Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD Sharp & Dohme GmbH

Modul 4A

Anhang 4-G: Weitere Ergebnisse

Adjuvante Behandlung von Erwachsenen mit NSCLC mit hohem Rezidivrisiko nach vollständiger Resektion und Platin-basierter Chemotherapie

Stand: 19.04.2024

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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-G1.1: Rücklaufquoten des EORTC QLQ-C30 und EORTC QLQ-LC13

Tabelle 4G-1: Gründe für das Fehlen von Werten im EORTC QLQ-C30 und EORTC QLQ-LC13

		Pembrolizumab N=496		Placebo N=499	
Treatment Visit	Category	n	(%)	n	(%)
BASELINE	**Expected to Complete Questionnaires**	**496**	**(100.0)**	**499**	**(100.0)**
	Completed	490	(98.8)	498	(99.8)
	Compliance (% in those expected to complete questionnaires)	490	(98.8)	498	(99.8)
	Not completed	6	(1.2)	1	(0.2)
	Administrative failure to distribute the questionnaire	4	(0.8)	1	(0.2)
	Patient felt too ill	0	(0.0)	0	(0.0)
	Clinician or nurse felt the patient was too ill	0	(0.0)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	0	(0.0)	0	(0.0)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	1	(0.2)	0	(0.0)
	With visit, no record	1	(0.2)	0	(0.0)
	Missing by Design	**0**	**(0.0)**	**0**	**(0.0)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	0	(0.0)	0	(0.0)
	Patient withdrew to follow-up with quality of life assessments	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Not required at this time point	0	(0.0)	0	(0.0)
WEEK 12	**Expected to Complete Questionnaires**	**489**	**(98.6)**	**497**	**(99.6)**
	Completed	453	(91.3)	473	(94.8)
	Compliance (% in those expected to complete questionnaires)	453	(92.6)	473	(95.2)
	Not completed	36	(7.3)	24	(4.8)
	Administrative failure to distribute the questionnaire	15	(3.0)	13	(2.6)

Treatment Visit	Category	Pembrolizumab N=496		Placebo N=499	
		n	(%)	n	(%)
WEEK 12	Patient felt too ill	2	(0.4)	0	(0.0)
	Clinician or nurse felt the patient was too ill	1	(0.2)	1	(0.2)
	Patient felt it was inconvenient, takes too much time	3	(0.6)	1	(0.2)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	15	(3.0)	8	(1.6)
	With visit, no record	0	(0.0)	1	(0.2)
	Missing by Design	**7**	**(1.4)**	**2**	**(0.4)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	0	(0.0)	0	(0.0)
	Patient withdrew to follow-up with quality of life assessments	1	(0.2)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Not required at this time point	6	(1.2)	2	(0.4)
WEEK 24	**Expected to Complete Questionnaires**	**473**	**(95.4)**	**492**	**(98.6)**
	Completed	422	(85.1)	446	(89.4)
	Compliance (% in those expected to complete questionnaires)	422	(89.2)	446	(90.7)
	Not completed	51	(10.3)	46	(9.2)
	Administrative failure to distribute the questionnaire	20	(4.0)	22	(4.4)
	Patient felt too ill	2	(0.4)	1	(0.2)
	Clinician or nurse felt the patient was too ill	1	(0.2)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	0	(0.0)	3	(0.6)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	24	(4.8)	18	(3.6)
	With visit, no record	4	(0.8)	2	(0.4)
	Missing by Design	**23**	**(4.6)**	**7**	**(1.4)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	8	(1.6)	1	(0.2)
	Patient withdrew to follow-up with quality of life assessments	4	(0.8)	1	(0.2)
	Visit not reached	4	(0.8)	1	(0.2)
	Not required at this time point	7	(1.4)	4	(0.8)
WEEK 36	**Expected to Complete Questionnaires**	**454**	**(91.5)**	**481**	**(96.4)**
	Completed	396	(79.8)	430	(86.2)

Treatment Visit	Category	Pembrolizumab N=496		Placebo N=499	
		n	(%)	n	(%)
WEEK 36	Compliance (% in those expected to complete questionnaires)	396	(87.2)	430	(89.4)
	Not completed	58	(11.7)	51	(10.2)
	Administrative failure to distribute the questionnaire	26	(5.2)	25	(5.0)
	Patient felt too ill	2	(0.4)	1	(0.2)
	Clinician or nurse felt the patient was too ill	0	(0.0)	1	(0.2)
	Patient felt it was inconvenient, takes too much time	0	(0.0)	0	(0.0)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	29	(5.8)	24	(4.8)
	With visit, no record	1	(0.2)	0	(0.0)
	Missing by Design	**42**	**(8.5)**	**18**	**(3.6)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	1	(0.2)
	Patient died	14	(2.8)	4	(0.8)
	Patient withdrew to follow-up with quality of life assessments	9	(1.8)	2	(0.4)
	Visit not reached	7	(1.4)	4	(0.8)
	Not required at this time point	12	(2.4)	7	(1.4)
WEEK 48	**Expected to Complete Questionnaires**	**452**	**(91.1)**	**469**	**(94.0)**
	Completed	387	(78.0)	423	(84.8)
	Compliance (% in those expected to complete questionnaires)	387	(85.6)	423	(90.2)
	Not completed	65	(13.1)	46	(9.2)
	Administrative failure to distribute the questionnaire	27	(5.4)	21	(4.2)
	Patient felt too ill	3	(0.6)	1	(0.2)
	Clinician or nurse felt the patient was too ill	0	(0.0)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	3	(0.6)	0	(0.0)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	31	(6.3)	24	(4.8)
	With visit, no record	1	(0.2)	0	(0.0)
	Missing by Design	**44**	**(8.9)**	**30**	**(6.0)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	1	(0.2)
	Patient died	19	(3.8)	20	(4.0)
	Patient withdrew to follow-up with quality of life assessments	12	(2.4)	3	(0.6)
	Visit not reached	10	(2.0)	3	(0.6)

Treatment Visit	Category	Pembrolizumab N=496		Placebo N=499	
		n	(%)	n	(%)
WEEK 48	Not required at this time point	3	(0.6)	3	(0.6)
WEEK 74	**Expected to Complete Questionnaires**	**443**	**(89.3)**	**444**	**(89.0)**
	Completed	356	(71.8)	350	(70.1)
	Compliance (% in those expected to complete questionnaires)	356	(80.4)	350	(78.8)
	Not completed	87	(17.5)	94	(18.8)
	Administrative failure to distribute the questionnaire	40	(8.1)	47	(9.4)
	Patient felt too ill	2	(0.4)	4	(0.8)
	Clinician or nurse felt the patient was too ill	0	(0.0)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	3	(0.6)	2	(0.4)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	41	(8.3)	39	(7.8)
	With visit, no record	1	(0.2)	2	(0.4)
	Missing by Design	**53**	**(10.7)**	**55**	**(11.0)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	25	(5.0)	34	(6.8)
	Patient withdrew to follow-up with quality of life assessments	10	(2.0)	8	(1.6)
	Visit not reached	13	(2.6)	5	(1.0)
	Not required at this time point	5	(1.0)	8	(1.6)
WEEK 100	**Expected to Complete Questionnaires**	**419**	**(84.5)**	**417**	**(83.6)**
	Completed	335	(67.5)	330	(66.1)
	Compliance (% in those expected to complete questionnaires)	335	(80.0)	330	(79.1)
	Not completed	84	(16.9)	87	(17.4)
	Administrative failure to distribute the questionnaire	36	(7.3)	39	(7.8)
	Patient felt too ill	1	(0.2)	2	(0.4)
	Clinician or nurse felt the patient was too ill	0	(0.0)	1	(0.2)
	Patient felt it was inconvenient, takes too much time	5	(1.0)	2	(0.4)
	Patient felt that it was a violation of privacy	0	(0.0)	1	(0.2)
	Other reason	42	(8.5)	41	(8.2)
	With visit, no record	0	(0.0)	1	(0.2)
	Missing by Design	**77**	**(15.5)**	**82**	**(16.4)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=496		Placebo N=499	
		n	(%)	n	(%)
WEEK 100	Patient died	44	(8.9)	57	(11.4)
	Patient withdrew to follow-up with quality of life assessments	18	(3.6)	11	(2.2)
	Visit not reached	12	(2.4)	10	(2.0)
	Not required at this time point	3	(0.6)	4	(0.8)
WEEK 152	**Expected to Complete Questionnaires**	**380**	**(76.6)**	**383**	**(76.8)**
	Completed	308	(62.1)	304	(60.9)
	Compliance (% in those expected to complete questionnaires)	308	(81.1)	304	(79.4)
	Not completed	72	(14.5)	79	(15.8)
	Administrative failure to distribute the questionnaire	24	(4.8)	35	(7.0)
	Patient felt too ill	0	(0.0)	9	(1.8)
	Clinician or nurse felt the patient was too ill	0	(0.0)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	10	(2.0)	2	(0.4)
	Patient felt that it was a violation of privacy	1	(0.2)	0	(0.0)
	Other reason	36	(7.3)	33	(6.6)
	With visit, no record	1	(0.2)	0	(0.0)
	Missing by Design	**116**	**(23.4)**	**116**	**(23.2)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	66	(13.3)	81	(16.2)
	Patient withdrew to follow-up with quality of life assessments	23	(4.6)	15	(3.0)
	Visit not reached	17	(3.4)	14	(2.8)
	Not required at this time point	10	(2.0)	6	(1.2)
WEEK 204	**Expected to Complete Questionnaires**	**230**	**(46.4)**	**222**	**(44.5)**
	Completed	175	(35.3)	165	(33.1)
	Compliance (% in those expected to complete questionnaires)	175	(76.1)	165	(74.3)
	Not completed	55	(11.1)	57	(11.4)
	Administrative failure to distribute the questionnaire	26	(5.2)	33	(6.6)
	Patient felt too ill	3	(0.6)	2	(0.4)
	Clinician or nurse felt the patient was too ill	0	(0.0)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	3	(0.6)	3	(0.6)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	23	(4.6)	19	(3.8)

Treatment Visit	Category	Pembrolizumab N=496		Placebo N=499	
		n	(%)	n	(%)
WEEK 204	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**266**	**(53.6)**	**277**	**(55.5)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	89	(17.9)	119	(23.8)
	Patient withdrew to follow-up with quality of life assessments	45	(9.1)	27	(5.4)
	Visit not reached	126	(25.4)	127	(25.5)
	Not required at this time point	6	(1.2)	4	(0.8)
WEEK 256	**Expected to Complete Questionnaires**	**79**	**(15.9)**	**81**	**(16.2)**
	Completed	51	(10.3)	61	(12.2)
	Compliance (% in those expected to complete questionnaires)	51	(64.6)	61	(75.3)
	Not completed	28	(5.6)	20	(4.0)
	Administrative failure to distribute the questionnaire	19	(3.8)	11	(2.2)
	Patient felt too ill	0	(0.0)	0	(0.0)
	Clinician or nurse felt the patient was too ill	0	(0.0)	1	(0.2)
	Patient felt it was inconvenient, takes too much time	2	(0.4)	0	(0.0)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	7	(1.4)	8	(1.6)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**417**	**(84.1)**	**418**	**(83.8)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	103	(20.8)	132	(26.5)
	Patient withdrew to follow-up with quality of life assessments	50	(10.1)	35	(7.0)
	Visit not reached	254	(51.2)	250	(50.1)
	Not required at this time point	10	(2.0)	1	(0.2)

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: death, withdrawal, and no visit scheduled.
Database Cutoff Date: 24JAN2023

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

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

Treatment Visit	Category	Pembrolizumab N=494 n	Pembrolizumab N=494 (%)	Placebo N=499 n	Placebo N=499 (%)
BASELINE	**Expected to Complete Questionnaires**	**494**	**(100.0)**	**499**	**(100.0)**
	Completed	484	(98.0)	494	(99.0)
	Compliance (% in those expected to complete questionnaires)	484	(98.0)	494	(99.0)
	Not completed	10	(2.0)	5	(1.0)
	Administrative failure to distribute the questionnaire	8	(1.6)	4	(0.8)
	Patient felt too ill	0	(0.0)	0	(0.0)
	Clinician or nurse felt the patient was too ill	0	(0.0)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	0	(0.0)	0	(0.0)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	1	(0.2)	1	(0.2)
	With visit, no record	1	(0.2)	0	(0.0)
	Missing by Design	**0**	**(0.0)**	**0**	**(0.0)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	0	(0.0)	0	(0.0)
	Patient withdrew to follow-up with quality of life assessments	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Not required at this time point	0	(0.0)	0	(0.0)
WEEK 12	**Expected to Complete Questionnaires**	**489**	**(99.0)**	**497**	**(99.6)**
	Completed	451	(91.3)	471	(94.4)
	Compliance (% in those expected to complete questionnaires)	451	(92.2)	471	(94.8)
	Not completed	38	(7.7)	26	(5.2)
	Administrative failure to distribute the questionnaire	15	(3.0)	15	(3.0)
	Patient felt too ill	2	(0.4)	0	(0.0)
	Clinician or nurse felt the patient was too ill	1	(0.2)	1	(0.2)
	Patient felt it was inconvenient, takes too much time	3	(0.6)	1	(0.2)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	17	(3.4)	8	(1.6)

Treatment Visit	Category	Pembrolizumab N=494 n	(%)	Placebo N=499 n	(%)
WEEK 12	With visit, no record	0	(0.0)	1	(0.2)
	Missing by Design	**5**	**(1.0)**	**2**	**(0.4)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	0	(0.0)	0	(0.0)
	Patient withdrew to follow-up with quality of life assessments	1	(0.2)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Not required at this time point	4	(0.8)	2	(0.4)
WEEK 24	**Expected to Complete Questionnaires**	**472**	**(95.5)**	**491**	**(98.4)**
	Completed	422	(85.4)	445	(89.2)
	Compliance (% in those expected to complete questionnaires)	422	(89.4)	445	(90.6)
	Not completed	50	(10.1)	46	(9.2)
	Administrative failure to distribute the questionnaire	18	(3.6)	23	(4.6)
	Patient felt too ill	2	(0.4)	1	(0.2)
	Clinician or nurse felt the patient was too ill	1	(0.2)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	0	(0.0)	3	(0.6)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	25	(5.1)	17	(3.4)
	With visit, no record	4	(0.8)	2	(0.4)
	Missing by Design	**22**	**(4.5)**	**8**	**(1.6)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	7	(1.4)	2	(0.4)
	Patient withdrew to follow-up with quality of life assessments	4	(0.8)	1	(0.2)
	Visit not reached	4	(0.8)	1	(0.2)
	Not required at this time point	7	(1.4)	4	(0.8)
WEEK 36	**Expected to Complete Questionnaires**	**453**	**(91.7)**	**481**	**(96.4)**
	Completed	394	(79.8)	430	(86.2)
	Compliance (% in those expected to complete questionnaires)	394	(87.0)	430	(89.4)
	Not completed	59	(11.9)	51	(10.2)
	Administrative failure to distribute the questionnaire	27	(5.5)	25	(5.0)
	Patient felt too ill	2	(0.4)	1	(0.2)
	Clinician or nurse felt the patient was too ill	0	(0.0)	1	(0.2)

Treatment Visit	Category	Pembrolizumab N=494		Placebo N=499	
		n	(%)	n	(%)
WEEK 36	Patient felt it was inconvenient, takes too much time	0	(0.0)	0	(0.0)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	29	(5.9)	24	(4.8)
	With visit, no record	1	(0.2)	0	(0.0)
	Missing by Design	**41**	**(8.3)**	**18**	**(3.6)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	1	(0.2)
	Patient died	13	(2.6)	4	(0.8)
	Patient withdrew to follow-up with quality of life assessments	9	(1.8)	2	(0.4)
	Visit not reached	7	(1.4)	4	(0.8)
	Not required at this time point	12	(2.4)	7	(1.4)
WEEK 48	**Expected to Complete Questionnaires**	**451**	**(91.3)**	**469**	**(94.0)**
	Completed	387	(78.3)	421	(84.4)
	Compliance (% in those expected to complete questionnaires)	387	(85.8)	421	(89.8)
	Not completed	64	(13.0)	48	(9.6)
	Administrative failure to distribute the questionnaire	27	(5.5)	23	(4.6)
	Patient felt too ill	3	(0.6)	1	(0.2)
	Clinician or nurse felt the patient was too ill	0	(0.0)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	3	(0.6)	0	(0.0)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	30	(6.1)	24	(4.8)
	With visit, no record	1	(0.2)	0	(0.0)
	Missing by Design	**43**	**(8.7)**	**30**	**(6.0)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	1	(0.2)
	Patient died	18	(3.6)	20	(4.0)
	Patient withdrew to follow-up with quality of life assessments	12	(2.4)	3	(0.6)
	Visit not reached	10	(2.0)	3	(0.6)
	Not required at this time point	3	(0.6)	3	(0.6)
WEEK 74	**Expected to Complete Questionnaires**	**442**	**(89.5)**	**444**	**(89.0)**
	Completed	355	(71.9)	351	(70.3)
	Compliance (% in those expected to complete questionnaires)	355	(80.3)	351	(79.1)
	Not completed	87	(17.6)	93	(18.6)

Treatment Visit	Category	Pembrolizumab N=494		Placebo N=499	
		n	(%)	n	(%)
WEEK 74	Administrative failure to distribute the questionnaire	40	(8.1)	46	(9.2)
	Patient felt too ill	2	(0.4)	4	(0.8)
	Clinician or nurse felt the patient was too ill	0	(0.0)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	3	(0.6)	2	(0.4)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	41	(8.3)	39	(7.8)
	With visit, no record	1	(0.2)	2	(0.4)
	Missing by Design	**52**	**(10.5)**	**55**	**(11.0)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	24	(4.9)	34	(6.8)
	Patient withdrew to follow-up with quality of life assessments	10	(2.0)	8	(1.6)
	Visit not reached	13	(2.6)	5	(1.0)
	Not required at this time point	5	(1.0)	8	(1.6)
WEEK 100	**Expected to Complete Questionnaires**	**418**	**(84.6)**	**417**	**(83.6)**
	Completed	335	(67.8)	328	(65.7)
	Compliance (% in those expected to complete questionnaires)	335	(80.1)	328	(78.7)
	Not completed	83	(16.8)	89	(17.8)
	Administrative failure to distribute the questionnaire	36	(7.3)	41	(8.2)
	Patient felt too ill	1	(0.2)	2	(0.4)
	Clinician or nurse felt the patient was too ill	0	(0.0)	1	(0.2)
	Patient felt it was inconvenient, takes too much time	5	(1.0)	2	(0.4)
	Patient felt that it was a violation of privacy	0	(0.0)	1	(0.2)
	Other reason	41	(8.3)	41	(8.2)
	With visit, no record	0	(0.0)	1	(0.2)
	Missing by Design	**76**	**(15.4)**	**82**	**(16.4)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	43	(8.7)	57	(11.4)
	Patient withdrew to follow-up with quality of life assessments	18	(3.6)	11	(2.2)
	Visit not reached	12	(2.4)	10	(2.0)
	Not required at this time point	3	(0.6)	4	(0.8)
WEEK 152	**Expected to Complete Questionnaires**	**379**	**(76.7)**	**383**	**(76.8)**

Treatment Visit	Category	Pembrolizumab N=494		Placebo N=499	
		n	(%)	n	(%)
WEEK 152	Completed	308	(62.3)	303	(60.7)
	Compliance (% in those expected to complete questionnaires)	308	(81.3)	303	(79.1)
	Not completed	71	(14.4)	80	(16.0)
	Administrative failure to distribute the questionnaire	25	(5.1)	36	(7.2)
	Patient felt too ill	0	(0.0)	9	(1.8)
	Clinician or nurse felt the patient was too ill	0	(0.0)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	10	(2.0)	2	(0.4)
	Patient felt that it was a violation of privacy	1	(0.2)	0	(0.0)
	Other reason	34	(6.9)	33	(6.6)
	With visit, no record	1	(0.2)	0	(0.0)
	Missing by Design	**115**	**(23.3)**	**116**	**(23.2)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	65	(13.2)	81	(16.2)
	Patient withdrew to follow-up with quality of life assessments	23	(4.7)	15	(3.0)
	Visit not reached	17	(3.4)	14	(2.8)
	Not required at this time point	10	(2.0)	6	(1.2)
WEEK 204	**Expected to Complete Questionnaires**	**230**	**(46.6)**	**222**	**(44.5)**
	Completed	172	(34.8)	165	(33.1)
	Compliance (% in those expected to complete questionnaires)	172	(74.8)	165	(74.3)
	Not completed	58	(11.7)	57	(11.4)
	Administrative failure to distribute the questionnaire	29	(5.9)	34	(6.8)
	Patient felt too ill	3	(0.6)	2	(0.4)
	Clinician or nurse felt the patient was too ill	0	(0.0)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	3	(0.6)	3	(0.6)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	23	(4.7)	18	(3.6)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**264**	**(53.4)**	**277**	**(55.5)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	88	(17.8)	119	(23.8)
	Patient withdrew to follow-up with quality of life assessments	45	(9.1)	27	(5.4)

Treatment Visit	Category	Pembrolizumab N=494		Placebo N=499	
		n	(%)	n	(%)
WEEK 256	Visit not reached	125	(25.3)	127	(25.5)
	Not required at this time point	6	(1.2)	4	(0.8)
	Expected to Complete Questionnaires	**79**	**(16.0)**	**81**	**(16.2)**
	Completed	49	(9.9)	60	(12.0)
	Compliance (% in those expected to complete questionnaires)	49	(62.0)	60	(74.1)
	Not completed	30	(6.1)	21	(4.2)
	Administrative failure to distribute the questionnaire	21	(4.3)	12	(2.4)
	Patient felt too ill	0	(0.0)	0	(0.0)
	Clinician or nurse felt the patient was too ill	0	(0.0)	1	(0.2)
	Patient felt it was inconvenient, takes too much time	2	(0.4)	0	(0.0)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	7	(1.4)	8	(1.6)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**415**	**(84.0)**	**418**	**(83.8)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	102	(20.6)	132	(26.5)
	Patient withdrew to follow-up with quality of life assessments	50	(10.1)	35	(7.0)
	Visit not reached	253	(51.2)	250	(50.1)
	Not required at this time point	10	(2.0)	1	(0.2)

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: death, withdrawal, and no visit scheduled.

