Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD Sharp & Dohme GmbH

Modul 4 A

Anhang 4-G: Weitere Ergebnisse

Monotherapie zur adjuvanten Behandlung des Nierenzellkarzinoms mit erhöhtem Rezidivrisiko nach Nephrektomie oder nach Nephrektomie und Resektion metastasierter Läsionen bei Erwachsenen

Stand: 18.07.2022

Inhaltsverzeichnis

Seite

Tabellenverzeichnis

Abbildungsverzeichnis

Anhang 4-G1: Ergänzende Analysen

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3 Analysen des früheren Datenschnitts vom 14. Dezember 2020 zur Studie KEYNOTE 564 dargestellt.

Anhang 4-G1.1: Mortalität

Ergänzende Analysen zum Endpunkt Gesamtüberleben

Tabelle 4G-1: Ergebnisse für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel (Datenschnitt 14. Dezember 2020)

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo	
	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]
Overall Survival	496	18 (3.6)	Not reached [-; -]	498	33 (6.6)	Not reached [-; -]	0.54 [0.30; 0.96]	0.036

a: Database Cutoff Date: 14DEC2020
b: Number of participants: intention-to-treat population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG Status (0 versus 1), US participant (Yes versus No) within M0 group by investigator in IVRS/ IWRS using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; IVRS: Interactive Voice Response System; IWRS: Interactive Web Response System; NED: No Evidence of Disease

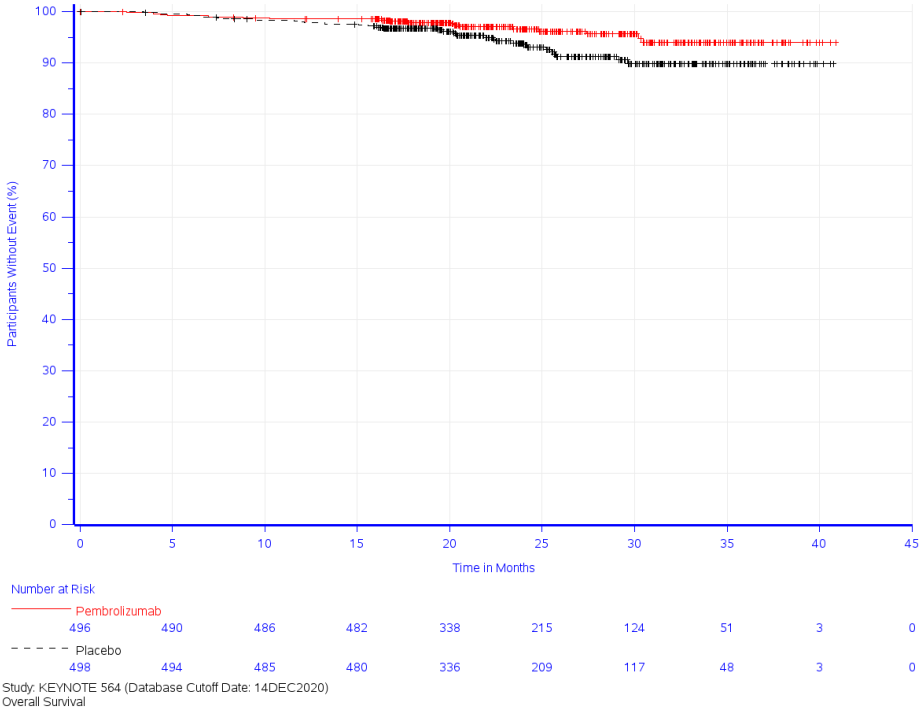

Abbildung 4G-1: Kaplan-Meier-Kurve für den Endpunkt Gesamtüberleben der Studie KEYNOTE 564 (Datenschnitt 14. Dezember 2020)

Anhang 4-G1.2: Morbidität

Ergänzende Analysen zum Endpunkt Krankheitsfreies Überleben

Tabelle 4G-2: Ergebnisse für den Endpunkt Krankheitsfreies Überleben aus RCT mit dem zu bewertenden Arzneimittel (Datenschnitt 14. Dezember 2020)

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo	
	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]
Disease-Free Survival Based on Investigator Assessment (Primary Censoring Rule)	496	109 (22.0)	Not reached [-; -]	498	151 (30.3)	Not reached [-; -]	0.68 [0.53; 0.87]	0.002

a: Database Cutoff Date: 14DEC2020
b: Number of participants: intention-to-treat population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG Status (0 versus 1), US participant (Yes versus No) within M0 group by investigator in IVRS/ IWRS using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; IVRS: Interactive Voice Response System; IWRS: Interactive Web Response System; NED: No Evidence of Disease

Tabelle 4G-3: Übersicht der Einzelkomponenten zum Endpunkt Krankheitsfreies Überleben in der Studie KEYNOTE 564 (Datenschnitt 14. Dezember 2020)

Study: KEYNOTE 564[a]	Pembrolizumab N[b] = 496	Placebo N[b] = 498
Type of First Event in Disease-Free Survival Analysis Based on Investigator Assessment (Primary Censoring Rule), n (%)		
No event	387 (78.0)	347 (69.7)
Event	109 (22.0)	151 (30.3)
Death	6 (1.2)	2 (0.4)
Distant Disease Metastases	87 (17.5)	119 (23.9)
Local Disease Recurrence	16 (3.2)	30 (6.0)

a: Database Cutoff Date: 14DEC2020
b: Number of participants: intention-to-treat population

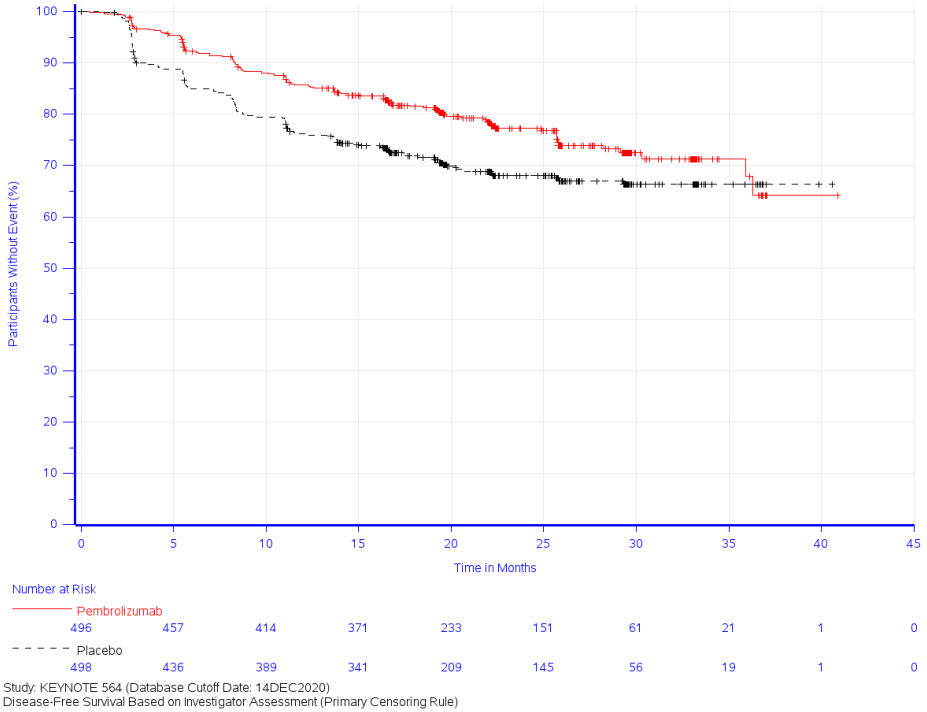

Abbildung 4G-2: Kaplan-Meier-Kurve für den Endpunkt Krankheitsfreies Überleben der Studie KEYNOTE 564 (Datenschnitt 14. Dezember 2020)

Ergänzende Analysen zum Endpunkt Zeit bis zur ersten Folgetherapie

Tabelle 4G-4: Ergebnisse für den Endpunkt Zeit bis zur ersten Folgetherapie aus RCT mit dem zu bewertenden Arzneimittel (Datenschnitt 14. Dezember 2020)

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo	
	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]
Subsequent Oncologic Therapy	496	67 (13.5)	Not reached [-; -]	498	92 (18.5)	Not reached [-; -]	0.69 [0.50; 0.95]	0.021

a: Database Cutoff Date: 14DEC2020
b: Number of participants: intention-to-treat population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG Status (0 versus 1), US participant (Yes versus No) within M0 group by investigator in IVRS/ IWRS using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; IVRS: Interactive Voice Response System; IWRS: Interactive Web Response System; NED: No Evidence of Disease

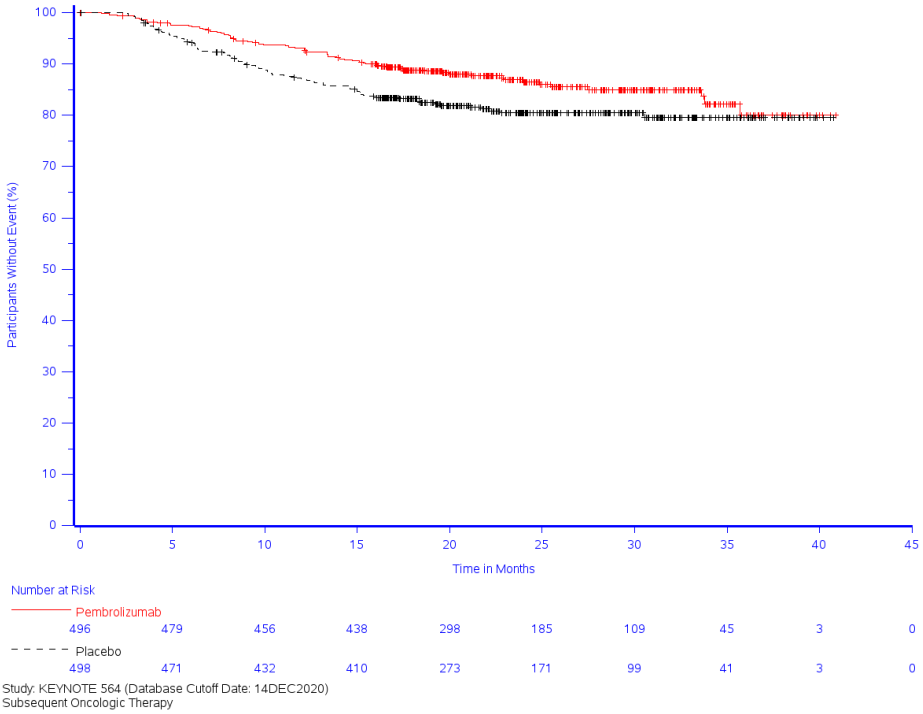

Abbildung 4G-3: Kaplan-Meier-Kurve für den Endpunkt Zeit bis zur ersten Folgetherapie der Studie KEYNOTE 564 (Datenschnitt 14. Dezember 2020)

Ergänzende Analysen zum Endpunkt Zeit bis zur ersten Folgeoperation

Tabelle 4G-5: Ergebnisse für den Endpunkt Zeit bis zur ersten Folgeoperation aus RCT mit dem zu bewertenden Arzneimittel (Datenschnitt 14. Dezember 2020)

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo	
	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]
Subsequent Oncologic Surgery	496	19 (3.8)	Not reached [-; -]	498	32 (6.4)	Not reached [-; -]	0.56 [0.32; 1.00]	0.048

a: Database Cutoff Date: 14DEC2020
b: Number of participants: intention-to-treat population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG Status (0 versus 1), US participant (Yes versus No) within M0 group by investigator in IVRS/ IWRS using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; IVRS: Interactive Voice Response System; IWRS: Interactive Web Response System; NED: No Evidence of Disease

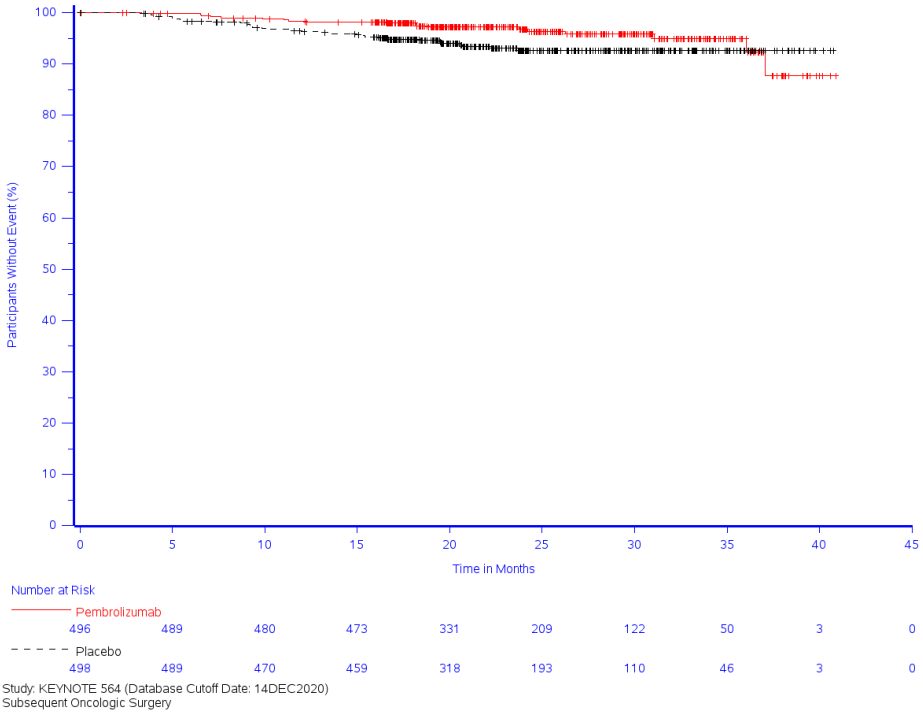

Abbildung 4G-4: Kaplan-Meier-Kurve für den Endpunkt Zeit bis zur ersten Folgeoperation der Studie KEYNOTE 564 (Datenschnitt 14. Dezember 2020)

Anhang 4-G1.3: Nebenwirkungen

Ergänzende Analysen zum Endpunkt Unerwünschte Ereignisse Gesamtraten

Tabelle 4G-6: Ergebnisse für den Endpunkt Unerwünschte Ereignisse Gesamtraten aus RCT mit dem zu bewertenden Arzneimittel (Datenschnitt 14. Dezember 2020)

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo	
	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]
Adverse Events	488	470 (96.3)	3.0 [2.9; 3.1]	496	452 (91.1)	4.4 [3.4; 5.9]	1.47 [1.29; 1.68]	< 0.001
Serious Adverse Events	488	100 (20.5)	Not reached [-; -]	496	56 (11.3)	Not reached [-; -]	1.95 [1.40; 2.70]	< 0.001
Severe Adverse Events (CTCAE-Grade 3-5)	488	158 (32.4)	Not reached [-; -]	496	88 (17.7)	83.9 [-; -]	2.07 [1.60; 2.70]	< 0.001
Adverse Events Leading to Treatment Discontinuation	488	101 (20.7)	Not reached [-; -]	496	10 (2.0)	Not reached [-; -]	11.23 [5.86; 21.51]	< 0.001

a: Database Cutoff Date: 14DEC2020
b: Number of participants: all-participants-as-treated population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero events in one treatment group)
CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events

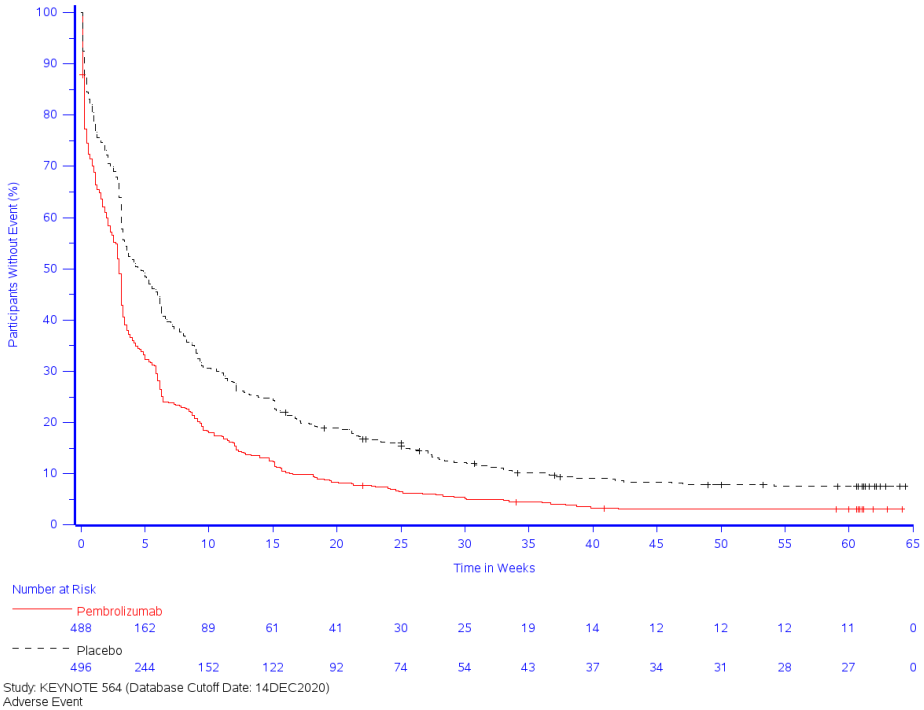

Abbildung 4G-5: Kaplan-Meier-Kurve für den Endpunkt Unerwünschte Ereignisse gesamt der Studie KEYNOTE 564 (Datenschnitt 14. Dezember 2020)

