-0.81	-	
Placebo + Chemotherapy[b] / Placebo	116	111	83.84 (19.44)	-7.10 (1.41)	[-4.69; 3.07]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	193	87.84 (15.88)	-7.74 (0.95)	-0.88	-	0.057
Placebo + Chemotherapy[b] / Placebo	215	203	85.78 (18.19)	-6.86 (0.95)	[-3.52; 1.76]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	178	88.39 (13.39)	-4.46 (0.87)	2.70	0.19	
Placebo + Chemotherapy[b] / Placebo	183	173	89.60 (11.88)	-7.16 (0.91)	[0.23; 5.18]	[0.02; 0.36]	
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	88.54 (14.53)	-5.37 (1.14)	3.02	-	0.199
Placebo + Chemotherapy[b] / Placebo	121	117	89.86 (12.15)	-8.39 (1.12)	[-0.13; 6.17]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	264	87.93 (14.82)	-6.38 (0.79)	0.18	-	
Placebo + Chemotherapy[b] / Placebo	277	259	86.49 (16.99)	-6.55 (0.82)	[-2.07; 2.42]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	123	88.18 (13.25)	-5.01 (1.04)	1.92	-	0.438

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Physical Functioning	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	132	126	88.15 (13.90)	-6.93 (1.05)	[-0.99; 4.83]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	88.06 (15.43)	-6.72 (0.83)	0.35	-	
Placebo + Chemotherapy[b] / Placebo	266	250	87.23 (16.55)	-7.07 (0.85)	[-1.98; 2.68]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	86.87 (15.66)	-6.75 (0.96)	1.03	-	0.966
Placebo + Chemotherapy[b] / Placebo	171	158	87.17 (15.19)	-7.77 (1.00)	[-1.70; 3.75]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	210	89.05 (13.93)	-5.61 (0.88)	0.94	-	
Placebo + Chemotherapy[b] / Placebo	227	218	87.80 (16.09)	-6.54 (0.89)	[-1.52; 3.39]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

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

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

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

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

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-35: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Rollenfunktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-C30 Role Functioning	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	262	85.94 (22.66)	-5.45 (0.99)	1.75	-	0.521
Placebo + Chemotherapy[b] / Placebo	282	265	86.67 (22.99)	-7.20 (1.00)	[-1.01; 4.52]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	109	85.93 (19.66)	-8.86 (1.79)	3.13	-	
Placebo + Chemotherapy[b] / Placebo	116	111	84.98 (24.72)	-11.99 (1.84)	[-1.93; 8.18]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	210	84.92 (22.94)	-4.32 (1.15)	4.14	0.20	0.053
Placebo + Chemotherapy[b] / Placebo	213	204	84.80 (24.44)	-8.46 (1.19)	[0.89; 7.39]	[0.04; 0.35]	
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	87.27 (20.20)	-9.17 (1.36)	-0.35	-	
Placebo + Chemotherapy[b] / Placebo	185	172	87.79 (22.28)	-8.82 (1.36)	[-4.12; 3.43]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	233	88.77 (18.67)	-7.48 (1.10)	0.95	-	0.292
Placebo + Chemotherapy[b] / Placebo	245	233	89.06 (19.77)	-8.44 (1.12)	[-2.13; 4.04]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	81.16 (25.62)	-4.65 (1.46)	4.19	0.18	
Placebo + Chemotherapy[b] / Placebo	153	143	81.47 (27.98)	-8.83 (1.49)	[0.08; 8.29]	[0.00; 0.36]	
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	193	82.47 (24.04)	-8.37 (1.30)	1.87	-	0.952

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Role Functioning	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	215	203	83.42 (25.98)	-10.25 (1.30)	[-1.74; 5.49]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	178	89.70 (18.41)	-4.37 (1.09)	2.26	-	
Placebo + Chemotherapy[b] / Placebo	183	173	89.40 (19.77)	-6.63 (1.14)	[-0.84; 5.36]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	88.63 (20.43)	-6.16 (1.61)	3.50	-	0.526
Placebo + Chemotherapy[b] / Placebo	121	117	90.46 (18.99)	-9.65 (1.57)	[-0.93; 7.92]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	264	84.85 (22.28)	-6.48 (1.05)	1.71	-	
Placebo + Chemotherapy[b] / Placebo	277	259	84.23 (25.06)	-8.19 (1.09)	[-1.27; 4.68]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	123	86.04 (22.11)	-6.05 (1.53)	3.07	-	0.617
Placebo + Chemotherapy[b] / Placebo	132	126	86.11 (24.20)	-9.12 (1.55)	[-1.22; 7.36]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	85.89 (21.69)	-6.63 (1.07)	1.72	-	
Placebo + Chemotherapy[b] / Placebo	266	250	86.20 (23.18)	-8.35 (1.10)	[-1.30; 4.75]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	84.99 (23.06)	-6.86 (1.30)	0.55	-	0.245
Placebo + Chemotherapy[b] / Placebo	171	158	85.97 (23.46)	-7.41 (1.36)	[-3.16; 4.26]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	210	86.67 (20.80)	-6.10 (1.19)	3.39	0.15	
Placebo + Chemotherapy[b] / Placebo	227	218	86.31 (23.57)	-9.49 (1.20)	[0.08; 6.70]	[0.00; 0.30]	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Role Functioning	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**

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

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

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

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

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

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

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-C30 Emotional Functioning	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	262	84.29 (18.89)	0.45 (0.77)	0.67	-	0.459
Placebo + Chemotherapy[b] / Placebo	282	265	85.35 (17.64)	-0.22 (0.79)	[-1.50; 2.84]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	109	75.99 (22.62)	2.44 (1.62)	2.11	-	
Placebo + Chemotherapy[b] / Placebo	116	111	75.83 (24.10)	0.33 (1.66)	[-2.46; 6.69]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	210	80.67 (20.97)	1.91 (0.98)	2.39	-	0.175
Placebo + Chemotherapy[b] / Placebo	213	204	80.23 (22.01)	-0.48 (1.02)	[-0.39; 5.16]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	83.39 (19.53)	-0.07 (1.09)	-0.53	-	
Placebo + Chemotherapy[b] / Placebo	185	172	85.27 (17.51)	0.45 (1.08)	[-3.54; 2.48]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	233	82.33 (19.62)	1.03 (0.90)	0.60	-	0.618
Placebo + Chemotherapy[b] / Placebo	245	233	84.73 (18.12)	0.44 (0.91)	[-1.92; 3.11]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	81.04 (21.64)	1.06 (1.22)	1.87	-	
Placebo + Chemotherapy[b] / Placebo	153	143	78.96 (22.83)	-0.81 (1.24)	[-1.57; 5.30]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	193	77.25 (21.65)	2.11 (1.09)	-0.68	-	0.096

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Emotional Functioning	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	215	203	77.71 (21.66)	2.78 (1.09)	[-3.71; 2.36]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	178	86.84 (17.64)	-0.18 (0.93)	3.14	0.20	
Placebo + Chemotherapy[b] / Placebo	183	173	88.20 (16.72)	-3.32 (0.97)	[0.50; 5.79]	[0.03; 0.37]	
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	84.74 (19.64)	0.09 (1.27)	-0.43	-	0.303
Placebo + Chemotherapy[b] / Placebo	121	117	85.54 (16.64)	0.52 (1.24)	[-3.91; 3.06]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	264	80.68 (20.59)	1.52 (0.88)	1.81	-	
Placebo + Chemotherapy[b] / Placebo	277	259	81.18 (21.51)	-0.28 (0.92)	[-0.69; 4.31]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	123	81.98 (22.31)	1.12 (1.29)	1.25	-	0.921
Placebo + Chemotherapy[b] / Placebo	132	126	81.48 (19.77)	-0.14 (1.31)	[-2.37; 4.88]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	81.79 (19.39)	1.02 (0.88)	1.04	-	
Placebo + Chemotherapy[b] / Placebo	266	250	83.07 (20.44)	-0.03 (0.90)	[-1.43; 3.52]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	82.87 (20.07)	-0.12 (1.02)	1.03	-	0.685
Placebo + Chemotherapy[b] / Placebo	171	158	85.28 (17.85)	-1.15 (1.06)	[-1.86; 3.92]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	210	81.07 (20.62)	2.00 (1.01)	1.45	-	
Placebo + Chemotherapy[b] / Placebo	227	218	80.54 (21.58)	0.55 (1.02)	[-1.38; 4.28]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Emotional Functioning	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**