Database Cutoff Date: 24JAN2023

Treatment Visit	Category	Pembrolizumab N=578 n	(%)	Placebo N=581 n	(%)
	Patient felt it was inconvenient, takes too much time	3	(0.5)	1	(0.2)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	20	(3.5)	9	(1.5)
	With visit, no record	1	(0.2)	2	(0.3)
	Missing by Design	**5**	**(0.9)**	**2**	**(0.3)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	0	(0.0)	0	(0.0)
	Patient withdrew to follow-up with quality of life assessments	1	(0.2)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Not required at this time point	4	(0.7)	2	(0.3)
WEEK 24	**Expected to Complete Questionnaires**	**555**	**(96.0)**	**571**	**(98.3)**
	Completed	495	(85.6)	520	(89.5)
	Compliance (% in those expected to complete questionnaires)	495	(89.2)	520	(91.1)
	Not completed	60	(10.4)	51	(8.8)
	Administrative failure to distribute the questionnaire	23	(4.0)	26	(4.5)
	Patient felt too ill	4	(0.7)	1	(0.2)
	Clinician or nurse felt the patient was too ill	1	(0.2)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	0	(0.0)	3	(0.5)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	27	(4.7)	19	(3.3)
	With visit, no record	5	(0.9)	2	(0.3)
	Missing by Design	**23**	**(4.0)**	**10**	**(1.7)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	7	(1.2)	2	(0.3)
	Patient withdrew to follow-up with quality of life assessments	4	(0.7)	1	(0.2)
	Visit not reached	4	(0.7)	1	(0.2)
	Not required at this time point	8	(1.4)	6	(1.0)

Treatment Visit	Category	Pembrolizumab N=578 n	(%)	Placebo N=581 n	(%)
WEEK 36	**Expected to Complete Questionnaires**	**530**	**(91.7)**	**562**	**(96.7)**
	Completed	460	(79.6)	502	(86.4)
	Compliance (% in those expected to complete questionnaires)	460	(86.8)	502	(89.3)
	Not completed	70	(12.1)	60	(10.3)
	Administrative failure to distribute the questionnaire	32	(5.5)	29	(5.0)
	Patient felt too ill	2	(0.3)	1	(0.2)
	Clinician or nurse felt the patient was too ill	1	(0.2)	1	(0.2)
	Patient felt it was inconvenient, takes too much time	1	(0.2)	0	(0.0)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	33	(5.7)	29	(5.0)
	With visit, no record	1	(0.2)	0	(0.0)
	Missing by Design	**48**	**(8.3)**	**19**	**(3.3)**
	Patient didn't understand the actual language / illiterate	1	(0.2)	1	(0.2)
	Patient died	15	(2.6)	5	(0.9)
	Patient withdrew to follow-up with quality of life assessments	9	(1.6)	2	(0.3)
	Visit not reached	10	(1.7)	4	(0.7)
	Not required at this time point	13	(2.2)	7	(1.2)
WEEK 48	**Expected to Complete Questionnaires**	**526**	**(91.0)**	**548**	**(94.3)**
	Completed	452	(78.2)	491	(84.5)
	Compliance (% in those expected to complete questionnaires)	452	(85.9)	491	(89.6)
	Not completed	74	(12.8)	57	(9.8)
	Administrative failure to distribute the questionnaire	34	(5.9)	27	(4.6)
	Patient felt too ill	3	(0.5)	1	(0.2)
	Clinician or nurse felt the patient was too ill	1	(0.2)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	3	(0.5)	0	(0.0)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	32	(5.5)	29	(5.0)
	With visit, no record	1	(0.2)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=578 n	(%)	Placebo N=581 n	(%)
	Missing by Design	**52**	**(9.0)**	**33**	**(5.7)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	1	(0.2)
	Patient died	23	(4.0)	23	(4.0)
	Patient withdrew to follow-up with quality of life assessments	13	(2.2)	3	(0.5)
	Visit not reached	11	(1.9)	3	(0.5)
	Not required at this time point	5	(0.9)	3	(0.5)
WEEK 74	**Expected to Complete Questionnaires**	**514**	**(88.9)**	**520**	**(89.5)**
	Completed	415	(71.8)	409	(70.4)
	Compliance (% in those expected to complete questionnaires)	415	(80.7)	409	(78.7)
	Not completed	99	(17.1)	111	(19.1)
	Administrative failure to distribute the questionnaire	49	(8.5)	58	(10.0)
	Patient felt too ill	2	(0.3)	4	(0.7)
	Clinician or nurse felt the patient was too ill	0	(0.0)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	3	(0.5)	2	(0.3)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	44	(7.6)	43	(7.4)
	With visit, no record	1	(0.2)	4	(0.7)
	Missing by Design	**64**	**(11.1)**	**61**	**(10.5)**
	Patient didn't understand the actual language / illiterate	1	(0.2)	0	(0.0)
	Patient died	32	(5.5)	38	(6.5)
	Patient withdrew to follow-up with quality of life assessments	11	(1.9)	8	(1.4)
	Visit not reached	15	(2.6)	7	(1.2)
	Not required at this time point	5	(0.9)	8	(1.4)
WEEK 100	**Expected to Complete Questionnaires**	**419**	**(72.5)**	**436**	**(75.0)**
	Completed	339	(58.7)	342	(58.9)
	Compliance (% in those expected to complete questionnaires)	339	(80.9)	342	(78.4)
	Not completed	80	(13.8)	94	(16.2)
	Administrative failure to distribute the questionnaire	38	(6.6)	46	(7.9)

Treatment Visit	Category	Pembrolizumab N=578 n	(%)	Placebo N=581 n	(%)
	Patient felt too ill	1	(0.2)	2	(0.3)
	Clinician or nurse felt the patient was too ill	0	(0.0)	1	(0.2)
	Patient felt it was inconvenient, takes too much time	5	(0.9)	2	(0.3)
	Patient felt that it was a violation of privacy	0	(0.0)	1	(0.2)
	Other reason	36	(6.2)	41	(7.1)
	With visit, no record	0	(0.0)	1	(0.2)
	Missing by Design	**159**	**(27.5)**	**145**	**(25.0)**
	Patient didn't understand the actual language / illiterate	1	(0.2)	0	(0.0)
	Patient died	53	(9.2)	61	(10.5)
	Patient withdrew to follow-up with quality of life assessments	21	(3.6)	16	(2.8)
	Visit not reached	77	(13.3)	62	(10.7)
	Not required at this time point	7	(1.2)	6	(1.0)
WEEK 152	**Expected to Complete Questionnaires**	**281**	**(48.6)**	**276**	**(47.5)**
	Completed	229	(39.6)	217	(37.3)
	Compliance (% in those expected to complete questionnaires)	229	(81.5)	217	(78.6)
	Not completed	52	(9.0)	59	(10.2)
	Administrative failure to distribute the questionnaire	23	(4.0)	29	(5.0)
	Patient felt too ill	0	(0.0)	4	(0.7)
	Clinician or nurse felt the patient was too ill	0	(0.0)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	4	(0.7)	2	(0.3)
	Patient felt that it was a violation of privacy	1	(0.2)	0	(0.0)
	Other reason	23	(4.0)	24	(4.1)
	With visit, no record	1	(0.2)	0	(0.0)
	Missing by Design	**297**	**(51.4)**	**305**	**(52.5)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	73	(12.6)	85	(14.6)
	Patient withdrew to follow-up with quality of life assessments	30	(5.2)	29	(5.0)
	Visit not reached	176	(30.4)	181	(31.2)

Treatment Visit	Category	Pembrolizumab N=578 n	(%)	Placebo N=581 n	(%)
	Not required at this time point	18	(3.1)	10	(1.7)
WEEK 204	**Expected to Complete Questionnaires**	**89**	**(15.4)**	**90**	**(15.5)**
	Completed	67	(11.6)	58	(10.0)
	Compliance (% in those expected to complete questionnaires)	67	(75.3)	58	(64.4)
	Not completed	22	(3.8)	32	(5.5)
	Administrative failure to distribute the questionnaire	10	(1.7)	15	(2.6)
	Patient felt too ill	0	(0.0)	1	(0.2)
	Clinician or nurse felt the patient was too ill	0	(0.0)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	0	(0.0)	2	(0.3)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	12	(2.1)	14	(2.4)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**489**	**(84.6)**	**491**	**(84.5)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	85	(14.7)	101	(17.4)
	Patient withdrew to follow-up with quality of life assessments	43	(7.4)	40	(6.9)
	Visit not reached	351	(60.7)	344	(59.2)
	Not required at this time point	10	(1.7)	6	(1.0)
WEEK 256	**Expected to Complete Questionnaires**	**19**	**(3.3)**	**17**	**(2.9)**
	Completed	8	(1.4)	12	(2.1)
	Compliance (% in those expected to complete questionnaires)	8	(42.1)	12	(70.6)
	Not completed	11	(1.9)	5	(0.9)
	Administrative failure to distribute the questionnaire	8	(1.4)	2	(0.3)
	Patient felt too ill	0	(0.0)	0	(0.0)
	Clinician or nurse felt the patient was too ill	0	(0.0)	0	(0.0)
	Patient felt it was inconvenient, takes too much time	1	(0.2)	0	(0.0)
	Patient felt that it was a violation of privacy	0	(0.0)	0	(0.0)
	Other reason	2	(0.3)	3	(0.5)

Treatment Visit	Category	Pembrolizumab N=578 n	Pembrolizumab N=578 (%)	Placebo N=581 n	Placebo N=581 (%)
	With visit, no record	0	(0.0)	0	(0.0)
	Missing by Design	**559**	**(96.7)**	**564**	**(97.1)**
	Patient didn't understand the actual language / illiterate	0	(0.0)	0	(0.0)
	Patient died	93	(16.1)	110	(18.9)
	Patient withdrew to follow-up with quality of life assessments	46	(8.0)	47	(8.1)
	Visit not reached	417	(72.1)	407	(70.1)
	Not required at this time point	3	(0.5)	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: death, withdrawal, and no visit scheduled.

Database Cutoff Date: 20SEP2021

Anhang 4-G2: 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-G2.1: Mortalität

Tabelle 4G-3: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 091[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Overall Survival	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Sex									
Male	339	82 (24.2)	Not reached [-; -]	347	94 (27.1)	Not reached [-; -]	0.88 [0.65; 1.18]	0.400	0.281
Female	167	31 (18.6)	Not reached [-; -]	157	44 (28.0)	Not reached [-; -]	0.65 [0.41; 1.03]	0.069	
Age									
< 65	264	55 (20.8)	Not reached [-; -]	252	58 (23.0)	Not reached [-; -]	0.93 [0.64; 1.35]	0.700	0.316
≥ 65	242	58 (24.0)	Not reached [-; -]	252	80 (31.7)	Not reached [-; -]	0.72 [0.51; 1.01]	0.057	
ECOG Performance Status									
0	326	70 (21.5)	Not reached [-; -]	292	70 (24.0)	Not reached [-; -]	0.89 [0.64; 1.24]	0.483	0.475
1	180	43 (23.9)	Not reached [63.9; -]	212	68 (32.1)	Not reached [-; -]	0.74 [0.50; 1.08]	0.122	
Region									
Western Europe	261	57 (21.8)	Not reached [-; -]	266	71 (26.7)	Not reached [-; -]	0.82 [0.58; 1.16]	0.255	0.606
Eastern Europe	105	31 (29.5)	Not reached [-; -]	96	34 (35.4)	Not reached [-; -]	0.80 [0.49; 1.31]	0.375	
Rest of World	53	8 (15.1)	Not reached [-; -]	55	16 (29.1)	Not reached [43.3; -]	0.50 [0.21; 1.16]	0.106	
Asia	87	17 (19.5)	Not reached [-; -]	87	17 (19.5)	Not reached [62.7; -]	1.01 [0.51; 1.97]	0.983	
Stage									
IB	60	9 (15.0)	Not reached [-; -]	57	12 (21.1)	Not reached [61.9; -]	0.68 [0.29; 1.63]	0.391	0.908
II	283	60 (21.2)	Not reached [-; -]	295	76 (25.8)	Not reached [-; -]	0.81 [0.58; 1.14]	0.229	
≥IIIA	163	44 (27.0)	Not reached [-; -]	152	50 (32.9)	Not reached [62.7; -]	0.82 [0.55; 1.23]	0.335	
Type of Adjuvant Chemotherapy									
Carboplatin + Vinorelbine	81	21 (25.9)	Not reached [-; -]	70	25 (35.7)	Not reached [51.6; -]	0.72 [0.40; 1.28]	0.259	0.912
Cisplatin + Vinorelbine	241	45 (18.7)	Not reached [-; -]	250	55 (22.0)	Not reached [-; -]	0.83 [0.56; 1.24]	0.363	
Other	184	47 (25.5)	Not reached [-; -]	184	58 (31.5)	Not reached [-; -]	0.81 [0.55; 1.19]	0.275	
Geographic Region									

Study: KEYNOTE 091[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Overall Survival	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
EU	343	82 (23.9)	Not reached [-; -]	342	97 (28.4)	Not reached [-; -]	0.84 [0.62; 1.12]	0.233	0.665
Non-EU	163	31 (19.0)	Not reached [-; -]	162	41 (25.3)	Not reached [62.7; -]	0.74 [0.46; 1.17]	0.198	
Histology									
Squamous	157	34 (21.7)	Not reached [-; -]	184	48 (26.1)	Not reached [-; -]	0.80 [0.52; 1.24]	0.321	0.952
Non-squamous	349	79 (22.6)	Not reached [-; -]	320	90 (28.1)	Not reached [-; -]	0.81 [0.60; 1.09]	0.160	
EGFR Mutation Status									
N	190	46 (24.2)	Not reached [-; -]	192	51 (26.6)	Not reached [-; -]	0.90 [0.61; 1.35]	0.623	0.349
Y	36	6 (16.7)	Not reached [59.0; -]	30	12 (40.0)	Not reached [43.3; -]	0.43 [0.16; 1.14]	0.088	
Unknown	280	61 (21.8)	Not reached [-; -]	282	75 (26.6)	Not reached [-; -]	0.81 [0.57; 1.13]	0.209	
Race									
White	387	87 (22.5)	Not reached [-; -]	392	111 (28.3)	Not reached [-; -]	0.78 [0.59; 1.04]	0.088	0.721
All Others	98	21 (21.4)	Not reached [-; -]	94	23 (24.5)	Not reached [62.7; -]	0.88 [0.48; 1.58]	0.662	
Smoking Status									
Never Smoker	80	18 (22.5)	Not reached [-; -]	57	18 (31.6)	Not reached [55.4; -]	0.67 [0.35; 1.30]	0.240	0.564
Former Smoker	362	84 (23.2)	Not reached [-; -]	375	100 (26.7)	Not reached [-; -]	0.87 [0.65; 1.16]	0.346	
Current Smoker	64	11 (17.2)	Not reached [-; -]	72	20 (27.8)	Not reached [61.2; -]	0.59 [0.28; 1.24]	0.165	
PD-L1 Status									
<1%	198	48 (24.2)	Not reached [-; -]	198	62 (31.3)	Not reached [-; -]	0.78 [0.53; 1.14]	0.193	0.495
1-49%	165	36 (21.8)	Not reached [-; -]	165	48 (29.1)	Not reached [-; -]	0.69 [0.45; 1.08]	0.105	
≥50%	143	29 (20.3)	Not reached [-; -]	141	28 (19.9)	Not reached [-; -]	0.93 [0.55; 1.57]	0.788	

a: Database Cutoff Date: 24JAN2023

b: Number of participants: intention-to-treat population with Adjuvant Chemotherapy

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

d: For PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment, adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current), using Wald confidence interval. For other subgroups, analysis is based on Cox regression model with treatment as a covariate using Wald confidence interval

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

f: For PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current), and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term). For other subgroups, analysis is based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

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

Anhang 4-G2.2: Morbidität

Krankheitsfreies Überleben

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

Study: KEYNOTE 091[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Disease-Free Survival Based on Investigator Assessment (Primary Censoring Rule)	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Sex									
Male	339	149 (44.0)	53.8 [42.1; 70.5]	347	175 (50.4)	41.5 [34.5; -]	0.85 [0.68; 1.06]	0.150	0.328
Female	167	76 (45.5)	59.5 [36.2; 74.7]	157	87 (55.4)	34.5 [18.0; 55.4]	0.69 [0.51; 0.95]	0.021	
Age									
< 65	264	113 (42.8)	59.5 [44.3; 74.7]	252	129 (51.2)	47.0 [29.1; 68.3]	0.77 [0.60; 0.99]	0.044	0.751
≥ 65	242	112 (46.3)	51.7 [36.2; 67.0]	252	133 (52.8)	35.2 [26.9; 47.4]	0.83 [0.65; 1.07]	0.155	
ECOG Performance Status									
0	326	145 (44.5)	58.7 [46.2; 70.5]	292	148 (50.7)	42.8 [34.5; 56.4]	0.80 [0.64; 1.01]	0.061	0.858
1	180	80 (44.4)	47.4 [35.6; -]	212	114 (53.8)	34.8 [23.2; 55.4]	0.80 [0.60; 1.07]	0.132	
Region									
Western Europe	261	117 (44.8)	58.7 [42.1; 74.7]	266	141 (53.0)	39.1 [27.6; 51.6]	0.78 [0.61; 1.00]	0.048	0.947
Eastern Europe	105	49 (46.7)	47.4 [29.4; -]	96	46 (47.9)	35.9 [16.6; -]	0.88 [0.59; 1.32]	0.541	
Rest of World	53	17 (32.1)	70.4 [35.6; -]	55	23 (41.8)	57.8 [35.4; -]	0.77 [0.41; 1.46]	0.424	
Asia	87	42 (48.3)	47.8 [28.8; -]	87	52 (59.8)	32.9 [19.8; 47.4]	0.75 [0.50; 1.13]	0.167	
Stage									
IB	60	19 (31.7)	74.7 [-; -]	57	21 (36.8)	Not reached [28.9; -]	0.75 [0.40; 1.40]	0.361	0.818
II	283	114 (40.3)	67.0 [47.4; 76.0]	295	143 (48.5)	47.2 [35.1; -]	0.77 [0.60; 0.99]	0.042	
≥IIIA	163	92 (56.4)	30.3 [22.3; 46.7]	152	98 (64.5)	22.7 [16.9; 35.0]	0.85 [0.64; 1.13]	0.251	
Type of Adjuvant Chemotherapy									
Carboplatin + Vinorelbine	81	37 (45.7)	58.7 [34.2; -]	70	44 (62.9)	24.1 [13.5; 45.4]	0.60 [0.39; 0.94]	0.024	0.463
Cisplatin + Vinorelbine	241	103 (42.7)	58.3 [46.7; 70.5]	250	123 (49.2)	47.0 [32.9; -]	0.83 [0.64; 1.08]	0.172	
Other	184	85 (46.2)	47.4 [35.2; 76.0]	184	95 (51.6)	40.5 [26.9; 57.8]	0.84 [0.62; 1.13]	0.241	
Geographic Region									
EU	343	153 (44.6)	58.7 [45.0; 74.7]	342	178 (52.0)	36.4 [27.6; 51.6]	0.79 [0.63; 0.98]	0.030	0.676
Non-EU	163	72 (44.2)	51.7 [35.2; -]	162	84 (51.9)	42.8 [31.0; 56.4]	0.82 [0.59; 1.12]	0.210	
Histology									

Study: KEYNOTE 091[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Disease-Free Survival Based on Investigator Assessment (Primary Censoring Rule)	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Squamous	157	57 (36.3)	67.0 [52.6; -]	184	75 (40.8)	Not reached [47.4; -]	0.87 [0.61; 1.23]	0.418	0.425
Non-squamous	349	168 (48.1)	46.4 [35.2; 59.5]	320	187 (58.4)	28.9 [22.5; 39.1]	0.74 [0.60; 0.91]	0.005	
EGFR Mutation Status									
N	190	90 (47.4)	58.3 [34.2; 70.5]	192	109 (56.8)	35.2 [23.3; 47.0]	0.79 [0.59; 1.04]	0.091	0.278
Y	36	20 (55.6)	35.2 [22.8; -]	30	24 (80.0)	13.6 [8.5; 29.4]	0.48 [0.27; 0.88]	0.017	
Unknown	280	115 (41.1)	58.7 [46.4; 74.7]	282	129 (45.7)	47.4 [34.8; -]	0.85 [0.66; 1.10]	0.209	
Race									
White	387	167 (43.2)	58.7 [46.7; 74.5]	392	194 (49.5)	45.4 [34.9; -]	0.83 [0.67; 1.02]	0.074	0.703
All Others	98	49 (50.0)	47.8 [28.8; -]	94	58 (61.7)	31.0 [17.6; 47.2]	0.73 [0.50; 1.08]	0.114	
Smoking Status									
Never Smoker	80	46 (57.5)	29.0 [19.1; -]	57	38 (66.7)	18.0 [11.6; 40.6]	0.71 [0.46; 1.09]	0.114	0.432
Former Smoker	362	157 (43.4)	53.8 [46.4; 70.5]	375	187 (49.9)	46.4 [34.9; 57.8]	0.84 [0.68; 1.04]	0.102	
Current Smoker	64	22 (34.4)	74.7 [44.3; -]	72	37 (51.4)	35.2 [22.5; -]	0.56 [0.32; 0.96]	0.035	
PD-L1 Status									
<1%	198	92 (46.5)	51.7 [42.1; 74.5]	198	108 (54.5)	34.8 [20.5; 51.6]	0.75 [0.56; 0.99]	0.043	0.497
1-49%	165	76 (46.1)	52.6 [34.2; 76.7]	165	91 (55.2)	32.9 [22.3; 47.2]	0.70 [0.51; 0.96]	0.027	
≥50%	143	57 (39.9)	67.0 [44.3; -]	141	63 (44.7)	57.8 [36.4; -]	0.83 [0.57; 1.19]	0.308	

a: Database Cutoff Date: 24JAN2023

b: Number of participants: intention-to-treat population with Adjuvant Chemotherapy

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

d: For PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment, adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current), using Wald confidence interval. For other subgroups, analysis is based on Cox regression model with treatment as a covariate using Wald confidence interval

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

f: For PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current), and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term). For other subgroups, analysis is based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal Growth Factor Receptor; EU: European Union; PD-L1: Programmed Cell Death - Ligand 1

Zeit bis zur ersten Folgetherapie

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

Study: KEYNOTE 091[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Time to Subsequent Oncologic Therapy	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Sex									
Male	339	79 (23.3)	Not reached [77.4; -]	347	125 (36.0)	Not reached [-; -]	0.60 [0.46; 0.80]	< 0.001	0.389
Female	167	46 (27.5)	Not reached [76.0; -]	157	55 (35.0)	Not reached [69.0; -]	0.74 [0.50; 1.10]	0.140	
Age									
< 65	264	64 (24.2)	77.4 [76.0; -]	252	95 (37.7)	Not reached [69.0; -]	0.60 [0.44; 0.83]	0.002	0.510
≥ 65	242	61 (25.2)	Not reached [-; -]	252	85 (33.7)	Not reached [-; -]	0.71 [0.51; 0.98]	0.039	
ECOG Performance Status									
0	326	84 (25.8)	Not reached [77.4; -]	292	101 (34.6)	Not reached [-; -]	0.71 [0.53; 0.95]	0.020	0.338
1	180	41 (22.8)	Not reached [-; -]	212	79 (37.3)	Not reached [69.0; -]	0.56 [0.38; 0.81]	0.002	
Region									
Western Europe	261	64 (24.5)	Not reached [76.0; -]	266	101 (38.0)	Not reached [69.0; -]	0.61 [0.44; 0.83]	0.002	0.880
Eastern Europe	105	30 (28.6)	77.4 [77.4; -]	96	36 (37.5)	Not reached [35.9; -]	0.68 [0.42; 1.10]	0.116	
Rest of World	53	9 (17.0)	Not reached [-; -]	55	10 (18.2)	Not reached [-; -]	0.90 [0.37; 2.21]	0.817	
Asia	87	22 (25.3)	Not reached [-; -]	87	33 (37.9)	Not reached [59.2; -]	0.65 [0.38; 1.12]	0.118	
Stage									
IB	60	8 (13.3)	76.0 [76.0; -]	57	12 (21.1)	Not reached [-; -]	0.64 [0.26; 1.56]	0.322	0.547
II	283	62 (21.9)	Not reached [77.4; -]	295	102 (34.6)	Not reached [-; -]	0.58 [0.42; 0.80]	< 0.001	
≥IIIA	163	55 (33.7)	Not reached [-; -]	152	66 (43.4)	Not reached [36.5; -]	0.76 [0.53; 1.08]	0.128	
PD-L1 Status									
<1%	198	50 (25.3)	77.4 [76.0; -]	198	75 (37.9)	Not reached [59.2; -]	0.62 [0.43; 0.89]	0.009	0.334
1-49%	165	39 (23.6)	Not reached [-; -]	165	61 (37.0)	Not reached [-; -]	0.53 [0.35; 0.80]	0.002	
≥50%	143	36 (25.2)	Not reached [-; -]	141	44 (31.2)	Not reached [-; -]	0.74 [0.47; 1.16]	0.191	

a: Database Cutoff Date: 24JAN2023

b: Number of participants: intention-to-treat population with Adjuvant Chemotherapy

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

d: For PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment, adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current), using Wald confidence interval. For other subgroups, analysis is based on Cox regression model with treatment as a covariate using Wald confidence interval

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

f: For PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current), and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term). For other subgroups, analysis is based on Cox regression model with treatment and subgroup as covariates, and

Study: KEYNOTE 091[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Time to Subsequent Oncologic Therapy	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1									

Zeit bis zur ersten Folgeoperation

Tabelle 4G-6: 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 091[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Time to Subsequent Oncologic Surgery	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Sex									
Male	339	24 (7.1)	Not reached [-; -]	347	29 (8.4)	Not reached [-; -]	0.84 [0.49; 1.44]	0.524	0.258
Female	167	12 (7.2)	Not reached [75.3; -]	157	21 (13.4)	Not reached [-; -]	0.50 [0.25; 1.01]	0.055	
Age									
< 65	264	20 (7.6)	Not reached [-; -]	252	26 (10.3)	Not reached [-; -]	0.72 [0.40; 1.29]	0.272	0.855
≥ 65	242	16 (6.6)	Not reached [-; -]	252	24 (9.5)	Not reached [-; -]	0.68 [0.36; 1.29]	0.238	
ECOG Performance Status									
0	326	26 (8.0)	Not reached [-; -]	292	32 (11.0)	Not reached [-; -]	0.69 [0.41; 1.16]	0.166	0.857
1	180	10 (5.6)	Not reached [-; -]	212	18 (8.5)	Not reached [-; -]	0.65 [0.30; 1.40]	0.267	
Region									
Western Europe	261	24 (9.2)	Not reached [-; -]	266	34 (12.8)	Not reached [-; -]	0.69 [0.41; 1.17]	0.170	0.360
Eastern Europe	105	8 (7.6)	Not reached [-; -]	96	5 (5.2)	Not reached [-; -]	1.45 [0.47; 4.43]	0.515	
Rest of World	53	1 (1.9)	Not reached [-; -]	55	2 (3.6)	Not reached [-; -]	0.51 [0.05; 5.66]	0.586	
Asia	87	3 (3.4)	Not reached [-; -]	87	9 (10.3)	Not reached [-; -]	0.33 [0.09; 1.22]	0.097	
Stage									
IB	60	4 (6.7)	75.3 [75.3; -]	57	6 (10.5)	Not reached [-; -]	0.62 [0.17; 2.20]	0.459	0.360
II	283	23 (8.1)	Not reached [-; -]	295	26 (8.8)	Not reached [-; -]	0.91 [0.52; 1.60]	0.747	
≥IIIA	163	9 (5.5)	Not reached [-; -]	152	18 (11.8)	Not reached [-; -]	0.45 [0.20; 1.00]	0.049	
PD-L1 Status									
<1%	198	13 (6.6)	Not reached [75.3; -]	198	24 (12.1)	Not reached [-; -]	0.49 [0.25; 0.97]	0.040	0.511
1-49%	165	14 (8.5)	Not reached [-; -]	165	15 (9.1)	Not reached [-; -]	0.88 [0.42; 1.85]	0.744	
≥50%	143	9 (6.3)	Not reached [-; -]	141	11 (7.8)	Not reached [-; -]	0.83 [0.34; 2.01]	0.682	

a: Database Cutoff Date: 24JAN2023

b: Number of participants: intention-to-treat population with Adjuvant Chemotherapy