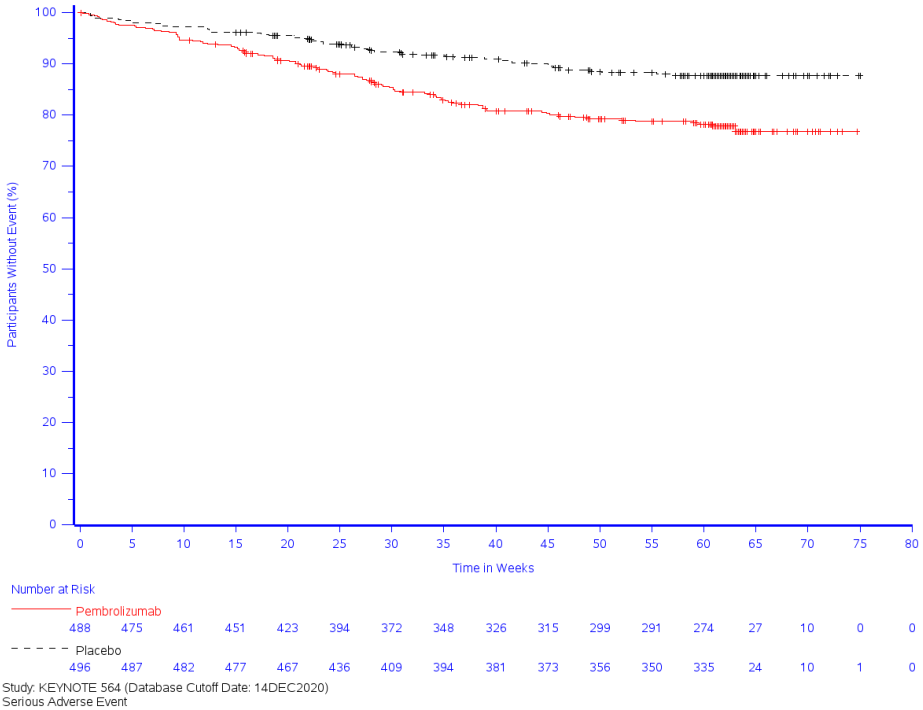

Abbildung 4G-6: Kaplan-Meier-Kurve für den Endpunkt Schwerwiegende unerwünschte Ereignisse der Studie KEYNOTE 564 (Datenschnitt 14. Dezember 2020)

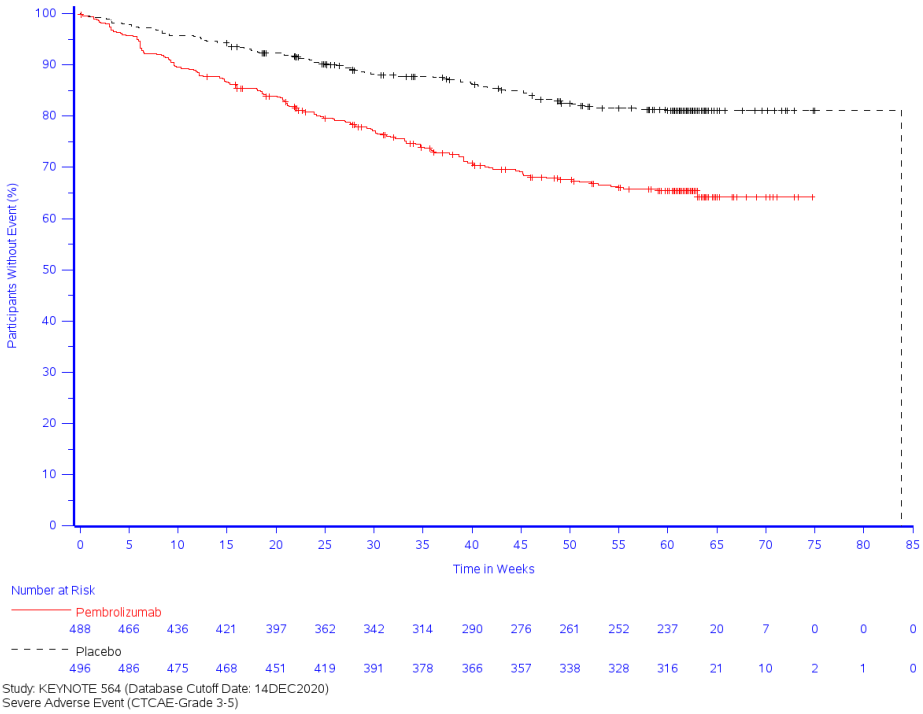

Abbildung 4G-7: Kaplan-Meier-Kurve für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) der Studie KEYNOTE 564 (Datenschnitt 14. Dezember 2020)

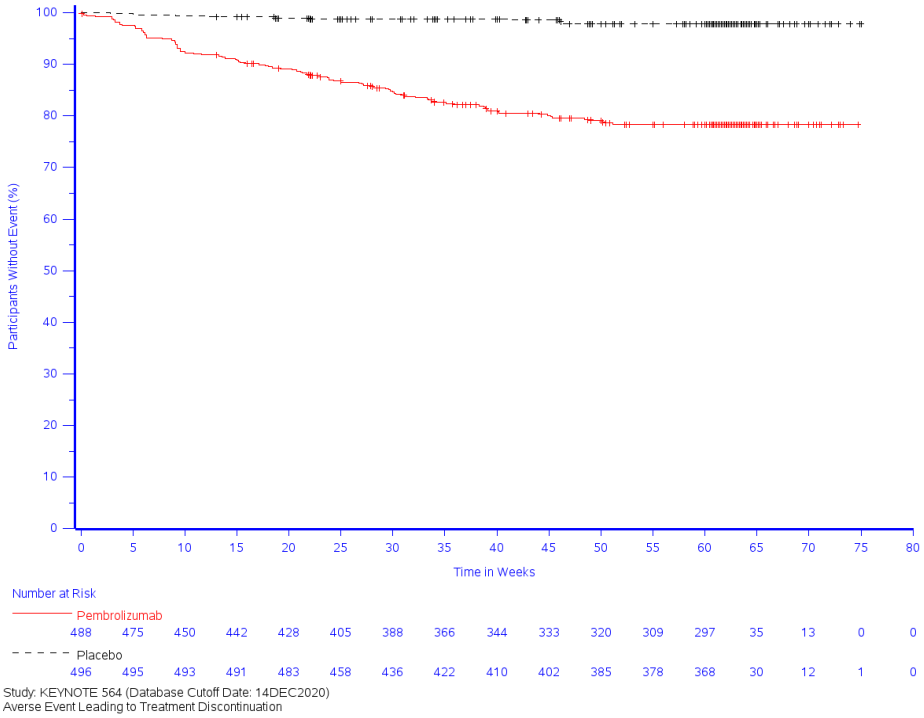

Abbildung 4G-8: Kaplan-Meier-Kurve für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse der Studie KEYNOTE 564 (Datenschnitt 14. Dezember 2020)

Anhang 4-G2: Rücklaufquoten des EORTC QLQ-C30, FKSI-DRS und EQ-5D VAS

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

Anhang 4-G2.1: Rücklaufquoten des EORTC QLQ-C30

Tabelle 4G-7: Gründe für das Fehlen von Werten im EORTC QLQ-C30

		Pembrolizumab N=484		Placebo N=493		Total N=977	
Treatment Visit	Category	n	(%)	n	(%)	n	(%)
BASELINE	**Expected to Complete Questionnaires**	**484**	**(100.0)**	**493**	**(100.0)**	**977**	**(100.0)**
	Completed	438	(90.5)	450	(91.3)	888	(90.9)
	Compliance (% in those expected to complete questionnaires)	438	(90.5)	450	(91.3)	888	(90.9)
	Not completed	46	(9.5)	43	(8.7)	89	(9.1)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)	0	(0.0)
	Not completed due to site staff error	9	(1.9)	12	(2.4)	21	(2.1)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	2	(0.4)	4	(0.4)
	Other	15	(3.1)	11	(2.2)	26	(2.7)
	With visit, no record	20	(4.1)	18	(3.7)	38	(3.9)

Treatment Visit	Category	Pembrolizumab N=484		Placebo N=493		Total N=977	
		n	(%)	n	(%)	n	(%)
	Missing by Design	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
	Discontinued due to death	0	(0.0)	0	(0.0)	0	(0.0)
	Discontinued due to progressive disease	0	(0.0)	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)	0	(0.0)
	Subject died, no reported disposition status	0	(0.0)	0	(0.0)	0	(0.0)
WEEK 12	**Expected to Complete Questionnaires**	**483**	**(99.8)**	**493**	**(100.0)**	**976**	**(99.9)**
	Completed	432	(89.3)	458	(92.9)	890	(91.1)
	Compliance (% in those expected to complete questionnaires)	432	(89.4)	458	(92.9)	890	(91.2)
	Not completed	51	(10.5)	35	(7.1)	86	(8.8)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)	1	(0.1)
	Not completed due to site staff error	13	(2.7)	15	(3.0)	28	(2.9)
	Subject in hospital or hospice	1	(0.2)	0	(0.0)	1	(0.1)
	Subject was physically unable to complete	0	(0.0)	1	(0.2)	1	(0.1)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.2)	1	(0.1)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	4	(0.8)	5	(1.0)	9	(0.9)
	Other	16	(3.3)	7	(1.4)	23	(2.4)
	With visit, no record	17	(3.5)	5	(1.0)	22	(2.3)

Treatment Visit	Category	Pembrolizumab N=484		Placebo N=493		Total N=977	
		n	(%)	n	(%)	n	(%)
	Missing by Design	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.1)**
	Discontinued due to death	0	(0.0)	0	(0.0)	0	(0.0)
	Discontinued due to progressive disease	0	(0.0)	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)	0	(0.0)
	Subject died	1	(0.2)	0	(0.0)	1	(0.1)
	Visit not reached	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)	0	(0.0)
	Subject died, no reported disposition status	0	(0.0)	0	(0.0)	0	(0.0)
WEEK 24	**Expected to Complete Questionnaires**	**459**	**(94.8)**	**452**	**(91.7)**	**911**	**(93.2)**
	Completed	384	(79.3)	415	(84.2)	799	(81.8)
	Compliance (% in those expected to complete questionnaires)	384	(83.7)	415	(91.8)	799	(87.7)
	Not completed	75	(15.5)	37	(7.5)	112	(11.5)
	Subject did not complete due to disease under study	1	(0.2)	1	(0.2)	2	(0.2)
	Not completed due to site staff error	14	(2.9)	18	(3.7)	32	(3.3)
	Subject in hospital or hospice	1	(0.2)	0	(0.0)	1	(0.1)
	Subject was physically unable to complete	1	(0.2)	1	(0.2)	2	(0.2)
	Subject lost to follow-up/unable to contact	1	(0.2)	0	(0.0)	1	(0.1)
	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)	1	(0.1)
	Subject refused for other reasons	4	(0.8)	2	(0.4)	6	(0.6)
	Other	12	(2.5)	11	(2.2)	23	(2.4)
	With visit, no record	40	(8.3)	4	(0.8)	44	(4.5)

Treatment Visit	Category	Pembrolizumab N=484		Placebo N=493		Total N=977	
		n	(%)	n	(%)	n	(%)
	Missing by Design	**25**	**(5.2)**	**41**	**(8.3)**	**66**	**(6.8)**
	Discontinued due to death	1	(0.2)	0	(0.0)	1	(0.1)
	Discontinued due to progressive disease	13	(2.7)	35	(7.1)	48	(4.9)
	Discontinued due to withdrawal by subject	3	(0.6)	2	(0.4)	5	(0.5)
	Subject died	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not reached	3	(0.6)	3	(0.6)	6	(0.6)
	Visit not scheduled	4	(0.8)	1	(0.2)	5	(0.5)
	Subject died, no reported disposition status	1	(0.2)	0	(0.0)	1	(0.1)
WEEK 36	**Expected to Complete Questionnaires**	**399**	**(82.4)**	**423**	**(85.8)**	**822**	**(84.1)**
	Completed	332	(68.6)	360	(73.0)	692	(70.8)
	Compliance (% in those expected to complete questionnaires)	332	(83.2)	360	(85.1)	692	(84.2)
	Not completed	67	(13.8)	63	(12.8)	130	(13.3)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)	0	(0.0)
	Not completed due to site staff error	13	(2.7)	18	(3.7)	31	(3.2)
	Subject in hospital or hospice	1	(0.2)	0	(0.0)	1	(0.1)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	6	(1.2)	4	(0.8)	10	(1.0)
	Other	13	(2.7)	20	(4.1)	33	(3.4)
	With visit, no record	34	(7.0)	21	(4.3)	55	(5.6)

Treatment Visit	Category	Pembrolizumab N=484		Placebo N=493		Total N=977	
		n	(%)	n	(%)	n	(%)
	Missing by Design	**85**	**(17.6)**	**70**	**(14.2)**	**155**	**(15.9)**
	Discontinued due to death	1	(0.2)	0	(0.0)	1	(0.1)
	Discontinued due to progressive disease	32	(6.6)	64	(13.0)	96	(9.8)
	Discontinued due to withdrawal by subject	10	(2.1)	2	(0.4)	12	(1.2)
	Subject died	1	(0.2)	0	(0.0)	1	(0.1)
	Visit not reached	18	(3.7)	3	(0.6)	21	(2.1)
	Visit not scheduled	22	(4.5)	1	(0.2)	23	(2.4)
	Subject died, no reported disposition status	1	(0.2)	0	(0.0)	1	(0.1)
WEEK 48	**Expected to Complete Questionnaires**	**358**	**(74.0)**	**394**	**(79.9)**	**752**	**(77.0)**
	Completed	248	(51.2)	311	(63.1)	559	(57.2)
	Compliance (% in those expected to complete questionnaires)	248	(69.3)	311	(78.9)	559	(74.3)
	Not completed	110	(22.7)	83	(16.8)	193	(19.8)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)	1	(0.1)
	Not completed due to site staff error	8	(1.7)	6	(1.2)	14	(1.4)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)	1	(0.1)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)	0	(0.0)
	Other	11	(2.3)	13	(2.6)	24	(2.5)
	With visit, no record	90	(18.6)	63	(12.8)	153	(15.7)

Treatment Visit	Category	Pembrolizumab N=484		Placebo N=493		Total N=977	
		n	(%)	n	(%)	n	(%)
	Missing by Design	**126**	**(26.0)**	**99**	**(20.1)**	**225**	**(23.0)**
	Discontinued due to death	2	(0.4)	0	(0.0)	2	(0.2)
	Discontinued due to progressive disease	48	(9.9)	84	(17.0)	132	(13.5)
	Discontinued due to withdrawal by subject	13	(2.7)	5	(1.0)	18	(1.8)
	Subject died	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not reached	28	(5.8)	7	(1.4)	35	(3.6)
	Visit not scheduled	33	(6.8)	3	(0.6)	36	(3.7)
	Subject died, no reported disposition status	2	(0.4)	0	(0.0)	2	(0.2)
WEEK 52	**Expected to Complete Questionnaires**	**353**	**(72.9)**	**385**	**(78.1)**	**738**	**(75.5)**
	Completed	301	(62.2)	325	(65.9)	626	(64.1)
	Compliance (% in those expected to complete questionnaires)	301	(85.3)	325	(84.4)	626	(84.8)
	Not completed	52	(10.7)	60	(12.2)	112	(11.5)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)	1	(0.1)
	Not completed due to site staff error	18	(3.7)	18	(3.7)	36	(3.7)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)	1	(0.1)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)	1	(0.1)
	Subject refused for other reasons	2	(0.4)	1	(0.2)	3	(0.3)
	Other	11	(2.3)	31	(6.3)	42	(4.3)
	With visit, no record	19	(3.9)	9	(1.8)	28	(2.9)

Treatment Visit	Category	Pembrolizumab N=484		Placebo N=493		Total N=977	
		n	(%)	n	(%)	n	(%)
	Missing by Design	**131**	**(27.1)**	**108**	**(21.9)**	**239**	**(24.5)**
	Discontinued due to death	2	(0.4)	0	(0.0)	2	(0.2)
	Discontinued due to progressive disease	56	(11.6)	92	(18.7)	148	(15.1)
	Discontinued due to withdrawal by subject	15	(3.1)	5	(1.0)	20	(2.0)
	Subject died	0	(0.0)	1	(0.2)	1	(0.1)
	Visit not reached	39	(8.1)	8	(1.6)	47	(4.8)
	Visit not scheduled	17	(3.5)	2	(0.4)	19	(1.9)
	Subject died, no reported disposition status	2	(0.4)	0	(0.0)	2	(0.2)
WEEK 104	**Expected to Complete Questionnaires**	**114**	**(23.6)**	**109**	**(22.1)**	**223**	**(22.8)**
	Completed	89	(18.4)	91	(18.5)	180	(18.4)
	Compliance (% in those expected to complete questionnaires)	89	(78.1)	91	(83.5)	180	(80.7)
	Not completed	25	(5.2)	18	(3.7)	43	(4.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)	0	(0.0)
	Not completed due to site staff error	5	(1.0)	2	(0.4)	7	(0.7)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.2)	1	(0.1)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	0	(0.0)	1	(0.1)
	Other	8	(1.7)	7	(1.4)	15	(1.5)
	With visit, no record	11	(2.3)	8	(1.6)	19	(1.9)