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

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

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

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

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-37: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Kognitive Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-C30 Cognitive Functioning	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	262	91.09 (14.56)	-2.81 (0.72)	1.29	-	0.432
Placebo + Chemotherapy[b] / Placebo	282	265	91.26 (13.77)	-4.10 (0.73)	[-0.73; 3.30]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	109	87.77 (19.06)	-6.11 (1.33)	-0.22	-	
Placebo + Chemotherapy[b] / Placebo	116	111	89.34 (19.57)	-5.89 (1.38)	[-4.01; 3.57]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	210	90.71 (16.54)	-3.07 (0.86)	1.93	-	0.154
Placebo + Chemotherapy[b] / Placebo	213	204	90.60 (17.59)	-5.00 (0.90)	[-0.51; 4.37]		
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	89.34 (15.43)	-4.85 (1.00)	-0.76	-	
Placebo + Chemotherapy[b] / Placebo	185	172	90.79 (13.15)	-4.09 (1.00)	[-3.54; 2.02]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	233	91.13 (15.08)	-3.81 (0.81)	1.37	-	0.337
Placebo + Chemotherapy[b] / Placebo	245	233	92.27 (11.47)	-5.18 (0.83)	[-0.92; 3.66]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	88.41 (17.51)	-3.89 (1.09)	-0.31	-	
Placebo + Chemotherapy[b] / Placebo	153	143	88.11 (20.61)	-3.58 (1.11)	[-3.38; 2.75]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	193	87.48 (19.02)	-4.84 (0.96)	-0.64	-	0.145

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Cognitive Functioning	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	215	203	89.08 (17.93)	-4.20 (0.96)	[-3.30; 2.02]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	178	92.98 (11.44)	-2.76 (0.86)	2.34	-	
Placebo + Chemotherapy[b] / Placebo	183	173	92.58 (12.37)	-5.10 (0.90)	[-0.11; 4.78]		
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	90.19 (17.58)	-4.71 (1.22)	-0.27	-	0.387
Placebo + Chemotherapy[b] / Placebo	121	117	92.31 (14.44)	-4.44 (1.19)	[-3.63; 3.09]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	264	90.09 (15.44)	-3.39 (0.77)	1.32	-	
Placebo + Chemotherapy[b] / Placebo	277	259	89.96 (16.21)	-4.72 (0.80)	[-0.86; 3.51]		
PD-L1 Status							
TPS ≥ 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	123	89.16 (17.07)	-3.38 (1.17)	1.49	-	0.635
Placebo + Chemotherapy[b] / Placebo	132	126	89.95 (17.39)	-4.87 (1.18)	[-1.79; 4.77]		
TPS < 50%							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	248	90.59 (15.55)	-4.05 (0.78)	0.43	-	
Placebo + Chemotherapy[b] / Placebo	266	250	91.07 (14.79)	-4.48 (0.81)	[-1.78; 2.64]		

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

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

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

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

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

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM: Mixed-effect Model Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error; TPS: Tumor Proportion Score; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Soziale Funktion

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

Study: KEYNOTE 671[a]					**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
EORTC QLQ-C30 Social Functioning	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Sex							
Male							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	277	262	87.28 (21.23)	-2.47 (0.86)	1.96	-	0.707
Placebo + Chemotherapy[b] / Placebo	282	265	89.75 (17.97)	-4.43 (0.88)	[-0.46; 4.38]		
Female							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	118	109	85.63 (19.17)	-3.01 (1.62)	2.54	-	
Placebo + Chemotherapy[b] / Placebo	116	111	86.34 (22.83)	-5.55 (1.67)	[-2.04; 7.12]		
Age							
< 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	221	210	86.03 (22.01)	-1.56 (1.08)	3.36	0.17	0.193
Placebo + Chemotherapy[b] / Placebo	213	204	87.58 (21.40)	-4.92 (1.12)	[0.31; 6.42]	[0.02; 0.33]	
≥ 65							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	174	161	87.78 (18.70)	-3.98 (1.12)	0.65	-	
Placebo + Chemotherapy[b] / Placebo	185	172	90.12 (17.08)	-4.63 (1.12)	[-2.46; 3.76]		
ECOG Performance Status							
0							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	253	233	88.77 (18.22)	-2.80 (0.88)	2.36	-	0.713
Placebo + Chemotherapy[b] / Placebo	245	233	91.63 (15.33)	-5.15 (0.90)	[-0.12; 4.83]		
1							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	142	138	83.45 (23.87)	-2.23 (1.46)	1.84	-	
Placebo + Chemotherapy[b] / Placebo	153	143	84.03 (24.30)	-4.06 (1.48)	[-2.25; 5.92]		
Region							
WHO Stratum A							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	203	193	84.54 (22.85)	-3.65 (1.18)	0.03	-	0.064

Study: KEYNOTE 671[a]					Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
EORTC QLQ-C30 Social Functioning	**N[c]**	**N[d]**	**Mean at Baseline (SD)[e]**	**Mean Change from Baseline (SE)[f]**	**Mean Difference[f] [95 %-CI]**	**Standardized Mean Difference[g] [95 %-CI]**	**p-Value for Interaction Test[h]**
Placebo + Chemotherapy[b] / Placebo	215	203	85.22 (22.69)	-3.68 (1.18)	[-3.24; 3.30]		
Rest of World							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	178	89.23 (17.66)	-1.73 (0.96)	4.14	0.25	
Placebo + Chemotherapy[b] / Placebo	183	173	92.87 (14.06)	-5.87 (1.01)	[1.39; 6.89]	[0.08; 0.41]	
Stage							
II							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	117	107	88.79 (18.99)	-2.91 (1.38)	1.76	-	0.772
Placebo + Chemotherapy[b] / Placebo	121	117	90.60 (15.22)	-4.66 (1.35)	[-2.06; 5.58]		
III							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	278	264	85.98 (21.24)	-2.47 (0.94)	2.36	-	
Placebo + Chemotherapy[b] / Placebo	277	259	87.90 (21.20)	-4.83 (0.98)	[-0.30; 5.02]		
Histology							
Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	170	161	87.68 (20.03)	-4.06 (1.16)	1.02	-	0.288
Placebo + Chemotherapy[b] / Placebo	171	158	89.87 (17.93)	-5.08 (1.21)	[-2.28; 4.32]		
Non-Squamous							
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	225	210	86.11 (21.11)	-1.55 (1.04)	3.06	0.16	
Placebo + Chemotherapy[b] / Placebo	227	218	87.92 (20.66)	-4.61 (1.05)	[0.16; 5.97]	[0.01; 0.31]	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Number of participants with data available for analysis

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM: Mixed-effect Model Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

Anhang 4-G5.4: Nebenwirkungen

Unerwünschte Ereignisse Gesamtraten

Unerwünschte Ereignisse gesamt

Tabelle 4G-39: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**		**Placebo + Chemotherapy[b] / Placebo**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		**p-Value for Interaction Test[f]**
	N[c]	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	
Adverse Events							
Sex							
Male	278	277 (99.6)	283	280 (98.9)	1.01 [0.99; 1.02]	0.325	0.827
Female	118	117 (99.2)	116	114 (98.3)	1.01 [0.98; 1.04]	0.552	
Age							
< 65	221	219 (99.1)	214	211 (98.6)	1.01 [0.98; 1.03]	0.627	0.307
≥ 65	175	175 (100.0)	185	183 (98.9)	1.01 [1.00; 1.03]	0.168	
ECOG Performance Status							
0	253	252 (99.6)	245	241 (98.4)	1.01 [0.99; 1.03]	0.167	0.388
1	143	142 (99.3)	154	153 (99.4)	1.00 [0.98; 1.02]	0.958	
Region							
WHO Stratum A	204	204 (100.0)	216	215 (99.5)	1.00 [1.00; 1.01]	0.331	0.516
Rest of World	192	190 (99.0)	183	179 (97.8)	1.01 [0.99; 1.04]	0.378	
Stage							
II	118	117 (99.2)	121	120 (99.2)	1.00 [0.98; 1.02]	0.986	0.417
III	278	277 (99.6)	278	274 (98.6)	1.01 [1.00; 1.03]	0.178	
PD-L1 Status							
TPS ≥ 50%	132	131 (99.2)	133	131 (98.5)	1.01 [0.98; 1.03]	0.567	0.810
TPS < 50%	264	263 (99.6)	266	263 (98.9)	1.01 [0.99; 1.02]	0.320	
Histology							
Squamous	171	171 (100.0)	172	171 (99.4)	1.01 [0.99; 1.02]	0.319	0.495
Non-Squamous	225	223 (99.1)	227	223 (98.2)	1.01 [0.99; 1.03]	0.418	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Based on 2x2 contingency table, using Wald confidence interval. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

e: Based on Mantel-Haenszel Chi-Squared test. In case no participant or all participants with event in both treatment groups, report 'n.a.'

f: Based on Breslow-Day test with subgroup as stratification factor. In case no participant or all participants with event in both treatment groups for a subgroup category, it is excluded from interaction test (if only one subgroup category remaining, report 'n.a.'). In case no participant with event in at least one treatment group across all subgroup categories, report 'n.a.'