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

d: For PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment, adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current), using Wald confidence interval. For other subgroups, analysis is based on Cox regression model with treatment as a covariate using Wald confidence interval

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

f: For PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current), and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term). For other subgroups, analysis is based on Cox regression model with treatment and subgroup as covariates, and

Study: KEYNOTE 091[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Time to Subsequent Oncologic Surgery	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1									

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30: Symptomskala Erschöpfung

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

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Fatigue	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	315	28.6 (21.50)	-2.42 (0.82)	1.84	-	0.251
Placebo	342	336	30.1 (22.39)	-4.26 (0.79)	[-0.40; 4.09]		
Female							
Pembrolizumab	164	157	32.6 (24.51)	-2.14 (1.24)	-0.41	-	
Placebo	157	156	31.4 (21.35)	-1.73 (1.26)	[-3.88; 3.06]		
Age							
< 65							
Pembrolizumab	260	250	32.0 (24.42)	-2.91 (1.01)	0.25	-	0.390
Placebo	251	246	30.9 (21.78)	-3.16 (1.02)	[-2.57; 3.07]		
≥ 65							
Pembrolizumab	236	222	27.7 (20.16)	-1.76 (0.92)	1.89	-	
Placebo	248	246	30.1 (22.36)	-3.65 (0.88)	[-0.61; 4.38]		
ECOG Performance Status							
0							
Pembrolizumab	321	310	27.9 (22.08)	-1.64 (0.84)	1.20	-	0.848
Placebo	289	283	26.6 (22.07)	-2.83 (0.88)	[-1.19; 3.58]		
1							
Pembrolizumab	175	162	34.0 (23.10)	-3.25 (1.20)	1.54	-	
Placebo	210	209	35.8 (20.96)	-4.79 (1.05)	[-1.60; 4.68]		
Region							
Western Europe							
Pembrolizumab	254	242	30.8 (23.72)	-3.01 (1.01)	0.85	-	0.720
Placebo	263	258	31.8 (23.76)	-3.86 (0.97)	[-1.91; 3.60]		
Eastern Europe							
Pembrolizumab	104	98	32.7 (23.17)	-1.12 (1.52)	2.00	-	
Placebo	95	95	31.9 (20.00)	-3.12 (1.55)	[-2.29; 6.28]		
Rest of World							
Pembrolizumab	51	46	25.8 (21.22)	-3.39 (2.21)	-1.25	-	
Placebo	54	52	29.3 (23.80)	-2.14 (2.08)	[-7.29; 4.79]		
Asia							
Pembrolizumab	87	86	26.6 (18.77)	-1.31 (1.40)	2.50	-	
Placebo	87	87	25.9 (16.92)	-3.81 (1.40)	[-1.42; 6.42]		
Stage							
IB							
Pembrolizumab	60	58	28.6 (22.56)	-1.78 (1.84)	2.15	-	0.629
Placebo	57	56	29.6 (22.05)	-3.93 (1.86)	[-3.05; 7.35]		
II							
Pembrolizumab	278	265	30.7 (23.42)	-3.13 (0.90)	0.37	-	
Placebo	293	292	30.8 (22.67)	-3.50 (0.86)	[-2.08; 2.83]		

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Fatigue	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
IIIA							
Pembrolizumab	158	149	29.1 (21.17)	-0.99 (1.30)	2.12	-	
Placebo	149	144	30.2 (20.89)	-3.11 (1.32)	[-1.52; 5.76]		
PD-L1 Status							
<1%							
Pembrolizumab	194	181	30.0 (22.62)	-1.11 (1.71)	1.83	-	0.154
Placebo	197	196	28.8 (22.02)	-2.94 (1.72)	[-1.26; 4.93]		
1-49%							
Pembrolizumab	163	155	31.2 (22.61)	-4.84 (1.86)	3.00	-	
Placebo	162	159	31.8 (21.37)	-7.83 (1.98)	[-0.41; 6.41]		
≥50%							
Pembrolizumab	139	136	28.5 (22.63)	-4.85 (2.22)	-1.59	-	
Placebo	140	137	31.4 (22.85)	-3.25 (2.28)	[-5.13; 1.95]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

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

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Nausea and Vomiting	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	315	4.9 (12.17)	-1.57 (0.37)	0.27	-	0.381
Placebo	342	336	6.1 (13.87)	-1.84 (0.36)	[-0.74; 1.28]		
Female							
Pembrolizumab	164	157	8.1 (17.26)	-1.86 (0.68)	1.20	-	
Placebo	157	156	7.9 (16.66)	-3.06 (0.69)	[-0.71; 3.11]		
Age							
< 65							
Pembrolizumab	260	250	7.3 (15.00)	-2.27 (0.53)	0.44	-	0.724
Placebo	251	246	7.5 (17.07)	-2.71 (0.53)	[-1.04; 1.92]		
≥ 65							
Pembrolizumab	236	222	4.4 (12.94)	-0.94 (0.39)	0.78	-	
Placebo	248	246	5.8 (12.14)	-1.72 (0.38)	[-0.29; 1.85]		
ECOG Performance Status							
0							
Pembrolizumab	321	310	5.0 (12.40)	-1.58 (0.40)	0.55	-	0.587
Placebo	289	283	6.6 (15.93)	-2.12 (0.42)	[-0.59; 1.68]		
1							
Pembrolizumab	175	162	7.8 (16.84)	-1.60 (0.60)	1.03	-	
Placebo	210	209	6.8 (13.20)	-2.63 (0.52)	[-0.54; 2.59]		
Region							
Western Europe							
Pembrolizumab	254	242	6.3 (14.51)	-1.57 (0.51)	0.64	-	0.964
Placebo	263	258	7.2 (15.67)	-2.21 (0.49)	[-0.76; 2.04]		
Eastern Europe							
Pembrolizumab	104	98	8.2 (16.62)	-2.16 (0.80)	0.29	-	
Placebo	95	95	6.7 (15.06)	-2.45 (0.81)	[-1.97; 2.54]		
Rest of World							
Pembrolizumab	51	46	4.7 (13.91)	-1.39 (1.04)	0.83	-	
Placebo	54	52	5.8 (11.85)	-2.22 (0.98)	[-2.00; 3.66]		
Asia							
Pembrolizumab	87	86	3.3 (8.79)	-1.58 (0.40)	0.86	-	
Placebo	87	87	5.7 (13.65)	-2.44 (0.41)	[-0.27; 1.99]		
Stage							
IB							
Pembrolizumab	60	58	4.9 (12.09)	-0.97 (1.06)	0.34	-	0.575
Placebo	57	56	6.5 (12.18)	-1.32 (1.07)	[-2.65; 3.33]		
II							
Pembrolizumab	278	265	5.5 (13.72)	-1.45 (0.41)	0.96	-	
Placebo	293	292	6.5 (14.61)	-2.41 (0.40)	[-0.17; 2.08]		
IIIA							
Pembrolizumab	158	149	7.2 (15.53)	-2.32 (0.64)	-0.02	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Nausea and Vomiting	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	149	144	7.1 (16.20)	-2.30 (0.64)	[-1.80; 1.76]		
PD-L1 Status							
<1%							
Pembrolizumab	194	181	6.8 (15.50)	-1.98 (0.88)	0.81	-	0.297
Placebo	197	196	6.6 (15.33)	-2.80 (0.89)	[-0.79; 2.41]		
1-49%							
Pembrolizumab	163	155	5.3 (14.43)	-2.30 (0.85)	1.52	-	
Placebo	162	159	7.1 (13.96)	-3.83 (0.91)	[-0.04; 3.09]		
≥50%							
Pembrolizumab	139	136	5.6 (11.69)	-1.21 (1.01)	-0.42	-	
Placebo	140	137	6.2 (15.13)	-0.79 (1.04)	[-2.04; 1.20]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-C30: Symptomskala Schmerzen

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

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Pain	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	315	14.2 (18.70)	0.83 (0.85)	-0.32	-	0.692
Placebo	342	337	15.9 (20.19)	1.16 (0.81)	[-2.63; 1.98]		
Female							
Pembrolizumab	164	158	18.4 (22.67)	3.84 (1.39)	0.63	-	
Placebo	157	156	17.0 (21.21)	3.21 (1.41)	[-3.26; 4.52]		
Age							
< 65							
Pembrolizumab	260	251	17.8 (21.85)	1.53 (1.07)	-0.39	-	0.742
Placebo	251	247	17.9 (22.05)	1.91 (1.07)	[-3.37; 2.59]		
≥ 65							
Pembrolizumab	236	222	13.1 (17.83)	2.19 (0.99)	0.31	-	
Placebo	248	246	14.6 (18.72)	1.88 (0.94)	[-2.38; 3.00]		
ECOG Performance Status							
0							
Pembrolizumab	321	310	13.7 (19.61)	1.85 (0.83)	1.75	-	0.086
Placebo	289	284	14.8 (20.07)	0.10 (0.87)	[-0.62; 4.12]		
1							
Pembrolizumab	175	163	19.3 (20.78)	2.07 (1.37)	-1.91	-	
Placebo	210	209	18.2 (20.97)	3.98 (1.20)	[-5.48; 1.66]		
Region							
Western Europe							
Pembrolizumab	254	242	16.5 (20.73)	2.72 (1.08)	-0.72	-	0.358
Placebo	263	259	16.3 (20.59)	3.44 (1.04)	[-3.66; 2.22]		
Eastern Europe							
Pembrolizumab	104	98	17.5 (21.05)	2.59 (1.70)	4.07	-	
Placebo	95	95	17.0 (21.19)	-1.48 (1.72)	[-0.70; 8.84]		
Rest of World							
Pembrolizumab	51	47	15.2 (22.48)	0.31 (2.29)	-1.57	-	
Placebo	54	52	19.9 (23.58)	1.88 (2.17)	[-7.85; 4.70]		
Asia							
Pembrolizumab	87	86	11.2 (15.43)	-0.35 (1.24)	-0.57	-	
Placebo	87	87	13.0 (17.13)	0.22 (1.24)	[-4.03; 2.89]		
Stage							
IB							
Pembrolizumab	60	58	15.8 (23.24)	3.55 (2.13)	4.53	-	0.198
Placebo	57	57	17.5 (23.24)	-0.99 (2.14)	[-1.45; 10.52]		
II							
Pembrolizumab	278	265	16.0 (20.53)	1.87 (1.02)	0.05	-	
Placebo	293	292	15.6 (19.90)	1.82 (0.97)	[-2.72; 2.81]		
IIIA							
Pembrolizumab	158	150	14.9 (18.33)	1.20 (1.19)	-1.86	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Pain	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	149	144	16.9 (20.67)	3.06 (1.21)	[-5.20; 1.47]		
PD-L1 Status							
<1%							
Pembrolizumab	194	182	15.6 (21.29)	2.92 (1.92)	1.02	-	0.493
Placebo	197	196	15.1 (20.44)	1.91 (1.94)	[-2.46; 4.49]		
1-49%							
Pembrolizumab	163	155	16.3 (19.23)	0.79 (1.85)	0.93	-	
Placebo	162	159	14.2 (19.14)	-0.14 (1.97)	[-2.47; 4.32]		
≥50%							
Pembrolizumab	139	136	14.8 (19.84)	-0.30 (2.29)	-1.54	-	
Placebo	140	138	20.3 (21.66)	1.24 (2.35)	[-5.21; 2.13]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-C30: Symptomskala Atemnot (Dyspnoe)

Tabelle 4G-10: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Dyspnoea	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	311	30.0 (26.63)	-2.06 (0.95)	0.96	-	0.732
Placebo	342	335	30.9 (28.51)	-3.02 (0.91)	[-1.64; 3.55]		
Female							
Pembrolizumab	164	155	28.0 (26.45)	-3.33 (1.40)	0.23	-	
Placebo	157	155	34.4 (27.50)	-3.56 (1.42)	[-3.72; 4.17]		
Age							
< 65							
Pembrolizumab	260	247	29.7 (26.89)	-2.06 (1.12)	-0.41	-	0.300
Placebo	251	244	32.4 (28.43)	-1.66 (1.12)	[-3.53; 2.71]		
≥ 65							
Pembrolizumab	236	219	28.9 (26.25)	-2.98 (1.10)	1.72	-	
Placebo	248	246	31.7 (28.04)	-4.70 (1.04)	[-1.26; 4.70]		
ECOG Performance Status							
0							
Pembrolizumab	321	306	26.3 (24.97)	-1.96 (0.94)	-0.12	-	0.204
Placebo	289	283	28.2 (26.57)	-1.84 (0.98)	[-2.78; 2.54]		
1							
Pembrolizumab	175	160	35.2 (28.53)	-3.06 (1.41)	2.59	-	
Placebo	210	207	37.4 (29.56)	-5.65 (1.24)	[-1.10; 6.28]		
Region							
Western Europe							
Pembrolizumab	254	238	32.2 (28.21)	-2.18 (1.17)	0.28	-	0.665
Placebo	263	256	31.9 (30.29)	-2.45 (1.12)	[-2.90; 3.45]		
Eastern Europe							
Pembrolizumab	104	97	28.5 (26.35)	-1.01 (1.58)	1.83	-	
Placebo	95	95	31.2 (25.64)	-2.84 (1.60)	[-2.61; 6.27]		
Rest of World							
Pembrolizumab	51	45	18.5 (24.16)	-4.47 (2.70)	-2.58	-	
Placebo	54	52	32.7 (31.30)	-1.90 (2.50)	[-9.98; 4.83]		
Asia							
Pembrolizumab	87	86	27.9 (21.61)	-4.09 (1.60)	2.28	-	
Placebo	87	87	33.0 (22.44)	-6.37 (1.60)	[-2.19; 6.75]		
Stage							
IB							
Pembrolizumab	60	58	27.0 (22.90)	-2.39 (2.18)	-0.54	-	0.249
Placebo	57	56	32.7 (30.15)	-1.84 (2.21)	[-6.71; 5.63]		
II							
Pembrolizumab	278	261	30.8 (26.99)	-3.32 (1.06)	-0.41	-	
Placebo	293	291	32.5 (28.69)	-2.91 (1.01)	[-3.29; 2.48]		
IIIA							
Pembrolizumab	158	147	27.7 (27.13)	-0.95 (1.39)	3.39	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Dyspnoea	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	149	143	30.8 (26.56)	-4.33 (1.41)	[-0.50; 7.28]		
PD-L1 Status							
<1%							
Pembrolizumab	194	176	29.9 (26.92)	-1.81 (2.01)	1.88	-	0.055
Placebo	197	196	29.4 (27.04)	-3.68 (2.00)	[-1.73; 5.48]		
1-49%							
Pembrolizumab	163	154	28.6 (25.40)	-4.92 (2.02)	3.35	-	
Placebo	162	157	33.5 (30.31)	-8.27 (2.14)	[-0.37; 7.07]		
≥50%							
Pembrolizumab	139	136	29.4 (27.53)	-10.34 (2.49)	-2.91	-	
Placebo	140	137	34.1 (27.26)	-7.43 (2.57)	[-6.89; 1.07]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

Tabelle 4G-11: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Insomnia	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	316	16.8 (24.42)	0.74 (0.94)	-0.04	-	0.693
Placebo	342	336	18.5 (26.20)	0.78 (0.91)	[-2.61; 2.53]		
Female							
Pembrolizumab	164	155	24.9 (28.83)	2.58 (1.44)	-1.05	-	
Placebo	157	156	23.7 (28.84)	3.63 (1.46)	[-5.08; 2.99]		
Age							
< 65							
Pembrolizumab	260	249	21.6 (27.35)	2.05 (1.19)	0.32	-	0.609
Placebo	251	246	21.5 (28.59)	1.73 (1.19)	[-3.00; 3.64]		
≥ 65							
Pembrolizumab	236	222	17.1 (24.71)	0.65 (1.05)	-0.90	-	
Placebo	248	246	18.7 (25.61)	1.55 (1.00)	[-3.75; 1.96]		
ECOG Performance Status							
0							
Pembrolizumab	321	308	18.2 (24.69)	2.51 (0.96)	1.23	-	0.147
Placebo	289	283	17.2 (26.08)	1.28 (1.01)	[-1.50; 3.96]		
1							
Pembrolizumab	175	163	21.9 (28.78)	-0.48 (1.42)	-2.26	-	
Placebo	210	209	24.1 (28.11)	1.77 (1.24)	[-5.96; 1.45]		
Region							
Western Europe							
Pembrolizumab	254	241	20.9 (27.42)	1.94 (1.26)	-1.50	-	0.266
Placebo	263	258	20.8 (29.00)	3.44 (1.21)	[-4.93; 1.93]		
Eastern Europe							
Pembrolizumab	104	98	22.4 (26.55)	1.26 (1.43)	4.20	0.21	
Placebo	95	95	21.8 (24.68)	-2.94 (1.46)	[0.16; 8.23]	[0.01; 0.40]	
Rest of World							
Pembrolizumab	51	46	18.1 (26.95)	-0.36 (2.24)	-0.46	-	
Placebo	54	52	25.0 (30.87)	0.10 (2.10)	[-6.58; 5.66]		
Asia							
Pembrolizumab	87	86	12.8 (20.56)	0.76 (1.49)	-0.21	-	
Placebo	87	87	13.4 (19.99)	0.97 (1.49)	[-4.38; 3.95]		
Stage							
IB							
Pembrolizumab	60	58	17.2 (22.72)	1.16 (2.35)	-0.60	-	0.978
Placebo	57	56	24.4 (29.47)	1.77 (2.37)	[-7.25; 6.04]		
II							
Pembrolizumab	278	265	20.5 (27.43)	1.11 (1.09)	-0.20	-	
Placebo	293	292	20.4 (27.17)	1.31 (1.04)	[-3.15; 2.76]		
IIIA							
Pembrolizumab	158	148	18.5 (25.28)	2.15 (1.37)	0.04	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Insomnia	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	149	144	17.8 (26.12)	2.12 (1.39)	[-3.81; 3.88]		
PD-L1 Status							
<1%							
Pembrolizumab	194	179	22.3 (27.09)	-1.27 (1.99)	-0.95	-	0.065
Placebo	197	196	20.7 (25.94)	-0.32 (2.00)	[-4.55; 2.65]		
1-49%							
Pembrolizumab	163	156	17.9 (24.36)	0.59 (2.05)	3.72	-	
Placebo	162	159	18.9 (27.18)	-3.13 (2.18)	[-0.05; 7.48]		
≥50%							
Pembrolizumab	139	136	17.4 (26.90)	2.20 (2.56)	-2.80	-	
Placebo	140	137	20.7 (28.90)	5.00 (2.63)	[-6.88; 1.28]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-C30: Symptomskala Appetitverlust

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

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Appetite Loss	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	314	10.9 (19.69)	-1.01 (0.79)	2.33	0.12	0.727
Placebo	342	333	14.1 (23.38)	-3.35 (0.76)	[0.19; 4.48]	[0.01; 0.23]	
Female							
Pembrolizumab	164	155	10.1 (19.14)	0.03 (1.11)	1.73	-	
Placebo	157	156	14.1 (22.41)	-1.70 (1.13)	[-1.40; 4.86]		
Age							
< 65							
Pembrolizumab	260	249	11.4 (19.85)	-0.58 (0.96)	2.90	0.14	0.422
Placebo	251	243	15.4 (23.90)	-3.48 (0.97)	[0.22; 5.58]	[0.01; 0.27]	
≥ 65							
Pembrolizumab	236	220	9.8 (19.09)	-0.74 (0.85)	1.36	-	
Placebo	248	246	12.9 (22.16)	-2.09 (0.81)	[-0.94; 3.66]		
ECOG Performance Status							
0							
Pembrolizumab	321	310	9.1 (18.16)	-0.57 (0.76)	1.58	-	0.230
Placebo	289	282	12.5 (21.98)	-2.16 (0.80)	[-0.59; 3.75]		
1							
Pembrolizumab	175	159	13.6 (21.61)	-0.45 (1.18)	3.62	0.17	
Placebo	210	207	16.3 (24.33)	-4.07 (1.03)	[0.53; 6.72]	[0.02; 0.31]	
Region							
Western Europe							
Pembrolizumab	254	241	9.1 (18.50)	-0.39 (0.96)	2.08	-	0.985
Placebo	263	256	14.5 (24.06)	-2.46 (0.92)	[-0.54; 4.70]		
Eastern Europe							
Pembrolizumab	104	98	10.5 (19.50)	2.58 (1.46)	3.10	-	
Placebo	95	95	13.3 (21.96)	-0.52 (1.50)	[-1.04; 7.23]		
Rest of World							
Pembrolizumab	51	45	11.1 (21.32)	-1.93 (1.99)	1.49	-	
Placebo	54	51	13.1 (25.89)	-3.42 (1.87)	[-3.93; 6.92]		
Asia							
Pembrolizumab	87	85	14.9 (20.90)	-3.79 (1.19)	2.15	-	
Placebo	87	87	14.6 (19.49)	-5.94 (1.19)	[-1.17; 5.47]		
Stage							
IB							
Pembrolizumab	60	58	8.6 (15.99)	0.45 (1.97)	1.33	-	0.918
Placebo	57	56	12.5 (23.41)	-0.88 (2.00)	[-4.25; 6.91]		
II							
Pembrolizumab	278	264	11.6 (21.16)	-1.08 (0.84)	2.32	0.12	
Placebo	293	289	13.4 (22.17)	-3.39 (0.80)	[0.03; 4.60]	[0.00; 0.23]	
IIIA							
Pembrolizumab	158	147	9.8 (17.54)	0.03 (1.14)	2.81	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Appetite Loss	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	149	144	16.2 (24.61)	-2.79 (1.15)	[-0.40; 6.03]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Errorsg0c0

EORTC QLQ-C30: Symptomskala Verstopfung

Tabelle 4G-13: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Constipation	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	315	14.3 (24.17)	-3.51 (0.75)	0.37	-	0.205
Placebo	341	336	12.5 (22.06)	-3.88 (0.72)	[-1.67; 2.40]		
Female							
Pembrolizumab	164	158	12.7 (24.56)	0.63 (1.16)	2.46	-	
Placebo	157	156	10.9 (21.81)	-1.83 (1.18)	[-0.80; 5.72]		
Age							
< 65							
Pembrolizumab	260	250	12.9 (22.88)	-2.44 (0.86)	1.04	-	0.975
Placebo	250	246	11.4 (21.65)	-3.48 (0.86)	[-1.34; 3.42]		
≥ 65							
Pembrolizumab	236	223	14.6 (25.79)	-1.82 (0.94)	0.96	-	
Placebo	248	246	12.6 (22.32)	-2.78 (0.90)	[-1.59; 3.51]		
ECOG Performance Status							
0							
Pembrolizumab	321	309	12.7 (22.87)	-2.56 (0.69)	2.17	0.13	0.276
Placebo	288	283	11.1 (20.32)	-4.74 (0.72)	[0.20; 4.14]	[0.01; 0.24]	
1							
Pembrolizumab	175	164	15.7 (26.73)	-1.10 (1.19)	0.17	-	
Placebo	210	209	13.2 (24.02)	-1.27 (1.05)	[-2.94; 3.29]		
Region							
Western Europe							
Pembrolizumab	254	243	14.8 (24.24)	-3.02 (0.92)	1.63	-	0.211
Placebo	263	258	14.3 (25.23)	-4.65 (0.89)	[-0.88; 4.14]		
Eastern Europe							
Pembrolizumab	104	97	10.7 (21.27)	-1.68 (1.18)	1.30	-	
Placebo	95	95	8.4 (16.82)	-2.98 (1.20)	[-2.02; 4.62]		
Rest of World							
Pembrolizumab	51	47	14.9 (29.33)	-4.25 (2.21)	-4.31	-	
Placebo	53	52	9.6 (19.06)	0.06 (2.09)	[-10.38; 1.75]		
Asia							
Pembrolizumab	87	86	13.6 (24.72)	0.81 (1.44)	1.93	-	
Placebo	87	87	10.3 (17.10)	-1.12 (1.44)	[-2.09; 5.94]		
Stage							
IB							
Pembrolizumab	60	57	7.6 (16.69)	1.46 (1.97)	1.60	-	0.820
Placebo	57	56	12.5 (23.41)	-0.14 (1.97)	[-3.95; 7.14]		
II							
Pembrolizumab	278	266	15.9 (25.77)	-3.10 (0.84)	1.23	-	
Placebo	293	292	11.8 (21.99)	-4.33 (0.80)	[-1.06; 3.52]		
IIIA							
Pembrolizumab	158	150	12.2 (23.62)	-1.71 (1.09)	0.26	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Constipation	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	148	144	12.3 (21.50)	-1.97 (1.11)	[-2.80; 3.33]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-C30: Symptomskala Diarrhoe