Treatment Visit	Category	Pembrolizumab N=484 n	Pembrolizumab N=484 (%)	Placebo N=493 n	Placebo N=493 (%)	Total N=977 n	Total N=977 (%)
	Missing by Design	**370**	**(76.4)**	**384**	**(77.9)**	**754**	**(77.2)**
	Discontinued due to death	3	(0.6)	2	(0.4)	5	(0.5)
	Discontinued due to progressive disease	93	(19.2)	142	(28.8)	235	(24.1)
	Discontinued due to withdrawal by subject	23	(4.8)	10	(2.0)	33	(3.4)
	Subject died	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not reached	246	(50.8)	230	(46.7)	476	(48.7)
	Visit not scheduled	3	(0.6)	0	(0.0)	3	(0.3)
	Subject died, no reported disposition status	2	(0.4)	0	(0.0)	2	(0.2)

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

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

Database Cutoff Date: 14DEC2020

Anhang 4-G2.2: Rücklaufquoten des FKSI-DRS

Tabelle 4G-8: Gründe für das Fehlen von Werten im FKSI-DRS

Treatment Visit	Category	Pembrolizumab N=483		Placebo N=493		Total N=976	
		n	(%)	n	(%)	n	(%)
BASELINE	**Expected to Complete Questionnaires**	**483**	**(100.0)**	**493**	**(100.0)**	**976**	**(100.0)**
	Completed	435	(90.1)	447	(90.7)	882	(90.4)
	Compliance (% in those expected to complete questionnaires)	435	(90.1)	447	(90.7)	882	(90.4)
	Not completed	48	(9.9)	46	(9.3)	94	(9.6)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)	0	(0.0)
	Not completed due to site staff error	10	(2.1)	14	(2.8)	24	(2.5)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	3	(0.6)	2	(0.4)	5	(0.5)
	Other	15	(3.1)	11	(2.2)	26	(2.7)
	With visit, no record	20	(4.1)	19	(3.9)	39	(4.0)
	Missing by Design	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
	Discontinued due to death	0	(0.0)	0	(0.0)	0	(0.0)
	Discontinued due to progressive disease	0	(0.0)	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)	0	(0.0)
	Subject died, no reported disposition status	0	(0.0)	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=483		Placebo N=493		Total N=976	
		n	(%)	n	(%)	n	(%)
WEEK 12	**Expected to Complete Questionnaires**	**482**	**(99.8)**	**493**	**(100.0)**	**975**	**(99.9)**
	Completed	431	(89.2)	454	(92.1)	885	(90.7)
	Compliance (% in those expected to complete questionnaires)	431	(89.4)	454	(92.1)	885	(90.8)
	Not completed	51	(10.6)	39	(7.9)	90	(9.2)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)	1	(0.1)
	Not completed due to site staff error	16	(3.3)	16	(3.2)	32	(3.3)
	Subject in hospital or hospice	1	(0.2)	0	(0.0)	1	(0.1)
	Subject was physically unable to complete	0	(0.0)	2	(0.4)	2	(0.2)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.2)	1	(0.1)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	4	(0.8)	5	(1.0)	9	(0.9)
	Other	14	(2.9)	9	(1.8)	23	(2.4)
	With visit, no record	16	(3.3)	5	(1.0)	21	(2.2)
	Missing by Design	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.1)**
	Discontinued due to death	0	(0.0)	0	(0.0)	0	(0.0)
	Discontinued due to progressive disease	0	(0.0)	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)	0	(0.0)
	Subject died	1	(0.2)	0	(0.0)	1	(0.1)
	Visit not reached	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)	0	(0.0)
	Subject died, no reported disposition status	0	(0.0)	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=483		Placebo N=493		Total N=976	
		n	(%)	n	(%)	n	(%)
WEEK 24	**Expected to Complete Questionnaires**	**458**	**(94.8)**	**452**	**(91.7)**	**910**	**(93.2)**
	Completed	383	(79.3)	414	(84.0)	797	(81.7)
	Compliance (% in those expected to complete questionnaires)	383	(83.6)	414	(91.6)	797	(87.6)
	Not completed	75	(15.5)	38	(7.7)	113	(11.6)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)	1	(0.1)
	Not completed due to site staff error	15	(3.1)	18	(3.7)	33	(3.4)
	Subject in hospital or hospice	1	(0.2)	0	(0.0)	1	(0.1)
	Subject was physically unable to complete	1	(0.2)	1	(0.2)	2	(0.2)
	Subject lost to follow-up/unable to contact	1	(0.2)	0	(0.0)	1	(0.1)
	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)	1	(0.1)
	Subject refused for other reasons	4	(0.8)	2	(0.4)	6	(0.6)
	Other	12	(2.5)	11	(2.2)	23	(2.4)
	With visit, no record	40	(8.3)	5	(1.0)	45	(4.6)
	Missing by Design	**25**	**(5.2)**	**41**	**(8.3)**	**66**	**(6.8)**
	Discontinued due to death	1	(0.2)	0	(0.0)	1	(0.1)
	Discontinued due to progressive disease	13	(2.7)	35	(7.1)	48	(4.9)
	Discontinued due to withdrawal by subject	3	(0.6)	2	(0.4)	5	(0.5)
	Subject died	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not reached	3	(0.6)	3	(0.6)	6	(0.6)
	Visit not scheduled	4	(0.8)	1	(0.2)	5	(0.5)
	Subject died, no reported disposition status	1	(0.2)	0	(0.0)	1	(0.1)

Treatment Visit	Category	Pembrolizumab N=483		Placebo N=493		Total N=976	
		n	(%)	n	(%)	n	(%)
WEEK 36	**Expected to Complete Questionnaires**	**399**	**(82.6)**	**423**	**(85.8)**	**822**	**(84.2)**
	Completed	331	(68.5)	360	(73.0)	691	(70.8)
	Compliance (% in those expected to complete questionnaires)	331	(83.0)	360	(85.1)	691	(84.1)
	Not completed	68	(14.1)	63	(12.8)	131	(13.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)	0	(0.0)
	Not completed due to site staff error	15	(3.1)	18	(3.7)	33	(3.4)
	Subject in hospital or hospice	1	(0.2)	0	(0.0)	1	(0.1)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	5	(1.0)	4	(0.8)	9	(0.9)
	Other	13	(2.7)	20	(4.1)	33	(3.4)
	With visit, no record	34	(7.0)	21	(4.3)	55	(5.6)
	Missing by Design	**84**	**(17.4)**	**70**	**(14.2)**	**154**	**(15.8)**
	Discontinued due to death	1	(0.2)	0	(0.0)	1	(0.1)
	Discontinued due to progressive disease	31	(6.4)	64	(13.0)	95	(9.7)
	Discontinued due to withdrawal by subject	10	(2.1)	2	(0.4)	12	(1.2)
	Subject died	1	(0.2)	0	(0.0)	1	(0.1)
	Visit not reached	18	(3.7)	3	(0.6)	21	(2.2)
	Visit not scheduled	22	(4.6)	1	(0.2)	23	(2.4)
	Subject died, no reported disposition status	1	(0.2)	0	(0.0)	1	(0.1)

		Pembrolizumab N=483		Placebo N=493		Total N=976	
Treatment Visit	Category	n	(%)	n	(%)	n	(%)
WEEK 48	**Expected to Complete Questionnaires**	**358**	**(74.1)**	**394**	**(79.9)**	**752**	**(77.0)**
	Completed	247	(51.1)	311	(63.1)	558	(57.2)
	Compliance (% in those expected to complete questionnaires)	247	(69.0)	311	(78.9)	558	(74.2)
	Not completed	111	(23.0)	83	(16.8)	194	(19.9)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)	1	(0.1)
	Not completed due to site staff error	8	(1.7)	6	(1.2)	14	(1.4)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)	1	(0.1)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)	0	(0.0)
	Other	11	(2.3)	13	(2.6)	24	(2.5)
	With visit, no record	91	(18.8)	63	(12.8)	154	(15.8)
	Missing by Design	**125**	**(25.9)**	**99**	**(20.1)**	**224**	**(23.0)**
	Discontinued due to death	2	(0.4)	0	(0.0)	2	(0.2)
	Discontinued due to progressive disease	47	(9.7)	84	(17.0)	131	(13.4)
	Discontinued due to withdrawal by subject	13	(2.7)	5	(1.0)	18	(1.8)
	Subject died	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not reached	28	(5.8)	7	(1.4)	35	(3.6)
	Visit not scheduled	33	(6.8)	3	(0.6)	36	(3.7)
	Subject died, no reported disposition status	2	(0.4)	0	(0.0)	2	(0.2)

		Pembrolizumab N=483		Placebo N=493		Total N=976	
Treatment Visit	Category	n	(%)	n	(%)	n	(%)
WEEK 52	**Expected to Complete Questionnaires**	**353**	**(73.1)**	**386**	**(78.3)**	**739**	**(75.7)**
	Completed	300	(62.1)	328	(66.5)	628	(64.3)
	Compliance (% in those expected to complete questionnaires)	300	(85.0)	328	(85.0)	628	(85.0)
	Not completed	53	(11.0)	58	(11.8)	111	(11.4)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)	1	(0.1)
	Not completed due to site staff error	18	(3.7)	18	(3.7)	36	(3.7)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)	1	(0.1)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)	1	(0.1)
	Subject refused for other reasons	2	(0.4)	1	(0.2)	3	(0.3)
	Other	12	(2.5)	29	(5.9)	41	(4.2)
	With visit, no record	19	(3.9)	9	(1.8)	28	(2.9)
	Missing by Design	**130**	**(26.9)**	**107**	**(21.7)**	**237**	**(24.3)**
	Discontinued due to death	2	(0.4)	0	(0.0)	2	(0.2)
	Discontinued due to progressive disease	55	(11.4)	91	(18.5)	146	(15.0)
	Discontinued due to withdrawal by subject	15	(3.1)	5	(1.0)	20	(2.0)
	Subject died	0	(0.0)	1	(0.2)	1	(0.1)
	Visit not reached	39	(8.1)	8	(1.6)	47	(4.8)
	Visit not scheduled	17	(3.5)	2	(0.4)	19	(1.9)
	Subject died, no reported disposition status	2	(0.4)	0	(0.0)	2	(0.2)

Treatment Visit	Category	Pembrolizumab N=483 n	Pembrolizumab N=483 (%)	Placebo N=493 n	Placebo N=493 (%)	Total N=976 n	Total N=976 (%)
WEEK 104	**Expected to Complete Questionnaires**	**114**	**(23.6)**	**109**	**(22.1)**	**223**	**(22.8)**
	Completed	88	(18.2)	91	(18.5)	179	(18.3)
	Compliance (% in those expected to complete questionnaires)	88	(77.2)	91	(83.5)	179	(80.3)
	Not completed	26	(5.4)	18	(3.7)	44	(4.5)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)	0	(0.0)
	Not completed due to site staff error	6	(1.2)	2	(0.4)	8	(0.8)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.2)	1	(0.1)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	0	(0.0)	1	(0.1)
	Other	8	(1.7)	7	(1.4)	15	(1.5)
	With visit, no record	11	(2.3)	8	(1.6)	19	(1.9)
	Missing by Design	**369**	**(76.4)**	**384**	**(77.9)**	**753**	**(77.2)**
	Discontinued due to death	3	(0.6)	2	(0.4)	5	(0.5)
	Discontinued due to progressive disease	92	(19.0)	142	(28.8)	234	(24.0)
	Discontinued due to withdrawal by subject	23	(4.8)	10	(2.0)	33	(3.4)
	Subject died	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not reached	246	(50.9)	230	(46.7)	476	(48.8)
	Visit not scheduled	3	(0.6)	0	(0.0)	3	(0.3)
	Subject died, no reported disposition status	2	(0.4)	0	(0.0)	2	(0.2)

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

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

Database Cutoff Date: 14DEC2020

Anhang 4-G2.3: Rücklaufquoten der EQ-5D VAS

Tabelle 4G-9: Gründe für das Fehlen von Werten in der EQ-5D VAS

Treatment Visit	Category	Pembrolizumab N=484		Placebo N=493		Total N=977	
		n	(%)	n	(%)	n	(%)
BASELINE	**Expected to Complete Questionnaires**	**484**	**(100.0)**	**493**	**(100.0)**	**977**	**(100.0)**
	Completed	446	(92.1)	460	(93.3)	906	(92.7)
	Compliance (% in those expected to complete questionnaires)	446	(92.1)	460	(93.3)	906	(92.7)
	Not completed	38	(7.9)	33	(6.7)	71	(7.3)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)	0	(0.0)
	Not completed due to site staff error	9	(1.9)	9	(1.8)	18	(1.8)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	0	(0.0)	2	(0.2)
	Other	10	(2.1)	6	(1.2)	16	(1.6)
	With visit, no record	17	(3.5)	18	(3.7)	35	(3.6)
	Missing by Design	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
	Discontinued due to death	0	(0.0)	0	(0.0)	0	(0.0)
	Discontinued due to progressive disease	0	(0.0)	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)	0	(0.0)
	Subject died, no reported disposition status	0	(0.0)	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=484		Placebo N=493		Total N=977	
		n	(%)	n	(%)	n	(%)
WEEK 12	**Expected to Complete Questionnaires**	**483**	**(99.8)**	**493**	**(100.0)**	**976**	**(99.9)**
	Completed	437	(90.3)	464	(94.1)	901	(92.2)
	Compliance (% in those expected to complete questionnaires)	437	(90.5)	464	(94.1)	901	(92.3)
	Not completed	46	(9.5)	29	(5.9)	75	(7.7)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)	1	(0.1)
	Not completed due to site staff error	13	(2.7)	15	(3.0)	28	(2.9)
	Subject in hospital or hospice	1	(0.2)	0	(0.0)	1	(0.1)
	Subject was physically unable to complete	0	(0.0)	1	(0.2)	1	(0.1)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.2)	1	(0.1)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	4	(0.8)	4	(0.8)	8	(0.8)
	Other	9	(1.9)	3	(0.6)	12	(1.2)
	With visit, no record	19	(3.9)	4	(0.8)	23	(2.4)
	Missing by Design	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.1)**
	Discontinued due to death	0	(0.0)	0	(0.0)	0	(0.0)
	Discontinued due to progressive disease	0	(0.0)	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)	0	(0.0)
	Subject died	1	(0.2)	0	(0.0)	1	(0.1)
	Visit not reached	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)	0	(0.0)
	Subject died, no reported disposition status	0	(0.0)	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab N=484		Placebo N=493		Total N=977	
		n	(%)	n	(%)	n	(%)
WEEK 24	**Expected to Complete Questionnaires**	**458**	**(94.6)**	**452**	**(91.7)**	**910**	**(93.1)**
	Completed	390	(80.6)	418	(84.8)	808	(82.7)
	Compliance (% in those expected to complete questionnaires)	390	(85.2)	418	(92.5)	808	(88.8)
	Not completed	68	(14.0)	34	(6.9)	102	(10.4)
	Subject did not complete due to disease under study	1	(0.2)	1	(0.2)	2	(0.2)
	Not completed due to site staff error	13	(2.7)	16	(3.2)	29	(3.0)
	Subject in hospital or hospice	1	(0.2)	0	(0.0)	1	(0.1)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)	1	(0.1)
	Subject lost to follow-up/unable to contact	1	(0.2)	0	(0.0)	1	(0.1)
	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)	1	(0.1)
	Subject refused for other reasons	2	(0.4)	2	(0.4)	4	(0.4)
	Other	9	(1.9)	11	(2.2)	20	(2.0)
	With visit, no record	39	(8.1)	4	(0.8)	43	(4.4)
	Missing by Design	**26**	**(5.4)**	**41**	**(8.3)**	**67**	**(6.9)**
	Discontinued due to death	1	(0.2)	0	(0.0)	1	(0.1)
	Discontinued due to progressive disease	13	(2.7)	35	(7.1)	48	(4.9)
	Discontinued due to withdrawal by subject	3	(0.6)	2	(0.4)	5	(0.5)
	Subject died	1	(0.2)	0	(0.0)	1	(0.1)
	Visit not reached	3	(0.6)	3	(0.6)	6	(0.6)
	Visit not scheduled	4	(0.8)	1	(0.2)	5	(0.5)
	Subject died, no reported disposition status	1	(0.2)	0	(0.0)	1	(0.1)

		Pembrolizumab N=484		Placebo N=493		Total N=977	
Treatment Visit	Category	n	(%)	n	(%)	n	(%)
WEEK 36	**Expected to Complete Questionnaires**	**399**	**(82.4)**	**423**	**(85.8)**	**822**	**(84.1)**
	Completed	333	(68.8)	361	(73.2)	694	(71.0)
	Compliance (% in those expected to complete questionnaires)	333	(83.5)	361	(85.3)	694	(84.4)
	Not completed	66	(13.6)	62	(12.6)	128	(13.1)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)	0	(0.0)
	Not completed due to site staff error	15	(3.1)	17	(3.4)	32	(3.3)
	Subject in hospital or hospice	1	(0.2)	0	(0.0)	1	(0.1)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	4	(0.8)	4	(0.8)	8	(0.8)
	Other	12	(2.5)	20	(4.1)	32	(3.3)
	With visit, no record	34	(7.0)	21	(4.3)	55	(5.6)
	Missing by Design	**85**	**(17.6)**	**70**	**(14.2)**	**155**	**(15.9)**
	Discontinued due to death	1	(0.2)	0	(0.0)	1	(0.1)
	Discontinued due to progressive disease	32	(6.6)	64	(13.0)	96	(9.8)
	Discontinued due to withdrawal by subject	10	(2.1)	2	(0.4)	12	(1.2)
	Subject died	1	(0.2)	0	(0.0)	1	(0.1)
	Visit not reached	18	(3.7)	3	(0.6)	21	(2.1)
	Visit not scheduled	22	(4.5)	1	(0.2)	23	(2.4)
	Subject died, no reported disposition status	1	(0.2)	0	(0.0)	1	(0.1)