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); PD-L1: Programmed Death-Ligand 1; TPS: Tumor Proportion Score; WHO: World Health Organization

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-40: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**		**Placebo + Chemotherapy[b] / Placebo**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		**p-Value for Interaction Test[f]**
	N[c]	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	
Serious Adverse Events							
Sex							
Male	278	112 (40.3)	283	98 (34.6)	1.16 [0.94; 1.44]	0.167	0.226
Female	118	53 (44.9)	116	35 (30.2)	1.49 [1.06; 2.09]	0.020	
Age							
< 65	221	77 (34.8)	214	63 (29.4)	1.18 [0.90; 1.56]	0.228	0.382
≥ 65	175	88 (50.3)	185	70 (37.8)	1.33 [1.05; 1.68]	0.018	
ECOG Performance Status							
0	253	113 (44.7)	245	77 (31.4)	1.42 [1.13; 1.79]	0.002	0.063
1	143	52 (36.4)	154	56 (36.4)	1.00 [0.74; 1.35]	>0.999	
Region							
WHO Stratum A	204	96 (47.1)	216	84 (38.9)	1.21 [0.97; 1.51]	0.091	0.754
Rest of World	192	69 (35.9)	183	49 (26.8)	1.34 [0.99; 1.82]	0.057	
Stage							
II	118	50 (42.4)	121	41 (33.9)	1.25 [0.90; 1.73]	0.178	0.985
III	278	115 (41.4)	278	92 (33.1)	1.25 [1.01; 1.55]	0.044	
PD-L1 Status							
TPS ≥ 50%	132	61 (46.2)	133	52 (39.1)	1.18 [0.89; 1.57]	0.243	0.737
TPS < 50%	264	104 (39.4)	266	81 (30.5)	1.29 [1.02; 1.64]	0.031	
Histology							
Squamous	171	74 (43.3)	172	63 (36.6)	1.18 [0.91; 1.53]	0.210	0.629
Non-Squamous	225	91 (40.4)	227	70 (30.8)	1.31 [1.02; 1.69]	0.033	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Based on 2x2 contingency table, using Wald confidence interval. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

e: Based on Mantel-Haenszel Chi-Squared test. In case no participant or all participants with event in both treatment groups, report 'n.a.'

f: Based on Breslow-Day test with subgroup as stratification factor. In case no participant or all participants with event in both treatment groups for a subgroup category, it is excluded from interaction test (if only one subgroup category remaining, report 'n.a.'). In case no participant with event in at least one treatment group across all subgroup categories, report 'n.a.'

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); PD-L1: Programmed Death-Ligand 1; TPS: Tumor Proportion Score; WHO: World Health Organization

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

Tabelle 4G-41: 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 671[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**		**Placebo + Chemotherapy[b] / Placebo**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		**p-Value for Interaction Test[f]**
	N[c]	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	
Severe Adverse Events							
Sex							
Male	278	178 (64.0)	283	156 (55.1)	1.16 [1.01; 1.33]	0.032	0.249
Female	118	79 (66.9)	116	57 (49.1)	1.36 [1.09; 1.71]	0.006	
Age							
< 65	221	130 (58.8)	214	102 (47.7)	1.23 [1.03; 1.48]	0.020	0.694
≥ 65	175	127 (72.6)	185	111 (60.0)	1.21 [1.04; 1.40]	0.012	
ECOG Performance Status							
0	253	170 (67.2)	245	125 (51.0)	1.32 [1.13; 1.53]	<0.001	0.081
1	143	87 (60.8)	154	88 (57.1)	1.06 [0.88; 1.29]	0.518	
Region							
WHO Stratum A	204	143 (70.1)	216	129 (59.7)	1.17 [1.02; 1.35]	0.026	0.770
Rest of World	192	114 (59.4)	183	84 (45.9)	1.29 [1.06; 1.57]	0.009	
Stage							
II	118	78 (66.1)	121	64 (52.9)	1.25 [1.01; 1.54]	0.038	0.744
III	278	179 (64.4)	278	149 (53.6)	1.20 [1.04; 1.38]	0.010	
PD-L1 Status							
TPS ≥ 50%	132	90 (68.2)	133	67 (50.4)	1.35 [1.10; 1.66]	0.003	0.198
TPS < 50%	264	167 (63.3)	266	146 (54.9)	1.15 [1.00; 1.33]	0.050[g]	
Histology							
Squamous	171	118 (69.0)	172	104 (60.5)	1.14 [0.98; 1.34]	0.098	0.535
Non-Squamous	225	139 (61.8)	227	109 (48.0)	1.29 [1.09; 1.52]	0.003	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Based on 2x2 contingency table, using Wald confidence interval. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

e: Based on Mantel-Haenszel Chi-Squared test. In case no participant or all participants with event in both treatment groups, report 'n.a.'

f: Based on Breslow-Day test with subgroup as stratification factor. In case no participant or all participants with event in both treatment groups for a subgroup category, it is excluded from interaction test (if only one subgroup category remaining, report 'n.a.'). In case no participant with event in at least one treatment group across all subgroup categories, report 'n.a.'

g: Unrounded p-value > 0.050

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); PD-L1: Programmed Death-Ligand 1; TPS: Tumor Proportion Score; WHO: World Health Organization

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-42: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**		**Placebo + Chemotherapy[b] / Placebo**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		**p-Value for Interaction Test[f]**
	N[c]	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	
Adverse Events Leading to Treatment Discontinuation							
Age							
< 65	221	47 (21.3)	214	28 (13.1)	1.63 [1.06; 2.49]	0.024	0.693
≥ 65	175	55 (31.4)	185	42 (22.7)	1.38 [0.98; 1.95]	0.063	
ECOG Performance Status							
0	253	70 (27.7)	245	38 (15.5)	1.78 [1.25; 2.54]	0.001	0.076
1	143	32 (22.4)	154	32 (20.8)	1.08 [0.70; 1.66]	0.738	
Region							
WHO Stratum A	204	61 (29.9)	216	44 (20.4)	1.47 [1.05; 2.06]	0.024	0.962
Rest of World	192	41 (21.4)	183	26 (14.2)	1.50 [0.96; 2.35]	0.071	
Stage							
II	118	36 (30.5)	121	22 (18.2)	1.68 [1.05; 2.67]	0.027	0.453
III	278	66 (23.7)	278	48 (17.3)	1.38 [0.99; 1.92]	0.059	
PD-L1 Status							
TPS ≥ 50%	132	27 (20.5)	133	23 (17.3)	1.18 [0.72; 1.95]	0.512	0.281
TPS < 50%	264	75 (28.4)	266	47 (17.7)	1.61 [1.16; 2.22]	0.003	
Histology							
Squamous	171	50 (29.2)	172	39 (22.7)	1.29 [0.90; 1.85]	0.166	0.395
Non-Squamous	225	52 (23.1)	227	31 (13.7)	1.69 [1.13; 2.54]	0.010	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Based on 2x2 contingency table, using Wald confidence interval. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

e: Based on Mantel-Haenszel Chi-Squared test. In case no participant or all participants with event in both treatment groups, report 'n.a.'

f: Based on Breslow-Day test with subgroup as stratification factor. In case no participant or all participants with event in both treatment groups for a subgroup category, it is excluded from interaction test (if only one subgroup category remaining, report 'n.a.'). In case no participant with event in at least one treatment group across all subgroup categories, report 'n.a.'

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); PD-L1: Programmed Death-Ligand 1; TPS: Tumor Proportion Score; WHO: World Health Organization

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

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

Study: KEYNOTE 671[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**		**Placebo + Chemotherapy[b] / Placebo**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	**p-Value for Interaction Test[f]**
SOC[g]: Endocrine disorders							
Sex							
Male	278	41 (14.7)	283	11 (3.9)	3.79 [1.99; 7.23]	<0.001	0.484
Female	118	23 (19.5)	116	4 (3.4)	5.65 [2.02; 15.84]	<0.001	
Age							
< 65	221	39 (17.6)	214	9 (4.2)	4.20 [2.08; 8.45]	<0.001	0.976
≥ 65	175	25 (14.3)	185	6 (3.2)	4.40 [1.85; 10.48]	<0.001	
ECOG Performance Status							
0	253	34 (13.4)	245	11 (4.5)	2.99 [1.55; 5.77]	0.001	0.085
1	143	30 (21.0)	154	4 (2.6)	8.08 [2.92; 22.36]	<0.001	
Region							
WHO Stratum A	204	36 (17.6)	216	6 (2.8)	6.35 [2.73; 14.76]	<0.001	0.169
Rest of World	192	28 (14.6)	183	9 (4.9)	2.97 [1.44; 6.11]	0.002	
Stage							
II	118	21 (17.8)	121	4 (3.3)	5.38 [1.91; 15.21]	<0.001	0.591
III	278	43 (15.5)	278	11 (4.0)	3.91 [2.06; 7.42]	<0.001	
PD-L1 Status							
TPS ≥ 50%	132	25 (18.9)	133	4 (3.0)	6.30 [2.25; 17.60]	<0.001	0.335
TPS < 50%	264	39 (14.8)	266	11 (4.1)	3.57 [1.87; 6.82]	<0.001	
Histology							
Squamous	171	33 (19.3)	172	11 (6.4)	3.02 [1.58; 5.77]	<0.001	0.145
Non-Squamous	225	31 (13.8)	227	4 (1.8)	7.82 [2.81; 21.79]	<0.001	
SOC[g]: Infections and infestations							
Age							
< 65	221	98 (44.3)	214	75 (35.0)	1.27 [1.00; 1.60]	0.048	0.987
≥ 65	175	79 (45.1)	185	66 (35.7)	1.27 [0.98; 1.63]	0.068	
ECOG Performance Status							
0	253	112 (44.3)	245	79 (32.2)	1.37 [1.09; 1.72]	0.006	0.317
1	143	65 (45.5)	154	62 (40.3)	1.13 [0.87; 1.47]	0.367	
Region							
WHO Stratum A	204	113 (55.4)	216	94 (43.5)	1.27 [1.05; 1.55]	0.015	0.720
Rest of World	192	64 (33.3)	183	47 (25.7)	1.30 [0.94; 1.78]	0.105	
Stage							
II	118	49 (41.5)	121	43 (35.5)	1.17 [0.85; 1.61]	0.343	0.537
III	278	128 (46.0)	278	98 (35.3)	1.31 [1.07; 1.60]	0.010	
PD-L1 Status							
TPS ≥ 50%	132	65 (49.2)	133	53 (39.8)	1.24 [0.94; 1.62]	0.125	0.954