Tabelle 4G-14: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Diarrhea	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	311	6.1 (14.49)	2.21 (0.61)	1.60	-	0.547
Placebo	342	334	5.1 (14.06)	0.61 (0.58)	[-0.07; 3.26]		
Female							
Pembrolizumab	164	157	7.0 (18.11)	2.32 (1.08)	0.52	-	
Placebo	157	156	7.7 (17.29)	1.80 (1.10)	[-2.50; 3.55]		
ECOG Performance Status							
0							
Pembrolizumab	321	305	6.6 (16.69)	1.98 (0.68)	1.04	-	0.804
Placebo	289	282	5.6 (13.94)	0.94 (0.71)	[-0.90; 2.99]		
1							
Pembrolizumab	175	163	6.1 (13.98)	2.65 (0.90)	1.61	-	
Placebo	210	208	6.4 (16.76)	1.04 (0.78)	[-0.73; 3.95]		
Region							
Western Europe							
Pembrolizumab	254	238	6.3 (16.27)	2.82 (0.82)	1.16	-	0.912
Placebo	263	256	6.2 (16.30)	1.67 (0.79)	[-1.08; 3.40]		
Eastern Europe							
Pembrolizumab	104	97	8.9 (18.95)	1.17 (1.27)	2.37	-	
Placebo	95	95	6.0 (13.73)	-1.19 (1.29)	[-1.22; 5.95]		
Rest of World							
Pembrolizumab	51	47	2.1 (8.24)	2.50 (1.47)	1.33	-	
Placebo	54	52	5.8 (17.11)	1.17 (1.40)	[-2.72; 5.38]		
Asia							
Pembrolizumab	87	86	6.2 (13.05)	1.89 (1.07)	0.92	-	
Placebo	87	87	5.0 (11.95)	0.97 (1.08)	[-2.07; 3.92]		
Stage							
IB							
Pembrolizumab	60	58	7.5 (18.78)	5.80 (1.64)	3.47	-	0.403
Placebo	57	57	2.9 (9.51)	2.33 (1.64)	[-1.15; 8.08]		
II							
Pembrolizumab	278	262	6.9 (16.10)	1.63 (0.72)	0.95	-	
Placebo	293	290	5.9 (15.93)	0.68 (0.69)	[-1.01; 2.92]		
IIIA							
Pembrolizumab	158	148	5.2 (13.86)	1.94 (0.99)	0.72	-	
Placebo	149	143	7.2 (15.39)	1.21 (1.00)	[-2.04; 3.49]		
PD-L1 Status							
<1%							
Pembrolizumab	194	178	7.3 (17.08)	1.29 (1.31)	-0.01	-	0.521
Placebo	197	196	6.8 (15.80)	1.30 (1.33)	[-2.41; 2.39]		
1-49%							
Pembrolizumab	163	155	5.6 (14.62)	2.00 (1.38)	2.80	0.16	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Diarrhea	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	162	158	5.3 (15.75)	-0.80 (1.47)	[0.26; 5.34]	[0.02; 0.31]	
≥50%							
Pembrolizumab	139	135	6.2 (15.34)	2.71 (1.88)	1.53	-	
Placebo	140	136	5.4 (13.59)	1.18 (1.93)	[-1.48; 4.53]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-LC13: Symptomskala Dyspnoe

Tabelle 4G-15: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Dyspnoea	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Age							
< 65							
Pembrolizumab	260	248	25.6 (20.49)	-0.16 (0.86)	-0.34	-	0.347
Placebo	251	244	25.8 (21.04)	0.18 (0.86)	[-2.72; 2.04]		
≥ 65							
Pembrolizumab	235	217	22.3 (17.06)	0.60 (0.84)	1.17	-	
Placebo	248	240	24.0 (19.19)	-0.56 (0.80)	[-1.12; 3.45]		
ECOG Performance Status							
0							
Pembrolizumab	320	303	21.5 (17.92)	0.74 (0.72)	0.51	-	0.853
Placebo	289	281	21.6 (18.70)	0.23 (0.75)	[-1.53; 2.54]		
1							
Pembrolizumab	175	162	28.7 (20.15)	-0.46 (1.08)	0.82	-	
Placebo	210	203	29.6 (21.17)	-1.28 (0.95)	[-2.01; 3.64]		
Region							
Western Europe							
Pembrolizumab	253	237	25.7 (20.70)	0.09 (0.85)	0.04	-	0.796
Placebo	263	255	24.3 (21.58)	0.05 (0.81)	[-2.26; 2.34]		
Eastern Europe							
Pembrolizumab	104	95	25.5 (16.99)	1.99 (1.27)	1.88	-	
Placebo	95	92	26.8 (16.48)	0.10 (1.29)	[-1.69; 5.46]		
Rest of World							
Pembrolizumab	51	47	18.2 (18.01)	-1.10 (2.41)	-1.93	-	
Placebo	54	51	29.8 (24.09)	0.83 (2.30)	[-8.66; 4.80]		
Asia							
Pembrolizumab	87	86	20.9 (15.84)	-1.04 (1.18)	1.08	-	
Placebo	87	86	22.0 (15.90)	-2.12 (1.19)	[-2.23; 4.38]		
Stage							
IB							
Pembrolizumab	60	58	21.5 (14.70)	0.36 (1.55)	1.38	-	0.452
Placebo	57	55	25.9 (22.74)	-1.02 (1.59)	[-3.03; 5.79]		
II							
Pembrolizumab	277	261	24.5 (19.95)	-0.07 (0.81)	-0.42	-	
Placebo	293	287	25.2 (20.04)	0.35 (0.77)	[-2.63; 1.78]		
IIIA							
Pembrolizumab	158	146	24.3 (18.87)	0.73 (1.08)	1.87	-	
Placebo	149	142	24.0 (19.39)	-1.13 (1.09)	[-1.16; 4.89]		
PD-L1 Status							
<1%							
Pembrolizumab	194	180	24.5 (19.64)	1.66 (1.52)	0.94	-	0.582
Placebo	197	194	22.7 (19.16)	0.72 (1.54)	[-1.82; 3.70]		
1-49%							
Pembrolizumab	163	154	24.6 (18.71)	-3.28 (1.55)	1.56	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Dyspnoea	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	162	155	26.2 (20.37)	-4.84 (1.65)	[-1.30; 4.41]		
≥50%							
Pembrolizumab	138	131	22.7 (18.59)	-2.76 (1.86)	-0.64	-	
Placebo	140	135	26.7 (21.09)	-2.13 (1.91)	[-3.63; 2.36]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; QoL: Quality of Life; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-LC13: Symptomskala Husten

Tabelle 4G-16: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Coughing	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	315	26.6 (23.87)	-2.47 (0.88)	0.87	-	0.233
Placebo	342	332	27.1 (23.64)	-3.34 (0.85)	[-1.53; 3.27]		
Female							
Pembrolizumab	163	156	25.6 (23.90)	-1.32 (1.22)	-1.70	-	
Placebo	157	156	26.5 (23.25)	0.38 (1.24)	[-5.12; 1.72]		
Age							
< 65							
Pembrolizumab	260	250	27.9 (22.97)	-2.73 (1.03)	0.85	-	0.443
Placebo	251	246	28.6 (24.84)	-3.59 (1.03)	[-2.00; 3.70]		
≥ 65							
Pembrolizumab	235	221	24.4 (24.75)	-1.33 (0.99)	-0.71	-	
Placebo	248	242	25.2 (21.96)	-0.61 (0.95)	[-3.42; 1.99]		
ECOG Performance Status							
0							
Pembrolizumab	320	306	23.7 (22.96)	-1.48 (0.86)	0.64	-	0.616
Placebo	289	282	25.2 (22.15)	-2.12 (0.90)	[-1.81; 3.08]		
1							
Pembrolizumab	175	165	30.9 (24.85)	-3.01 (1.26)	-0.42	-	
Placebo	210	206	29.3 (25.07)	-2.58 (1.12)	[-3.74; 2.89]		
Region							
Western Europe							
Pembrolizumab	253	241	29.0 (25.73)	-1.99 (1.04)	-0.35	-	0.793
Placebo	263	257	26.8 (25.02)	-1.64 (1.00)	[-3.18; 2.48]		
Eastern Europe							
Pembrolizumab	104	97	27.1 (18.21)	-0.20 (1.50)	-0.44	-	
Placebo	95	93	29.7 (21.12)	0.24 (1.54)	[-4.68; 3.80]		
Rest of World							
Pembrolizumab	51	47	22.0 (28.89)	-5.62 (2.44)	-0.58	-	
Placebo	54	51	30.7 (27.36)	-5.03 (2.35)	[-7.34; 6.18]		
Asia							
Pembrolizumab	87	86	19.8 (19.39)	-2.86 (1.38)	2.07	-	
Placebo	87	87	21.8 (17.48)	-4.93 (1.38)	[-1.79; 5.93]		
Stage							
IB							
Pembrolizumab	60	58	27.0 (24.55)	-3.51 (2.11)	-3.70	-	0.347
Placebo	57	56	30.4 (26.42)	0.19 (2.13)	[-9.64; 2.24]		
II							
Pembrolizumab	277	263	26.1 (23.90)	-1.93 (0.98)	0.94	-	
Placebo	293	289	27.1 (22.04)	-2.87 (0.93)	[-1.71; 3.59]		
IIIA							
Pembrolizumab	158	150	26.2 (23.68)	-1.77 (1.20)	-0.08	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Coughing	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	149	143	25.2 (25.09)	-1.69 (1.22)	[-3.45; 3.29]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; QoL: Quality of Life; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-LC13: Symptomskala Hämoptoe

Tabelle 4G-17: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Haemoptysis	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	315	0.4 (4.59)	0.33 (0.18)	0.04	-	0.510
Placebo	342	333	0.7 (6.56)	0.29 (0.17)	[-0.45; 0.53]		
Female							
Pembrolizumab	163	155	0.0 (0.00)	0.62 (0.21)	0.25	-	
Placebo	157	155	0.4 (3.77)	0.38 (0.22)	[-0.35; 0.84]		
Age							
< 65							
Pembrolizumab	260	250	0.4 (4.71)	0.65 (0.20)	0.20	-	0.531
Placebo	251	246	0.4 (3.67)	0.45 (0.20)	[-0.35; 0.76]		
≥ 65							
Pembrolizumab	235	220	0.2 (2.25)	0.14 (0.18)	-0.02	-	
Placebo	248	242	0.8 (7.39)	0.17 (0.18)	[-0.52; 0.47]		
ECOG Performance Status							
0							
Pembrolizumab	320	307	0.2 (2.69)	0.27 (0.14)	0.24	-	0.275
Placebo	289	283	0.6 (4.40)	0.03 (0.15)	[-0.16; 0.63]		
1							
Pembrolizumab	175	163	0.4 (5.22)	0.66 (0.26)	-0.06	-	
Placebo	210	205	0.7 (7.35)	0.73 (0.23)	[-0.74; 0.61]		
Region							
Western Europe							
Pembrolizumab	253	240	0.6 (5.25)	0.49 (0.22)	0.04	-	0.359
Placebo	263	258	0.6 (6.87)	0.45 (0.21)	[-0.55; 0.62]		
Eastern Europe							
Pembrolizumab	104	97	0.0 (0.00)	0.21 (0.29)	-0.35	-	
Placebo	95	92	0.4 (3.48)	0.56 (0.29)	[-1.16; 0.46]		
Rest of World							
Pembrolizumab	51	47	0.0 (0.00)	0.35 (0.13)	0.02	-	
Placebo	54	51	0.0 (0.00)	0.33 (0.12)	[-0.33; 0.37]		
Asia							
Pembrolizumab	87	86	0.0 (0.00)	0.31 (0.24)	0.47	-	
Placebo	87	87	1.1 (6.12)	-0.17 (0.25)	[-0.20; 1.15]		
Stage							
IB							
Pembrolizumab	60	58	0.0 (0.00)	0.09 (0.55)	-0.72	-	0.605
Placebo	57	56	0.6 (4.45)	0.81 (0.56)	[-2.25; 0.81]		
II							
Pembrolizumab	277	263	0.1 (2.06)	0.52 (0.18)	0.19	-	
Placebo	293	288	0.6 (6.50)	0.33 (0.18)	[-0.31; 0.69]		
IIIA							
Pembrolizumab	158	149	0.7 (6.09)	0.36 (0.24)	0.17	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Haemoptysis	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	149	144	0.7 (4.78)	0.19 (0.24)	[-0.49; 0.83]		
PD-L1 Status							
<1%							
Pembrolizumab	194	182	0.5 (5.51)	0.16 (0.28)	0.19	-	0.463
Placebo	197	194	0.5 (7.18)	-0.04 (0.28)	[-0.32; 0.70]		
1-49%							
Pembrolizumab	163	155	0.0 (0.00)	0.52 (0.37)	0.54	-	
Placebo	162	158	0.6 (4.56)	-0.02 (0.40)	[-0.15; 1.23]		
≥50%							
Pembrolizumab	138	133	0.3 (2.89)	-0.16 (0.55)	-0.42	-	
Placebo	140	136	0.7 (4.91)	0.26 (0.57)	[-1.26; 0.43]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; QoL: Quality of Life; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-LC13: Symptomskala Mundschmerzen

Tabelle 4G-18: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Sore Mouth	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	315	3.3 (11.28)	-0.68 (0.43)	0.07	-	0.096
Placebo	342	333	4.9 (15.06)	-0.75 (0.41)	[-1.10; 1.25]		
Female							
Pembrolizumab	163	155	6.0 (18.01)	1.85 (0.87)	2.12	-	
Placebo	157	155	5.6 (15.11)	-0.26 (0.89)	[-0.33; 4.56]		
Age							
< 65							
Pembrolizumab	260	250	4.5 (14.54)	0.75 (0.59)	1.25	-	0.503
Placebo	251	245	4.9 (15.49)	-0.50 (0.59)	[-0.39; 2.89]		
≥ 65							
Pembrolizumab	235	220	3.8 (13.16)	-0.36 (0.58)	0.43	-	
Placebo	248	243	5.3 (14.65)	-0.79 (0.55)	[-1.14; 2.00]		
ECOG Performance Status							
0							
Pembrolizumab	320	306	3.2 (11.49)	-0.38 (0.49)	0.76	-	0.955
Placebo	289	282	6.3 (16.99)	-1.15 (0.52)	[-0.65; 2.17]		
1							
Pembrolizumab	175	164	6.1 (17.42)	1.07 (0.74)	0.79	-	
Placebo	210	206	3.6 (11.79)	0.28 (0.66)	[-1.16; 2.75]		
Region							
Western Europe							
Pembrolizumab	253	240	4.0 (14.22)	-0.01 (0.57)	1.19	-	0.431
Placebo	263	257	5.7 (15.93)	-1.19 (0.54)	[-0.36; 2.74]		
Eastern Europe							
Pembrolizumab	104	97	3.1 (10.85)	1.72 (0.85)	1.54	-	
Placebo	95	93	3.6 (11.49)	0.18 (0.87)	[-0.86; 3.94]		
Rest of World							
Pembrolizumab	51	47	3.5 (12.50)	-0.83 (0.65)	0.87	-	
Placebo	54	51	3.3 (12.03)	-1.70 (0.63)	[-0.94; 2.67]		
Asia							
Pembrolizumab	87	86	6.2 (16.58)	-0.20 (1.16)	-1.17	-	
Placebo	87	87	6.1 (17.26)	0.97 (1.17)	[-4.43; 2.09]		
PD-L1 Status							
<1%							
Pembrolizumab	194	183	3.6 (13.94)	0.95 (1.05)	1.11	-	0.566
Placebo	197	194	6.0 (17.74)	-0.16 (1.06)	[-0.80; 3.03]		
1-49%							
Pembrolizumab	163	154	4.1 (11.64)	-0.29 (1.05)	0.76	-	
Placebo	162	158	4.4 (12.54)	-1.05 (1.11)	[-1.14; 2.67]		
≥50%							
Pembrolizumab	138	133	5.0 (16.15)	-0.23 (1.31)	0.37	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Sore Mouth	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	140	136	4.7 (13.56)	-0.60 (1.35)	[-1.71; 2.45]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; QoL: Quality of Life; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-LC13: Symptomskala Dysphagie

Tabelle 4G-19: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Dysphagia	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	314	3.8 (13.04)	-0.19 (0.44)	-0.14	-	0.286
Placebo	342	333	4.0 (13.09)	-0.05 (0.42)	[-1.34; 1.05]		
Female							
Pembrolizumab	163	156	5.6 (14.58)	0.84 (0.65)	1.12	-	
Placebo	157	154	3.0 (10.34)	-0.28 (0.67)	[-0.74; 2.97]		
Age							
< 65							
Pembrolizumab	260	250	4.8 (12.46)	0.02 (0.50)	0.18	-	0.950
Placebo	251	245	3.5 (12.67)	-0.16 (0.50)	[-1.22; 1.57]		
≥ 65							
Pembrolizumab	235	220	3.9 (14.76)	0.23 (0.53)	0.24	-	
Placebo	248	242	3.9 (11.91)	-0.01 (0.51)	[-1.21; 1.70]		
ECOG Performance Status							
0							
Pembrolizumab	320	306	3.7 (12.40)	0.44 (0.44)	0.10	-	0.730
Placebo	289	283	3.2 (11.65)	0.35 (0.46)	[-1.15; 1.34]		
1							
Pembrolizumab	175	164	5.7 (15.49)	-0.35 (0.65)	0.53	-	
Placebo	210	204	4.4 (13.12)	-0.88 (0.58)	[-1.18; 2.24]		
Region							
Western Europe							
Pembrolizumab	253	240	4.7 (13.84)	-0.18 (0.52)	-0.24	-	0.671
Placebo	263	257	4.0 (13.70)	0.06 (0.49)	[-1.65; 1.16]		
Eastern Europe							
Pembrolizumab	104	97	3.4 (10.19)	2.01 (0.91)	1.41	-	
Placebo	95	93	3.2 (11.06)	0.60 (0.94)	[-1.17; 4.00]		
Rest of World							
Pembrolizumab	51	47	3.5 (15.90)	-1.27 (0.72)	-0.11	-	
Placebo	54	51	2.6 (9.05)	-1.17 (0.69)	[-2.09; 1.87]		
Asia							
Pembrolizumab	87	86	5.0 (14.92)	-0.08 (0.78)	0.52	-	
Placebo	87	86	3.9 (10.75)	-0.59 (0.79)	[-1.66; 2.70]		
Stage							
IB							
Pembrolizumab	60	58	2.3 (8.52)	2.38 (0.99)	1.12	-	0.547
Placebo	57	56	2.4 (10.74)	1.26 (1.00)	[-1.68; 3.92]		
II							
Pembrolizumab	277	263	4.4 (13.71)	-0.77 (0.47)	-0.20	-	
Placebo	293	289	4.2 (12.96)	-0.57 (0.45)	[-1.48; 1.08]		
IIIA							
Pembrolizumab	158	149	5.1 (14.87)	0.88 (0.69)	0.53	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Dysphagia	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	149	142	3.3 (11.44)	0.36 (0.70)	[-1.41; 2.46]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; QoL: Quality of Life; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-LC13: Periphere Neuropathie

Tabelle 4G-20: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Peripheral Neuropathy	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	315	14.7 (22.55)	2.48 (1.04)	-0.14	-	0.467
Placebo	341	331	17.2 (27.13)	2.62 (1.01)	[-2.98; 2.70]		
Female							
Pembrolizumab	162	154	14.7 (25.56)	7.72 (1.55)	2.05	-	
Placebo	157	153	16.3 (27.34)	5.67 (1.58)	[-2.31; 6.40]		
Age							
< 65							
Pembrolizumab	259	250	15.2 (23.71)	4.45 (1.28)	1.02	-	0.689
Placebo	250	243	19.3 (29.16)	3.43 (1.29)	[-2.54; 4.58]		
≥ 65							
Pembrolizumab	235	219	14.2 (23.41)	3.85 (1.17)	0.00	-	
Placebo	248	241	14.5 (24.84)	3.84 (1.12)	[-3.18; 3.18]		
ECOG Performance Status							
0							
Pembrolizumab	320	306	12.3 (21.70)	4.56 (1.01)	2.09	-	0.251
Placebo	288	282	15.7 (26.10)	2.47 (1.05)	[-0.77; 4.95]		
1							
Pembrolizumab	174	163	19.2 (26.16)	3.88 (1.61)	-0.85	-	
Placebo	210	202	18.6 (28.58)	4.73 (1.44)	[-5.09; 3.39]		
Region							
Western Europe							
Pembrolizumab	252	239	14.8 (23.96)	5.73 (1.28)	1.00	-	0.279
Placebo	263	254	16.9 (27.28)	4.73 (1.24)	[-2.50; 4.51]		
Eastern Europe							
Pembrolizumab	104	97	17.5 (24.58)	2.46 (1.69)	3.42	-	
Placebo	95	93	16.8 (24.39)	-0.95 (1.74)	[-1.36; 8.20]		
Rest of World							
Pembrolizumab	51	47	12.1 (22.44)	2.13 (3.10)	-4.09	-	
Placebo	53	50	28.7 (35.00)	6.22 (3.01)	[-12.84; 4.67]		
Asia							
Pembrolizumab	87	86	12.8 (21.79)	3.35 (1.73)	0.61	-	
Placebo	87	87	10.3 (22.34)	2.74 (1.73)	[-4.22; 5.44]		
Stage							
IB							
Pembrolizumab	60	57	14.6 (24.41)	2.53 (2.10)	2.12	-	0.872
Placebo	57	55	20.6 (28.32)	0.42 (2.13)	[-3.82; 8.06]		
II							
Pembrolizumab	277	263	15.6 (24.15)	4.61 (1.23)	0.16	-	
Placebo	293	287	15.6 (26.40)	4.45 (1.19)	[-3.20; 3.53]		
IIIA							
Pembrolizumab	157	149	13.2 (22.20)	4.26 (1.43)	1.21	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Peripheral Neuropathy	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	148	142	18.3 (28.23)	3.05 (1.47)	[-2.83; 5.26]		
PD-L1 Status							
<1%							
Pembrolizumab	193	181	14.5 (25.16)	5.31 (2.10)	0.96	-	0.190
Placebo	197	192	16.3 (27.29)	4.35 (2.12)	[-2.86; 4.78]		
1-49%							
Pembrolizumab	163	155	14.2 (21.47)	5.38 (2.30)	3.17	-	
Placebo	161	156	15.4 (26.88)	2.21 (2.45)	[-1.06; 7.40]		
≥50%							
Pembrolizumab	138	133	15.5 (23.77)	1.74 (2.91)	-2.26	-	
Placebo	140	136	19.6 (27.36)	3.99 (3.00)	[-6.90; 2.39]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; QoL: Quality of Life; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-LC13: Alopezie