		Pembrolizumab N=484		Placebo N=493		Total N=977	
Treatment Visit	Category	n	(%)	n	(%)	n	(%)
WEEK 48	**Expected to Complete Questionnaires**	**358**	**(74.0)**	**394**	**(79.9)**	**752**	**(77.0)**
	Completed	252	(52.1)	311	(63.1)	563	(57.6)
	Compliance (% in those expected to complete questionnaires)	252	(70.4)	311	(78.9)	563	(74.9)
	Not completed	106	(21.9)	83	(16.8)	189	(19.3)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)	1	(0.1)
	Not completed due to site staff error	8	(1.7)	6	(1.2)	14	(1.4)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)	0	(0.0)
	Other	9	(1.9)	13	(2.6)	22	(2.3)
	With visit, no record	89	(18.4)	63	(12.8)	152	(15.6)
	Missing by Design	**126**	**(26.0)**	**99**	**(20.1)**	**225**	**(23.0)**
	Discontinued due to death	2	(0.4)	0	(0.0)	2	(0.2)
	Discontinued due to progressive disease	48	(9.9)	84	(17.0)	132	(13.5)
	Discontinued due to withdrawal by subject	13	(2.7)	5	(1.0)	18	(1.8)
	Subject died	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not reached	28	(5.8)	7	(1.4)	35	(3.6)
	Visit not scheduled	33	(6.8)	3	(0.6)	36	(3.7)
	Subject died, no reported disposition status	2	(0.4)	0	(0.0)	2	(0.2)

Treatment Visit	Category	Pembrolizumab N=484		Placebo N=493		Total N=977	
		n	(%)	n	(%)	n	(%)
WEEK 52	**Expected to Complete Questionnaires**	**353**	**(72.9)**	**384**	**(77.9)**	**737**	**(75.4)**
	Completed	301	(62.2)	327	(66.3)	628	(64.3)
	Compliance (% in those expected to complete questionnaires)	301	(85.3)	327	(85.2)	628	(85.2)
	Not completed	52	(10.7)	57	(11.6)	109	(11.2)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)	1	(0.1)
	Not completed due to site staff error	17	(3.5)	17	(3.4)	34	(3.5)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)	1	(0.1)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)	1	(0.1)
	Subject refused for other reasons	2	(0.4)	1	(0.2)	3	(0.3)
	Other	11	(2.3)	29	(5.9)	40	(4.1)
	With visit, no record	20	(4.1)	9	(1.8)	29	(3.0)
	Missing by Design	**131**	**(27.1)**	**109**	**(22.1)**	**240**	**(24.6)**
	Discontinued due to death	2	(0.4)	0	(0.0)	2	(0.2)
	Discontinued due to progressive disease	56	(11.6)	93	(18.9)	149	(15.3)
	Discontinued due to withdrawal by subject	15	(3.1)	5	(1.0)	20	(2.0)
	Subject died	0	(0.0)	1	(0.2)	1	(0.1)
	Visit not reached	39	(8.1)	8	(1.6)	47	(4.8)
	Visit not scheduled	17	(3.5)	2	(0.4)	19	(1.9)
	Subject died, no reported disposition status	2	(0.4)	0	(0.0)	2	(0.2)

Treatment Visit	Category	Pembrolizumab N=484		Placebo N=493		Total N=977	
		n	(%)	n	(%)	n	(%)
WEEK 104	**Expected to Complete Questionnaires**	**115**	**(23.8)**	**109**	**(22.1)**	**224**	**(22.9)**
	Completed	91	(18.8)	91	(18.5)	182	(18.6)
	Compliance (% in those expected to complete questionnaires)	91	(79.1)	91	(83.5)	182	(81.3)
	Not completed	24	(5.0)	18	(3.7)	42	(4.3)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)	0	(0.0)
	Not completed due to site staff error	5	(1.0)	2	(0.4)	7	(0.7)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	1	(0.2)	1	(0.1)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	0	(0.0)	2	(0.2)
	Other	8	(1.7)	7	(1.4)	15	(1.5)
	With visit, no record	9	(1.9)	8	(1.6)	17	(1.7)
	Missing by Design	**369**	**(76.2)**	**384**	**(77.9)**	**753**	**(77.1)**
	Discontinued due to death	3	(0.6)	2	(0.4)	5	(0.5)
	Discontinued due to progressive disease	92	(19.0)	142	(28.8)	234	(24.0)
	Discontinued due to withdrawal by subject	23	(4.8)	10	(2.0)	33	(3.4)
	Subject died	0	(0.0)	0	(0.0)	0	(0.0)
	Visit not reached	246	(50.8)	230	(46.7)	476	(48.7)
	Visit not scheduled	3	(0.6)	0	(0.0)	3	(0.3)
	Subject died, no reported disposition status	2	(0.4)	0	(0.0)	2	(0.2)

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

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

Database Cutoff Date: 14DEC2020

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

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

Anhang 4-G3.1: Mortalität

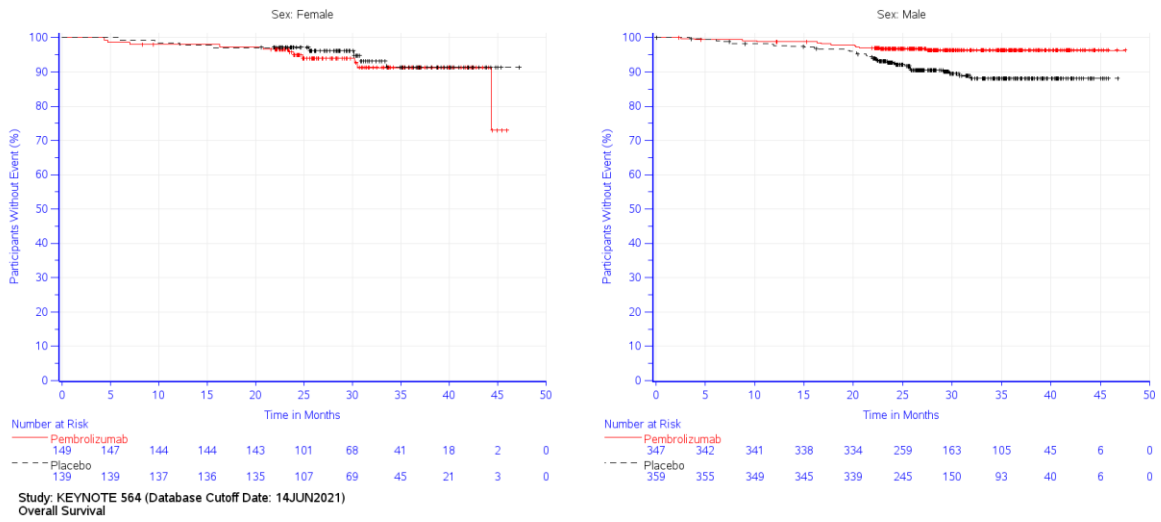

Abbildung 4G-9: Kaplan-Meier-Kurven für die Subgruppenanalyse Geschlecht für den Endpunkt Gesamtüberleben der Studie KEYNOTE 564

Anhang 4-G3.2: Morbidität

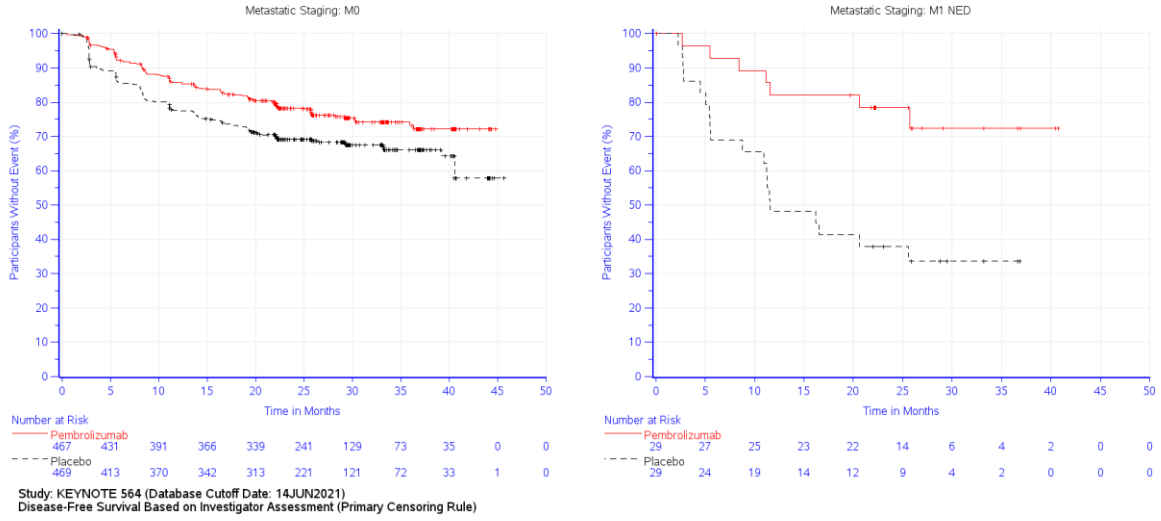

Abbildung 4G-10: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Metastasenstatus für den Endpunkt Krankheitsfreies Überleben der Studie KEYNOTE 564

Anhang 4-G3.3: Nebenwirkungen

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

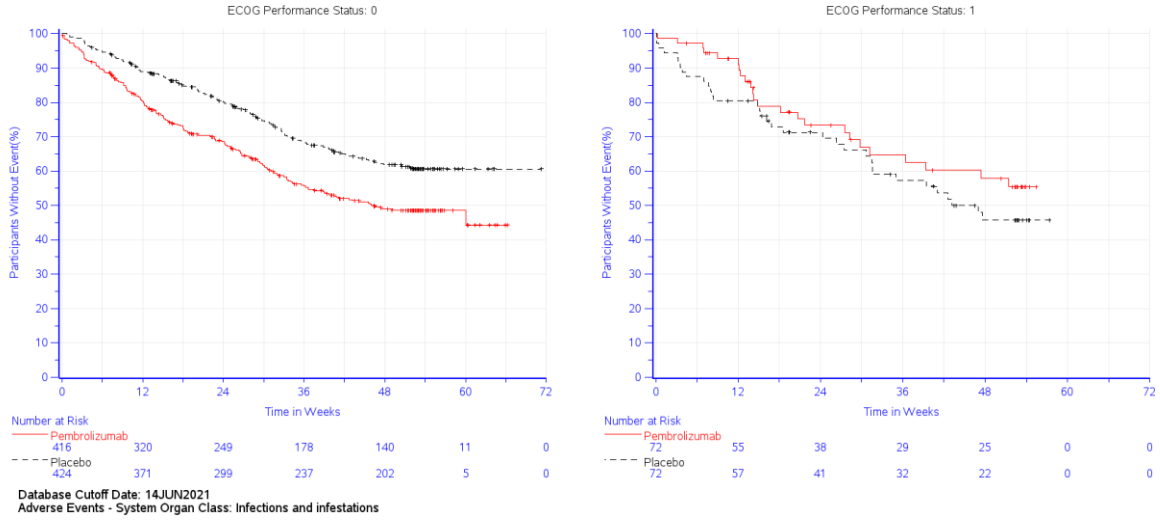

Abbildung 4G-11: Kaplan-Meier-Kurven für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC Infektionen und parasitäre Erkrankungen der Studie KEYNOTE 564

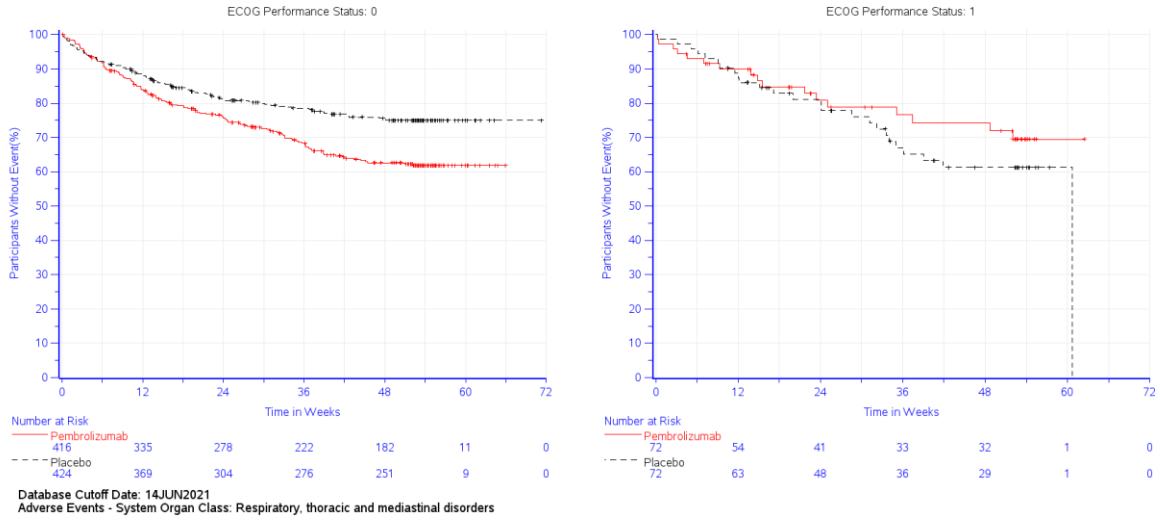

Abbildung 4G-12: Kaplan-Meier-Kurven für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC Erkrankungen der Atemwege, des Brustraums und Mediastinums der Studie KEYNOTE 564

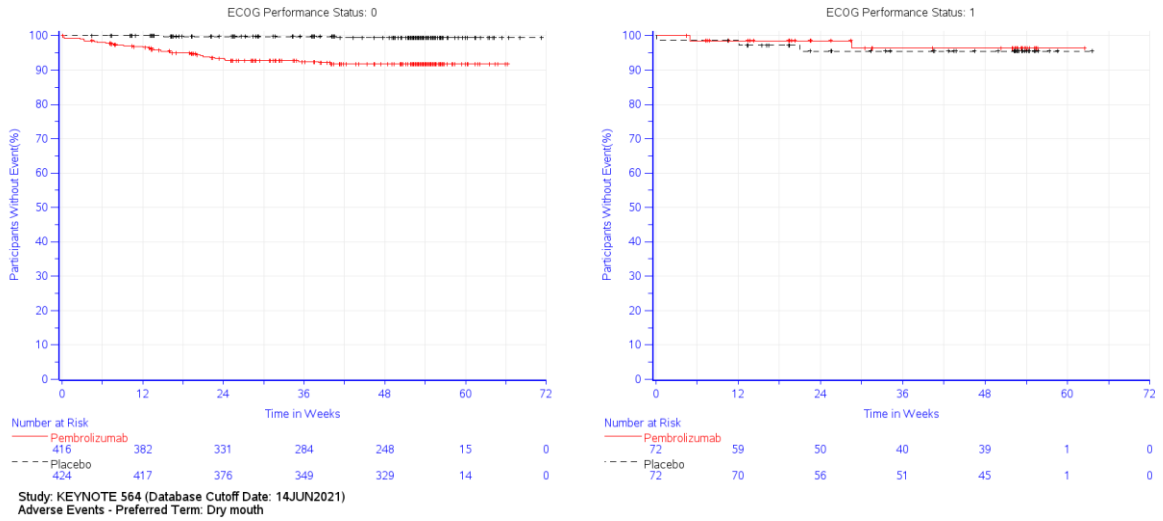

Abbildung 4G-13: Kaplan-Meier-Kurven für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT Mundtrockenheit der Studie KEYNOTE 564

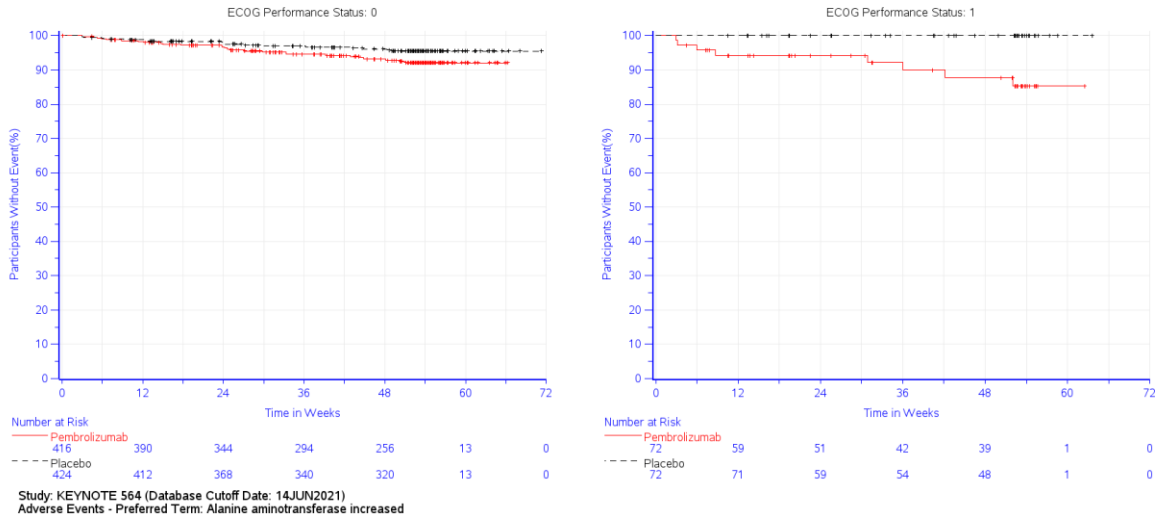

Abbildung 4G-14: Kaplan-Meier-Kurven für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT Alaninaminotransferase erhöht der Studie KEYNOTE 564