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab		Placebo + Chemotherapy[b] / Placebo		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	**p-Value for Interaction Test[f]**
TPS < 50%	264	112 (42.4)	266	88 (33.1)	1.28 [1.03; 1.60]	0.027	
Histology							
Squamous	171	71 (41.5)	172	63 (36.6)	1.13 [0.87; 1.48]	0.354	0.268
Non-Squamous	225	106 (47.1)	227	78 (34.4)	1.37 [1.09; 1.72]	0.006	
SOC[g]: Psychiatric disorders							
Sex							
Male	278	51 (18.3)	283	33 (11.7)	1.57 [1.05; 2.36]	0.027	0.689
Female	118	26 (22.0)	116	19 (16.4)	1.35 [0.79; 2.29]	0.274	
Age							
< 65	221	47 (21.3)	214	29 (13.6)	1.57 [1.03; 2.40]	0.034	0.672
≥ 65	175	30 (17.1)	185	23 (12.4)	1.38 [0.83; 2.28]	0.208	
ECOG Performance Status							
0	253	50 (19.8)	245	35 (14.3)	1.38 [0.93; 2.05]	0.105	0.563
1	143	27 (18.9)	154	17 (11.0)	1.71 [0.97; 3.00]	0.058	
Region							
WHO Stratum A	204	55 (27.0)	216	39 (18.1)	1.49 [1.04; 2.15]	0.029	0.981
Rest of World	192	22 (11.5)	183	13 (7.1)	1.61 [0.84; 3.11]	0.148	
Stage							
II	118	20 (16.9)	121	15 (12.4)	1.37 [0.74; 2.54]	0.321	0.726
III	278	57 (20.5)	278	37 (13.3)	1.54 [1.05; 2.25]	0.024	
PD-L1 Status							
TPS ≥ 50%	132	29 (22.0)	133	17 (12.8)	1.72 [0.99; 2.97]	0.049	0.512
TPS < 50%	264	48 (18.2)	266	35 (13.2)	1.38 [0.93; 2.06]	0.112	
Histology							
Squamous	171	29 (17.0)	172	19 (11.0)	1.54 [0.90; 2.63]	0.115	0.939
Non-Squamous	225	48 (21.3)	227	33 (14.5)	1.47 [0.98; 2.20]	0.060	
SOC[g]: Respiratory, thoracic and mediastinal disorders							
Sex							
Male	278	156 (56.1)	283	146 (51.6)	1.09 [0.93; 1.27]	0.283	0.117
Female	118	82 (69.5)	116	62 (53.4)	1.30 [1.06; 1.60]	0.012	
Age							
< 65	221	131 (59.3)	214	111 (51.9)	1.14 [0.96; 1.35]	0.120	0.848
≥ 65	175	107 (61.1)	185	97 (52.4)	1.17 [0.97; 1.40]	0.096	
ECOG Performance Status							
0	253	159 (62.8)	245	132 (53.9)	1.17 [1.00; 1.35]	0.043	0.652
1	143	79 (55.2)	154	76 (49.4)	1.12 [0.90; 1.39]	0.310	
Region							
WHO Stratum A	204	147 (72.1)	216	131 (60.6)	1.19 [1.04; 1.36]	0.014	0.310
Rest of World	192	91 (47.4)	183	77 (42.1)	1.13 [0.90; 1.41]	0.301	
Stage							
II	118	68 (57.6)	121	67 (55.4)	1.04 [0.83; 1.30]	0.726	0.286
III	278	170 (61.2)	278	141 (50.7)	1.21 [1.04; 1.40]	0.013	
PD-L1 Status							

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab		Placebo + Chemotherapy[b] / Placebo		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	**p-Value for Interaction Test[f]**
TPS ≥ 50%	132	85 (64.4)	133	71 (53.4)	1.21 [0.98; 1.48]	0.069	0.522
TPS < 50%	264	153 (58.0)	266	137 (51.5)	1.13 [0.96; 1.31]	0.136	
Histology							
Squamous	171	91 (53.2)	172	83 (48.3)	1.10 [0.89; 1.36]	0.359	0.424
Non-Squamous	225	147 (65.3)	227	125 (55.1)	1.19 [1.02; 1.38]	0.026	
SOC[g]: Skin and subcutaneous tissue disorders							
Sex							
Male	278	128 (46.0)	283	92 (32.5)	1.42 [1.15; 1.75]	0.001	0.409
Female	118	60 (50.8)	116	50 (43.1)	1.18 [0.90; 1.55]	0.236	
Age							
< 65	221	107 (48.4)	214	84 (39.3)	1.23 [0.99; 1.53]	0.054	0.372
≥ 65	175	81 (46.3)	185	58 (31.4)	1.48 [1.13; 1.93]	0.004	
ECOG Performance Status							
0	253	119 (47.0)	245	82 (33.5)	1.41 [1.13; 1.75]	0.002	0.527
1	143	69 (48.3)	154	60 (39.0)	1.24 [0.95; 1.61]	0.107	
Region							
WHO Stratum A	204	127 (62.3)	216	96 (44.4)	1.40 [1.17; 1.68]	<0.001	0.192
Rest of World	192	61 (31.8)	183	46 (25.1)	1.26 [0.91; 1.75]	0.156	
Stage							
II	118	58 (49.2)	121	44 (36.4)	1.35 [1.00; 1.82]	0.046	0.881
III	278	130 (46.8)	278	98 (35.3)	1.33 [1.08; 1.62]	0.006	
PD-L1 Status							
TPS ≥ 50%	132	70 (53.0)	133	57 (42.9)	1.24 [0.96; 1.59]	0.098	0.662
TPS < 50%	264	118 (44.7)	266	85 (32.0)	1.40 [1.12; 1.74]	0.003	
Histology							
Squamous	171	75 (43.9)	172	62 (36.0)	1.22 [0.94; 1.58]	0.140	0.321
Non-Squamous	225	113 (50.2)	227	80 (35.2)	1.43 [1.14; 1.77]	0.001	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Based on 2x2 contingency table, using Wald confidence interval. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

e: Based on Mantel-Haenszel Chi-Squared test. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

f: Based on Breslow-Day test with subgroup as stratification factor. In case no participant or all participants with event in both treatment groups for a subgroup category, it is excluded from interaction test (if only one subgroup category remaining, report 'n.a.'). In case no participant with event in at least one treatment group across all subgroup categories, report 'n.a.'

g: A system organ class or 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 smaller than 0.05

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); PD-L1: Programmed Death-Ligand 1; SOC: System Organ Class; TPS: Tumor Proportion Score; WHO: World Health Organization