Tabelle 4G-21: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Alopecia	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Age							
< 65							
Pembrolizumab	260	250	27.9 (33.28)	-21.84 (0.73)	0.46	-	0.770
Placebo	251	246	27.9 (33.37)	-22.30 (0.72)	[-1.55; 2.48]		
≥ 65							
Pembrolizumab	235	216	24.7 (32.75)	-18.19 (0.71)	0.89	-	
Placebo	248	238	25.1 (32.72)	-19.08 (0.69)	[-1.05; 2.83]		
ECOG Performance Status							
0							
Pembrolizumab	320	304	26.2 (32.90)	-18.66 (0.59)	1.57	-	0.123
Placebo	289	283	23.7 (30.51)	-20.23 (0.62)	[-0.10; 3.25]		
1							
Pembrolizumab	175	162	26.7 (33.40)	-22.68 (0.95)	-0.74	-	
Placebo	210	201	30.5 (36.02)	-21.93 (0.84)	[-3.24; 1.75]		
Region							
Western Europe							
Pembrolizumab	253	238	23.1 (30.21)	-18.76 (0.70)	0.91	-	0.533
Placebo	263	254	25.3 (32.89)	-19.67 (0.67)	[-1.01; 2.82]		
Eastern Europe							
Pembrolizumab	104	96	34.7 (39.27)	-23.90 (0.93)	1.00	-	
Placebo	95	92	30.4 (37.52)	-24.90 (0.96)	[-1.64; 3.64]		
Rest of World							
Pembrolizumab	51	47	22.7 (36.85)	-20.68 (1.95)	-1.83	-	
Placebo	54	51	29.4 (35.68)	-18.85 (1.88)	[-7.18; 3.53]		
Asia							
Pembrolizumab	87	85	28.2 (29.32)	-19.30 (1.29)	1.52	-	
Placebo	87	87	24.1 (26.26)	-20.83 (1.29)	[-2.09; 5.14]		
Stage							
IB							
Pembrolizumab	60	56	29.8 (35.78)	-16.21 (1.63)	1.23	-	0.418
Placebo	57	54	22.2 (31.72)	-17.44 (1.64)	[-3.35; 5.81]		
II							
Pembrolizumab	277	261	25.8 (32.66)	-20.10 (0.62)	-0.13	-	
Placebo	293	286	24.5 (32.67)	-19.97 (0.59)	[-1.81; 1.55]		
IIIA							
Pembrolizumab	158	149	26.2 (32.78)	-21.63 (1.02)	1.96	-	
Placebo	149	144	32.2 (33.78)	-23.59 (1.03)	[-0.90; 4.81]		
PD-L1 Status							
<1%							
Pembrolizumab	194	181	25.0 (31.80)	-18.90 (1.24)	0.85	-	0.383
Placebo	197	193	26.3 (33.18)	-19.76 (1.26)	[-1.42; 3.13]		
1-49%							
Pembrolizumab	163	153	27.5 (32.70)	-22.33 (1.28)	1.83	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Alopecia	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	162	157	29.7 (35.32)	-24.16 (1.38)	[-0.55; 4.20]		
≥50%							
Pembrolizumab	138	132	27.0 (35.22)	-17.35 (1.70)	-0.90	-	
Placebo	140	134	23.1 (29.82)	-16.45 (1.74)	[-3.58; 1.78]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; QoL: Quality of Life; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-LC13: Schmerzen (Brust)

Tabelle 4G-22: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Pain in Chest	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Age							
< 65							
Pembrolizumab	259	248	14.4 (21.51)	-2.39 (0.90)	-0.02	-	0.690
Placebo	251	245	15.8 (24.62)	-2.37 (0.90)	[-2.52; 2.49]		
≥ 65							
Pembrolizumab	235	219	12.8 (20.17)	-3.35 (0.74)	-0.65	-	
Placebo	248	240	11.8 (19.39)	-2.70 (0.71)	[-2.67; 1.37]		
ECOG Performance Status							
0							
Pembrolizumab	320	306	13.4 (21.39)	-3.04 (0.70)	0.45	-	0.382
Placebo	289	282	13.4 (21.94)	-3.49 (0.73)	[-1.54; 2.44]		
1							
Pembrolizumab	174	161	14.1 (19.94)	-2.32 (1.06)	-0.95	-	
Placebo	210	203	14.4 (22.72)	-1.37 (0.94)	[-3.74; 1.84]		
Region							
Western Europe							
Pembrolizumab	252	238	12.5 (21.18)	-2.46 (0.83)	-0.14	-	0.317
Placebo	263	257	12.3 (22.81)	-2.32 (0.80)	[-2.40; 2.12]		
Eastern Europe							
Pembrolizumab	104	97	16.5 (21.58)	-2.00 (1.23)	0.72	-	
Placebo	95	90	14.4 (18.73)	-2.73 (1.28)	[-2.78; 4.23]		
Rest of World							
Pembrolizumab	51	46	10.9 (21.15)	-3.58 (2.16)	-4.74	-	
Placebo	54	51	13.7 (25.97)	1.16 (2.05)	[-10.65; 1.18]		
Asia							
Pembrolizumab	87	86	15.1 (18.90)	-4.34 (1.35)	0.20	-	
Placebo	87	87	17.6 (21.47)	-4.54 (1.35)	[-3.57; 3.98]		
Stage							
IB							
Pembrolizumab	60	58	9.8 (18.74)	1.28 (1.77)	-0.11	-	0.387
Placebo	57	54	11.7 (24.36)	1.39 (1.83)	[-5.16; 4.94]		
II							
Pembrolizumab	276	261	13.8 (21.21)	-3.81 (0.78)	-1.17	-	
Placebo	293	287	13.2 (22.19)	-2.64 (0.75)	[-3.30; 0.95]		
IIIA							
Pembrolizumab	158	148	14.9 (21.04)	-2.74 (1.03)	1.35	-	
Placebo	149	144	15.7 (21.57)	-4.09 (1.04)	[-1.53; 4.22]		
PD-L1 Status							
<1%							
Pembrolizumab	194	180	13.9 (21.10)	-1.50 (1.46)	-0.55	-	0.317
Placebo	197	193	12.4 (20.00)	-0.95 (1.47)	[-3.20; 2.09]		
1-49%							
Pembrolizumab	162	155	12.9 (20.24)	-1.14 (1.56)	1.88	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Pain in Chest	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	162	157	11.0 (18.64)	-3.02 (1.67)	[-1.00; 4.76]		
≥50%							
Pembrolizumab	138	132	14.1 (21.45)	-7.52 (1.94)	-1.64	-	
Placebo	140	135	19.0 (27.78)	-5.88 (2.00)	[-4.75; 1.48]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; QoL: Quality of Life; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-LC13: Schmerzen (Arm/Schulter)

Tabelle 4G-23: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Pain in Arm or Shoulder	**N[b]**	**N[c]**	**Mean at Baseline (SD)[d]**	**Mean Change from Baseline (SE)[e]**	**Mean Difference[e] [95 %-CI]**	**Standardized Mean Difference[f] [95 %-CI]**	**p-Value for Interaction Test[g]**
Sex							
Male							
Pembrolizumab	332	313	8.7 (17.35)	2.43 (0.79)	0.88	-	0.983
Placebo	342	331	13.1 (21.63)	1.54 (0.76)	[-1.28; 3.05]		
Female							
Pembrolizumab	163	153	13.5 (24.01)	5.27 (1.32)	0.90	-	
Placebo	157	155	10.8 (20.08)	4.36 (1.34)	[-2.81; 4.62]		
Age							
< 65							
Pembrolizumab	260	247	11.9 (21.53)	3.19 (1.01)	0.61	-	0.678
Placebo	251	245	12.1 (20.09)	2.58 (1.00)	[-2.18; 3.40]		
≥ 65							
Pembrolizumab	235	219	8.5 (17.73)	3.64 (0.93)	1.44	-	
Placebo	248	241	12.6 (22.22)	2.20 (0.90)	[-1.12; 3.99]		
ECOG Performance Status							
0							
Pembrolizumab	320	304	10.3 (19.43)	2.47 (0.79)	1.21	-	0.898
Placebo	289	280	11.2 (19.80)	1.27 (0.82)	[-1.03; 3.45]		
1							
Pembrolizumab	175	162	10.3 (20.78)	5.40 (1.29)	1.58	-	
Placebo	210	206	13.9 (22.82)	3.82 (1.14)	[-1.81; 4.98]		
Region							
Western Europe							
Pembrolizumab	253	237	9.8 (19.81)	3.04 (0.98)	0.69	-	0.110
Placebo	263	258	12.7 (22.08)	2.36 (0.93)	[-1.97; 3.35]		
Eastern Europe							
Pembrolizumab	104	97	12.4 (19.44)	3.31 (1.49)	4.88	0.23	
Placebo	95	91	16.1 (21.29)	-1.57 (1.55)	[0.63; 9.13]	[0.03; 0.44]	
Rest of World							
Pembrolizumab	51	46	5.8 (17.64)	4.73 (2.59)	-3.66	-	
Placebo	54	51	9.2 (17.74)	8.40 (2.47)	[-10.79; 3.46]		
Asia							
Pembrolizumab	87	86	11.6 (21.55)	3.55 (1.38)	0.54	-	
Placebo	87	86	9.3 (19.57)	3.01 (1.40)	[-3.35; 4.43]		
Stage							
IB							
Pembrolizumab	60	58	11.5 (21.22)	2.66 (1.95)	2.70	-	0.730
Placebo	57	55	17.0 (26.35)	-0.05 (1.98)	[-2.82; 8.22]		
II							
Pembrolizumab	277	259	10.2 (20.43)	2.91 (0.94)	0.72	-	
Placebo	293	289	11.8 (20.60)	2.19 (0.89)	[-1.82; 3.27]		
IIIA							

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Pain in Arm or Shoulder	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Pembrolizumab	158	149	10.1 (18.46)	4.53 (1.19)	0.68	-	
Placebo	149	142	11.7 (19.93)	3.85 (1.22)	[-2.68; 4.03]		
PD-L1 Status							
<1%							
Pembrolizumab	194	181	9.8 (18.17)	4.98 (1.71)	0.72	-	0.365
Placebo	197	195	12.6 (20.85)	4.27 (1.73)	[-2.41; 3.84]		
1-49%							
Pembrolizumab	163	155	12.7 (22.24)	1.95 (1.81)	3.16	-	
Placebo	162	156	10.5 (19.97)	-1.21 (1.93)	[-0.18; 6.49]		
≥50%							
Pembrolizumab	138	130	8.2 (19.05)	3.80 (2.23)	-0.38	-	
Placebo	140	135	14.1 (22.84)	4.18 (2.31)	[-4.00; 3.24]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; QoL: Quality of Life; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-LC13: Schmerzen (andere)

Tabelle 4G-24: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Pain in Other Parts	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	331	302	12.1 (20.51)	0.58 (0.91)	1.01	-	0.580
Placebo	341	317	16.1 (25.93)	-0.44 (0.88)	[-1.47; 3.50]		
Female							
Pembrolizumab	163	148	17.8 (25.91)	4.42 (1.56)	-0.22	-	
Placebo	157	149	18.3 (26.97)	4.65 (1.58)	[-4.60; 4.16]		
Age							
< 65							
Pembrolizumab	260	246	14.2 (23.54)	1.82 (1.18)	-0.67	-	0.216
Placebo	250	236	18.1 (27.90)	2.49 (1.19)	[-3.98; 2.64]		
≥ 65							
Pembrolizumab	234	204	13.7 (21.37)	1.88 (1.08)	2.07	-	
Placebo	248	230	15.5 (24.45)	-0.19 (1.03)	[-0.86; 5.00]		
ECOG Performance Status							
0							
Pembrolizumab	320	291	12.6 (22.52)	2.32 (0.94)	2.49	-	0.085
Placebo	289	273	14.5 (23.84)	-0.17 (0.97)	[-0.16; 5.15]		
1							
Pembrolizumab	174	159	16.6 (22.46)	1.19 (1.49)	-1.50	-	
Placebo	209	193	20.0 (29.10)	2.69 (1.34)	[-5.44; 2.44]		
Region							
Western Europe							
Pembrolizumab	252	233	14.7 (22.04)	2.73 (1.21)	0.66	-	0.753
Placebo	262	243	17.6 (26.64)	2.07 (1.17)	[-2.64; 3.96]		
Eastern Europe							
Pembrolizumab	104	93	17.9 (27.61)	-1.91 (1.74)	1.18	-	
Placebo	95	89	17.2 (24.68)	-3.09 (1.80)	[-3.77; 6.13]		
Rest of World							
Pembrolizumab	51	42	13.5 (23.35)	1.78 (2.81)	-1.91	-	
Placebo	54	50	19.3 (31.65)	3.69 (2.61)	[-9.55; 5.73]		
Asia							
Pembrolizumab	87	82	7.7 (15.09)	3.48 (1.45)	2.90	-	
Placebo	87	84	12.7 (23.09)	0.58 (1.45)	[-1.16; 6.95]		
Stage							
IB							
Pembrolizumab	60	57	15.8 (24.48)	5.75 (2.43)	5.53	-	0.160
Placebo	57	52	17.3 (30.60)	0.22 (2.51)	[-1.41; 12.48]		
II							
Pembrolizumab	276	252	14.4 (22.84)	1.42 (1.08)	1.01	-	
Placebo	293	276	16.3 (25.18)	0.41 (1.03)	[-1.93; 3.94]		
IIIA							
Pembrolizumab	158	141	12.5 (21.28)	1.15 (1.42)	-1.87	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-LC13 Pain in Other Parts	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	148	138	17.6 (26.77)	3.02 (1.44)	[-5.86; 2.12]		
PD-L1 Status							
<1%							
Pembrolizumab	193	176	14.4 (22.70)	2.15 (2.12)	-0.24	-	0.936
Placebo	196	187	17.8 (26.38)	2.39 (2.13)	[-4.06; 3.59]		
1-49%							
Pembrolizumab	163	145	16.1 (24.25)	0.57 (2.09)	1.52	-	
Placebo	162	152	14.0 (24.42)	-0.95 (2.20)	[-2.23; 5.28]		
≥50%							
Pembrolizumab	138	129	11.1 (20.13)	4.67 (2.50)	1.04	-	
Placebo	140	127	18.6 (28.06)	3.63 (2.55)	[-2.98; 5.05]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; QoL: Quality of Life; SD: Standard Deviation; SE: Standard Error

EQ-5D VAS

Tabelle 4G-25: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EQ-5D VAS	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	331	307	74.4 (16.44)	0.35 (0.70)	-1.04	-	0.618
Placebo	342	322	72.9 (16.27)	1.39 (0.68)	[-2.96; 0.88]		
Female							
Pembrolizumab	162	150	75.1 (18.16)	0.21 (0.99)	-0.03	-	
Placebo	157	150	72.7 (16.70)	0.23 (1.00)	[-2.81; 2.75]		
Age							
< 65							
Pembrolizumab	259	240	72.9 (18.74)	0.48 (0.82)	-1.11	-	0.609
Placebo	251	242	72.5 (16.57)	1.59 (0.81)	[-3.36; 1.15]		
≥ 65							
Pembrolizumab	234	217	76.6 (14.66)	0.16 (0.80)	-0.19	-	
Placebo	248	230	73.2 (16.22)	0.35 (0.78)	[-2.40; 2.02]		
ECOG Performance Status							
0							
Pembrolizumab	319	300	76.4 (17.09)	-0.44 (0.67)	-1.02	-	0.919
Placebo	289	271	75.8 (15.51)	0.58 (0.71)	[-2.93; 0.89]		
1							
Pembrolizumab	174	157	71.4 (16.41)	1.36 (1.05)	-0.68	-	
Placebo	210	201	68.8 (16.73)	2.04 (0.92)	[-3.42; 2.06]		
Region							
Western Europe							
Pembrolizumab	252	232	74.4 (16.37)	1.26 (0.83)	-0.72	-	0.935
Placebo	263	242	71.3 (17.95)	1.98 (0.81)	[-3.00; 1.56]		
Eastern Europe							
Pembrolizumab	103	95	70.9 (19.03)	-0.87 (1.18)	-1.05	-	
Placebo	95	92	73.4 (14.25)	0.19 (1.19)	[-4.37; 2.26]		
Rest of World							
Pembrolizumab	51	44	77.5 (18.59)	-1.20 (1.94)	0.97	-	
Placebo	54	51	73.9 (14.30)	-2.17 (1.81)	[-4.31; 6.26]		
Asia							
Pembrolizumab	87	86	78.0 (14.73)	0.56 (1.23)	-0.59	-	
Placebo	87	87	75.7 (14.80)	1.14 (1.23)	[-4.03; 2.86]		
Stage							
IB							
Pembrolizumab	60	57	78.6 (15.97)	-2.64 (1.46)	-1.28	-	0.985
Placebo	57	51	74.5 (15.49)	-1.36 (1.54)	[-5.51; 2.95]		
II							
Pembrolizumab	276	254	73.0 (18.00)	1.34 (0.80)	-0.69	-	
Placebo	293	280	72.2 (16.71)	2.03 (0.77)	[-2.87; 1.49]		
IIIA							
Pembrolizumab	157	146	76.0 (15.26)	-0.49 (0.96)	-0.67	-	
Placebo	149	141	73.5 (16.10)	0.18 (0.97)	[-3.35; 2.01]		

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EQ-5D VAS	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
PD-L1 Status							
<1%							
Pembrolizumab	193	179	75.6 (17.21)	-1.49 (1.47)	-2.69	-0.17	0.123
Placebo	197	190	73.4 (15.94)	1.20 (1.48)	[-5.36; -0.01]	[-0.33; -0.00]	
1-49%							
Pembrolizumab	163	149	72.8 (17.77)	1.11 (1.47)	-0.59	-	
Placebo	162	151	71.4 (17.04)	1.70 (1.55)	[-3.28; 2.09]		
≥50%							
Pembrolizumab	137	129	75.5 (15.73)	0.23 (1.85)	1.51	-	
Placebo	140	131	73.6 (16.28)	-1.27 (1.90)	[-1.46; 4.47]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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; VAS: Visual Analog Scale

Anhang 4-G2.3: Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-26: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Global Health Status/QoL	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	310	68.7 (18.38)	1.21 (0.75)	-1.56	-	0.907
Placebo	342	336	66.4 (19.82)	2.78 (0.72)	[-3.60; 0.47]		
Female							
Pembrolizumab	164	157	69.2 (20.03)	-0.06 (1.05)	-1.44	-	
Placebo	157	156	65.1 (19.76)	1.38 (1.07)	[-4.39; 1.52]		
Age							
< 65							
Pembrolizumab	260	247	68.3 (20.19)	0.75 (0.86)	-1.86	-	0.696
Placebo	251	248	65.3 (19.57)	2.62 (0.85)	[-4.24; 0.51]		
≥ 65							
Pembrolizumab	236	220	69.5 (17.43)	0.89 (0.88)	-1.05	-	
Placebo	248	244	66.7 (20.02)	1.94 (0.84)	[-3.43; 1.33]		
ECOG Performance Status							
0							
Pembrolizumab	321	305	71.0 (18.81)	0.05 (0.73)	-1.63	-	0.906
Placebo	289	284	69.2 (20.28)	1.68 (0.76)	[-3.70; 0.44]		
1							
Pembrolizumab	175	162	64.9 (18.57)	1.93 (1.09)	-1.76	-	
Placebo	210	208	61.6 (18.26)	3.69 (0.96)	[-4.62; 1.10]		
Region							
Western Europe							
Pembrolizumab	254	238	68.6 (18.80)	1.62 (0.87)	-1.24	-	0.859
Placebo	263	258	65.8 (20.62)	2.86 (0.83)	[-3.60; 1.12]		
Eastern Europe							
Pembrolizumab	104	96	65.5 (21.00)	-0.61 (1.29)	-2.97	-	
Placebo	95	95	62.7 (17.10)	2.36 (1.30)	[-6.58; 0.64]		
Rest of World							
Pembrolizumab	51	47	73.2 (15.34)	-1.64 (1.75)	-1.29	-	
Placebo	54	52	70.8 (17.58)	-0.34 (1.66)	[-6.09; 3.51]		
Asia							
Pembrolizumab	87	86	71.0 (18.20)	1.92 (1.50)	-0.70	-	
Placebo	87	87	67.1 (20.86)	2.62 (1.50)	[-4.88; 3.49]		
Stage							
IB							
Pembrolizumab	60	56	71.6 (18.31)	0.91 (1.86)	-1.88	-	0.980
Placebo	57	57	65.4 (21.06)	2.79 (1.81)	[-7.05; 3.29]		
II							

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Global Health Status/QoL	**N[b]**	**N[c]**	**Mean at Baseline (SD)[d]**	**Mean Change from Baseline (SE)[e]**	**Mean Difference[e] [95 %-CI]**	**Standardized Mean Difference[f] [95 %-CI]**	**p-Value for Interaction Test[g]**
Pembrolizumab	278	262	67.9 (19.80)	1.09 (0.83)	-1.39	-	
Placebo	293	291	66.2 (20.47)	2.49 (0.79)	[-3.65; 0.86]		
IIIA							
Pembrolizumab	158	149	69.6 (17.54)	0.16 (1.03)	-1.71	-	
Placebo	149	144	65.9 (17.91)	1.87 (1.03)	[-4.58; 1.17]		
PD-L1 Status							
<1%							
Pembrolizumab	194	180	69.0 (18.82)	-0.81 (1.57)	-1.93	-	0.390
Placebo	197	196	68.7 (19.18)	1.12 (1.58)	[-4.78; 0.92]		
1-49%							
Pembrolizumab	163	153	69.5 (19.29)	2.16 (1.47)	-3.50	-0.21	
Placebo	162	160	62.8 (18.22)	5.67 (1.53)	[-6.16; -0.85]	[-0.37; -0.05]	
≥50%							
Pembrolizumab	139	134	68.0 (18.78)	2.65 (2.01)	0.29	-	
Placebo	140	136	65.7 (21.89)	2.35 (2.07)	[-2.94; 3.52]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; QoL: Quality of Life; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-27: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Physical Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	315	81.2 (16.40)	0.44 (0.64)	-0.43	-	0.138
Placebo	342	338	80.5 (16.21)	0.87 (0.62)	[-2.17; 1.32]		
Female							
Pembrolizumab	164	157	79.5 (16.05)	1.00 (1.00)	1.99	-	
Placebo	157	156	78.0 (17.56)	-1.00 (1.01)	[-0.79; 4.78]		
Age							
< 65							
Pembrolizumab	260	250	80.3 (16.78)	0.86 (0.76)	0.60	-	0.722
Placebo	251	248	79.3 (16.70)	0.26 (0.76)	[-1.51; 2.71]		
≥ 65							
Pembrolizumab	236	222	80.9 (15.74)	0.36 (0.77)	0.10	-	
Placebo	248	246	80.2 (16.67)	0.26 (0.74)	[-2.00; 2.20]		
ECOG Performance Status							
0							
Pembrolizumab	321	310	83.2 (15.30)	0.10 (0.62)	-0.02	-	0.845
Placebo	289	285	83.3 (15.57)	0.12 (0.65)	[-1.79; 1.74]		
1							
Pembrolizumab	175	162	75.5 (16.95)	1.19 (1.02)	0.30	-	
Placebo	210	209	74.8 (16.92)	0.89 (0.90)	[-2.38; 2.98]		
Region							
Western Europe							
Pembrolizumab	254	242	79.6 (16.82)	0.88 (0.78)	0.64	-	0.256
Placebo	263	260	79.6 (17.52)	0.24 (0.75)	[-1.50; 2.78]		
Eastern Europe							
Pembrolizumab	104	98	77.1 (17.38)	-0.85 (1.26)	-1.91	-	
Placebo	95	95	77.6 (15.15)	1.06 (1.28)	[-5.46; 1.64]		
Rest of World							
Pembrolizumab	51	46	82.2 (15.78)	1.50 (1.66)	3.20	-	
Placebo	54	52	74.5 (18.72)	-1.71 (1.56)	[-1.37; 7.78]		
Asia							
Pembrolizumab	87	86	86.6 (11.66)	0.71 (1.04)	-0.55	-	
Placebo	87	87	85.7 (12.39)	1.27 (1.05)	[-3.47; 2.36]		
Stage							
IB							
Pembrolizumab	60	58	82.0 (15.79)	-1.18 (1.64)	-1.45	-	0.205
Placebo	57	57	80.4 (16.62)	0.27 (1.64)	[-6.05; 3.15]		
II							
Pembrolizumab	278	265	79.1 (16.75)	1.86 (0.73)	1.49	-	
Placebo	293	292	79.2 (17.22)	0.38 (0.70)	[-0.51; 3.48]		
IIIA							
Pembrolizumab	158	149	82.6 (15.45)	-1.05 (0.91)	-1.15	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Physical Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	149	145	80.6 (15.60)	0.10 (0.92)	[-3.71; 1.40]		
PD-L1 Status							
<1%							
Pembrolizumab	194	181	80.8 (16.78)	-0.03 (1.39)	-1.37	-	0.060
Placebo	197	196	80.3 (17.38)	1.35 (1.40)	[-3.89; 1.14]		
1-49%							
Pembrolizumab	163	155	80.7 (15.76)	1.87 (1.33)	-0.32	-	
Placebo	162	160	78.4 (16.78)	2.19 (1.40)	[-2.75; 2.11]		
≥50%							
Pembrolizumab	139	136	80.2 (16.32)	0.41 (1.72)	2.84	0.19	
Placebo	140	138	80.5 (15.51)	-2.43 (1.76)	[0.10; 5.57]	[0.01; 0.37]	