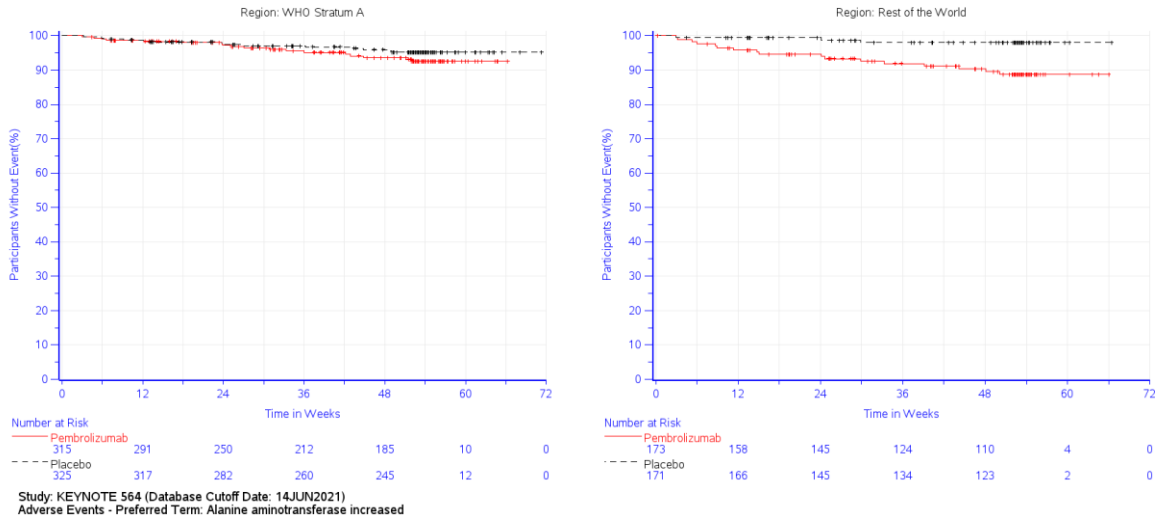

Abbildung 4G-15: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT Alaninaminotransferase erhöht der Studie KEYNOTE 564

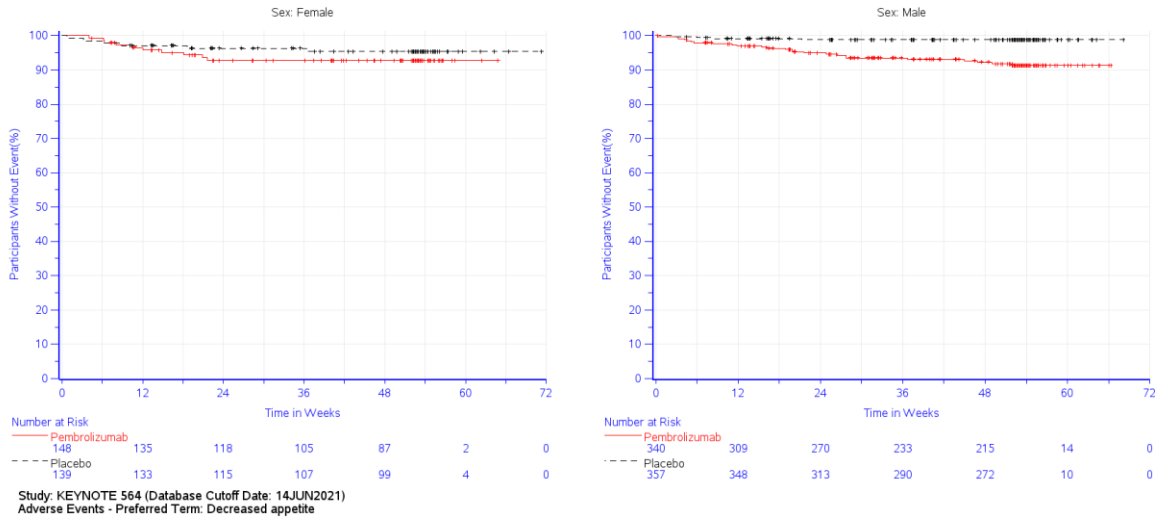

Abbildung 4G-16: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Geschlecht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT Appetit vermindert der Studie KEYNOTE 564

Anhang 4-G4: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest (p ≥ 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 ≥ 0,05) vorliegt, dargestellt.

Anhang 4-G4.1: Mortalität

Tabelle 4G-10: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 564[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]
Age									
<65	338	11 (3.3)	Not reached [-; -]	326	26 (8.0)	Not reached [-; -]	0.41 [0.20; 0.82]	0.0122	0.250
≥65	158	12 (7.6)	Not reached [44.4; -]	172	17 (9.9)	Not reached [-; -]	0.73 [0.35; 1.54]	0.4108	
ECOG Performance Status									
0	421	15 (3.6)	Not reached [-; -]	426	31 (7.3)	Not reached [-; -]	0.48 [0.26; 0.88]	0.0182	0.594
1	75	8 (10.7)	Not reached [-; -]	72	12 (16.7)	Not reached [-; -]	0.64 [0.26; 1.56]	0.3219	
Region									
WHO Stratum A	322	9 (2.8)	Not reached [44.4; -]	327	22 (6.7)	Not reached [-; -]	0.40 [0.18; 0.86]	0.0192	0.339
Rest of the World	174	14 (8.0)	Not reached [-; -]	171	21 (12.3)	Not reached [-; -]	0.66 [0.34; 1.30]	0.2325	

a: Database Cutoff Date: 14JUN2021
b: Number of participants: intention-to-treat population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization

Anhang 4-G4.2: Morbidität

Krankheitsfreies Überleben

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

Study: KEYNOTE 564[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									
Female	149	38 (25.5)	Not reached [-; -]	139	46 (33.1)	Not reached [-; -]	0.73 [0.48; 1.13]	0.1562	0.436
Male	347	76 (21.9)	Not reached [-; -]	359	123 (34.3)	Not reached [40.5; -]	0.60 [0.45; 0.80]	0.0004	
Age									
<65	338	71 (21.0)	Not reached [-; -]	326	109 (33.4)	Not reached [40.5; -]	0.58 [0.43; 0.79]	0.0004	0.307
≥65	158	43 (27.2)	Not reached [-; -]	172	60 (34.9)	Not reached [39.2; -]	0.75 [0.51; 1.11]	0.1529	
ECOG Performance Status									
0	421	91 (21.6)	Not reached [-; -]	426	141 (33.1)	Not reached [-; -]	0.61 [0.47; 0.79]	0.0002	0.363
1	75	23 (30.7)	Not reached [30.2; -]	72	28 (38.9)	40.5 [22.2; -]	0.79 [0.45; 1.37]	0.3918	
Region									
WHO Stratum A	322	73 (22.7)	Not reached [-; -]	327	112 (34.3)	Not reached [40.5; -]	0.64 [0.47; 0.86]	0.0027	0.988
Rest of the World	174	41 (23.6)	Not reached [-; -]	171	57 (33.3)	Not reached [-; -]	0.64 [0.43; 0.96]	0.0300	
Type of Nephrectomy									
Partial	37	2 (5.4)	Not reached [-; -]	38	8 (21.1)	Not reached [-; -]	0.22 [0.05; 1.04]	0.0553	0.112
Radical	459	112 (24.4)	Not reached [-; -]	460	161 (35.0)	Not reached [40.5; -]	0.66 [0.52; 0.85]	0.0009	

Study: KEYNOTE 564[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]
PD-L1 Status									
CPS<1	124	19 (15.3)	Not reached [-; -]	113	25 (22.1)	Not reached [-; -]	0.68 [0.37; 1.24]	0.2067	0.837
CPS≥1	365	93 (25.5)	Not reached [-; -]	383	143 (37.3)	40.5 [40.5; -]	0.63 [0.49; 0.82]	0.0006	
Race									
White	372	87 (23.4)	Not reached [-; -]	377	128 (34.0)	Not reached [40.5; -]	0.65 [0.50; 0.86]	0.0022	0.684
Non-White	88	19 (21.6)	Not reached [-; -]	87	30 (34.5)	Not reached [-; -]	0.57 [0.32; 1.02]	0.0572	
Baseline Disease Status by BICR									
Non-NED	19	12 (63.2)	5.6 [2.9; -]	29	26 (89.7)	4.7 [2.8; 8.2]	0.51 [0.25; 1.02]	0.0582	0.299
NED	476	101 (21.2)	Not reached [-; -]	468	143 (30.6)	Not reached [40.5; -]	0.67 [0.52; 0.86]	0.0017	

a: Database Cutoff Date: 14JUN2021

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

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

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

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

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

BICR: Blinded Independent Central Review; CI: Confidence Interval; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; NED: No Evidence of Disease; PD-L1: Programmed Cell Death - Ligand 1; WHO: World Health Organization

Zeit bis zur ersten Folgetherapie

Tabelle 4G-12: 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 564[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									
Female	149	19 (12.8)	Not reached [-; -]	139	27 (19.4)	Not reached [-; -]	0.64 [0.36; 1.16]	0.1429	0.872
Male	347	55 (15.9)	Not reached [-; -]	359	78 (21.7)	Not reached [-; -]	0.68 [0.48; 0.97]	0.0307	
Age									
<65	338	45 (13.3)	Not reached [-; -]	326	69 (21.2)	Not reached [-; -]	0.60 [0.41; 0.87]	0.0074	0.311
≥65	158	29 (18.4)	Not reached [-; -]	172	36 (20.9)	Not reached [-; -]	0.82 [0.50; 1.33]	0.4206	
ECOG Performance Status									
0	421	58 (13.8)	Not reached [-; -]	426	90 (21.1)	Not reached [-; -]	0.61 [0.44; 0.86]	0.0039	0.212
1	75	16 (21.3)	Not reached [40.0; -]	72	15 (20.8)	43.6 [43.6; -]	1.07 [0.52; 2.19]	0.8537	
Region									
WHO Stratum A	322	50 (15.5)	Not reached [-; -]	327	66 (20.2)	Not reached [-; -]	0.73 [0.51; 1.06]	0.0972	0.420
Rest of the World	174	24 (13.8)	Not reached [-; -]	171	39 (22.8)	Not reached [-; -]	0.57 [0.34; 0.95]	0.0305	

a: Database Cutoff Date: 14JUN2021
b: Number of participants: intention-to-treat population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization

Zeit bis zur ersten Folgeoperation

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

Study: KEYNOTE 564[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									
Female	149	9 (6.0)	Not reached [-; -]	139	13 (9.4)	Not reached [-; -]	0.65 [0.28; 1.52]	0.3183	0.897
Male	347	14 (4.0)	Not reached [-; -]	359	23 (6.4)	Not reached [-; -]	0.61 [0.31; 1.18]	0.1386	
Age									
<65	338	14 (4.1)	Not reached [-; -]	326	29 (8.9)	Not reached [-; -]	0.45 [0.24; 0.85]	0.0143	0.063
≥65	158	9 (5.7)	Not reached [-; -]	172	7 (4.1)	Not reached [-; -]	1.33 [0.49; 3.58]	0.5709	
ECOG Performance Status									
0	421	20 (4.8)	Not reached [-; -]	426	32 (7.5)	Not reached [-; -]	0.61 [0.35; 1.07]	0.0838	0.824
1	75	3 (4.0)	Not reached [-; -]	72	4 (5.6)	Not reached [42.3; -]	0.77 [0.17; 3.44]	0.7286	
Region									
WHO Stratum A	322	18 (5.6)	Not reached [-; -]	327	25 (7.6)	Not reached [-; -]	0.71 [0.39; 1.29]	0.2606	0.431
Rest of the World	174	5 (2.9)	Not reached [-; -]	171	11 (6.4)	Not reached [-; -]	0.44 [0.15; 1.27]	0.1298	

a: Database Cutoff Date: 14JUN2021
b: Number of participants: intention-to-treat population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30: Symptomskala Erschöpfung

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

Study: KEYNOTE 564[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							
Female							
Pembrolizumab	147	126	21.43 (18.92)	5.49 (1.34)	3.15	-	0.616
Placebo	139	121	21.76 (18.05)	2.35 (1.36)	[-0.61; 6.91]		
Male							
Pembrolizumab	337	300	17.56 (18.92)	4.44 (0.81)	2.22	0.13	
Placebo	354	322	17.63 (18.36)	2.22 (0.77)	[0.02; 4.41]	[0.00; 0.25]	
Age							
<65							
Pembrolizumab	331	291	19.01 (19.31)	4.76 (0.85)	1.62	-	0.205
Placebo	322	289	18.42 (19.72)	3.15 (0.85)	[-0.75; 3.98]		
≥65							
Pembrolizumab	153	135	18.02 (18.31)	4.69 (1.18)	4.19	0.24	
Placebo	171	154	19.41 (15.48)	0.50 (1.10)	[1.02; 7.36]	[0.06; 0.43]	
ECOG Performance Status							
0							
Pembrolizumab	414	363	17.11 (17.73)	4.71 (0.72)	2.78	0.16	0.518
Placebo	421	377	16.95 (17.30)	1.93 (0.70)	[0.81; 4.75]	[0.05; 0.28]	
1							
Pembrolizumab	70	63	27.87 (23.09)	4.81 (2.15)	1.11	-	
Placebo	72	66	29.12 (20.70)	3.70 (2.09)	[-4.82; 7.03]		

Study: KEYNOTE 564[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]
Region							
WHO Stratum A							
Pembrolizumab	311	268	18.12 (19.14)	5.86 (0.85)	3.32	0.19	0.384
Placebo	323	286	19.27 (19.46)	2.54 (0.81)	[1.02; 5.61]	[0.06; 0.32]	
Rest of the World							
Pembrolizumab	173	158	19.69 (18.72)	3.19 (1.18)	1.71	-	
Placebo	170	157	17.83 (16.15)	1.48 (1.19)	[-1.58; 5.00]		

a: Database Cutoff Date: 14DEC2020
b: Number of participants: full-analysis-set population
c: Number of participants with data available for analysis
d: Mean and SD at baseline are calculated based on number of participants with data available for analysis
e: Based on MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed
f: Standardized mean difference (Hedges' g) is only calculated if confidence interval for mean difference does not include zero
g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-15: 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 564[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							
Female							
Pembrolizumab	147	126	2.51 (7.91)	3.26 (0.82)	1.63	-	0.601
Placebo	139	121	3.72 (12.64)	1.62 (0.82)	[-0.65; 3.92]		
Male							
Pembrolizumab	337	300	1.83 (7.43)	1.48 (0.33)	1.00	0.12	

Study: KEYNOTE 564[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	354	322	1.55 (6.25)	0.47 (0.32)	[0.10; 1.90]	[0.01; 0.22]	
Age							
<65							
Pembrolizumab	331	291	2.06 (7.16)	2.44 (0.44)	1.32	0.13	0.637
Placebo	322	289	2.08 (8.53)	1.12 (0.43)	[0.12; 2.53]	[0.01; 0.25]	
≥65							
Pembrolizumab	153	135	1.98 (8.41)	1.02 (0.50)	0.81	-	
Placebo	171	154	2.27 (8.54)	0.22 (0.46)	[-0.53; 2.15]		
ECOG Performance Status							
0							
Pembrolizumab	414	363	2.07 (7.81)	2.04 (0.36)	1.39	0.14	0.520
Placebo	421	377	1.72 (7.54)	0.65 (0.35)	[0.40; 2.37]	[0.04; 0.25]	
1							
Pembrolizumab	70	63	1.85 (6.07)	2.16 (1.07)	0.43	-	
Placebo	72	66	4.55 (12.59)	1.73 (1.03)	[-2.53; 3.39]		
Region							
WHO Stratum A							
Pembrolizumab	311	268	1.68 (5.42)	1.80 (0.37)	0.78	-	0.284
Placebo	323	286	1.92 (7.72)	1.02 (0.35)	[-0.23; 1.78]		
Rest of the World							
Pembrolizumab	173	158	2.64 (10.22)	2.34 (0.65)	1.87	0.17	
Placebo	170	157	2.55 (9.84)	0.48 (0.66)	[0.05; 3.69]	[0.00; 0.33]	

a: Database Cutoff Date: 14DEC2020

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

c: Number of participants with data available for analysis

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

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

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

g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Schmerzen

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

Study: KEYNOTE 564[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							
Female							
Pembrolizumab	147	126	17.46 (22.00)	4.97 (1.42)	2.30	-	0.451
Placebo	139	121	17.36 (20.46)	2.67 (1.43)	[-1.67; 6.27]		
Male							
Pembrolizumab	337	300	15.17 (21.09)	1.30 (0.82)	0.71	-	
Placebo	354	322	12.68 (16.60)	0.59 (0.78)	[-1.51; 2.93]		
Age							
<65							
Pembrolizumab	331	291	16.38 (21.46)	2.19 (0.90)	1.00	-	0.749
Placebo	322	289	14.19 (18.44)	1.19 (0.89)	[-1.49; 3.49]		
≥65							
Pembrolizumab	153	135	14.69 (21.17)	2.73 (1.17)	1.56	-	
Placebo	171	154	13.53 (16.70)	1.17 (1.09)	[-1.59; 4.70]		
ECOG Performance Status							
0							
Pembrolizumab	414	363	13.77 (19.07)	2.49 (0.73)	1.10	-	0.821
Placebo	421	377	12.11 (16.46)	1.39 (0.71)	[-0.89; 3.09]		
1							
Pembrolizumab	70	63	27.78 (28.87)	1.33 (2.46)	1.75	-	
Placebo	72	66	24.49 (21.53)	-0.42 (2.39)	[-5.04; 8.54]		