Tabelle 4G-44: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für PT aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**		**Placebo + Chemotherapy[b] / Placebo**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	**p-Value for Interaction Test[f]**
SOC: Endocrine disorders - PT[g]: Hyperthyroidism							
Sex							
Male	278	14 (5.0)	283	8 (2.8)	1.78 [0.76; 4.18]	0.178	0.083
Female	118	6 (5.1)	116	0	n.a. [n.a.; n.a.]	n.a.	
Age							
< 65	221	10 (4.5)	214	4 (1.9)	2.42 [0.77; 7.60]	0.117	0.909
≥ 65	175	10 (5.7)	185	4 (2.2)	2.64 [0.84; 8.27]	0.082	
ECOG Performance Status							
0	253	11 (4.3)	245	7 (2.9)	1.52 [0.60; 3.86]	0.373	0.079
1	143	9 (6.3)	154	1 (0.6)	9.69 [1.24; 75.55]	0.007	
Region							
WHO Stratum A	204	12 (5.9)	216	2 (0.9)	6.35 [1.44; 28.04]	0.005	0.069
Rest of World	192	8 (4.2)	183	6 (3.3)	1.27 [0.45; 3.59]	0.651	
Stage							
II	118	6 (5.1)	121	1 (0.8)	6.15 [0.75; 50.33]	0.051	0.320
III	278	14 (5.0)	278	7 (2.5)	2.00 [0.82; 4.88]	0.120	
PD-L1 Status							
TPS ≥ 50%	132	6 (4.5)	133	2 (1.5)	3.02 [0.62; 14.71]	0.149	0.794
TPS < 50%	264	14 (5.3)	266	6 (2.3)	2.35 [0.92; 6.03]	0.066	
Histology							
Squamous	171	10 (5.8)	172	7 (4.1)	1.44 [0.56; 3.69]	0.449	0.066
Non-Squamous	225	10 (4.4)	227	1 (0.4)	10.09 [1.30; 78.16]	0.006	
SOC: Endocrine disorders - PT[g]: Hypothyroidism							
Sex							
Male	278	26 (9.4)	283	3 (1.1)	8.82 [2.70; 28.81]	<0.001	0.636
Female	118	17 (14.4)	116	3 (2.6)	5.57 [1.68; 18.50]	0.001	
Age							
< 65	221	26 (11.8)	214	4 (1.9)	6.29 [2.23; 17.73]	<0.001	0.714
≥ 65	175	17 (9.7)	185	2 (1.1)	8.99 [2.11; 38.33]	<0.001	
ECOG Performance Status							
0	253	20 (7.9)	245	4 (1.6)	4.84 [1.68; 13.96]	0.001	0.256
1	143	23 (16.1)	154	2 (1.3)	12.38 [2.97; 51.59]	<0.001	
Region							
WHO Stratum A	204	20 (9.8)	216	4 (1.9)	5.29 [1.84; 15.22]	<0.001	0.406
Rest of World	192	23 (12.0)	183	2 (1.1)	10.96 [2.62; 45.83]	<0.001	
Stage							
II	118	15 (12.7)	121	3 (2.5)	5.13 [1.52; 17.25]	0.003	0.509
III	278	28 (10.1)	278	3 (1.1)	9.33 [2.87; 30.34]	<0.001	
PD-L1 Status							
TPS ≥ 50%	132	19 (14.4)	133	2 (1.5)	9.57 [2.27; 40.28]	<0.001	0.575

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab		Placebo + Chemotherapy[b] / Placebo		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		p-Value for Interaction Test[f]
Adverse Events	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	
TPS < 50%	264	24 (9.1)	266	4 (1.5)	6.05 [2.13; 17.18]	<0.001	
Histology							
Squamous	171	24 (14.0)	172	4 (2.3)	6.04 [2.14; 17.03]	<0.001	0.654
Non-Squamous	225	19 (8.4)	227	2 (0.9)	9.58 [2.26; 40.67]	<0.001	
SOC: Gastrointestinal disorders - PT[g]: Oesophagitis							
Sex							
Male	278	1 (0.4)	283	8 (2.8)	n.c. [n.c.; n.c.]	n.c.	n.c.
Female	118	0	116	2 (1.7)	n.c. [n.c.; n.c.]	n.c.	
Age							
< 65	221	1 (0.5)	214	9 (4.2)	0.11 [0.01; 0.84]	0.009	0.754
≥ 65	175	0	185	1 (0.5)	n.a. [n.a.; n.a.]	n.a.	
ECOG Performance Status							
0	253	0	245	7 (2.9)	n.c. [n.c.; n.c.]	n.c.	n.c.
1	143	1 (0.7)	154	3 (1.9)	n.c. [n.c.; n.c.]	n.c.	
Region							
WHO Stratum A	204	1 (0.5)	216	6 (2.8)	n.c. [n.c.; n.c.]	n.c.	n.c.
Rest of World	192	0	183	4 (2.2)	n.c. [n.c.; n.c.]	n.c.	
Stage							
II	118	0	121	4 (3.3)	n.c. [n.c.; n.c.]	n.c.	n.c.
III	278	1 (0.4)	278	6 (2.2)	n.c. [n.c.; n.c.]	n.c.	
PD-L1 Status							
TPS ≥ 50%	132	0	133	2 (1.5)	n.c. [n.c.; n.c.]	n.c.	n.c.
TPS < 50%	264	1 (0.4)	266	8 (3.0)	n.c. [n.c.; n.c.]	n.c.	
Histology							
Squamous	171	1 (0.6)	172	6 (3.5)	n.c. [n.c.; n.c.]	n.c.	n.c.
Non-Squamous	225	0	227	4 (1.8)	n.c. [n.c.; n.c.]	n.c.	
SOC: General disorders and administration site conditions - PT[g]: Chills							
Sex							
Male	278	6 (2.2)	283	2 (0.7)	n.c. [n.c.; n.c.]	n.c.	n.c.
Female	118	6 (5.1)	116	1 (0.9)	n.c. [n.c.; n.c.]	n.c.	
Age							
< 65	221	7 (3.2)	214	3 (1.4)	2.26 [0.59; 8.62]	0.220	0.156
≥ 65	175	5 (2.9)	185	0	n.a. [n.a.; n.a.]	n.a.	
ECOG Performance Status							
0	253	7 (2.8)	245	2 (0.8)	n.c. [n.c.; n.c.]	n.c.	n.c.
1	143	5 (3.5)	154	1 (0.6)	n.c. [n.c.; n.c.]	n.c.	
Region							
WHO Stratum A	204	10 (4.9)	216	3 (1.4)	3.53 [0.99; 12.64]	0.038	0.475
Rest of World	192	2 (1.0)	183	0	n.a. [n.a.; n.a.]	n.a.	
Stage							
II	118	5 (4.2)	121	1 (0.8)	n.c. [n.c.; n.c.]	n.c.	n.c.
III	278	7 (2.5)	278	2 (0.7)	n.c. [n.c.; n.c.]	n.c.	

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab		Placebo + Chemotherapy[b] / Placebo		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	**p-Value for Interaction Test[f]**
PD-L1 Status							
TPS ≥ 50%	132	7 (5.3)	133	2 (1.5)	n.c. [n.c.; n.c.]	n.c.	n.c.
TPS < 50%	264	5 (1.9)	266	1 (0.4)	n.c. [n.c.; n.c.]	n.c.	
Histology							
Squamous	171	4 (2.3)	172	1 (0.6)	4.02 [0.45; 35.63]	0.175	0.993
Non-Squamous	225	8 (3.6)	227	2 (0.9)	4.04 [0.87; 18.80]	0.054	
SOC: General disorders and administration site conditions - PT[g]: Oedema peripheral							
Sex							
Male	278	27 (9.7)	283	15 (5.3)	1.83 [1.00; 3.37]	0.047	0.636
Female	118	13 (11.0)	116	9 (7.8)	1.42 [0.63; 3.19]	0.394	
Age							
< 65	221	19 (8.6)	214	9 (4.2)	2.04 [0.95; 4.42]	0.062	0.551
≥ 65	175	21 (12.0)	185	15 (8.1)	1.48 [0.79; 2.78]	0.219	
ECOG Performance Status							
0	253	23 (9.1)	245	11 (4.5)	2.02 [1.01; 4.06]	0.042	0.489
1	143	17 (11.9)	154	13 (8.4)	1.41 [0.71; 2.79]	0.326	
Region							
WHO Stratum A	204	32 (15.7)	216	18 (8.3)	1.88 [1.09; 3.25]	0.020	0.459
Rest of World	192	8 (4.2)	183	6 (3.3)	1.27 [0.45; 3.59]	0.651	
Stage							
II	118	18 (15.3)	121	8 (6.6)	2.31 [1.04; 5.10]	0.032	0.290
III	278	22 (7.9)	278	16 (5.8)	1.38 [0.74; 2.56]	0.314	
PD-L1 Status							
TPS ≥ 50%	132	13 (9.8)	133	12 (9.0)	1.09 [0.52; 2.30]	0.818	0.154
TPS < 50%	264	27 (10.2)	266	12 (4.5)	2.27 [1.17; 4.38]	0.012	
Histology							
Squamous	171	18 (10.5)	172	9 (5.2)	2.01 [0.93; 4.35]	0.069	0.547
Non-Squamous	225	22 (9.8)	227	15 (6.6)	1.48 [0.79; 2.78]	0.220	
SOC: General disorders and administration site conditions - PT[g]: Pyrexia							
Age							
< 65	221	26 (11.8)	214	18 (8.4)	1.40 [0.79; 2.48]	0.247	0.544
≥ 65	175	24 (13.7)	185	14 (7.6)	1.81 [0.97; 3.39]	0.058	
ECOG Performance Status							
0	253	33 (13.0)	245	16 (6.5)	2.00 [1.13; 3.53]	0.015	0.208
1	143	17 (11.9)	154	16 (10.4)	1.14 [0.60; 2.18]	0.682	
Region							
WHO Stratum A	204	32 (15.7)	216	22 (10.2)	1.54 [0.93; 2.56]	0.093	0.863
Rest of World	192	18 (9.4)	183	10 (5.5)	1.72 [0.81; 3.62]	0.150	
Stage							
II	118	15 (12.7)	121	11 (9.1)	1.40 [0.67; 2.92]	0.370	0.708
III	278	35 (12.6)	278	21 (7.6)	1.67 [1.00; 2.79]	0.049	
PD-L1 Status							
TPS ≥ 50%	132	17 (12.9)	133	11 (8.3)	1.56 [0.76; 3.20]	0.223	0.974