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-28: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Role Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	314	78.5 (25.33)	0.22 (0.94)	-2.81	-0.12	0.084
Placebo	342	337	77.5 (25.31)	3.03 (0.91)	[-5.38; -0.24]	[-0.24; -0.01]	
Female							
Pembrolizumab	164	157	77.7 (24.79)	1.31 (1.37)	1.08	-	
Placebo	157	156	76.8 (24.43)	0.23 (1.39)	[-2.76; 4.92]		
Age							
< 65							
Pembrolizumab	260	250	75.9 (26.55)	0.65 (1.12)	-1.56	-	0.965
Placebo	251	247	76.0 (25.39)	2.21 (1.12)	[-4.67; 1.55]		
≥ 65							
Pembrolizumab	236	221	80.8 (23.21)	0.44 (1.06)	-1.55	-	
Placebo	248	246	78.5 (24.62)	1.99 (1.01)	[-4.44; 1.34]		
ECOG Performance Status							
0							
Pembrolizumab	321	309	80.4 (24.53)	-0.50 (0.91)	-2.89	-0.13	0.242
Placebo	289	284	81.6 (23.42)	2.40 (0.95)	[-5.49; -0.30]	[-0.26; -0.01]	
1							
Pembrolizumab	175	162	74.1 (25.81)	2.16 (1.41)	-0.18	-	
Placebo	210	209	71.5 (25.96)	2.34 (1.23)	[-3.87; 3.51]		
Region							
Western Europe							
Pembrolizumab	254	242	75.1 (27.84)	1.39 (1.17)	-2.20	-	0.492
Placebo	263	259	73.8 (28.10)	3.60 (1.12)	[-5.38; 0.98]		
Eastern Europe							
Pembrolizumab	104	97	77.8 (23.16)	-2.70 (1.71)	-4.02	-	
Placebo	95	95	79.3 (21.15)	1.32 (1.72)	[-8.80; 0.77]		
Rest of World							
Pembrolizumab	51	46	83.3 (23.31)	0.05 (2.40)	0.62	-	
Placebo	54	52	79.8 (23.65)	-0.57 (2.26)	[-5.94; 7.18]		
Asia							
Pembrolizumab	87	86	84.5 (17.86)	2.39 (1.43)	1.08	-	
Placebo	87	87	83.9 (17.32)	1.32 (1.44)	[-2.92; 5.08]		
Stage							
IB							
Pembrolizumab	60	58	80.7 (22.90)	-3.83 (2.42)	-5.18	-	0.117
Placebo	57	56	81.8 (21.62)	1.35 (2.45)	[-12.01; 1.65]		
II							
Pembrolizumab	278	264	75.3 (26.95)	2.91 (1.05)	0.29	-	
Placebo	293	292	76.3 (26.60)	2.62 (1.00)	[-2.57; 3.14]		
IIIA							
Pembrolizumab	158	149	82.3 (21.85)	-2.06 (1.30)	-3.62	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Role Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	149	145	77.6 (22.77)	1.56 (1.31)	[-7.26; 0.02]		
PD-L1 Status							
<1%							
Pembrolizumab	194	181	77.4 (26.10)	0.76 (1.95)	-3.01	-	0.550
Placebo	197	196	78.0 (25.73)	3.76 (1.97)	[-6.55; 0.54]		
1-49%							
Pembrolizumab	163	155	77.4 (24.60)	2.91 (1.99)	-1.20	-	
Placebo	162	160	76.6 (24.96)	4.11 (2.11)	[-4.84; 2.43]		
≥50%							
Pembrolizumab	139	135	80.1 (24.48)	-0.23 (2.53)	-0.33	-	
Placebo	140	137	77.1 (24.17)	0.09 (2.61)	[-4.39; 3.74]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-29: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Emotional Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	313	85.2 (17.52)	0.85 (0.72)	-0.68	-	0.239
Placebo	342	335	82.5 (20.16)	1.53 (0.69)	[-2.64; 1.29]		
Female							
Pembrolizumab	164	158	78.1 (22.80)	1.60 (1.09)	1.51	-	
Placebo	157	156	79.8 (21.37)	0.09 (1.11)	[-1.55; 4.56]		
Age							
< 65							
Pembrolizumab	260	249	80.9 (21.48)	0.47 (0.87)	-0.80	-	0.241
Placebo	251	247	80.6 (21.59)	1.28 (0.87)	[-3.23; 1.62]		
≥ 65							
Pembrolizumab	236	222	84.9 (17.34)	1.68 (0.82)	0.84	-	
Placebo	248	244	82.8 (19.46)	0.84 (0.78)	[-1.38; 3.07]		
ECOG Performance Status							
0							
Pembrolizumab	321	307	83.1 (20.07)	0.79 (0.72)	-0.59	-	0.956
Placebo	289	283	84.6 (18.58)	1.37 (0.75)	[-2.63; 1.46]		
1							
Pembrolizumab	175	164	82.2 (19.07)	1.11 (1.09)	-0.17	-	
Placebo	210	208	77.6 (22.41)	1.28 (0.96)	[-3.04; 2.70]		
Region							
Western Europe							
Pembrolizumab	254	241	80.8 (20.36)	1.18 (0.89)	-0.02	-	0.539
Placebo	263	257	79.3 (22.00)	1.20 (0.86)	[-2.46; 2.42]		
Eastern Europe							
Pembrolizumab	104	97	85.2 (17.41)	-0.87 (1.21)	-2.62	-	
Placebo	95	95	85.7 (17.18)	1.75 (1.22)	[-6.01; 0.78]		
Rest of World							
Pembrolizumab	51	47	80.0 (24.98)	3.12 (2.13)	1.42	-	
Placebo	54	52	76.4 (23.92)	1.70 (2.03)	[-4.43; 7.26]		
Asia							
Pembrolizumab	87	86	87.1 (16.05)	1.82 (1.17)	0.93	-	
Placebo	87	87	87.3 (14.97)	0.89 (1.17)	[-2.33; 4.19]		
Stage							
IB							
Pembrolizumab	60	58	83.6 (17.86)	1.78 (1.84)	-1.23	-	0.936
Placebo	57	57	77.5 (21.36)	3.01 (1.83)	[-6.41; 3.94]		
II							
Pembrolizumab	278	263	82.5 (19.52)	1.45 (0.81)	0.18	-	
Placebo	293	291	81.1 (21.31)	1.27 (0.78)	[-2.03; 2.39]		
IIIA							
Pembrolizumab	158	150	83.0 (20.82)	-0.14 (1.05)	-0.27	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Emotional Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	149	143	84.4 (18.37)	0.13 (1.08)	[-3.23; 2.70]		
PD-L1 Status							
<1%							
Pembrolizumab	194	180	80.9 (19.94)	1.84 (1.45)	-0.77	-	0.329
Placebo	197	196	81.2 (21.84)	2.62 (1.47)	[-3.42; 1.87]		
1-49%							
Pembrolizumab	163	156	83.9 (19.22)	2.77 (1.74)	-1.46	-	
Placebo	162	159	80.8 (20.05)	4.23 (1.85)	[-4.66; 1.73]		
≥50%							
Pembrolizumab	139	135	84.0 (19.93)	2.50 (1.79)	1.40	-	
Placebo	140	136	83.3 (19.29)	1.09 (1.84)	[-1.46; 4.27]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-30: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Cognitive Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	313	90.0 (15.42)	-2.10 (0.63)	-0.31	-	0.837
Placebo	342	336	88.0 (17.61)	-1.79 (0.60)	[-2.03; 1.41]		
Female							
Pembrolizumab	164	158	86.8 (20.26)	-1.73 (1.05)	0.27	-	
Placebo	157	156	85.0 (19.51)	-2.00 (1.07)	[-2.69; 3.23]		
Age							
< 65							
Pembrolizumab	260	249	89.0 (17.77)	-2.85 (0.78)	0.17	-	0.648
Placebo	251	248	88.1 (17.83)	-3.02 (0.77)	[-1.98; 2.32]		
≥ 65							
Pembrolizumab	236	222	88.8 (16.67)	-0.99 (0.76)	-0.19	-	
Placebo	248	244	86.1 (18.69)	-0.81 (0.73)	[-2.25; 1.88]		
ECOG Performance Status							
0							
Pembrolizumab	321	307	89.7 (17.17)	-2.36 (0.64)	-0.43	-	0.805
Placebo	289	284	89.4 (17.44)	-1.93 (0.66)	[-2.24; 1.38]		
1							
Pembrolizumab	175	164	87.4 (17.33)	-1.42 (1.02)	0.13	-	
Placebo	210	208	83.9 (18.92)	-1.55 (0.90)	[-2.55; 2.81]		
Region							
Western Europe							
Pembrolizumab	254	241	88.0 (16.76)	-1.89 (0.84)	0.31	-	0.552
Placebo	263	258	86.0 (20.67)	-2.20 (0.80)	[-1.98; 2.59]		
Eastern Europe							
Pembrolizumab	104	97	92.1 (14.45)	-2.78 (0.93)	-2.11	-	
Placebo	95	95	90.0 (13.18)	-0.66 (0.94)	[-4.72; 0.49]		
Rest of World							
Pembrolizumab	51	47	84.4 (22.90)	-0.58 (1.96)	1.21	-	
Placebo	54	52	87.5 (15.79)	-1.79 (1.86)	[-4.17; 6.59]		
Asia							
Pembrolizumab	87	86	90.3 (17.43)	-2.18 (1.13)	-0.12	-	
Placebo	87	87	86.8 (16.69)	-2.06 (1.13)	[-3.29; 3.05]		
Stage							
IB							
Pembrolizumab	60	58	89.4 (14.54)	-2.89 (1.58)	-0.43	-	0.781
Placebo	57	57	88.6 (17.01)	-2.46 (1.59)	[-4.87; 4.01]		
II							
Pembrolizumab	278	263	88.6 (17.38)	-1.32 (0.75)	0.31	-	
Placebo	293	291	86.4 (18.83)	-1.63 (0.71)	[-1.72; 2.34]		
IIIA							
Pembrolizumab	158	150	89.3 (18.04)	-2.93 (0.94)	-0.90	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Cognitive Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	149	144	87.8 (17.65)	-2.03 (0.95)	[-3.53; 1.73]		
PD-L1 Status							
<1%							
Pembrolizumab	194	180	88.3 (17.78)	-1.59 (1.35)	-0.49	-	0.816
Placebo	197	196	87.7 (19.09)	-1.10 (1.36)	[-2.94; 1.95]		
1-49%							
Pembrolizumab	163	156	89.0 (16.56)	-1.16 (1.53)	-0.33	-	
Placebo	162	160	86.5 (17.35)	-0.83 (1.62)	[-3.12; 2.46]		
≥50%							
Pembrolizumab	139	135	89.6 (17.38)	-0.33 (1.72)	0.56	-	
Placebo	140	136	87.0 (18.22)	-0.89 (1.78)	[-2.20; 3.32]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error

EORTC QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-31: 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 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Social Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Sex							
Male							
Pembrolizumab	332	313	82.3 (22.04)	1.91 (0.91)	-2.34	-	0.581
Placebo	342	336	81.8 (22.68)	4.25 (0.87)	[-4.81; 0.14]		
Female							
Pembrolizumab	164	158	81.5 (26.64)	3.78 (1.33)	-1.06	-	
Placebo	157	156	80.8 (23.58)	4.84 (1.35)	[-4.78; 2.67]		
Age							
< 65							
Pembrolizumab	260	249	80.4 (25.84)	1.81 (1.12)	-3.50	-0.16	0.099
Placebo	251	248	80.2 (23.84)	5.31 (1.12)	[-6.60; -0.39]	[-0.30; -0.02]	
≥ 65							
Pembrolizumab	236	222	83.9 (20.85)	3.39 (0.97)	0.00	-	
Placebo	248	244	82.7 (21.98)	3.39 (0.93)	[-2.64; 2.65]		
ECOG Performance Status							
0							
Pembrolizumab	321	307	83.1 (23.02)	2.87 (0.87)	-2.47	-0.13	0.819
Placebo	289	284	83.6 (22.59)	5.34 (0.90)	[-4.93; -0.02]	[-0.26; -0.00]	
1							
Pembrolizumab	175	164	80.1 (24.76)	1.60 (1.39)	-1.90	-	
Placebo	210	208	78.6 (23.18)	3.49 (1.22)	[-5.54; 1.74]		
Region							
Western Europe							
Pembrolizumab	254	241	79.5 (25.39)	2.35 (1.13)	-2.58	-	0.164
Placebo	263	258	79.1 (25.22)	4.93 (1.09)	[-5.67; 0.51]		
Eastern Europe							
Pembrolizumab	104	97	82.5 (23.62)	0.68 (1.70)	-4.37	-	
Placebo	95	95	84.7 (18.46)	5.05 (1.72)	[-9.15; 0.41]		
Rest of World							
Pembrolizumab	51	47	87.6 (20.99)	0.26 (2.46)	-3.95	-	
Placebo	54	52	81.4 (21.81)	4.20 (2.33)	[-10.71; 2.82]		
Asia							
Pembrolizumab	87	86	85.9 (18.88)	6.08 (1.15)	2.86	-	
Placebo	87	87	84.9 (20.27)	3.23 (1.15)	[-0.35; 6.06]		
Stage							
IB							
Pembrolizumab	60	58	83.0 (24.68)	0.57 (2.10)	-2.00	-	0.848
Placebo	57	57	84.8 (22.11)	2.57 (2.10)	[-7.89; 3.89]		
II							
Pembrolizumab	278	263	81.6 (22.75)	3.08 (1.04)	-1.41	-	
Placebo	293	291	80.8 (23.02)	4.49 (0.99)	[-4.23; 1.40]		
IIIA							
Pembrolizumab	158	150	82.4 (24.94)	2.28 (1.25)	-2.63	-	

Study: KEYNOTE 091[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Social Functioning	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]	p-Value for Interaction Test[g]
Placebo	149	144	81.5 (23.16)	4.91 (1.27)	[-6.13; 0.87]		
PD-L1 Status							
<1%							
Pembrolizumab	194	180	81.9 (24.17)	2.38 (1.91)	-4.55	-0.21	0.057
Placebo	197	196	80.4 (24.77)	6.93 (1.93)	[-8.02; -1.08]	[-0.37; -0.05]	
1-49%							
Pembrolizumab	163	156	81.5 (22.21)	4.54 (2.02)	-2.31	-	
Placebo	162	160	81.5 (21.64)	6.85 (2.14)	[-6.00; 1.38]		
≥50%							
Pembrolizumab	139	135	83.0 (24.73)	4.84 (2.25)	1.28	-	
Placebo	140	136	83.1 (21.75)	3.56 (2.31)	[-2.32; 4.88]		

a: Database Cutoff Date: 24JAN2023

b: Number of participants: full-analysis-set population with Adjuvant Chemotherapy

c: Number of participants with data available for analysis

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

e: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates. For other subgroups, analysis is based on 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

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

g: For PD-L1 subgroup, analysis is based on MMRM of change from baseline with treatment, subgroup, time, baseline endpoint score, stage (IB vs. II vs. IIIA), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current) as covariates, and treatment-by-subgroup interaction. For other subgroups, analysis is based on 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 Model for Repeated Measures; PD-L1: Programmed Cell Death - Ligand 1; SD: Standard Deviation; SE: Standard Error

Anhang 4-G2.4: Nebenwirkungen

Unerwünschte Ereignisse Gesamtraten

Unerwünschte Ereignisse gesamt

Tabelle 4G-32: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 091[a]	**Pembrolizumab**		**Placebo**		**Pembrolizumab vs. Placebo**		
Adverse Events	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
Sex							
Male	332	314 (94.6)	342	309 (90.4)	1.05 [1.00; 1.09]	0.038	0.221
Female	164	161 (98.2)	157	145 (92.4)	1.06 [1.01; 1.12]	0.014	
Age							
< 65	260	247 (95.0)	251	232 (92.4)	1.03 [0.98; 1.08]	0.231	0.168
≥ 65	236	228 (96.6)	248	222 (89.5)	1.08 [1.03; 1.13]	0.002	
ECOG Performance Status							
0	321	306 (95.3)	289	262 (90.7)	1.05 [1.01; 1.10]	0.023	0.697
1	175	169 (96.6)	210	192 (91.4)	1.06 [1.00; 1.11]	0.038	
Region							
Western Europe	254	247 (97.2)	263	253 (96.2)	1.01 [0.98; 1.04]	0.505	0.057
Eastern Europe	104	95 (91.3)	95	71 (74.7)	1.22 [1.07; 1.39]	0.002	
Rest of World	51	48 (94.1)	54	53 (98.1)	0.96 [0.89; 1.04]	0.283	
Asia	87	85 (97.7)	87	77 (88.5)	1.10 [1.02; 1.20]	0.017	
Stage							
IB	60	58 (96.7)	57	53 (93.0)	1.04 [0.95; 1.13]	0.369	0.982
II	278	266 (95.7)	293	267 (91.1)	1.05 [1.01; 1.10]	0.029	
IIIA	158	151 (95.6)	149	134 (89.9)	1.06 [1.00; 1.13]	0.056	
PD-L1 Status							
<1%	194	187 (96.4)	197	178 (90.4)	1.07 [1.01; 1.13]	0.017	0.662
1-49%	163	153 (93.9)	162	146 (90.1)	1.04 [0.98; 1.11]	0.215	
≥50%	139	135 (97.1)	140	130 (92.9)	1.05 [0.99; 1.10]	0.103	

a: Database Cutoff Date: 24JAN2023

b: Number of participants: all-participants-as-treated population with Adjuvant Chemotherapy

c: 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.'

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

e: 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 Cell Death - Ligand 1

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-33: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 091[a]	**Pembrolizumab**		**Placebo**		**Pembrolizumab vs. Placebo**		
Serious Adverse Events	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
Sex							
Male	332	93 (28.0)	342	56 (16.4)	1.71 [1.27; 2.30]	<0.001	0.774
Female	164	34 (20.7)	157	20 (12.7)	1.63 [0.98; 2.70]	0.056	
Age							
< 65	260	59 (22.7)	251	42 (16.7)	1.36 [0.95; 1.94]	0.091	0.086
≥ 65	236	68 (28.8)	248	34 (13.7)	2.10 [1.45; 3.05]	<0.001	
ECOG Performance Status							
0	321	77 (24.0)	289	34 (11.8)	2.04 [1.41; 2.95]	<0.001	0.233
1	175	50 (28.6)	210	42 (20.0)	1.43 [1.00; 2.04]	0.050[f]	
Region							
Western Europe	254	80 (31.5)	263	55 (20.9)	1.51 [1.12; 2.03]	0.006	0.338
Eastern Europe	104	21 (20.2)	95	13 (13.7)	1.48 [0.78; 2.78]	0.224	
Rest of World	51	11 (21.6)	54	4 (7.4)	2.91 [0.99; 8.56]	0.039	
Asia	87	15 (17.2)	87	4 (4.6)	3.75 [1.30; 10.85]	0.008	
Stage							
IB	60	14 (23.3)	57	10 (17.5)	1.33 [0.64; 2.75]	0.440	0.719
II	278	80 (28.8)	293	47 (16.0)	1.79 [1.30; 2.47]	<0.001	
IIIA	158	33 (20.9)	149	19 (12.8)	1.64 [0.98; 2.75]	0.058	

a: Database Cutoff Date: 24JAN2023

b: Number of participants: all-participants-as-treated population with Adjuvant Chemotherapy

c: 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.'

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

e: 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.'

f: Unrounded p-value < 0.050

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

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

Tabelle 4G-34: 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 091[a]	**Pembrolizumab**		**Placebo**		**Pembrolizumab vs. Placebo**		
Severe Adverse Events	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
Sex							
Male	332	123 (37.0)	342	85 (24.9)	1.49 [1.18; 1.88]	0.001	0.087
Female	164	47 (28.7)	157	43 (27.4)	1.05 [0.74; 1.49]	0.800	
Age							
< 65	260	87 (33.5)	251	66 (26.3)	1.27 [0.97; 1.67]	0.077	0.607
≥ 65	236	83 (35.2)	248	62 (25.0)	1.41 [1.07; 1.85]	0.015	
ECOG Performance Status							
0	321	102 (31.8)	289	54 (18.7)	1.70 [1.27; 2.27]	<0.001	0.054
1	175	68 (38.9)	210	74 (35.2)	1.10 [0.85; 1.43]	0.464	
Region							
Western Europe	254	104 (40.9)	263	91 (34.6)	1.18 [0.95; 1.48]	0.137	0.456
Eastern Europe	104	32 (30.8)	95	16 (16.8)	1.83 [1.07; 3.11]	0.022	
Rest of World	51	16 (31.4)	54	12 (22.2)	1.41 [0.74; 2.69]	0.292	
Asia	87	18 (20.7)	87	9 (10.3)	2.00 [0.95; 4.20]	0.060	
Stage							
IB	60	21 (35.0)	57	21 (36.8)	0.95 [0.59; 1.54]	0.836	0.213
II	278	99 (35.6)	293	80 (27.3)	1.30 [1.02; 1.67]	0.033	
IIIA	158	50 (31.6)	149	27 (18.1)	1.75 [1.16; 2.63]	0.006	
PD-L1 Status							
<1%	194	69 (35.6)	197	53 (26.9)	1.32 [0.98; 1.78]	0.065	0.606
1-49%	163	47 (28.8)	162	39 (24.1)	1.20 [0.83; 1.72]	0.331	
≥50%	139	54 (38.8)	140	36 (25.7)	1.51 [1.06; 2.14]	0.019	

a: Database Cutoff Date: 24JAN2023

b: Number of participants: all-participants-as-treated population with Adjuvant Chemotherapy

c: 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.'

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

e: 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 Cell Death - Ligand 1

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-35: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 091[a]	**Pembrolizumab**		**Placebo**		**Pembrolizumab vs. Placebo**		
Adverse Events Leading to Treatment Discontinuation	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
Sex							
Male	332	73 (22.0)	342	19 (5.6)	3.96 [2.44; 6.41]	<0.001	0.423
Female	164	30 (18.3)	157	10 (6.4)	2.87 [1.45; 5.68]	0.001	
Age							
< 65	260	46 (17.7)	251	9 (3.6)	4.93 [2.47; 9.87]	<0.001	0.318
≥ 65	236	57 (24.2)	248	20 (8.1)	2.99 [1.86; 4.83]	<0.001	
ECOG Performance Status							
0	321	62 (19.3)	289	11 (3.8)	5.07 [2.73; 9.44]	<0.001	0.171
1	175	41 (23.4)	210	18 (8.6)	2.73 [1.63; 4.58]	<0.001	
Stage							
IB	60	12 (20.0)	57	4 (7.0)	2.85 [0.98; 8.33]	0.042	0.903
II	278	63 (22.7)	293	18 (6.1)	3.69 [2.24; 6.07]	<0.001	
IIIA	158	28 (17.7)	149	7 (4.7)	3.77 [1.70; 8.37]	<0.001	
PD-L1 Status							
<1%	194	39 (20.1)	197	10 (5.1)	3.96 [2.03; 7.71]	<0.001	0.411
1-49%	163	28 (17.2)	162	11 (6.8)	2.53 [1.30; 4.91]	0.004	
≥50%	139	36 (25.9)	140	8 (5.7)	4.53 [2.19; 9.40]	<0.001	

a: Database Cutoff Date: 24JAN2023

b: Number of participants: all-participants-as-treated population with Adjuvant Chemotherapy

c: 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.'