Study: KEYNOTE 564[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]
Region							
WHO Stratum A							
Pembrolizumab	311	268	16.04 (22.20)	2.33 (0.90)	1.21	-	0.916
Placebo	323	286	14.22 (18.25)	1.12 (0.86)	[-1.25; 3.66]		
Rest of the World							
Pembrolizumab	173	158	15.51 (19.92)	2.44 (1.17)	1.18	-	
Placebo	170	157	13.48 (17.10)	1.26 (1.17)	[-2.08; 4.44]		

a: Database Cutoff Date: 14DEC2020
b: Number of participants: full-analysis-set population
c: Number of participants with data available for analysis
d: Mean and SD at baseline are calculated based on number of participants with data available for analysis
e: Based on MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed
f: Standardized mean difference (Hedges' g) is only calculated if confidence interval for mean difference does not include zero
g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Atemnot (Dyspnoe)

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

Study: KEYNOTE 564[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Dyspnea	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							
Female							
Pembrolizumab	147	126	8.47 (17.86)	4.12 (1.20)	3.28	-	0.429
Placebo	139	121	11.85 (19.18)	0.84 (1.20)	[-0.07; 6.62]		
Male							

Study: KEYNOTE 564[a]					Pembrolizumab vs. Placebo		
EORTC QLQ-C30 Dyspnea	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	337	300	9.22 (18.69)	4.39 (0.83)	1.95	-	
Placebo	354	322	7.14 (15.81)	2.44 (0.79)	[-0.30; 4.20]		
Age							
<65							
Pembrolizumab	331	291	9.62 (19.35)	3.83 (0.84)	2.06	-	0.467
Placebo	322	289	8.30 (17.13)	1.77 (0.83)	[-0.25; 4.37]		
≥65							
Pembrolizumab	153	135	7.65 (16.26)	5.69 (1.20)	3.51	0.19	
Placebo	171	154	8.66 (16.53)	2.18 (1.12)	[0.29; 6.74]	[0.02; 0.37]	
ECOG Performance Status							
0							
Pembrolizumab	414	363	8.17 (16.91)	4.30 (0.70)	3.00	0.17	0.236
Placebo	421	377	7.43 (16.06)	1.30 (0.68)	[1.08; 4.91]	[0.06; 0.28]	
1							
Pembrolizumab	70	63	13.76 (25.14)	5.38 (2.26)	0.00	-	
Placebo	72	66	14.14 (20.31)	5.37 (2.19)	[-6.23; 6.24]		
Region							
WHO Stratum A							
Pembrolizumab	311	268	9.33 (18.47)	4.78 (0.88)	3.00	0.17	0.512
Placebo	323	286	8.74 (17.36)	1.78 (0.83)	[0.63; 5.37]	[0.03; 0.30]	
Rest of the World							
Pembrolizumab	173	158	8.44 (18.41)	3.83 (1.10)	1.73	-	
Placebo	170	157	7.86 (16.08)	2.10 (1.11)	[-1.34; 4.79]		

a: Database Cutoff Date: 14DEC2020

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

c: Number of participants with data available for analysis

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

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

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

g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

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

Study: KEYNOTE 564[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							
Female							
Pembrolizumab	147	126	21.69 (26.44)	3.66 (1.66)	2.70	-	0.583
Placebo	139	121	27.55 (28.76)	0.96 (1.68)	[-1.96; 7.36]		
Male							
Pembrolizumab	337	300	16.78 (24.15)	1.77 (0.99)	1.17	-	
Placebo	354	322	18.84 (24.76)	0.60 (0.95)	[-1.54; 3.87]		
Age							
<65							
Pembrolizumab	331	291	19.24 (25.45)	2.36 (1.05)	1.16	-	0.551
Placebo	322	289	20.42 (25.35)	1.20 (1.04)	[-1.76; 4.07]		
≥65							
Pembrolizumab	153	135	16.05 (23.69)	2.54 (1.48)	3.00	-	
Placebo	171	154	22.73 (27.67)	-0.46 (1.37)	[-0.99; 6.98]		
Region							
WHO Stratum A							
Pembrolizumab	311	268	19.40 (25.90)	2.39 (1.08)	1.68	-	0.856
Placebo	323	286	21.79 (26.25)	0.70 (1.03)	[-1.25; 4.61]		
Rest of the World							
Pembrolizumab	173	158	16.24 (23.11)	2.27 (1.39)	1.70	-	
Placebo	170	157	20.17 (26.08)	0.57 (1.41)	[-2.20; 5.59]		

a: Database Cutoff Date: 14DEC2020
b: Number of participants: full-analysis-set population
c: Number of participants with data available for analysis
d: Mean and SD at baseline are calculated based on number of participants with data available for analysis
e: Based on MMRM of change from baseline with treatment, time, baseline endpoint score as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed

Study: KEYNOTE 564[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]

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

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

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

EORTC QLQ-C30: Symptomskala Appetitverlust

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

Study: KEYNOTE 564[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							
Female							
Pembrolizumab	147	126	6.08 (14.85)	1.87 (1.14)	3.77	0.23	0.497
Placebo	139	121	9.09 (19.25)	-1.90 (1.15)	[0.57; 6.96]	[0.03; 0.42]	
Male							
Pembrolizumab	337	300	5.33 (15.22)	2.55 (0.64)	2.67	0.18	
Placebo	354	322	4.14 (11.62)	-0.12 (0.62)	[0.92; 4.41]	[0.06; 0.30]	
Age							
<65							
Pembrolizumab	331	291	5.73 (15.09)	2.53 (0.69)	2.87	0.19	0.743
Placebo	322	289	5.31 (13.98)	-0.35 (0.68)	[0.97; 4.78]	[0.06; 0.32]	
≥65							
Pembrolizumab	153	135	5.19 (15.16)	2.12 (0.96)	3.42	0.22	
Placebo	171	154	5.84 (14.83)	-1.30 (0.90)	[0.82; 6.01]	[0.05; 0.39]	

Study: KEYNOTE 564[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]
ECOG Performance Status							
0							
Pembrolizumab	414	363	5.33 (14.52)	2.23 (0.58)	3.05	0.21	0.854
Placebo	421	377	4.51 (12.88)	-0.81 (0.56)	[1.46; 4.64]	[0.10; 0.31]	
1							
Pembrolizumab	70	63	6.88 (18.12)	4.18 (1.80)	4.53	-	
Placebo	72	66	11.11 (19.68)	-0.36 (1.75)	[-0.45; 9.52]		
Region							
WHO Stratum A							
Pembrolizumab	311	268	5.22 (14.91)	2.54 (0.74)	2.52	0.16	0.372
Placebo	323	286	5.13 (13.28)	0.02 (0.70)	[0.53; 4.51]	[0.03; 0.29]	
Rest of the World							
Pembrolizumab	173	158	6.12 (15.44)	2.13 (0.86)	3.99	0.27	
Placebo	170	157	6.16 (15.93)	-1.86 (0.87)	[1.57; 6.40]	[0.11; 0.43]	

a: Database Cutoff Date: 14DEC2020

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

c: Number of participants with data available for analysis

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

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

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

g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Symptomskala Verstopfung

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

Study: KEYNOTE 564[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]
Age							
<65							
Pembrolizumab	331	291	7.45 (15.72)	0.73 (0.74)	-0.78	-	0.096
Placebo	322	289	6.00 (14.52)	1.51 (0.73)	[-2.82; 1.26]		
≥65							
Pembrolizumab	153	135	11.11 (21.16)	0.45 (1.21)	2.43	-	
Placebo	171	154	11.69 (19.63)	-1.98 (1.13)	[-0.84; 5.70]		
ECOG Performance Status							
0							
Pembrolizumab	414	363	8.45 (17.23)	0.22 (0.66)	-0.05	-	0.357
Placebo	421	377	7.43 (16.42)	0.27 (0.64)	[-1.87; 1.76]		
1							
Pembrolizumab	70	63	9.52 (20.24)	3.02 (2.03)	2.28	-	
Placebo	72	66	11.11 (17.86)	0.74 (1.97)	[-3.34; 7.89]		
Region							
WHO Stratum A							
Pembrolizumab	311	268	8.33 (18.50)	0.41 (0.82)	0.13	-	0.832
Placebo	323	286	8.28 (16.91)	0.28 (0.78)	[-2.10; 2.35]		
Rest of the World							
Pembrolizumab	173	158	9.07 (16.25)	1.07 (0.99)	0.70	-	
Placebo	170	157	7.43 (16.28)	0.37 (1.00)	[-2.08; 3.47]		

a: Database Cutoff Date: 14DEC2020

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

c: Number of participants with data available for analysis

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

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

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

Study: KEYNOTE 564[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]
g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization							

EORTC QLQ-C30: Symptomskala Diarrhoe

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

Study: KEYNOTE 564[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							
Female							
Pembrolizumab	147	126	4.50 (12.89)	2.51 (1.13)	0.55	-	0.978
Placebo	139	121	4.96 (11.91)	1.96 (1.13)	[-2.60; 3.70]		
Male							
Pembrolizumab	337	300	4.22 (11.43)	3.77 (0.69)	0.58	-	
Placebo	354	322	3.62 (10.72)	3.19 (0.66)	[-1.30; 2.47]		
Age							
<65							
Pembrolizumab	331	291	3.89 (11.42)	3.77 (0.74)	0.01	-	0.346
Placebo	322	289	3.58 (10.70)	3.76 (0.73)	[-2.04; 2.06]		
≥65							
Pembrolizumab	153	135	5.19 (12.79)	2.62 (0.93)	1.69	-	
Placebo	171	154	4.76 (11.70)	0.92 (0.87)	[-0.82; 4.20]		

Study: KEYNOTE 564[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]
ECOG Performance Status							
0							
Pembrolizumab	414	363	4.04 (11.44)	3.58 (0.63)	1.00	-	0.204
Placebo	421	377	3.80 (10.89)	2.58 (0.61)	[-0.71; 2.71]		
1							
Pembrolizumab	70	63	5.82 (14.09)	2.35 (1.68)	-1.96	-	
Placebo	72	66	5.05 (12.04)	4.31 (1.63)	[-6.58; 2.66]		
Region							
WHO Stratum A							
Pembrolizumab	311	268	4.98 (12.58)	4.30 (0.78)	0.62	-	0.985
Placebo	323	286	3.73 (10.53)	3.68 (0.74)	[-1.49; 2.73]		
Rest of the World							
Pembrolizumab	173	158	3.16 (10.50)	1.88 (0.86)	0.65	-	
Placebo	170	157	4.46 (11.99)	1.23 (0.87)	[-1.76; 3.06]		

a: Database Cutoff Date: 14DEC2020

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

c: Number of participants with data available for analysis

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

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

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

g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

FKSI-DRS

Tabelle 4G-22: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den FKSI-DRS aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 564[a]					Pembrolizumab vs. Placebo		
FKSI DRS	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							
Female							
Pembrolizumab	147	125	32.21 (3.61)	-1.22 (0.27)	-0.57	-	0.749
Placebo	139	120	32.23 (3.67)	-0.65 (0.27)	[-1.31; 0.17]		
Male							
Pembrolizumab	336	298	33.13 (3.43)	-1.05 (0.16)	-0.71	-0.21	
Placebo	354	320	33.05 (3.35)	-0.35 (0.15)	[-1.14; -0.27]	[-0.34; -0.08]	
Age							
<65							
Pembrolizumab	330	288	32.97 (3.36)	-1.19 (0.17)	-0.70	-0.20	0.819
Placebo	322	289	32.74 (3.60)	-0.49 (0.17)	[-1.16; -0.23]	[-0.34; -0.07]	
≥65							
Pembrolizumab	153	135	32.62 (3.79)	-0.93 (0.24)	-0.61	-	
Placebo	171	151	32.99 (3.18)	-0.32 (0.22)	[-1.25; 0.04]		
ECOG Performance Status							
0							
Pembrolizumab	413	360	33.24 (3.23)	-1.14 (0.14)	-0.71	-0.21	0.616
Placebo	421	375	33.19 (3.13)	-0.43 (0.14)	[-1.10; -0.32]	[-0.33; -0.10]	
1							
Pembrolizumab	70	63	30.67 (4.19)	-0.84 (0.43)	-0.46	-	
Placebo	72	65	30.71 (4.41)	-0.38 (0.42)	[-1.64; 0.73]		
Region							
WHO Stratum A							
Pembrolizumab	310	267	32.77 (3.46)	-1.05 (0.16)	-0.60	-0.19	0.633
Placebo	323	283	32.76 (3.48)	-0.45 (0.15)	[-1.04; -0.17]	[-0.32; -0.05]	
Rest of the World							
Pembrolizumab	173	156	33.01 (3.59)	-1.21 (0.25)	-0.79	-0.21	
Placebo	170	157	32.96 (3.42)	-0.41 (0.25)	[-1.49; -0.09]	[-0.40; -0.02]	

Study: KEYNOTE 564[a]					Pembrolizumab vs. Placebo		
FKSI DRS	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]

a: Database Cutoff Date: 14DEC2020

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

c: Number of participants with data available for analysis

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

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

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

g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; FKSI-DRS: Functional Assessment of Cancer Therapy Kidney Symptom Index - Disease-Related Symptoms; MMRM: Mixed Model for Repeated Measures; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EQ-5D VAS

Tabelle 4G-23: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die EQ-5D VAS aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 564[a]					Pembrolizumab vs. Placebo		
EQ5D 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							
Female							
Pembrolizumab	147	133	83.08 (15.38)	-4.76 (0.97)	-0.39	-	0.564
Placebo	139	125	84.89 (14.58)	-4.37 (0.98)	[-3.11; 2.33]		
Male							
Pembrolizumab	337	303	84.50 (13.33)	-2.25 (0.60)	-1.31	-	
Placebo	354	329	82.58 (14.41)	-0.94 (0.58)	[-2.94; 0.33]		
Age							
<65							
Pembrolizumab	331	300	84.42 (13.37)	-3.17 (0.61)	-0.94	-	0.848
Placebo	322	295	83.81 (13.95)	-2.23 (0.61)	[-2.63; 0.75]		

Study: KEYNOTE 564[a]					Pembrolizumab vs. Placebo		
EQ5D 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]
≥65							
Pembrolizumab	153	136	83.30 (15.28)	-2.52 (0.95)	-1.19	-	
Placebo	171	159	82.11 (15.40)	-1.33 (0.88)	[-3.73; 1.36]		
ECOG Performance Status							
0							
Pembrolizumab	414	372	85.52 (12.56)	-2.95 (0.53)	-1.21	-	0.609
Placebo	421	387	84.63 (13.75)	-1.74 (0.51)	[-2.66; 0.23]		
1							
Pembrolizumab	70	64	75.64 (18.35)	-2.82 (1.57)	-0.22	-	
Placebo	72	67	75.07 (15.97)	-2.60 (1.51)	[-4.53; 4.09]		
Region							
WHO Stratum A							
Pembrolizumab	311	277	84.31 (13.53)	-3.19 (0.64)	-0.97	-	0.736
Placebo	323	296	83.34 (14.75)	-2.23 (0.62)	[-2.72; 0.78]		
Rest of the World							
Pembrolizumab	173	159	83.65 (14.78)	-2.68 (0.84)	-1.40	-	
Placebo	170	158	82.99 (14.01)	-1.28 (0.84)	[-3.74; 0.93]		

a: Database Cutoff Date: 14DEC2020

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

c: Number of participants with data available for analysis

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

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

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

g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; SD: Standard Deviation; SE: Standard Error; VAS: Visual Analog Scale; WHO: World Health Organization

Anhang 4-G4.3: Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-24: 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 564[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							
Female							
Pembrolizumab	147	126	78.24 (18.26)	-4.48 (1.18)	-2.67	-	0.684
Placebo	139	121	75.83 (19.11)	-1.81 (1.19)	[-5.98; 0.64]		
Male							
Pembrolizumab	337	300	79.72 (18.70)	-4.42 (0.77)	-3.75	-0.22	
Placebo	354	322	77.85 (16.66)	-0.67 (0.74)	[-5.85; -1.64]	[-0.34; -0.10]	
Age							
<65							
Pembrolizumab	331	291	79.70 (17.94)	-4.71 (0.78)	-2.92	-0.17	0.319
Placebo	322	289	77.85 (16.53)	-1.79 (0.78)	[-5.09; -0.75]	[-0.30; -0.04]	
≥65							
Pembrolizumab	153	135	78.40 (19.88)	-3.94 (1.15)	-4.55	-0.25	
Placebo	171	154	76.24 (18.83)	0.61 (1.07)	[-7.64; -1.47]	[-0.42; -0.08]	
ECOG Performance Status							
0							
Pembrolizumab	414	363	80.81 (17.55)	-4.29 (0.68)	-3.61	-0.21	0.587
Placebo	421	377	78.89 (16.64)	-0.68 (0.66)	[-5.47; -1.74]	[-0.32; -0.10]	
1							
Pembrolizumab	70	63	70.50 (21.73)	-4.86 (1.83)	-2.38	-	
Placebo	72	66	68.18 (18.66)	-2.48 (1.79)	[-7.46; 2.70]		
Region							
WHO Stratum A							
Pembrolizumab	311	268	78.73 (19.21)	-3.69 (0.83)	-3.66	-0.21	0.786
Placebo	323	286	76.69 (18.26)	-0.03 (0.79)	[-5.92; -1.41]	[-0.34; -0.08]	