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab		Placebo + Chemotherapy[b] / Placebo		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		p-Value for Interaction Test[f]
Adverse Events	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	
TPS < 50%	264	33 (12.5)	266	21 (7.9)	1.58 [0.94; 2.66]	0.080	
Histology							
Squamous	171	23 (13.5)	172	19 (11.0)	1.22 [0.69; 2.15]	0.498	0.225
Non-Squamous	225	27 (12.0)	227	13 (5.7)	2.10 [1.11; 3.96]	0.019	
SOC: Infections and infestations - PT[g]: Bronchitis							
Sex							
Male	278	7 (2.5)	283	5 (1.8)	1.43 [0.46; 4.44]	0.539	0.125
Female	118	8 (6.8)	116	1 (0.9)	7.86 [1.00; 61.89]	0.019	
Age							
< 65	221	7 (3.2)	214	2 (0.9)	3.39 [0.71; 16.13]	0.102	0.643
≥ 65	175	8 (4.6)	185	4 (2.2)	2.11 [0.65; 6.90]	0.204	
ECOG Performance Status							
0	253	9 (3.6)	245	4 (1.6)	2.18 [0.68; 6.98]	0.179	0.693
1	143	6 (4.2)	154	2 (1.3)	3.23 [0.66; 15.75]	0.124	
Region							
WHO Stratum A	204	10 (4.9)	216	3 (1.4)	3.53 [0.99; 12.64]	0.038	0.402
Rest of World	192	5 (2.6)	183	3 (1.6)	1.59 [0.39; 6.55]	0.519	
Stage							
II	118	2 (1.7)	121	1 (0.8)	2.05 [0.19; 22.32]	0.547	0.847
III	278	13 (4.7)	278	5 (1.8)	2.60 [0.94; 7.20]	0.055	
PD-L1 Status							
TPS ≥ 50%	132	4 (3.0)	133	1 (0.8)	4.03 [0.46; 35.58]	0.174	0.630
TPS < 50%	264	11 (4.2)	266	5 (1.9)	2.22 [0.78; 6.29]	0.124	
Histology							
Squamous	171	6 (3.5)	172	3 (1.7)	2.01 [0.51; 7.91]	0.307	0.670
Non-Squamous	225	9 (4.0)	227	3 (1.3)	3.03 [0.83; 11.03]	0.077	
SOC: Investigations - PT[g]: Alanine aminotransferase increased							
Sex							
Male	278	38 (13.7)	283	31 (11.0)	1.25 [0.80; 1.95]	0.328	0.230
Female	118	21 (17.8)	116	10 (8.6)	2.06 [1.02; 4.19]	0.039	
Age							
< 65	221	39 (17.6)	214	30 (14.0)	1.26 [0.81; 1.95]	0.301	0.350
≥ 65	175	20 (11.4)	185	11 (5.9)	1.92 [0.95; 3.89]	0.064	
ECOG Performance Status							
0	253	39 (15.4)	245	30 (12.2)	1.26 [0.81; 1.96]	0.306	0.308
1	143	20 (14.0)	154	11 (7.1)	1.96 [0.97; 3.94]	0.054	
Region							
WHO Stratum A	204	31 (15.2)	216	21 (9.7)	1.56 [0.93; 2.63]	0.089	0.681
Rest of World	192	28 (14.6)	183	20 (10.9)	1.33 [0.78; 2.28]	0.290	
Stage							
II	118	20 (16.9)	121	14 (11.6)	1.46 [0.78; 2.76]	0.235	0.952
III	278	39 (14.0)	278	27 (9.7)	1.44 [0.91; 2.29]	0.116	

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab		Placebo + Chemotherapy[b] / Placebo		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	**p-Value for Interaction Test[f]**
PD-L1 Status							
TPS ≥ 50%	132	16 (12.1)	133	14 (10.5)	1.15 [0.59; 2.26]	0.683	0.411
TPS < 50%	264	43 (16.3)	266	27 (10.2)	1.60 [1.02; 2.52]	0.037	
SOC: Psychiatric disorders - PT[g]: Insomnia							
Sex							
Male	278	38 (13.7)	283	21 (7.4)	1.84 [1.11; 3.06]	0.016	0.590
Female	118	13 (11.0)	116	5 (4.3)	2.56 [0.94; 6.94]	0.055	
Age							
< 65	221	29 (13.1)	214	16 (7.5)	1.76 [0.98; 3.14]	0.054	0.563
≥ 65	175	22 (12.6)	185	10 (5.4)	2.33 [1.13; 4.77]	0.017	
Region							
WHO Stratum A	204	36 (17.6)	216	17 (7.9)	2.24 [1.30; 3.86]	0.003	0.425
Rest of World	192	15 (7.8)	183	9 (4.9)	1.59 [0.71; 3.54]	0.253	
Stage							
II	118	15 (12.7)	121	8 (6.6)	1.92 [0.85; 4.36]	0.111	0.937
III	278	36 (12.9)	278	18 (6.5)	2.00 [1.16; 3.43]	0.010	
PD-L1 Status							
TPS ≥ 50%	132	17 (12.9)	133	8 (6.0)	2.14 [0.96; 4.79]	0.056	0.816
TPS < 50%	264	34 (12.9)	266	18 (6.8)	1.90 [1.10; 3.28]	0.018	
Histology							
Squamous	171	22 (12.9)	172	14 (8.1)	1.58 [0.84; 2.98]	0.154	0.359
Non-Squamous	225	29 (12.9)	227	12 (5.3)	2.44 [1.28; 4.66]	0.005	
SOC: Renal and urinary disorders - PT[g]: Proteinuria							
Sex							
Male	278	5 (1.8)	283	2 (0.7)	n.c. [n.c.; n.c.]	n.c.	n.c.
Female	118	6 (5.1)	116	1 (0.9)	n.c. [n.c.; n.c.]	n.c.	
Age							
< 65	221	7 (3.2)	214	3 (1.4)	2.26 [0.59; 8.62]	0.220	0.200
≥ 65	175	4 (2.3)	185	0	n.a. [n.a.; n.a.]	n.a.	
ECOG Performance Status							
0	253	9 (3.6)	245	3 (1.2)	2.91 [0.80; 10.60]	0.090	0.405
1	143	2 (1.4)	154	0	n.a. [n.a.; n.a.]	n.a.	
Region							
WHO Stratum A	204	6 (2.9)	216	1 (0.5)	n.c. [n.c.; n.c.]	n.c.	n.c.
Rest of World	192	5 (2.6)	183	2 (1.1)	n.c. [n.c.; n.c.]	n.c.	
Stage							
II	118	4 (3.4)	121	1 (0.8)	n.c. [n.c.; n.c.]	n.c.	n.c.
III	278	7 (2.5)	278	2 (0.7)	n.c. [n.c.; n.c.]	n.c.	
PD-L1 Status							
TPS ≥ 50%	132	6 (4.5)	133	1 (0.8)	n.c. [n.c.; n.c.]	n.c.	n.c.
TPS < 50%	264	5 (1.9)	266	2 (0.8)	n.c. [n.c.; n.c.]	n.c.	
Histology							
Squamous	171	6 (3.5)	172	0	n.c. [n.c.; n.c.]	n.c.	n.c.

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab		Placebo + Chemotherapy[b] / Placebo		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	**p-Value for Interaction Test[f]**
Non-Squamous	225	5 (2.2)	227	3 (1.3)	n.c. [n.c.; n.c.]	n.c.	
SOC: Respiratory, thoracic and mediastinal disorders - PT[g]: Dyspnoea							
Sex							
Male	278	47 (16.9)	283	35 (12.4)	1.37 [0.91; 2.05]	0.128	0.753
Female	118	26 (22.0)	116	17 (14.7)	1.50 [0.86; 2.62]	0.146	
Age							
< 65	221	34 (15.4)	214	25 (11.7)	1.32 [0.81; 2.13]	0.260	0.614
≥ 65	175	39 (22.3)	185	27 (14.6)	1.53 [0.98; 2.38]	0.060	
ECOG Performance Status							
0	253	44 (17.4)	245	29 (11.8)	1.47 [0.95; 2.27]	0.080	0.844
1	143	29 (20.3)	154	23 (14.9)	1.36 [0.83; 2.23]	0.227	
Region							
WHO Stratum A	204	59 (28.9)	216	43 (19.9)	1.45 [1.03; 2.05]	0.032	0.882
Rest of World	192	14 (7.3)	183	9 (4.9)	1.48 [0.66; 3.34]	0.339	
Stage							
II	118	21 (17.8)	121	17 (14.0)	1.27 [0.70; 2.28]	0.429	0.661
III	278	52 (18.7)	278	35 (12.6)	1.49 [1.00; 2.21]	0.047	
PD-L1 Status							
TPS ≥ 50%	132	28 (21.2)	133	19 (14.3)	1.48 [0.87; 2.52]	0.141	0.793
TPS < 50%	264	45 (17.0)	266	33 (12.4)	1.37 [0.91; 2.08]	0.132	
SOC: Respiratory, thoracic and mediastinal disorders - PT[g]: Pneumonitis							
Sex							
Male	278	10 (3.6)	283	3 (1.1)	3.39 [0.94; 12.20]	0.046	0.652
Female	118	6 (5.1)	116	1 (0.9)	5.90 [0.72; 48.24]	0.059	
Age							
< 65	221	7 (3.2)	214	1 (0.5)	6.78 [0.84; 54.63]	0.036	0.548
≥ 65	175	9 (5.1)	185	3 (1.6)	3.17 [0.87; 11.52]	0.063	
ECOG Performance Status							
0	253	10 (4.0)	245	3 (1.2)	3.23 [0.90; 11.59]	0.057	0.577
1	143	6 (4.2)	154	1 (0.6)	6.46 [0.79; 53.02]	0.044	
Region							
WHO Stratum A	204	8 (3.9)	216	2 (0.9)	4.24 [0.91; 19.71]	0.044	0.926
Rest of World	192	8 (4.2)	183	2 (1.1)	3.81 [0.82; 17.72]	0.065	
Stage							
II	118	4 (3.4)	121	1 (0.8)	4.10 [0.47; 36.16]	0.167	0.989
III	278	12 (4.3)	278	3 (1.1)	4.00 [1.14; 14.02]	0.019	
PD-L1 Status							
TPS ≥ 50%	132	6 (4.5)	133	1 (0.8)	6.05 [0.74; 49.53]	0.055	0.635
TPS < 50%	264	10 (3.8)	266	3 (1.1)	3.36 [0.93; 12.07]	0.048	
Histology							
Squamous	171	6 (3.5)	172	0	n.a. [n.a.; n.a.]	n.a.	0.144
Non-Squamous	225	10 (4.4)	227	4 (1.8)	2.52 [0.80; 7.92]	0.100	