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

e: 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 Cell Death - Ligand 1

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-36: 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 091[a]	**Pembrolizumab**		**Placebo**		**Pembrolizumab vs. Placebo**		
Adverse Event	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
SOC[f]: Endocrine disorders							
Sex							
Male	332	86 (25.9)	342	22 (6.4)	4.03 [2.58; 6.27]	<0.001	0.374
Female	164	52 (31.7)	157	18 (11.5)	2.77 [1.70; 4.51]	<0.001	
Age							
< 65	260	77 (29.6)	251	22 (8.8)	3.38 [2.17; 5.25]	<0.001	0.965
≥ 65	236	61 (25.8)	248	18 (7.3)	3.56 [2.17; 5.84]	<0.001	
ECOG Performance Status							
0	321	94 (29.3)	289	23 (8.0)	3.68 [2.40; 5.64]	<0.001	0.564
1	175	44 (25.1)	210	17 (8.1)	3.11 [1.84; 5.24]	<0.001	
Region							
Western Europe	254	69 (27.2)	263	22 (8.4)	3.25 [2.08; 5.08]	<0.001	0.538
Eastern Europe	104	26 (25.0)	95	3 (3.2)	7.92 [2.48; 25.31]	<0.001	
Rest of World	51	18 (35.3)	54	7 (13.0)	2.72 [1.24; 5.97]	0.008	
Asia	87	25 (28.7)	87	8 (9.2)	3.13 [1.49; 6.54]	0.001	
Stage							
IB	60	13 (21.7)	57	3 (5.3)	4.12 [1.24; 13.69]	0.010	0.937
II	278	81 (29.1)	293	24 (8.2)	3.56 [2.33; 5.44]	<0.001	
IIIA	158	44 (27.8)	149	13 (8.7)	3.19 [1.79; 5.68]	<0.001	
PD-L1 Status							
<1%	194	52 (26.8)	197	16 (8.1)	3.30 [1.95; 5.57]	<0.001	0.873
1-49%	163	49 (30.1)	162	15 (9.3)	3.25 [1.90; 5.55]	<0.001	
≥50%	139	37 (26.6)	140	9 (6.4)	4.14 [2.08; 8.25]	<0.001	
SOC[f]: Gastrointestinal disorders							
Sex							
Male	332	135 (40.7)	342	103 (30.1)	1.35 [1.10; 1.66]	0.004	0.244
Female	164	81 (49.4)	157	72 (45.9)	1.08 [0.86; 1.36]	0.527	
Age							
< 65	260	119 (45.8)	251	99 (39.4)	1.16 [0.95; 1.42]	0.149	0.450
≥ 65	236	97 (41.1)	248	76 (30.6)	1.34 [1.05; 1.71]	0.017	
ECOG Performance Status							
0	321	133 (41.4)	289	88 (30.4)	1.36 [1.09; 1.69]	0.005	0.377
1	175	83 (47.4)	210	87 (41.4)	1.14 [0.92; 1.43]	0.238	
Region							
Western Europe	254	128 (50.4)	263	124 (47.1)	1.07 [0.90; 1.28]	0.461	0.118
Eastern Europe	104	26 (25.0)	95	11 (11.6)	2.16 [1.13; 4.13]	0.015	
Rest of World	51	22 (43.1)	54	15 (27.8)	1.55 [0.91; 2.65]	0.101	
Asia	87	40 (46.0)	87	25 (28.7)	1.60 [1.07; 2.39]	0.019	

Study: KEYNOTE 091[a]	Pembrolizumab		Placebo		Pembrolizumab vs. Placebo		
Adverse Event	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
PD-L1 Status							
<1%	194	76 (39.2)	197	69 (35.0)	1.12 [0.86; 1.45]	0.396	0.300
1-49%	163	75 (46.0)	162	50 (30.9)	1.49 [1.12; 1.98]	0.005	
≥50%	139	65 (46.8)	140	56 (40.0)	1.17 [0.89; 1.53]	0.255	
SOC[f]: Skin and subcutaneous tissue disorders							
Sex							
Male	332	135 (40.7)	342	88 (25.7)	1.58 [1.27; 1.97]	<0.001	0.161
Female	164	73 (44.5)	157	59 (37.6)	1.18 [0.91; 1.54]	0.208	
Age							
< 65	260	112 (43.1)	251	87 (34.7)	1.24 [1.00; 1.55]	0.051	0.129
≥ 65	236	96 (40.7)	248	60 (24.2)	1.68 [1.29; 2.20]	<0.001	
ECOG Performance Status							
0	321	133 (41.4)	289	79 (27.3)	1.52 [1.21; 1.90]	<0.001	0.505
1	175	75 (42.9)	210	68 (32.4)	1.32 [1.02; 1.72]	0.034	
Region							
Western Europe	254	112 (44.1)	263	97 (36.9)	1.20 [0.97; 1.48]	0.095	0.073
Eastern Europe	104	21 (20.2)	95	10 (10.5)	1.92 [0.95; 3.86]	0.061	
Rest of World	51	24 (47.1)	54	13 (24.1)	1.95 [1.12; 3.41]	0.014	
Asia	87	51 (58.6)	87	27 (31.0)	1.89 [1.32; 2.71]	<0.001	
Stage							
IB	60	22 (36.7)	57	15 (26.3)	1.39 [0.81; 2.41]	0.231	0.881
II	278	125 (45.0)	293	90 (30.7)	1.46 [1.18; 1.82]	<0.001	
IIIA	158	61 (38.6)	149	42 (28.2)	1.37 [0.99; 1.89]	0.054	
PD-L1 Status							
<1%	194	75 (38.7)	197	50 (25.4)	1.52 [1.13; 2.05]	0.005	0.919
1-49%	163	76 (46.6)	162	55 (34.0)	1.37 [1.05; 1.80]	0.020	
≥50%	139	57 (41.0)	140	42 (30.0)	1.37 [0.99; 1.89]	0.055	

a: Database Cutoff Date: 24JAN2023

b: Number of participants: all-participants-as-treated population with Adjuvant Chemotherapy

c: 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.'

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

e: 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.'

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); PD-L1: Programmed Cell Death - Ligand 1; SOC: System Organ Class

Tabelle 4G-37: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für PT aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 091[a]	**Pembrolizumab**		**Placebo**		**Pembrolizumab vs. Placebo**		
Adverse Event	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
SOC: Endocrine disorders - PT[f]: Adrenal insufficiency							
Sex							
Male	332	10 (3.0)	342	0	n.a. [n.a.; n.a.]	n.a.	n.a.
Female	164	0	157	0	n.a. [n.a.; n.a.]	n.a.	
Age							
< 65	260	4 (1.5)	251	0	n.c. [n.c.; n.c.]	n.c.	n.c.
≥ 65	236	6 (2.5)	248	0	n.c. [n.c.; n.c.]	n.c.	
ECOG Performance Status							
0	321	5 (1.6)	289	0	n.c. [n.c.; n.c.]	n.c.	n.c.
1	175	5 (2.9)	210	0	n.c. [n.c.; n.c.]	n.c.	
Region							
Western Europe	254	4 (1.6)	263	0	n.c. [n.c.; n.c.]	n.c.	n.c.
Eastern Europe	104	1 (1.0)	95	0	n.c. [n.c.; n.c.]	n.c.	
Rest of World	51	2 (3.9)	54	0	n.c. [n.c.; n.c.]	n.c.	
Asia	87	3 (3.4)	87	0	n.c. [n.c.; n.c.]	n.c.	
Stage							
IB	60	2 (3.3)	57	0	n.c. [n.c.; n.c.]	n.c.	n.c.
II	278	4 (1.4)	293	0	n.c. [n.c.; n.c.]	n.c.	
IIIA	158	4 (2.5)	149	0	n.c. [n.c.; n.c.]	n.c.	
PD-L1 Status							
<1%	194	5 (2.6)	197	0	n.c. [n.c.; n.c.]	n.c.	n.c.
1-49%	163	2 (1.2)	162	0	n.c. [n.c.; n.c.]	n.c.	
≥50%	139	3 (2.2)	140	0	n.c. [n.c.; n.c.]	n.c.	
SOC: Endocrine disorders - PT[f]: Hyperthyroidism							
Sex							
Male	332	40 (12.0)	342	10 (2.9)	4.12 [2.10; 8.10]	<0.001	0.339
Female	164	15 (9.1)	157	6 (3.8)	2.39 [0.95; 6.01]	0.054	
Age							
< 65	260	34 (13.1)	251	9 (3.6)	3.65 [1.79; 7.45]	<0.001	0.754
≥ 65	236	21 (8.9)	248	7 (2.8)	3.15 [1.37; 7.28]	0.004	
ECOG Performance Status							
0	321	38 (11.8)	289	9 (3.1)	3.80 [1.87; 7.72]	<0.001	0.624
1	175	17 (9.7)	210	7 (3.3)	2.91 [1.24; 6.87]	0.010	
Region							
Western Europe	254	32 (12.6)	263	8 (3.0)	4.14 [1.95; 8.81]	<0.001	0.888
Eastern Europe	104	7 (6.7)	95	2 (2.1)	3.20 [0.68; 15.01]	0.118	
Rest of World	51	9 (17.6)	54	3 (5.6)	3.18 [0.91; 11.08]	0.053	
Asia	87	7 (8.0)	87	3 (3.4)	2.33 [0.62; 8.73]	0.194	
Stage							
IB	60	5 (8.3)	57	2 (3.5)	2.38 [0.48; 11.75]	0.273	0.789
II	278	34 (12.2)	293	9 (3.1)	3.98 [1.95; 8.15]	<0.001	
IIIA	158	16 (10.1)	149	5 (3.4)	3.02 [1.13; 8.03]	0.019	

Study: KEYNOTE 091[a]	Pembrolizumab		Placebo		Pembrolizumab vs. Placebo		
Adverse Event	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
PD-L1 Status							
<1%	194	19 (9.8)	197	6 (3.0)	3.22 [1.31; 7.88]	0.006	0.890
1-49%	163	19 (11.7)	162	6 (3.7)	3.15 [1.29; 7.68]	0.007	
≥50%	139	17 (12.2)	140	4 (2.9)	4.28 [1.48; 12.40]	0.003	
SOC: Endocrine disorders - PT[f]: Hypothyroidism							
Sex							
Male	332	58 (17.5)	342	14 (4.1)	4.27 [2.43; 7.50]	<0.001	0.967
Female	164	42 (25.6)	157	10 (6.4)	4.02 [2.09; 7.73]	<0.001	
Age							
< 65	260	59 (22.7)	251	13 (5.2)	4.38 [2.47; 7.79]	<0.001	0.720
≥ 65	236	41 (17.4)	248	11 (4.4)	3.92 [2.06; 7.44]	<0.001	
ECOG Performance Status							
0	321	69 (21.5)	289	14 (4.8)	4.44 [2.55; 7.71]	<0.001	0.648
1	175	31 (17.7)	210	10 (4.8)	3.72 [1.88; 7.37]	<0.001	
Region							
Western Europe	254	50 (19.7)	263	13 (4.9)	3.98 [2.22; 7.15]	<0.001	0.253
Eastern Europe	104	22 (21.2)	95	1 (1.1)	20.10 [2.76; 146.22]	<0.001	
Rest of World	51	14 (27.5)	54	5 (9.3)	2.96 [1.15; 7.64]	0.016	
Asia	87	14 (16.1)	87	5 (5.7)	2.80 [1.05; 7.44]	0.029	
Stage							
IB	60	10 (16.7)	57	1 (1.8)	9.50 [1.26; 71.86]	0.006	0.703
II	278	58 (20.9)	293	16 (5.5)	3.82 [2.25; 6.48]	<0.001	
IIIA	158	32 (20.3)	149	7 (4.7)	4.31 [1.96; 9.47]	<0.001	
PD-L1 Status							
<1%	194	38 (19.6)	197	12 (6.1)	3.22 [1.73; 5.97]	<0.001	0.564
1-49%	163	36 (22.1)	162	7 (4.3)	5.11 [2.34; 11.15]	<0.001	
≥50%	139	26 (18.7)	140	5 (3.6)	5.24 [2.07; 13.25]	<0.001	
SOC: Gastrointestinal disorders - PT[f]: Colitis							
Sex							
Male	332	6 (1.8)	342	3 (0.9)	2.06 [0.52; 8.17]	0.293	0.542
Female	164	8 (4.9)	157	2 (1.3)	3.83 [0.83; 17.75]	0.064	
Age							
< 65	260	9 (3.5)	251	2 (0.8)	4.34 [0.95; 19.91]	0.038	0.383
≥ 65	236	5 (2.1)	248	3 (1.2)	1.75 [0.42; 7.25]	0.434	
ECOG Performance Status							
0	321	10 (3.1)	289	3 (1.0)	3.00 [0.83; 10.80]	0.076	0.833
1	175	4 (2.3)	210	2 (1.0)	2.40 [0.44; 12.95]	0.294	
Region							
Western Europe	254	10 (3.9)	263	4 (1.5)	2.59 [0.82; 8.15]	0.091	0.121
Eastern Europe	104	4 (3.8)	95	0	n.a. [n.a.; n.a.]	n.a.	
Rest of World	51	0	54	0	n.a. [n.a.; n.a.]	n.a.	
Asia	87	0	87	1 (1.1)	n.a. [n.a.; n.a.]	n.a.	
Stage							
IB	60	1 (1.7)	57	1 (1.8)	0.95 [0.06; 14.83]	0.971	0.675
II	278	10 (3.6)	293	3 (1.0)	3.51 [0.98; 12.63]	0.040	
IIIA	158	3 (1.9)	149	1 (0.7)	2.83 [0.30; 26.90]	0.344	

Study: KEYNOTE 091[a]	Pembrolizumab		Placebo		Pembrolizumab vs. Placebo		
Adverse Event	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
PD-L1 Status							
<1%	194	4 (2.1)	197	2 (1.0)	n.c. [n.c.; n.c.]	n.c.	n.c.
1-49%	163	5 (3.1)	162	2 (1.2)	n.c. [n.c.; n.c.]	n.c.	
≥50%	139	5 (3.6)	140	1 (0.7)	n.c. [n.c.; n.c.]	n.c.	
SOC: Gastrointestinal disorders - PT[f]: Diarrhoea							
Sex							
Male	332	59 (17.8)	342	43 (12.6)	1.41 [0.98; 2.03]	0.060	0.677
Female	164	36 (22.0)	157	28 (17.8)	1.23 [0.79; 1.92]	0.357	
Age							
< 65	260	53 (20.4)	251	35 (13.9)	1.46 [0.99; 2.16]	0.054	0.533
≥ 65	236	42 (17.8)	248	36 (14.5)	1.23 [0.82; 1.84]	0.327	
ECOG Performance Status							
0	321	55 (17.1)	289	32 (11.1)	1.55 [1.03; 2.32]	0.033	0.480
1	175	40 (22.9)	210	39 (18.6)	1.23 [0.83; 1.82]	0.300	
Stage							
IB	60	16 (26.7)	57	4 (7.0)	3.80 [1.35; 10.69]	0.005	0.061
II	278	53 (19.1)	293	50 (17.1)	1.12 [0.79; 1.59]	0.535	
IIIA	158	26 (16.5)	149	17 (11.4)	1.44 [0.82; 2.55]	0.204	
PD-L1 Status							
<1%	194	31 (16.0)	197	23 (11.7)	1.37 [0.83; 2.26]	0.218	0.711
1-49%	163	33 (20.2)	162	21 (13.0)	1.56 [0.95; 2.58]	0.078	
≥50%	139	31 (22.3)	140	27 (19.3)	1.16 [0.73; 1.83]	0.535	
SOC: Gastrointestinal disorders - PT[f]: Dry mouth							
Sex							
Male	332	10 (3.0)	342	3 (0.9)	3.43 [0.95; 12.37]	0.044	0.935
Female	164	4 (2.4)	157	1 (0.6)	3.83 [0.43; 33.89]	0.193	
Age							
< 65	260	9 (3.5)	251	3 (1.2)	2.90 [0.79; 10.57]	0.091	0.645
≥ 65	236	5 (2.1)	248	1 (0.4)	5.25 [0.62; 44.64]	0.089	
ECOG Performance Status							
0	321	10 (3.1)	289	2 (0.7)	4.50 [0.99; 20.37]	0.032	0.580
1	175	4 (2.3)	210	2 (1.0)	2.40 [0.44; 12.95]	0.294	
Region							
Western Europe	254	11 (4.3)	263	3 (1.1)	3.80 [1.07; 13.45]	0.026	0.502
Eastern Europe	104	2 (1.9)	95	0	n.a. [n.a.; n.a.]	n.a.	
Rest of World	51	1 (2.0)	54	1 (1.9)	1.06 [0.07; 16.48]	0.968	
Asia	87	0	87	0	n.a. [n.a.; n.a.]	n.a.	
Stage							
IB	60	1 (1.7)	57	0	n.a. [n.a.; n.a.]	n.a.	0.515
II	278	10 (3.6)	293	4 (1.4)	2.63 [0.84; 8.30]	0.085	
IIIA	158	3 (1.9)	149	0	n.a. [n.a.; n.a.]	n.a.	
PD-L1 Status							
<1%	194	4 (2.1)	197	1 (0.5)	n.c. [n.c.; n.c.]	n.c.	n.c.
1-49%	163	5 (3.1)	162	2 (1.2)	n.c. [n.c.; n.c.]	n.c.	
≥50%	139	5 (3.6)	140	1 (0.7)	n.c. [n.c.; n.c.]	n.c.	

Study: KEYNOTE 091[a]	Pembrolizumab		Placebo		Pembrolizumab vs. Placebo		
Adverse Event	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	p-Value[d]	p-Value for Interaction Test[e]
SOC: Gastrointestinal disorders - PT[f]: Gastritis							
Sex							
Male	332	4 (1.2)	342	1 (0.3)	n.c. [n.c.; n.c.]	n.c.	n.c.
Female	164	6 (3.7)	157	2 (1.3)	n.c. [n.c.; n.c.]	n.c.	
Age							
< 65	260	4 (1.5)	251	3 (1.2)	n.c. [n.c.; n.c.]	n.c.	n.c.
≥ 65	236	6 (2.5)	248	0	n.c. [n.c.; n.c.]	n.c.	
ECOG Performance Status							
0	321	7 (2.2)	289	2 (0.7)	n.c. [n.c.; n.c.]	n.c.	n.c.
1	175	3 (1.7)	210	1 (0.5)	n.c. [n.c.; n.c.]	n.c.	
Region							
Western Europe	254	5 (2.0)	263	0	n.c. [n.c.; n.c.]	n.c.	n.c.
Eastern Europe	104	1 (1.0)	95	0	n.c. [n.c.; n.c.]	n.c.	
Rest of World	51	0	54	2 (3.7)	n.c. [n.c.; n.c.]	n.c.	
Asia	87	4 (4.6)	87	1 (1.1)	n.c. [n.c.; n.c.]	n.c.	
Stage							
IB	60	0	57	0	n.c. [n.c.; n.c.]	n.c.	n.c.
II	278	6 (2.2)	293	2 (0.7)	n.c. [n.c.; n.c.]	n.c.	
IIIA	158	4 (2.5)	149	1 (0.7)	n.c. [n.c.; n.c.]	n.c.	
PD-L1 Status							
<1%	194	2 (1.0)	197	1 (0.5)	n.c. [n.c.; n.c.]	n.c.	n.c.
1-49%	163	5 (3.1)	162	0	n.c. [n.c.; n.c.]	n.c.	
≥50%	139	3 (2.2)	140	2 (1.4)	n.c. [n.c.; n.c.]	n.c.	
SOC: Infections and infestations - PT[f]: Nasopharyngitis							
Sex							
Male	332	30 (9.0)	342	17 (5.0)	1.82 [1.02; 3.23]	0.038	0.636
Female	164	15 (9.1)	157	10 (6.4)	1.44 [0.67; 3.10]	0.354	
Age							
< 65	260	24 (9.2)	251	18 (7.2)	1.29 [0.72; 2.31]	0.397	0.192
≥ 65	236	21 (8.9)	248	9 (3.6)	2.45 [1.15; 5.24]	0.016	
ECOG Performance Status							
0	321	29 (9.0)	289	16 (5.5)	1.63 [0.91; 2.94]	0.099	0.890
1	175	16 (9.1)	210	11 (5.2)	1.75 [0.83; 3.66]	0.136	
Region							
Western Europe	254	26 (10.2)	263	19 (7.2)	1.42 [0.80; 2.50]	0.225	0.105
Eastern Europe	104	1 (1.0)	95	3 (3.2)	0.30 [0.03; 2.88]	0.271	
Rest of World	51	5 (9.8)	54	1 (1.9)	5.29 [0.64; 43.78]	0.081	
Asia	87	13 (14.9)	87	4 (4.6)	3.25 [1.10; 9.58]	0.022	
Stage							
IB	60	3 (5.0)	57	3 (5.3)	0.95 [0.20; 4.52]	0.949	0.729
II	278	26 (9.4)	293	16 (5.5)	1.71 [0.94; 3.12]	0.075	
IIIA	158	16 (10.1)	149	8 (5.4)	1.89 [0.83; 4.28]	0.121	
PD-L1 Status							
<1%	194	17 (8.8)	197	10 (5.1)	1.73 [0.81; 3.67]	0.151	0.497
1-49%	163	15 (9.2)	162	12 (7.4)	1.24 [0.60; 2.57]	0.558	
≥50%	139	13 (9.4)	140	5 (3.6)	2.62 [0.96; 7.15]	0.050[g]	

Study: KEYNOTE 091[a]	Pembrolizumab		Placebo		Pembrolizumab vs. Placebo		
Adverse Event	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	p-Value[d]	p-Value for Interaction Test[e]
SOC: Musculoskeletal and connective tissue disorders - PT[f]: Arthralgia							
Sex							
Male	332	47 (14.2)	342	36 (10.5)	1.34 [0.90; 2.02]	0.152	0.802
Female	164	41 (25.0)	157	28 (17.8)	1.40 [0.91; 2.15]	0.119	
Age							
< 65	260	50 (19.2)	251	36 (14.3)	1.34 [0.91; 1.98]	0.140	0.870
≥ 65	236	38 (16.1)	248	28 (11.3)	1.43 [0.91; 2.25]	0.124	
ECOG Performance Status							
0	321	45 (14.0)	289	33 (11.4)	1.23 [0.81; 1.87]	0.337	0.268
1	175	43 (24.6)	210	31 (14.8)	1.66 [1.10; 2.52]	0.015	
Region							
Western Europe	254	59 (23.2)	263	53 (20.2)	1.15 [0.83; 1.60]	0.396	0.066
Eastern Europe	104	5 (4.8)	95	4 (4.2)	1.14 [0.32; 4.13]	0.840	
Rest of World	51	12 (23.5)	54	5 (9.3)	2.54 [0.96; 6.71]	0.048	
Asia	87	12 (13.8)	87	2 (2.3)	6.00 [1.38; 26.02]	0.005	
Stage							
IB	60	14 (23.3)	57	8 (14.0)	1.66 [0.75; 3.66]	0.200	0.420
II	278	50 (18.0)	293	34 (11.6)	1.55 [1.04; 2.32]	0.032	
IIIA	158	24 (15.2)	149	22 (14.8)	1.03 [0.60; 1.75]	0.917	
PD-L1 Status							
<1%	194	34 (17.5)	197	23 (11.7)	1.50 [0.92; 2.45]	0.102	0.452
1-49%	163	35 (21.5)	162	22 (13.6)	1.58 [0.97; 2.57]	0.062	
≥50%	139	19 (13.7)	140	19 (13.6)	1.01 [0.56; 1.82]	0.981	
SOC: Musculoskeletal and connective tissue disorders - PT[f]: Myalgia							
Sex							
Male	332	21 (6.3)	342	7 (2.0)	3.09 [1.33; 7.17]	0.005	0.173
Female	164	11 (6.7)	157	8 (5.1)	1.32 [0.54; 3.19]	0.541	
Age							
< 65	260	18 (6.9)	251	8 (3.2)	2.17 [0.96; 4.91]	0.055	0.951
≥ 65	236	14 (5.9)	248	7 (2.8)	2.10 [0.86; 5.12]	0.094	
ECOG Performance Status							
0	321	16 (5.0)	289	7 (2.4)	2.06 [0.86; 4.93]	0.097	0.774
1	175	16 (9.1)	210	8 (3.8)	2.40 [1.05; 5.47]	0.031	
Region							
Western Europe	254	11 (4.3)	263	9 (3.4)	1.27 [0.53; 3.00]	0.593	0.418
Eastern Europe	104	4 (3.8)	95	1 (1.1)	3.65 [0.42; 32.12]	0.210	
Rest of World	51	6 (11.8)	54	2 (3.7)	3.18 [0.67; 15.02]	0.121	
Asia	87	11 (12.6)	87	3 (3.4)	3.67 [1.06; 12.69]	0.026	
Stage							
IB	60	5 (8.3)	57	1 (1.8)	4.75 [0.57; 39.42]	0.108	0.569
II	278	12 (4.3)	293	8 (2.7)	1.58 [0.66; 3.81]	0.303	
IIIA	158	15 (9.5)	149	6 (4.0)	2.36 [0.94; 5.92]	0.058	
PD-L1 Status							
<1%	194	10 (5.2)	197	7 (3.6)	1.45 [0.56; 3.73]	0.438	0.577
1-49%	163	12 (7.4)	162	4 (2.5)	2.98 [0.98; 9.05]	0.042	
≥50%	139	10 (7.2)	140	4 (2.9)	2.52 [0.81; 7.84]	0.098	