Study: KEYNOTE 564[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]
Rest of the World							
Pembrolizumab	173	158	80.22 (17.43)	-5.71 (1.04)	-3.11	-0.18	
Placebo	170	157	78.40 (15.59)	-2.60 (1.05)	[-6.01; -0.20]	[-0.35; -0.01]	

a: Database Cutoff Date: 14DEC2020

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

c: Number of participants with data available for analysis

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

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

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

g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; QoL: Quality of Life; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-25: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 564[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							
Female							
Pembrolizumab	147	126	85.66 (15.89)	-1.99 (0.89)	-1.83	-	0.675
Placebo	139	121	84.30 (17.59)	-0.17 (0.90)	[-4.33; 0.67]		
Male							
Pembrolizumab	337	300	89.96 (14.29)	-2.02 (0.55)	-1.25	-	
Placebo	354	322	90.60 (11.68)	-0.77 (0.53)	[-2.76; 0.26]		

Study: KEYNOTE 564[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]
Age							
<65							
Pembrolizumab	331	291	89.37 (14.46)	-1.40 (0.58)	-0.88	-	0.194
Placebo	322	289	89.85 (13.33)	-0.51 (0.58)	[-2.49; 0.73]		
≥65							
Pembrolizumab	153	135	87.21 (15.73)	-3.33 (0.79)	-2.63	-0.22	
Placebo	171	154	87.06 (14.57)	-0.70 (0.73)	[-4.74; -0.51]	[-0.40; -0.04]	
ECOG Performance Status							
0							
Pembrolizumab	414	363	90.58 (12.76)	-2.07 (0.48)	-1.77	-0.15	0.209
Placebo	421	377	90.82 (11.98)	-0.30 (0.47)	[-3.08; -0.46]	[-0.27; -0.04]	
1							
Pembrolizumab	70	63	77.78 (20.67)	-1.59 (1.53)	0.52	-	
Placebo	72	66	77.78 (17.94)	-2.11 (1.49)	[-3.71; 4.76]		
Region							
WHO Stratum A							
Pembrolizumab	311	268	89.33 (15.19)	-2.28 (0.58)	-1.49	-	0.922
Placebo	323	286	89.51 (14.06)	-0.78 (0.55)	[-3.07; 0.08]		
Rest of the World							
Pembrolizumab	173	158	87.59 (14.35)	-1.62 (0.80)	-1.33	-	
Placebo	170	157	87.73 (13.34)	-0.29 (0.81)	[-3.56; 0.91]		

a: Database Cutoff Date: 14DEC2020

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

c: Number of participants with data available for analysis

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

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

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

g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-26: 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 564[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							
Female							
Pembrolizumab	147	126	87.83 (18.67)	-4.00 (1.36)	-3.14	-	0.465
Placebo	139	121	86.23 (22.53)	-0.85 (1.37)	[-6.95; 0.66]		
Male							
Pembrolizumab	337	300	88.00 (20.46)	-2.16 (0.82)	-1.78	-	
Placebo	354	322	88.56 (17.58)	-0.38 (0.79)	[-4.02; 0.46]		
Age							
<65							
Pembrolizumab	331	291	87.06 (21.18)	-1.90 (0.87)	-1.48	-	0.244
Placebo	322	289	87.14 (20.10)	-0.42 (0.86)	[-3.88; 0.91]		
≥65							
Pembrolizumab	153	135	89.88 (16.80)	-4.39 (1.23)	-3.77	-0.21	
Placebo	171	154	89.39 (16.92)	-0.62 (1.14)	[-7.07; -0.48]	[-0.39; -0.03]	
ECOG Performance Status							
0							
Pembrolizumab	414	363	89.72 (17.82)	-2.56 (0.73)	-2.48	-0.14	0.573
Placebo	421	377	89.52 (17.49)	-0.08 (0.71)	[-4.47; -0.49]	[-0.25; -0.03]	
1							
Pembrolizumab	70	63	77.78 (27.27)	-3.37 (2.19)	-0.93	-	
Placebo	72	66	78.79 (24.56)	-2.45 (2.13)	[-6.97; 5.12]		
Region							
WHO Stratum A							
Pembrolizumab	311	268	86.57 (21.92)	-2.50 (0.91)	-2.28	-	0.992
Placebo	323	286	87.06 (20.27)	-0.22 (0.87)	[-4.75; 0.18]		
Rest of the World							
Pembrolizumab	173	158	90.30 (15.76)	-3.11 (1.12)	-2.29	-	
Placebo	170	157	89.49 (16.59)	-0.82 (1.13)	[-5.42; 0.85]		

Study: KEYNOTE 564[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]

a: Database Cutoff Date: 14DEC2020

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

c: Number of participants with data available for analysis

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

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

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

g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

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

Study: KEYNOTE 564[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							
Female							
Pembrolizumab	147	126	81.68 (19.89)	-2.65 (1.27)	-1.81	-	0.873
Placebo	139	121	80.72 (21.36)	-0.84 (1.28)	[-5.36; 1.74]		
Male							
Pembrolizumab	337	300	86.44 (16.37)	-1.90 (0.73)	-2.10	-0.13	
Placebo	354	322	85.79 (16.13)	0.20 (0.70)	[-4.09; -0.11]	[-0.26; -0.01]	
Age							
<65							
Pembrolizumab	331	291	84.22 (18.31)	-2.69 (0.82)	-1.60	-	0.512
Placebo	322	289	83.56 (18.75)	-1.10 (0.82)	[-3.88; 0.69]		

Study: KEYNOTE 564[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]
≥65							
Pembrolizumab	153	135	86.79 (15.88)	-0.85 (0.92)	-2.68	-0.19	
Placebo	171	154	85.98 (15.91)	1.82 (0.86)	[-5.16; -0.19]	[-0.37; -0.01]	
ECOG Performance Status							
0							
Pembrolizumab	414	363	86.16 (16.10)	-1.94 (0.68)	-1.51	-	0.112
Placebo	421	377	85.48 (16.93)	-0.44 (0.66)	[-3.38; 0.36]		
1							
Pembrolizumab	70	63	78.57 (23.65)	-3.18 (1.77)	-5.25	-0.29	
Placebo	72	66	78.28 (21.43)	2.08 (1.72)	[-10.15; -0.36]	[-0.57; -0.02]	
Region							
WHO Stratum A							
Pembrolizumab	311	268	85.45 (16.94)	-2.11 (0.77)	-2.54	-0.16	0.570
Placebo	323	286	84.15 (17.22)	0.43 (0.73)	[-4.62; -0.46]	[-0.30; -0.03]	
Rest of the World							
Pembrolizumab	173	158	84.34 (18.70)	-2.31 (1.10)	-1.53	-	
Placebo	170	157	84.87 (18.94)	-0.78 (1.11)	[-4.61; 1.55]		

a: Database Cutoff Date: 14DEC2020

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

c: Number of participants with data available for analysis

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

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

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

g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-28: 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 564[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							
Female							
Pembrolizumab	147	126	90.08 (13.20)	-5.42 (1.23)	-2.49	-	0.542
Placebo	139	121	89.26 (17.19)	-2.92 (1.24)	[-5.93; 0.94]		
Male							
Pembrolizumab	337	300	92.33 (13.51)	-3.27 (0.67)	-1.47	-	
Placebo	354	322	90.89 (13.79)	-1.80 (0.65)	[-3.30; 0.36]		
Age							
<65							
Pembrolizumab	331	291	91.75 (14.00)	-4.37 (0.75)	-1.95	-	0.809
Placebo	322	289	90.60 (15.87)	-2.42 (0.75)	[-4.04; 0.13]		
≥65							
Pembrolizumab	153	135	91.48 (12.19)	-2.90 (0.97)	-1.46	-	
Placebo	171	154	90.15 (12.58)	-1.44 (0.91)	[-4.08; 1.16]		
ECOG Performance Status							
0							
Pembrolizumab	414	363	92.38 (12.39)	-3.88 (0.63)	-1.94	-0.13	0.601
Placebo	421	377	91.25 (14.18)	-1.94 (0.61)	[-3.65; -0.23]	[-0.24; -0.02]	
1							
Pembrolizumab	70	63	87.57 (17.95)	-4.11 (1.83)	-1.09	-	
Placebo	72	66	85.86 (17.36)	-3.02 (1.78)	[-6.15; 3.97]		
Region							
WHO Stratum A							
Pembrolizumab	311	268	92.35 (13.32)	-4.05 (0.74)	-1.88	-	0.956
Placebo	323	286	90.73 (15.12)	-2.17 (0.70)	[-3.88; 0.11]		
Rest of the World							
Pembrolizumab	173	158	90.51 (13.61)	-3.79 (1.03)	-1.79	-	
Placebo	170	157	89.92 (14.22)	-2.00 (1.04)	[-4.66; 1.08]		

Study: KEYNOTE 564[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]

a: Database Cutoff Date: 14DEC2020

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

c: Number of participants with data available for analysis

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

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

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

g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

EORTC QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-29: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Soziale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 564[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							
Female							
Pembrolizumab	147	126	90.74 (16.67)	-2.20 (1.19)	-1.93	-	0.327
Placebo	139	121	87.88 (20.07)	-0.27 (1.20)	[-5.26; 1.40]		
Male							
Pembrolizumab	337	300	90.06 (17.35)	-2.75 (0.82)	-3.92	-0.22	
Placebo	354	322	88.98 (18.47)	1.17 (0.79)	[-6.16; -1.68]	[-0.35; -0.10]	
Age							
<65							
Pembrolizumab	331	291	89.29 (18.23)	-2.62 (0.88)	-3.01	-0.16	0.690
Placebo	322	289	87.54 (20.00)	0.38 (0.87)	[-5.44; -0.57]	[-0.30; -0.03]	

Study: KEYNOTE 564[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]
≥65							
Pembrolizumab	153	135	92.35 (14.36)	-2.31 (1.00)	-3.67	-0.24	
Placebo	171	154	90.80 (16.51)	1.36 (0.93)	[-6.36; -0.98]	[-0.42; -0.07]	
ECOG Performance Status							
0							
Pembrolizumab	414	363	91.32 (15.78)	-1.97 (0.68)	-3.49	-0.21	0.457
Placebo	421	377	89.43 (18.10)	1.52 (0.67)	[-5.36; -1.61]	[-0.33; -0.10]	
1							
Pembrolizumab	70	63	84.13 (22.68)	-5.40 (2.16)	-1.36	-	
Placebo	72	66	84.34 (22.62)	-4.04 (2.10)	[-7.31; 4.60]		
Region							
WHO Stratum A							
Pembrolizumab	311	268	90.11 (17.86)	-2.89 (0.86)	-3.19	-0.18	0.684
Placebo	323	286	88.34 (19.20)	0.30 (0.82)	[-5.52; -0.86]	[-0.32; -0.05]	
Rest of the World							
Pembrolizumab	173	158	90.51 (15.89)	-2.13 (1.07)	-3.76	-0.22	
Placebo	170	157	89.28 (18.39)	1.64 (1.08)	[-6.76; -0.76]	[-0.40; -0.05]	

a: Database Cutoff Date: 14DEC2020

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

c: Number of participants with data available for analysis

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

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

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

g: Based on MMRM of change from baseline with treatment, time, baseline endpoint score and subgroup 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; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

Anhang 4-G4.4: Nebenwirkungen

Unerwünschte Ereignisse Gesamtraten

Unerwünschte Ereignisse gesamt

Tabelle 4G-30: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 564[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Adverse Events	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Sex									
Female	148	148 (100.0)	2.9 [2.1; 3.1]	139	130 (93.5)	3.4 [3.1; 5.0]	1.75 [1.37; 2.23]	< 0.001	0.194
Male	340	322 (94.7)	3.1 [2.6; 3.3]	357	323 (90.5)	5.3 [3.7; 6.3]	1.40 [1.20; 1.63]	< 0.001	
Age									
<65	333	322 (96.7)	2.9 [2.3; 3.1]	324	294 (90.7)	5.1 [3.6; 6.1]	1.56 [1.33; 1.83]	< 0.001	0.225
≥65	155	148 (95.5)	3.1 [2.9; 3.3]	172	159 (92.4)	3.7 [3.1; 5.3]	1.31 [1.05; 1.64]	0.018	
ECOG Performance Status									
0	416	403 (96.9)	3.0 [2.6; 3.1]	424	384 (90.6)	5.0 [3.6; 6.1]	1.53 [1.33; 1.76]	< 0.001	0.203
1	72	67 (93.1)	3.1 [2.9; 3.4]	72	69 (95.8)	3.4 [3.1; 5.3]	1.19 [0.85; 1.67]	0.313	
Region									
WHO Stratum A	315	305 (96.8)	2.1 [1.6; 2.9]	325	308 (94.8)	3.3 [3.1; 4.1]	1.48 [1.26; 1.73]	< 0.001	0.944
Rest of the World	173	165 (95.4)	4.9 [3.3; 6.3]	171	145 (84.8)	7.7 [5.7; 10.1]	1.58 [1.26; 1.99]	< 0.001	

a: Database Cutoff Date: 14JUN2021
b: Number of participants: all-participants-as-treated population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero events in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-31: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 564[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Serious Adverse Events	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Sex									
Female	148	32 (21.6)	Not reached [66.4; -]	139	10 (7.2)	Not reached [-; -]	3.27 [1.61; 6.65]	0.001	0.088
Male	340	69 (20.3)	Not reached [-; -]	357	47 (13.2)	Not reached [-; -]	1.65 [1.14; 2.39]	0.008	
Age									
<65	333	63 (18.9)	Not reached [-; -]	324	30 (9.3)	Not reached [-; -]	2.15 [1.39; 3.33]	< 0.001	0.518
≥65	155	38 (24.5)	Not reached [-; -]	172	27 (15.7)	Not reached [-; -]	1.74 [1.06; 2.85]	0.028	
ECOG Performance Status									
0	416	79 (19.0)	Not reached [-; -]	424	44 (10.4)	Not reached [-; -]	1.95 [1.35; 2.82]	< 0.001	0.936
1	72	22 (30.6)	66.4 [66.4; -]	72	13 (18.1)	Not reached [-; -]	1.85 [0.93; 3.68]	0.079	
Region									
WHO Stratum A	315	74 (23.5)	Not reached [-; -]	325	40 (12.3)	Not reached [-; -]	2.11 [1.44; 3.10]	< 0.001	0.436
Rest of the World	173	27 (15.6)	Not reached [-; -]	171	17 (9.9)	Not reached [-; -]	1.59 [0.86; 2.91]	0.137	

a: Database Cutoff Date: 14JUN2021

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

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

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

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

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

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

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

Tabelle 4G-32: 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 564[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Sex									
Female	148	52 (35.1)	Not reached [-; -]	139	21 (15.1)	Not reached [-; -]	2.68 [1.62; 4.46]	< 0.001	0.258
Male	340	105 (30.9)	Not reached [-; -]	357	67 (18.8)	83.9 [-; -]	1.86 [1.37; 2.54]	< 0.001	
Age									
<65	333	104 (31.2)	Not reached [-; -]	324	45 (13.9)	Not reached [-; -]	2.54 [1.79; 3.60]	< 0.001	0.074
≥65	155	53 (34.2)	Not reached [63.0; -]	172	43 (25.0)	83.9 [-; -]	1.58 [1.05; 2.37]	0.027	
ECOG Performance Status									
0	416	128 (30.8)	Not reached [-; -]	424	69 (16.3)	83.9 [-; -]	2.14 [1.60; 2.87]	< 0.001	0.558
1	72	29 (40.3)	Not reached [35.9; -]	72	19 (26.4)	Not reached [-; -]	1.79 [1.00; 3.20]	0.049	
Region									
WHO Stratum A	315	112 (35.6)	Not reached [-; -]	325	60 (18.5)	83.9 [-; -]	2.29 [1.67; 3.15]	< 0.001	0.268
Rest of the World	173	45 (26.0)	Not reached [-; -]	171	28 (16.4)	Not reached [-; -]	1.66 [1.04; 2.66]	0.035	

a: Database Cutoff Date: 14JUN2021

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

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

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

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

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

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

Therapieabbruch wegen unerwünschter Ereignisse

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

Study: KEYNOTE 564[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Adverse Events Leading to Treatment Discontinuation	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Sex									
Female	148	33 (22.3)	Not reached [-; -]	139	4 (2.9)	Not reached [-; -]	8.51 [3.02; 24.04]	< 0.001	0.644
Male	340	70 (20.6)	Not reached [-; -]	357	7 (2.0)	Not reached [-; -]	11.47 [5.27; 24.94]	< 0.001	
Age									
<65	333	60 (18.0)	Not reached [-; -]	324	6 (1.9)	Not reached [-; -]	10.40 [4.49; 24.07]	< 0.001	0.915
≥65	155	43 (27.7)	Not reached [-; -]	172	5 (2.9)	Not reached [-; -]	10.94 [4.33; 27.63]	< 0.001	
ECOG Performance Status									
0	416	83 (20.0)	Not reached [-; -]	424	7 (1.7)	Not reached [-; -]	13.18 [6.09; 28.50]	< 0.001	0.243
1	72	20 (27.8)	Not reached [-; -]	72	4 (5.6)	Not reached [-; -]	5.58 [1.91; 16.33]	0.002	
Region									
WHO Stratum A	315	76 (24.1)	Not reached [-; -]	325	9 (2.8)	Not reached [-; -]	9.78 [4.90; 19.52]	< 0.001	0.665
Rest of the World	173	27 (15.6)	Not reached [-; -]	171	2 (1.2)	Not reached [-; -]	13.82 [3.29; 58.13]	< 0.001	