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab		Placebo + Chemotherapy[b] / Placebo		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	**p-Value for Interaction Test[f]**
SOC: Skin and subcutaneous tissue disorders - PT[g]: Dermatitis acneiform							
Sex							
Male	278	10 (3.6)	283	3 (1.1)	3.39 [0.94; 12.20]	0.046	0.685
Female	118	2 (1.7)	116	1 (0.9)	1.97 [0.18; 21.39]	0.572	
Age							
< 65	221	5 (2.3)	214	4 (1.9)	n.c. [n.c.; n.c.]	n.c.	n.c.
≥ 65	175	7 (4.0)	185	0	n.c. [n.c.; n.c.]	n.c.	
ECOG Performance Status							
0	253	7 (2.8)	245	4 (1.6)	1.69 [0.50; 5.72]	0.390	0.103
1	143	5 (3.5)	154	0	n.a. [n.a.; n.a.]	n.a.	
Region							
WHO Stratum A	204	10 (4.9)	216	4 (1.9)	2.65 [0.84; 8.31]	0.082	0.411
Rest of World	192	2 (1.0)	183	0	n.a. [n.a.; n.a.]	n.a.	
Stage							
II	118	5 (4.2)	121	1 (0.8)	5.13 [0.61; 43.23]	0.093	0.530
III	278	7 (2.5)	278	3 (1.1)	2.33 [0.61; 8.93]	0.202	
PD-L1 Status							
TPS ≥ 50%	132	3 (2.3)	133	2 (1.5)	1.51 [0.26; 8.90]	0.646	0.346
TPS < 50%	264	9 (3.4)	266	2 (0.8)	4.53 [0.99; 20.79]	0.032	
Histology							
Squamous	171	4 (2.3)	172	1 (0.6)	4.02 [0.45; 35.63]	0.175	0.762
Non-Squamous	225	8 (3.6)	227	3 (1.3)	2.69 [0.72; 10.01]	0.124	
SOC: Skin and subcutaneous tissue disorders - PT[g]: Pruritus							
Sex							
Male	278	35 (12.6)	283	23 (8.1)	1.55 [0.94; 2.55]	0.083	0.930
Female	118	18 (15.3)	116	12 (10.3)	1.47 [0.74; 2.92]	0.262	
Age							
< 65	221	33 (14.9)	214	23 (10.7)	1.39 [0.84; 2.29]	0.193	0.611
≥ 65	175	20 (11.4)	185	12 (6.5)	1.76 [0.89; 3.50]	0.100	
ECOG Performance Status							
0	253	36 (14.2)	245	22 (9.0)	1.58 [0.96; 2.61]	0.068	0.773
1	143	17 (11.9)	154	13 (8.4)	1.41 [0.71; 2.79]	0.326	
Region							
WHO Stratum A	204	45 (22.1)	216	27 (12.5)	1.76 [1.14; 2.73]	0.009	0.198
Rest of World	192	8 (4.2)	183	8 (4.4)	0.95 [0.37; 2.49]	0.922	
Stage							
II	118	15 (12.7)	121	10 (8.3)	1.54 [0.72; 3.29]	0.262	0.986
III	278	38 (13.7)	278	25 (9.0)	1.52 [0.94; 2.45]	0.082	
Histology							
Squamous	171	14 (8.2)	172	14 (8.1)	1.01 [0.49; 2.05]	0.987	0.142
Non-Squamous	225	39 (17.3)	227	21 (9.3)	1.87 [1.14; 3.08]	0.011	
SOC: Skin and subcutaneous tissue disorders - PT[g]: Rash							
Sex							

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab		Placebo + Chemotherapy[b] / Placebo		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	**p-Value for Interaction Test[f]**
Male	278	43 (15.5)	283	17 (6.0)	2.57 [1.51; 4.40]	<0.001	0.224
Female	118	26 (22.0)	116	17 (14.7)	1.50 [0.86; 2.62]	0.146	
Age							
< 65	221	36 (16.3)	214	22 (10.3)	1.58 [0.96; 2.60]	0.066	0.137
≥ 65	175	33 (18.9)	185	12 (6.5)	2.91 [1.55; 5.45]	<0.001	
ECOG Performance Status							
0	253	43 (17.0)	245	20 (8.2)	2.08 [1.26; 3.43]	0.003	0.937
1	143	26 (18.2)	154	14 (9.1)	2.00 [1.09; 3.68]	0.022	
Region							
WHO Stratum A	204	46 (22.5)	216	27 (12.5)	1.80 [1.17; 2.79]	0.007	0.315
Rest of World	192	23 (12.0)	183	7 (3.8)	3.13 [1.38; 7.12]	0.004	
Stage							
II	118	18 (15.3)	121	9 (7.4)	2.05 [0.96; 4.38]	0.057	0.976
III	278	51 (18.3)	278	25 (9.0)	2.04 [1.30; 3.20]	0.001	
PD-L1 Status							
TPS ≥ 50%	132	25 (18.9)	133	10 (7.5)	2.52 [1.26; 5.04]	0.006	0.460
TPS < 50%	264	44 (16.7)	266	24 (9.0)	1.85 [1.16; 2.95]	0.009	
Histology							
Squamous	171	26 (15.2)	172	13 (7.6)	2.01 [1.07; 3.78]	0.026	0.904
Non-Squamous	225	43 (19.1)	227	21 (9.3)	2.07 [1.27; 3.37]	0.003	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Based on 2x2 contingency table, using Wald confidence interval. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

e: Based on Mantel-Haenszel Chi-Squared test. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

f: Based on Breslow-Day test with subgroup as stratification factor. In case no participant or all participants with event in both treatment groups for a subgroup category, it is excluded from interaction test (if only one subgroup category remaining, report 'n.a.'). In case no participant with event in at least one treatment group across all subgroup categories, report 'n.a.'

g: A system organ class or 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 smaller than 0.05