Study: KEYNOTE 091[a]	Pembrolizumab		Placebo		Pembrolizumab vs. Placebo		
Adverse Event	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
SOC: Respiratory, thoracic and mediastinal disorders - PT[f]: Pneumonitis							
Age							
< 65	260	13 (5.0)	251	6 (2.4)	2.09 [0.81; 5.42]	0.119	0.962
≥ 65	236	19 (8.1)	248	10 (4.0)	2.00 [0.95; 4.20]	0.063	
ECOG Performance Status							
0	321	22 (6.9)	289	9 (3.1)	2.20 [1.03; 4.70]	0.036	0.682
1	175	10 (5.7)	210	7 (3.3)	1.71 [0.67; 4.41]	0.258	
Region							
Western Europe	254	25 (9.8)	263	11 (4.2)	2.35 [1.18; 4.68]	0.012	0.611
Eastern Europe	104	3 (2.9)	95	1 (1.1)	2.74 [0.29; 25.90]	0.359	
Rest of World	51	2 (3.9)	54	3 (5.6)	0.71 [0.12; 4.05]	0.696	
Asia	87	2 (2.3)	87	1 (1.1)	2.00 [0.18; 21.65]	0.561	
Stage							
IB	60	3 (5.0)	57	4 (7.0)	0.71 [0.17; 3.04]	0.647	0.242
II	278	18 (6.5)	293	9 (3.1)	2.11 [0.96; 4.61]	0.056	
IIIA	158	11 (7.0)	149	3 (2.0)	3.46 [0.98; 12.15]	0.038	
PD-L1 Status							
<1%	194	6 (3.1)	197	8 (4.1)	0.76 [0.27; 2.15]	0.607	0.073
1-49%	163	13 (8.0)	162	4 (2.5)	3.23 [1.08; 9.70]	0.026	
≥50%	139	13 (9.4)	140	4 (2.9)	3.27 [1.09; 9.79]	0.024	
SOC: Respiratory, thoracic and mediastinal disorders - PT[f]: Productive cough							
Sex							
Male	332	21 (6.3)	342	10 (2.9)	2.16 [1.03; 4.52]	0.035	0.715
Female	164	9 (5.5)	157	3 (1.9)	2.87 [0.79; 10.41]	0.092	
ECOG Performance Status							
0	321	15 (4.7)	289	9 (3.1)	1.50 [0.67; 3.38]	0.323	0.102
1	175	15 (8.6)	210	4 (1.9)	4.50 [1.52; 13.31]	0.003	
Region							
Western Europe	254	16 (6.3)	263	11 (4.2)	1.51 [0.71; 3.18]	0.280	0.242
Eastern Europe	104	3 (2.9)	95	0	n.a. [n.a.; n.a.]	n.a.	
Rest of World	51	2 (3.9)	54	0	n.a. [n.a.; n.a.]	n.a.	
Asia	87	9 (10.3)	87	2 (2.3)	4.50 [1.00; 20.23]	0.030	
Stage							
IB	60	6 (10.0)	57	2 (3.5)	2.85 [0.60; 13.55]	0.166	0.855
II	278	15 (5.4)	293	8 (2.7)	1.98 [0.85; 4.59]	0.106	
IIIA	158	9 (5.7)	149	3 (2.0)	2.83 [0.78; 10.25]	0.097	
SOC: Skin and subcutaneous tissue disorders - PT[f]: Pruritus							
Sex							
Male	332	62 (18.7)	342	39 (11.4)	1.64 [1.13; 2.37]	0.008	0.524
Female	164	36 (22.0)	157	26 (16.6)	1.33 [0.84; 2.09]	0.222	
Age							
< 65	260	51 (19.6)	251	33 (13.1)	1.49 [1.00; 2.23]	0.049	0.908
≥ 65	236	47 (19.9)	248	32 (12.9)	1.54 [1.02; 2.33]	0.037	
ECOG Performance Status							
0	321	62 (19.3)	289	34 (11.8)	1.64 [1.12; 2.42]	0.011	0.607

Study: KEYNOTE 091[a]	Pembrolizumab		Placebo		Pembrolizumab vs. Placebo		
Adverse Event	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
1	175	36 (20.6)	210	31 (14.8)	1.39 [0.90; 2.16]	0.135	
Region							
Western Europe	254	62 (24.4)	263	48 (18.3)	1.34 [0.96; 1.87]	0.087	0.391
Eastern Europe	104	2 (1.9)	95	2 (2.1)	0.91 [0.13; 6.36]	0.927	
Rest of World	51	9 (17.6)	54	4 (7.4)	2.38 [0.78; 7.26]	0.113	
Asia	87	25 (28.7)	87	11 (12.6)	2.27 [1.19; 4.33]	0.009	
Stage							
IB	60	12 (20.0)	57	11 (19.3)	1.04 [0.50; 2.16]	0.924	0.557
II	278	55 (19.8)	293	37 (12.6)	1.57 [1.07; 2.30]	0.020	
IIIA	158	31 (19.6)	149	17 (11.4)	1.72 [0.99; 2.97]	0.048	
PD-L1 Status							
<1%	194	35 (18.0)	197	18 (9.1)	1.97 [1.16; 3.36]	0.010	0.489
1-49%	163	33 (20.2)	162	26 (16.0)	1.26 [0.79; 2.01]	0.327	
≥50%	139	30 (21.6)	140	21 (15.0)	1.44 [0.87; 2.39]	0.156	
SOC: Skin and subcutaneous tissue disorders - PT[f]: Rash							
Sex							
Male	332	30 (9.0)	342	17 (5.0)	1.82 [1.02; 3.23]	0.038	0.873
Female	164	14 (8.5)	157	8 (5.1)	1.68 [0.72; 3.88]	0.223	
Age							
< 65	260	25 (9.6)	251	18 (7.2)	1.34 [0.75; 2.40]	0.320	0.155
≥ 65	236	19 (8.1)	248	7 (2.8)	2.85 [1.22; 6.66]	0.011	
ECOG Performance Status							
0	321	28 (8.7)	289	13 (4.5)	1.94 [1.02; 3.67]	0.038	0.703
1	175	16 (9.1)	210	12 (5.7)	1.60 [0.78; 3.29]	0.198	
Region							
Western Europe	254	26 (10.2)	263	18 (6.8)	1.50 [0.84; 2.66]	0.167	0.158
Eastern Europe	104	8 (7.7)	95	2 (2.1)	3.65 [0.80; 16.78]	0.072	
Rest of World	51	5 (9.8)	54	0	n.a. [n.a.; n.a.]	n.a.	
Asia	87	5 (5.7)	87	5 (5.7)	1.00 [0.30; 3.33]	>0.999	
Stage							
IB	60	7 (11.7)	57	3 (5.3)	2.22 [0.60; 8.16]	0.218	0.769
II	278	27 (9.7)	293	15 (5.1)	1.90 [1.03; 3.49]	0.036	
IIIA	158	10 (6.3)	149	7 (4.7)	1.35 [0.53; 3.45]	0.533	
PD-L1 Status							
<1%	194	16 (8.2)	197	7 (3.6)	2.32 [0.98; 5.52]	0.049	0.294
1-49%	163	18 (11.0)	162	8 (4.9)	2.24 [1.00; 5.00]	0.043	
≥50%	139	10 (7.2)	140	10 (7.1)	1.01 [0.43; 2.34]	0.987	
SOC: Skin and subcutaneous tissue disorders - PT[f]: Rash maculo-papular							
Sex							
Male	332	24 (7.2)	342	10 (2.9)	2.47 [1.20; 5.09]	0.011	0.253
Female	164	9 (5.5)	157	7 (4.5)	1.23 [0.47; 3.22]	0.672	
Age							
< 65	260	17 (6.5)	251	12 (4.8)	1.37 [0.67; 2.81]	0.391	0.147
≥ 65	236	16 (6.8)	248	5 (2.0)	3.36 [1.25; 9.03]	0.010	
ECOG Performance Status							
0	321	18 (5.6)	289	10 (3.5)	1.62 [0.76; 3.45]	0.206	0.423

Study: KEYNOTE 091[a]	**Pembrolizumab**		**Placebo**		**Pembrolizumab vs. Placebo**		
Adverse Event	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
1	175	15 (8.6)	210	7 (3.3)	2.57 [1.07; 6.17]	0.028	
Stage							
IB	60	2 (3.3)	57	1 (1.8)	1.90 [0.18; 20.38]	0.591	0.759
II	278	20 (7.2)	293	9 (3.1)	2.34 [1.09; 5.06]	0.025	
IIIA	158	11 (7.0)	149	7 (4.7)	1.48 [0.59; 3.72]	0.399	
PD-L1 Status							
<1%	194	7 (3.6)	197	3 (1.5)	2.37 [0.62; 9.03]	0.192	0.264
1-49%	163	12 (7.4)	162	10 (6.2)	1.19 [0.53; 2.68]	0.670	
≥50%	139	14 (10.1)	140	4 (2.9)	3.53 [1.19; 10.44]	0.014	

a: Database Cutoff Date: 24JAN2023

b: Number of participants: all-participants-as-treated population with Adjuvant Chemotherapy

c: 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.'

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

e: 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.'

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

g: Unrounded p-value < 0.050

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 Cell Death - Ligand 1; PT: Preferred Term; SOC: System Organ Class

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-38: 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 091[a]	**Pembrolizumab**		**Placebo**		**Pembrolizumab vs. Placebo**		
Serious Adverse Event	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
SOC[f]: Endocrine disorders							
Sex							
Male	332	8 (2.4)	342	0	n.c. [n.c.; n.c.]	n.c.	n.c.
Female	164	2 (1.2)	157	0	n.c. [n.c.; n.c.]	n.c.	
Age							
< 65	260	4 (1.5)	251	0	n.c. [n.c.; n.c.]	n.c.	n.c.
≥ 65	236	6 (2.5)	248	0	n.c. [n.c.; n.c.]	n.c.	
ECOG Performance Status							
0	321	7 (2.2)	289	0	n.c. [n.c.; n.c.]	n.c.	n.c.
1	175	3 (1.7)	210	0	n.c. [n.c.; n.c.]	n.c.	
Region							
Western Europe	254	6 (2.4)	263	0	n.c. [n.c.; n.c.]	n.c.	n.c.
Eastern Europe	104	0	95	0	n.c. [n.c.; n.c.]	n.c.	
Rest of World	51	1 (2.0)	54	0	n.c. [n.c.; n.c.]	n.c.	
Asia	87	3 (3.4)	87	0	n.c. [n.c.; n.c.]	n.c.	
Stage							
IB	60	2 (3.3)	57	0	n.c. [n.c.; n.c.]	n.c.	n.c.
II	278	5 (1.8)	293	0	n.c. [n.c.; n.c.]	n.c.	
IIIA	158	3 (1.9)	149	0	n.c. [n.c.; n.c.]	n.c.	
PD-L1 Status							
<1%	194	3 (1.5)	197	0	n.c. [n.c.; n.c.]	n.c.	n.c.
1-49%	163	2 (1.2)	162	0	n.c. [n.c.; n.c.]	n.c.	
≥50%	139	5 (3.6)	140	0	n.c. [n.c.; n.c.]	n.c.	
SOC[f]: Hepatobiliary disorders							
Sex							
Male	332	11 (3.3)	342	1 (0.3)	11.33 [1.47; 87.28]	0.003	0.565
Female	164	4 (2.4)	157	0	n.a. [n.a.; n.a.]	n.a.	
Age							
< 65	260	7 (2.7)	251	1 (0.4)	n.c. [n.c.; n.c.]	n.c.	n.c.
≥ 65	236	8 (3.4)	248	0	n.c. [n.c.; n.c.]	n.c.	
ECOG Performance Status							
0	321	10 (3.1)	289	1 (0.3)	9.00 [1.16; 69.90]	0.010	0.433
1	175	5 (2.9)	210	0	n.a. [n.a.; n.a.]	n.a.	
Region							
Western Europe	254	8 (3.1)	263	1 (0.4)	n.c. [n.c.; n.c.]	n.c.	n.c.
Eastern Europe	104	3 (2.9)	95	0	n.c. [n.c.; n.c.]	n.c.	
Rest of World	51	1 (2.0)	54	0	n.c. [n.c.; n.c.]	n.c.	
Asia	87	3 (3.4)	87	0	n.c. [n.c.; n.c.]	n.c.	
Stage							
IB	60	2 (3.3)	57	0	n.a. [n.a.; n.a.]	n.a.	0.803
II	278	10 (3.6)	293	1 (0.3)	10.54 [1.36; 81.79]	0.005	

Study: KEYNOTE 091[a]	Pembrolizumab		Placebo		Pembrolizumab vs. Placebo		
Serious Adverse Event	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	p-Value[d]	p-Value for Interaction Test[e]
IIIA	158	3 (1.9)	149	0	n.a. [n.a.; n.a.]	n.a.	
PD-L1 Status							
<1%	194	7 (3.6)	197	0	n.c. [n.c.; n.c.]	n.c.	n.c.
1-49%	163	4 (2.5)	162	0	n.c. [n.c.; n.c.]	n.c.	
≥50%	139	4 (2.9)	140	1 (0.7)	n.c. [n.c.; n.c.]	n.c.	
SOC[f]: Infections and infestations							
Sex							
Male	332	24 (7.2)	342	16 (4.7)	1.55 [0.84; 2.86]	0.161	0.418
Female	164	11 (6.7)	157	4 (2.5)	2.63 [0.86; 8.09]	0.078	
Age							
< 65	260	18 (6.9)	251	8 (3.2)	2.17 [0.96; 4.91]	0.055	0.500
≥ 65	236	17 (7.2)	248	12 (4.8)	1.49 [0.73; 3.05]	0.274	
ECOG Performance Status							
0	321	19 (5.9)	289	10 (3.5)	1.71 [0.81; 3.62]	0.155	0.813
1	175	16 (9.1)	210	10 (4.8)	1.92 [0.89; 4.12]	0.088	
Region							
Western Europe	254	25 (9.8)	263	17 (6.5)	1.52 [0.84; 2.75]	0.160	0.462
Eastern Europe	104	6 (5.8)	95	3 (3.2)	1.83 [0.47; 7.10]	0.377	
Rest of World	51	3 (5.9)	54	0	n.a. [n.a.; n.a.]	n.a.	
Asia	87	1 (1.1)	87	0	n.a. [n.a.; n.a.]	n.a.	
Stage							
IB	60	4 (6.7)	57	1 (1.8)	3.80 [0.44; 32.99]	0.191	0.493
II	278	20 (7.2)	293	15 (5.1)	1.41 [0.73; 2.69]	0.302	
IIIA	158	11 (7.0)	149	4 (2.7)	2.59 [0.84; 7.97]	0.083	
PD-L1 Status							
<1%	194	15 (7.7)	197	11 (5.6)	1.38 [0.65; 2.94]	0.395	0.382
1-49%	163	5 (3.1)	162	4 (2.5)	1.24 [0.34; 4.54]	0.743	
≥50%	139	15 (10.8)	140	5 (3.6)	3.02 [1.13; 8.09]	0.020	
SOC[f]: Respiratory, thoracic and mediastinal disorders							
Sex							
Male	332	20 (6.0)	342	5 (1.5)	4.12 [1.56; 10.85]	0.002	0.069
Female	164	7 (4.3)	157	6 (3.8)	1.12 [0.38; 3.25]	0.839	
Age							
< 65	260	9 (3.5)	251	7 (2.8)	1.24 [0.47; 3.28]	0.663	0.060
≥ 65	236	18 (7.6)	248	4 (1.6)	4.73 [1.62; 13.77]	0.002	
Region							
Western Europe	254	21 (8.3)	263	7 (2.7)	3.11 [1.34; 7.18]	0.005	0.632
Eastern Europe	104	1 (1.0)	95	1 (1.1)	0.91 [0.06; 14.40]	0.949	
Rest of World	51	2 (3.9)	54	2 (3.7)	1.06 [0.15; 7.24]	0.954	
Asia	87	3 (3.4)	87	1 (1.1)	3.00 [0.32; 28.28]	0.313	
Stage							
IB	60	2 (3.3)	57	3 (5.3)	0.63 [0.11; 3.65]	0.607	0.119
II	278	16 (5.8)	293	7 (2.4)	2.41 [1.01; 5.77]	0.041	
IIIA	158	9 (5.7)	149	1 (0.7)	8.49 [1.09; 66.18]	0.013	
PD-L1 Status							
<1%	194	13 (6.7)	197	2 (1.0)	6.60 [1.51; 28.86]	0.003	0.212

Study: KEYNOTE 091[a]	Pembrolizumab		Placebo		Pembrolizumab vs. Placebo		
Serious Adverse Event	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	p-Value[d]	p-Value for Interaction Test[e]
1-49%	163	6 (3.7)	162	4 (2.5)	1.49 [0.43; 5.18]	0.528	
≥50%	139	8 (5.8)	140	5 (3.6)	1.61 [0.54; 4.80]	0.388	

a: Database Cutoff Date: 24JAN2023

b: Number of participants: all-participants-as-treated population with Adjuvant Chemotherapy

c: 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.'

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

e: 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.'

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

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 Cell Death - Ligand 1; SOC: System Organ Class

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-39: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) für PT aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 091[a]	**Pembrolizumab**		**Placebo**		**Pembrolizumab vs. Placebo**		
Serious Adverse Event	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
SOC: Respiratory, thoracic and mediastinal disorders - PT[f]: Pneumonitis							
Sex							
Male	332	10 (3.0)	342	2 (0.6)	5.15 [1.14; 23.33]	0.017	0.158
Female	164	2 (1.2)	157	2 (1.3)	0.96 [0.14; 6.71]	0.965	
Age							
< 65	260	4 (1.5)	251	2 (0.8)	1.93 [0.36; 10.45]	0.437	0.495
≥ 65	236	8 (3.4)	248	2 (0.8)	4.20 [0.90; 19.59]	0.046	
Region							
Western Europe	254	11 (4.3)	263	3 (1.1)	3.80 [1.07; 13.45]	0.026	0.181
Eastern Europe	104	0	95	0	n.a. [n.a.; n.a.]	n.a.	
Rest of World	51	0	54	1 (1.9)	n.a. [n.a.; n.a.]	n.a.	
Asia	87	1 (1.1)	87	0	n.a. [n.a.; n.a.]	n.a.	
Stage							
IB	60	2 (3.3)	57	2 (3.5)	n.c. [n.c.; n.c.]	n.c.	n.c.
II	278	4 (1.4)	293	2 (0.7)	n.c. [n.c.; n.c.]	n.c.	
IIIA	158	6 (3.8)	149	0	n.c. [n.c.; n.c.]	n.c.	
PD-L1 Status							
<1%	194	2 (1.0)	197	1 (0.5)	n.c. [n.c.; n.c.]	n.c.	n.c.
1-49%	163	5 (3.1)	162	1 (0.6)	n.c. [n.c.; n.c.]	n.c.	
≥50%	139	5 (3.6)	140	2 (1.4)	n.c. [n.c.; n.c.]	n.c.	

a: Database Cutoff Date: 24JAN2023

b: Number of participants: all-participants-as-treated population with Adjuvant Chemotherapy

c: 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.'

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

e: 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.'

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

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 Cell Death - Ligand 1; PT: Preferred Term; SOC: System Organ Class

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

Tabelle 4G-40: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für SOC aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 091[a]	**Pembrolizumab**		**Placebo**		**Pembrolizumab vs. Placebo**		
Severe Adverse Event	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
SOC[f]: Hepatobiliary disorders							
Sex							
Male	332	10 (3.0)	342	1 (0.3)	10.30 [1.33; 80.02]	0.005	0.546
Female	164	4 (2.4)	157	0	n.a. [n.a.; n.a.]	n.a.	
Age							
< 65	260	6 (2.3)	251	0	n.c. [n.c.; n.c.]	n.c.	n.c.
≥ 65	236	8 (3.4)	248	1 (0.4)	n.c. [n.c.; n.c.]	n.c.	
ECOG Performance Status							
0	321	9 (2.8)	289	1 (0.3)	8.10 [1.03; 63.57]	0.017	0.411
1	175	5 (2.9)	210	0	n.a. [n.a.; n.a.]	n.a.	
Region							
Western Europe	254	7 (2.8)	263	1 (0.4)	n.c. [n.c.; n.c.]	n.c.	n.c.
Eastern Europe	104	3 (2.9)	95	0	n.c. [n.c.; n.c.]	n.c.	
Rest of World	51	1 (2.0)	54	0	n.c. [n.c.; n.c.]	n.c.	
Asia	87	3 (3.4)	87	0	n.c. [n.c.; n.c.]	n.c.	
Stage							
IB	60	2 (3.3)	57	1 (1.8)	n.c. [n.c.; n.c.]	n.c.	n.c.
II	278	9 (3.2)	293	0	n.c. [n.c.; n.c.]	n.c.	
IIIA	158	3 (1.9)	149	0	n.c. [n.c.; n.c.]	n.c.	
PD-L1 Status							
<1%	194	6 (3.1)	197	1 (0.5)	n.c. [n.c.; n.c.]	n.c.	n.c.
1-49%	163	4 (2.5)	162	0	n.c. [n.c.; n.c.]	n.c.	
≥50%	139	4 (2.9)	140	0	n.c. [n.c.; n.c.]	n.c.	
SOC[f]: Infections and infestations							
Sex							
Male	332	24 (7.2)	342	15 (4.4)	1.65 [0.88; 3.09]	0.114	0.581
Female	164	10 (6.1)	157	4 (2.5)	2.39 [0.77; 7.47]	0.120	
Age							
< 65	260	15 (5.8)	251	8 (3.2)	1.81 [0.78; 4.19]	0.160	0.981
≥ 65	236	19 (8.1)	248	11 (4.4)	1.82 [0.88; 3.73]	0.100	
ECOG Performance Status							
0	321	20 (6.2)	289	10 (3.5)	1.80 [0.86; 3.78]	0.114	0.937
1	175	14 (8.0)	210	9 (4.3)	1.87 [0.83; 4.21]	0.126	
Region							
Western Europe	254	21 (8.3)	263	16 (6.1)	1.36 [0.73; 2.54]	0.336	0.231
Eastern Europe	104	7 (6.7)	95	3 (3.2)	2.13 [0.57; 8.01]	0.250	
Rest of World	51	4 (7.8)	54	0	n.a. [n.a.; n.a.]	n.a.	
Asia	87	2 (2.3)	87	0	n.a. [n.a.; n.a.]	n.a.	
Stage							
IB	60	5 (8.3)	57	2 (3.5)	2.38 [0.48; 11.75]	0.273	0.918
II	278	19 (6.8)	293	12 (4.1)	1.67 [0.83; 3.37]	0.149	

Study: KEYNOTE 091[a]	**Pembrolizumab**		**Placebo**		**Pembrolizumab vs. Placebo**		
Severe Adverse Event	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**p-Value[d]**	**p-Value for Interaction Test[e]**
IIIA	158	10 (6.3)	149	5 (3.4)	1.89 [0.66; 5.39]	0.228	
PD-L1 Status							
<1%	194	14 (7.2)	197	11 (5.6)	1.29 [0.60; 2.78]	0.510	0.460
1-49%	163	6 (3.7)	162	3 (1.9)	1.99 [0.51; 7.81]	0.316	
≥50%	139	14 (10.1)	140	5 (3.6)	2.82 [1.04; 7.62]	0.031	

a: Database Cutoff Date: 24JAN2023

b: Number of participants: all-participants-as-treated population with Adjuvant Chemotherapy

c: 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.'

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

e: 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.'

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

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 Cell Death - Ligand 1; SOC: System Organ Class

Anhang 4-G3: 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-41: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT in der Studie KEYNOTE 091

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, Immune-mediated adrenal insuficiency	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis, Immune-mediated hypophysitis	Yes
Hyperthyroidism	Hyperthyroidism, Basedow's disease, Thyrotoxic crisis, Immune-mediated hyperthyroidism	Yes
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism, Autoimmune hypothyroidism, Immune-mediated hypothyroidism	Yes
Thyroiditis	Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute, Silent thyroiditis, Autoimmune thyroid disorder, Immune-mediated thyroiditis	Yes
Type 1 Diabetes Mellitus	Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus, Euglycaemic diabetic ketoacidosis, Diabetic ketosis, Ketosis-prone diabetes mellitus	Yes
Severe Skin Reactions Including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): or	Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Pemphigoid, Pemphigus, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, SJS-TEN overlap	Yes
Severe Skin (continued): If Grade 3 or higher:	Rash, Rash erythematous, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus genital, Lichen planus, Oral lichen planus, Cutaneous vasculitis, Vasculitic rash	Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis, Vogt-Koyanagi-Harada disease, Chorioretinitis, Choroiditis, Immune-mediated uveitis, Choroidal effusion, Choroidal detachment, Serous retinal detachment	Yes
Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Immune-mediated pancreatitis	Yes
Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated myositis, Rhabdomyolysis, Myopathy, Dermatomyositis, Autoimmune myositis	Yes

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Guillain-Barre Syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome, Subacute inflammatory demyelinating polyneuropathy	Yes
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis	Yes
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis, Immune-mediated encephalitis	Yes
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis	Yes
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction, Infusion related hypersensitivity reaction	No
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia	Yes
Myelitis	Myelitis, Myelitis transverse	Yes
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