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

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-45: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) für SOC aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**		**Placebo + Chemotherapy[b] / Placebo**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
Serious Adverse Events	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	**p-Value for Interaction Test[f]**
SOC[g]: General disorders and administration site conditions							
Sex							
Male	278	13 (4.7)	283	4 (1.4)	3.31 [1.09; 10.02]	0.024	0.441
Female	118	7 (5.9)	116	4 (3.4)	1.72 [0.52; 5.72]	0.370	
Age							
< 65	221	10 (4.5)	214	6 (2.8)	1.61 [0.60; 4.36]	0.341	0.186
≥ 65	175	10 (5.7)	185	2 (1.1)	5.29 [1.17; 23.79]	0.015	
ECOG Performance Status							
0	253	13 (5.1)	245	4 (1.6)	3.15 [1.04; 9.52]	0.031	0.540
1	143	7 (4.9)	154	4 (2.6)	1.88 [0.56; 6.30]	0.296	
Region							
WHO Stratum A	204	15 (7.4)	216	7 (3.2)	2.27 [0.94; 5.45]	0.059	0.541
Rest of World	192	5 (2.6)	183	1 (0.5)	4.77 [0.56; 40.40]	0.113	
Stage							
II	118	9 (7.6)	121	1 (0.8)	9.23 [1.19; 71.71]	0.009	0.093
III	278	11 (4.0)	278	7 (2.5)	1.57 [0.62; 3.99]	0.338	
PD-L1 Status							
TPS ≥ 50%	132	4 (3.0)	133	4 (3.0)	1.01 [0.26; 3.94]	0.991	0.106
TPS < 50%	264	16 (6.1)	266	4 (1.5)	4.03 [1.37; 11.90]	0.006	
Histology							
Squamous	171	8 (4.7)	172	1 (0.6)	8.05 [1.02; 63.65]	0.018	0.159
Non-Squamous	225	12 (5.3)	227	7 (3.1)	1.73 [0.69; 4.31]	0.234	
SOC[g]: Metabolism and nutrition disorders							
Sex							
Male	278	5 (1.8)	283	2 (0.7)	n.c. [n.c.; n.c.]	n.c.	n.c.
Female	118	5 (4.2)	116	1 (0.9)	n.c. [n.c.; n.c.]	n.c.	
Age							
< 65	221	4 (1.8)	214	1 (0.5)	n.c. [n.c.; n.c.]	n.c.	n.c.
≥ 65	175	6 (3.4)	185	2 (1.1)	n.c. [n.c.; n.c.]	n.c.	
ECOG Performance Status							
0	253	9 (3.6)	245	3 (1.2)	2.91 [0.80; 10.60]	0.090	0.552
1	143	1 (0.7)	154	0	n.a. [n.a.; n.a.]	n.a.	
Region							
WHO Stratum A	204	8 (3.9)	216	3 (1.4)	2.82 [0.76; 10.50]	0.105	0.426
Rest of World	192	2 (1.0)	183	0	n.a. [n.a.; n.a.]	n.a.	
Stage							
II	118	2 (1.7)	121	2 (1.7)	n.c. [n.c.; n.c.]	n.c.	n.c.
III	278	8 (2.9)	278	1 (0.4)	n.c. [n.c.; n.c.]	n.c.	

Study: KEYNOTE 671[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab		Placebo + Chemotherapy[b] / Placebo		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo		
Serious Adverse Events	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	**p-Value for Interaction Test[f]**
PD-L1 Status							
TPS ≥ 50%	132	4 (3.0)	133	1 (0.8)	n.c. [n.c.; n.c.]	n.c.	n.c.
TPS < 50%	264	6 (2.3)	266	2 (0.8)	n.c. [n.c.; n.c.]	n.c.	
Histology							
Squamous	171	3 (1.8)	172	0	n.a. [n.a.; n.a.]	n.a.	0.281
Non-Squamous	225	7 (3.1)	227	3 (1.3)	2.35 [0.62; 8.99]	0.196	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Based on 2x2 contingency table, using Wald confidence interval. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

e: Based on Mantel-Haenszel Chi-Squared test. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

f: Based on Breslow-Day test with subgroup as stratification factor. In case no participant or all participants with event in both treatment groups for a subgroup category, it is excluded from interaction test (if only one subgroup category remaining, report 'n.a.'). In case no participant with event in at least one treatment group across all subgroup categories, report 'n.a.'

g: A system organ class or 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 smaller than 0.05

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); PD-L1: Programmed Death-Ligand 1; SOC: System Organ Class; TPS: Tumor Proportion Score; WHO: World Health Organization

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

Tabelle 4G-46: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für SOC aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 671[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**		**Placebo + Chemotherapy[b] / Placebo**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[b] / Placebo**		
Severe Adverse Events	**N[c]**	**Participants with Event n (%)**	**N[c]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][d]**	**p-Value[e]**	**p-Value for Interaction Test[f]**
SOC[g]: General disorders and administration site conditions							
Sex							
Male	278	20 (7.2)	283	10 (3.5)	2.04 [0.97; 4.27]	0.054	0.837
Female	118	9 (7.6)	116	5 (4.3)	1.77 [0.61; 5.12]	0.286	
Age							
< 65	221	13 (5.9)	214	9 (4.2)	1.40 [0.61; 3.20]	0.425	0.257
≥ 65	175	16 (9.1)	185	6 (3.2)	2.82 [1.13; 7.04]	0.020	
ECOG Performance Status							
0	253	17 (6.7)	245	5 (2.0)	3.29 [1.23; 8.79]	0.011	0.153
1	143	12 (8.4)	154	10 (6.5)	1.29 [0.58; 2.90]	0.533	
Region							
WHO Stratum A	204	17 (8.3)	216	12 (5.6)	1.50 [0.73; 3.06]	0.262	0.204
Rest of World	192	12 (6.3)	183	3 (1.6)	3.81 [1.09; 13.29]	0.023	
Stage							
II	118	9 (7.6)	121	4 (3.3)	2.31 [0.73; 7.29]	0.142	0.731
III	278	20 (7.2)	278	11 (4.0)	1.82 [0.89; 3.72]	0.097	
PD-L1 Status							
TPS ≥ 50%	132	9 (6.8)	133	2 (1.5)	4.53 [1.00; 20.59]	0.030	0.195
TPS < 50%	264	20 (7.6)	266	13 (4.9)	1.55 [0.79; 3.05]	0.201	
Histology							
Squamous	171	13 (7.6)	172	6 (3.5)	2.18 [0.85; 5.60]	0.096	0.757
Non-Squamous	225	16 (7.1)	227	9 (4.0)	1.79 [0.81; 3.97]	0.144	

a: Database Cutoff Date: 10JUL2023

b: Cisplatin plus gemcitabine (for squamous histology) or cisplatin plus pemetrexed (for non-squamous histology)

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

d: Based on 2x2 contingency table, using Wald confidence interval. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

e: Based on Mantel-Haenszel Chi-Squared test. In case of no participant with event in at least one treatment group or all participants with event in both treatment groups, report 'n.a.'

f: Based on Breslow-Day test with subgroup as stratification factor. In case no participant or all participants with event in both treatment groups for a subgroup category, it is excluded from interaction test (if only one subgroup category remaining, report 'n.a.'). In case no participant with event in at least one treatment group across all subgroup categories, report 'n.a.'

g: A system organ class or 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 smaller than 0.05

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); PD-L1: Programmed Death-Ligand 1; SOC: System Organ Class; TPS: Tumor Proportion Score; WHO: World Health Organization

Anhang 4-G6: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI)

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

Tabelle 4G-47: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT in der Studie KEYNOTE 671

AEOSI	**Preferred Terms**	**Immune-mediated (Yes/No)**
Pneumonitis	Acute interstitial pneumonitis, Autoimmune lung disease, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organising pneumonia, Immune-mediated lung disease	Yes
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive, Autoimmune colitis, Immune-mediated enterocolitis	Yes
Hepatitis	Hepatitis, Immune-mediated hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitis fulminant, Drug-induced liver injury	Yes
Nephritis	Nephritis, Autoimmune nephritis, Chronic autoimmune glomerulonephritis, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Mesangioproliferative glomerulonephritis, Nephritis haemorrhagic, Tubulointerstitial nephritis, Nephrotic syndrome, Immune-mediated nephritis	Yes
Adrenal Insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency, Primary adrenal insufficiency, Addison's disease, Immune-mediated adrenal insufficiency	Yes

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

AEOSI	Preferred Terms	Immune-mediated (Yes/No)
	uveitis, Choroidal effusion, Choroidal detachment, Serous retinal detachment	
Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Immune-mediated pancreatitis	Yes
Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated myositis, Rhabdomyolysis, Myopathy, Dermatomyositis, Autoimmune myositis	Yes
Guillain-Barre Syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome, Subacute inflammatory demyelinating polyneuropathy	Yes
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis	Yes
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis, Immune-mediated encephalitis	Yes
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis, Sarcoidosis of lymph node	Yes
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction, Infusion related hypersensitivity reaction	No
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia,	Yes

AEOSI	Preferred Terms	Immune-mediated (Yes/No)
	Immune-mediated myasthenia gravis	
Myelitis	Myelitis, Myelitis transverse, Acute necrotising myelitis, Immune-mediated myelitis	Yes
Vasculitis	Anti-neutrophil cytoplasmic antibody positive vasculitis, Aortitis, Arteritis, Arteritis coronary, Behcet's syndrome, Central nervous system vasculitis, Cerebral arteritis, Diffuse vasculitis, Eosinophilic granulomatosis with polyangiitis, Granulomatosis with polyangiitis, Haemorrhagic vasculitis, Hypersensitivity vasculitis, Microscopic polyangiitis, Ocular vasculitis, Polyarteritis nodosa, Pulmonary vasculitis, Renal arteritis, Renal vasculitis, Retinal vasculitis, Takayasu's arteritis, Giant cell arteritis, Vasculitis, Vasculitis gastrointestinal, Vasculitis necrotising	Yes
Cholangitis Sclerosing	Cholangitis sclerosing, Autoimmune cholangitis, Immune-mediated cholangitis	Yes
Hypoparathyroidism	Hypoparathyroidism, Primary hypoparathyroidism	Yes
Arthritis	Autoimmune arthritis, Immune-mediated arthritis	Yes
HLH	Haemophagocytic lymphohistiocytosis	Yes
Optic Neuritis	Optic neuritis, Immune-mediated optic neuritis	Yes
Gastritis	Gastritis, Gastritis erosive, Gastritis haemorrhagic, Haemorrhagic erosive gastritis, Immune-mediated gastritis, Ulcerative gastritis	Yes