a: Database Cutoff Date: 14JUN2021

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

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

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

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

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

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

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-34: 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 564[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Adverse Events	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
SOC[g]: Endocrine disorders									
Sex									
Female	148	56 (37.8)	Not reached [-; -]	139	7 (5.0)	Not reached [-; -]	9.70 [4.42; 21.30]	< 0.001	0.423
Male	340	76 (22.4)	Not reached [-; -]	357	14 (3.9)	Not reached [-; -]	6.70 [3.79; 11.85]	< 0.001	
Age									
<65	333	91 (27.3)	Not reached [-; -]	324	15 (4.6)	Not reached [-; -]	7.10 [4.11; 12.26]	< 0.001	0.566
≥65	155	41 (26.5)	60.9 [60.9; -]	172	6 (3.5)	Not reached [-; -]	9.56 [4.05; 22.56]	< 0.001	
ECOG Performance Status									
0	416	113 (27.2)	Not reached [-; -]	424	18 (4.2)	Not reached [-; -]	7.67 [4.66; 12.61]	< 0.001	0.926
1	72	19 (26.4)	Not reached [-; -]	72	3 (4.2)	Not reached [-; -]	8.16 [2.41; 27.62]	< 0.001	
Region									
WHO Stratum A	315	83 (26.3)	Not reached [60.9; -]	325	11 (3.4)	Not reached [-; -]	9.66 [5.15; 18.13]	< 0.001	0.259
Rest of the World	173	49 (28.3)	Not reached [-; -]	171	10 (5.8)	Not reached [-; -]	5.62 [2.85; 11.10]	< 0.001	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC[g]: Gastrointestinal disorders									
Sex									
Female	148	92 (62.2)	20.6 [12.3; 25.1]	139	73 (52.5)	36.0 [22.3; -]	1.38 [1.02; 1.88]	0.038	0.782
Male	340	170 (50.0)	39.1 [26.9; -]	357	155 (43.4)	Not reached [51.0; -]	1.30 [1.05; 1.62]	0.017	
Age									
<65	333	184 (55.3)	27.0 [19.6; 40.1]	324	149 (46.0)	Not reached [37.1; -]	1.36 [1.10; 1.69]	0.005	0.719
≥65	155	78 (50.3)	36.7 [21.0; -]	172	79 (45.9)	Not reached [31.3; -]	1.29 [0.94; 1.76]	0.115	
ECOG Performance Status									
0	416	226 (54.3)	30.0 [21.1; 40.1]	424	194 (45.8)	Not reached [40.1; -]	1.36 [1.12; 1.65]	0.002	0.691
1	72	36 (50.0)	32.3 [9.6; -]	72	34 (47.2)	Not reached [17.1; -]	1.22 [0.76; 1.95]	0.406	
Region									
WHO Stratum A	315	191 (60.6)	17.4 [12.3; 23.4]	325	170 (52.3)	37.1 [24.3; -]	1.41 [1.15; 1.73]	0.001	0.550
Rest of the World	173	71 (41.0)	Not reached [41.4; -]	171	58 (33.9)	Not reached [-; -]	1.27 [0.90; 1.80]	0.178	
SOC[g]: General disorders and administration site conditions									
Sex									
Female	148	84 (56.8)	21.1 [15.6; 47.3]	139	59 (42.4)	Not reached [36.1; -]	1.56 [1.12; 2.18]	0.009	0.272
Male	340	167 (49.1)	40.4 [28.1; -]	357	156 (43.7)	Not reached [42.9; -]	1.24 [1.00; 1.55]	0.051	
Age									
<65	333	179 (53.8)	32.1 [21.6; 45.0]	324	144 (44.4)	Not reached [43.3; -]	1.35 [1.08; 1.68]	0.008	0.780
≥65	155	72 (46.5)	49.1 [21.0; -]	172	71 (41.3)	Not reached [37.7; -]	1.27 [0.92; 1.77]	0.148	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
ECOG Performance Status									
0	416	215 (51.7)	35.9 [24.9; 52.0]	424	186 (43.9)	Not reached [47.3; -]	1.33 [1.09; 1.62]	0.005	0.953
1	72	36 (50.0)	31.9 [16.6; -]	72	29 (40.3)	Not reached [29.7; -]	1.35 [0.83; 2.20]	0.233	
Region									
WHO Stratum A	315	184 (58.4)	21.0 [16.7; 31.9]	325	165 (50.8)	42.7 [27.4; -]	1.33 [1.08; 1.65]	0.007	0.806
Rest of the World	173	67 (38.7)	Not reached [53.1; -]	171	50 (29.2)	Not reached [-; -]	1.41 [0.98; 2.04]	0.064	
SOC[g]: Hepatobiliary disorders									
Sex									
Female	148	8 (5.4)	Not reached [-; -]	139	2 (1.4)	Not reached [-; -]	4.07 [0.86; 19.19]	0.076	0.554
Male	340	17 (5.0)	Not reached [-; -]	357	8 (2.2)	Not reached [-; -]	2.44 [1.05; 5.65]	0.038	
Age									
<65	333	16 (4.8)	Not reached [-; -]	324	8 (2.5)	Not reached [-; -]	2.06 [0.88; 4.81]	0.096	0.228
≥65	155	9 (5.8)	Not reached [-; -]	172	2 (1.2)	Not reached [-; -]	5.91 [1.27; 27.40]	0.023	
ECOG Performance Status									
0	416	20 (4.8)	Not reached [-; -]	424	7 (1.7)	Not reached [-; -]	3.20 [1.35; 7.57]	0.008	0.553
1	72	5 (6.9)	Not reached [-; -]	72	3 (4.2)	Not reached [-; -]	1.78 [0.43; 7.47]	0.428	
Region									
WHO Stratum A	315	14 (4.4)	Not reached [-; -]	325	7 (2.2)	Not reached [-; -]	2.27 [0.92; 5.63]	0.076	0.538
Rest of the World	173	11 (6.4)	Not reached [-; -]	171	3 (1.8)	Not reached [-; -]	3.80 [1.06; 13.61]	0.041	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC[g]: Infections and infestations									
Sex									
Female	148	70 (47.3)	42.7 [31.1; -]	139	56 (40.3)	Not reached [41.6; -]	1.32 [0.93; 1.87]	0.126	0.725
Male	340	145 (42.6)	Not reached [39.3; -]	357	126 (35.3)	Not reached [-; -]	1.43 [1.12; 1.81]	0.004	
Age									
<65	333	154 (46.2)	45.6 [34.6; -]	324	117 (36.1)	Not reached [-; -]	1.48 [1.16; 1.88]	0.002	0.412
≥65	155	61 (39.4)	60.0 [39.3; -]	172	65 (37.8)	Not reached [47.6; -]	1.22 [0.86; 1.74]	0.257	
Region									
WHO Stratum A	315	155 (49.2)	36.6 [29.9; 47.4]	325	133 (40.9)	Not reached [47.3; -]	1.47 [1.17; 1.86]	0.001	0.556
Rest of the World	173	60 (34.7)	Not reached [-; -]	171	49 (28.7)	Not reached [-; -]	1.30 [0.89; 1.89]	0.179	
SOC[g]: Investigations									
Sex									
Female	148	55 (37.2)	Not reached [51.1; -]	139	30 (21.6)	Not reached [-; -]	2.05 [1.31; 3.20]	0.002	0.213
Male	340	107 (31.5)	Not reached [-; -]	357	86 (24.1)	Not reached [-; -]	1.45 [1.09; 1.93]	0.010	
Age									
<65	333	114 (34.2)	Not reached [-; -]	324	82 (25.3)	Not reached [-; -]	1.49 [1.12; 1.98]	0.006	0.388
≥65	155	48 (31.0)	Not reached [-; -]	172	34 (19.8)	Not reached [-; -]	1.87 [1.20; 2.90]	0.005	
ECOG Performance Status									
0	416	134 (32.2)	Not reached [-; -]	424	94 (22.2)	Not reached [-; -]	1.64 [1.26; 2.14]	< 0.001	0.668
1	72	28 (38.9)	Not reached [33.4; -]	72	22 (30.6)	Not reached [-; -]	1.45 [0.83; 2.54]	0.192	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Region									
WHO Stratum A	315	106 (33.7)	Not reached [-; -]	325	86 (26.5)	Not reached [-; -]	1.46 [1.10; 1.94]	0.009	0.238
Rest of the World	173	56 (32.4)	Not reached [-; -]	171	30 (17.5)	Not reached [-; -]	2.03 [1.30; 3.16]	0.002	
SOC[g]: Musculoskeletal and connective tissue disorders									
Sex									
Female	148	80 (54.1)	29.0 [20.9; 52.9]	139	63 (45.3)	Not reached [33.1; -]	1.41 [1.01; 1.96]	0.043	0.369
Male	340	151 (44.4)	53.0 [36.1; -]	357	146 (40.9)	Not reached [-; -]	1.17 [0.93; 1.47]	0.167	
Age									
<65	333	162 (48.6)	41.9 [32.1; -]	324	138 (42.6)	Not reached [44.9; -]	1.27 [1.02; 1.60]	0.036	0.727
≥65	155	69 (44.5)	53.0 [25.9; -]	172	71 (41.3)	Not reached [37.1; -]	1.18 [0.85; 1.64]	0.330	
ECOG Performance Status									
0	416	193 (46.4)	52.9 [37.0; -]	424	178 (42.0)	Not reached [52.4; -]	1.21 [0.99; 1.49]	0.062	0.514
1	72	38 (52.8)	25.0 [18.0; -]	72	31 (43.1)	Not reached [26.1; -]	1.43 [0.89; 2.30]	0.141	
Region									
WHO Stratum A	315	176 (55.9)	29.0 [22.6; 38.7]	325	169 (52.0)	39.1 [28.9; -]	1.22 [0.99; 1.51]	0.066	0.429
Rest of the World	173	55 (31.8)	Not reached [-; -]	171	40 (23.4)	Not reached [-; -]	1.46 [0.97; 2.20]	0.068	
SOC[g]: Nervous system disorders									
Sex									
Female	148	61 (41.2)	Not reached [44.1; -]	139	35 (25.2)	Not reached [-; -]	1.82 [1.20; 2.76]	0.005	0.088
Male	340	92 (27.1)	Not reached [-; -]	357	88 (24.6)	Not reached [-; -]	1.18 [0.88; 1.58]	0.274	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age									
<65	333	116 (34.8)	Not reached [-; -]	324	87 (26.9)	Not reached [-; -]	1.38 [1.05; 1.82]	0.023	0.740
≥65	155	37 (23.9)	Not reached [-; -]	172	36 (20.9)	Not reached [-; -]	1.26 [0.80; 2.00]	0.317	
ECOG Performance Status									
0	416	134 (32.2)	Not reached [-; -]	424	102 (24.1)	Not reached [-; -]	1.45 [1.12; 1.88]	0.005	0.234
1	72	19 (26.4)	Not reached [-; -]	72	21 (29.2)	Not reached [-; -]	0.96 [0.52; 1.79]	0.909	
Region									
WHO Stratum A	315	110 (34.9)	Not reached [-; -]	325	95 (29.2)	Not reached [-; -]	1.31 [1.00; 1.73]	0.053	0.502
Rest of the World	173	43 (24.9)	Not reached [-; -]	171	28 (16.4)	Not reached [-; -]	1.60 [1.00; 2.58]	0.052	
SOC[g]: Respiratory, thoracic and mediastinal disorders									
Sex									
Female	148	59 (39.9)	Not reached [42.0; -]	139	32 (23.0)	Not reached [-; -]	1.97 [1.28; 3.03]	0.002	0.069
Male	340	100 (29.4)	Not reached [-; -]	357	92 (25.8)	Not reached [60.7; -]	1.22 [0.92; 1.62]	0.168	
Age									
<65	333	116 (34.8)	Not reached [-; -]	324	78 (24.1)	Not reached [-; -]	1.56 [1.17; 2.08]	0.002	0.250
≥65	155	43 (27.7)	Not reached [-; -]	172	46 (26.7)	Not reached [60.7; -]	1.18 [0.78; 1.80]	0.431	
Region									
WHO Stratum A	315	122 (38.7)	Not reached [48.7; -]	325	97 (29.8)	Not reached [60.7; -]	1.49 [1.14; 1.95]	0.003	0.728
Rest of the World	173	37 (21.4)	Not reached [-; -]	171	27 (15.8)	Not reached [-; -]	1.36 [0.83; 2.23]	0.226	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC[g]: Skin and subcutaneous tissue disorders									
Sex									
Female	148	73 (49.3)	36.6 [20.1; -]	139	48 (34.5)	Not reached [54.1; -]	1.70 [1.18; 2.44]	0.005	0.436
Male	340	178 (52.4)	28.9 [21.3; 48.7]	357	115 (32.2)	60.4 [60.4; -]	2.05 [1.62; 2.59]	< 0.001	
Age									
<65	333	175 (52.6)	28.9 [22.0; 50.6]	324	101 (31.2)	60.4 [60.4; -]	2.12 [1.66; 2.71]	< 0.001	0.238
≥65	155	76 (49.0)	30.1 [18.9; -]	172	62 (36.0)	Not reached [-; -]	1.68 [1.20; 2.35]	0.003	
ECOG Performance Status									
0	416	218 (52.4)	30.1 [23.9; 47.1]	424	132 (31.1)	Not reached [60.4; -]	2.10 [1.69; 2.61]	< 0.001	0.068
1	72	33 (45.8)	27.9 [15.0; -]	72	31 (43.1)	Not reached [26.1; -]	1.30 [0.80; 2.13]	0.292	
Region									
WHO Stratum A	315	180 (57.1)	20.1 [15.3; 28.9]	325	120 (36.9)	Not reached [60.4; -]	2.03 [1.61; 2.56]	< 0.001	0.668
Rest of the World	173	71 (41.0)	57.1 [37.3; -]	171	43 (25.1)	Not reached [-; -]	1.88 [1.28; 2.74]	0.001	

a: Database Cutoff Date: 14JUN2021

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

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

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

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

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

g: A system organ class appears on this report only if its incidence ≥ 10% or (incidence ≥ 1% and in at least 10 participants) in one or more 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 the rule of 10 is not met

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; SOC: System Organ Class; WHO: World Health Organization

Tabelle 4G-35: 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 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC: Endocrine disorders - PT[g]: Adrenal insufficiency									
Sex									
Female	148	2 (1.4)	n.c.	139	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Male	340	8 (2.4)	n.c.	357	1 (0.3)	n.c.	n.c.	n.c.	
Age									
<65	333	5 (1.5)	n.c.	324	1 (0.3)	n.c.	n.c.	n.c.	n.c.
≥65	155	5 (3.2)	n.c.	172	0 (0.0)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	416	8 (1.9)	n.c.	424	0 (0.0)	n.c.	n.c.	n.c.	n.c.
1	72	2 (2.8)	n.c.	72	1 (1.4)	n.c.	n.c.	n.c.	
Region									
WHO Stratum A	315	8 (2.5)	n.c.	325	1 (0.3)	n.c.	n.c.	n.c.	n.c.
Rest of the World	173	2 (1.2)	n.c.	171	0 (0.0)	n.c.	n.c.	n.c.	
SOC: Endocrine disorders - PT[g]: Hyperthyroidism									
Sex									
Female	148	23 (15.5)	Not reached [-; -]	139	1 (0.7)	Not reached [-; -]	23.81 [3.22; 176.37]	0.002	0.153
Male	340	39 (11.5)	Not reached [-; -]	357	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age									
<65	333	45 (13.5)	Not reached [-; -]	324	1 (0.3)	Not reached [-; -]	47.62 [6.57; 345.24]	< 0.001	0.391
≥65	155	17 (11.0)	60.9 [60.9; -]	172	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
ECOG Performance Status									
0	416	54 (13.0)	Not reached [-; -]	424	1 (0.2)	Not reached [-; -]	59.73 [8.26; 431.77]	< 0.001	0.599
1	72	8 (11.1)	Not reached [-; -]	72	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.003	
Region									
WHO Stratum A	315	42 (13.3)	Not reached [-; -]	325	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.127
Rest of the World	173	20 (11.6)	Not reached [-; -]	171	1 (0.6)	Not reached [-; -]	21.13 [2.84; 157.48]	0.003	
SOC: Endocrine disorders - PT[g]: Hypothyroidism									
Sex									
Female	148	52 (35.1)	Not reached [-; -]	139	6 (4.3)	Not reached [-; -]	10.28 [4.41; 23.94]	< 0.001	0.167
Male	340	51 (15.0)	Not reached [-; -]	357	12 (3.4)	Not reached [-; -]	5.12 [2.73; 9.60]	< 0.001	
Age									
<65	333	73 (21.9)	Not reached [-; -]	324	12 (3.7)	Not reached [-; -]	6.86 [3.72; 12.63]	< 0.001	0.988
≥65	155	30 (19.4)	Not reached [-; -]	172	6 (3.5)	Not reached [-; -]	6.72 [2.80; 16.16]	< 0.001	
ECOG Performance Status									
0	416	89 (21.4)	Not reached [-; -]	424	16 (3.8)	Not reached [-; -]	6.58 [3.87; 11.21]	< 0.001	0.673
1	72	14 (19.4)	Not reached [-; -]	72	2 (2.8)	Not reached [-; -]	8.96 [2.03; 39.50]	0.004	
Region									

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
WHO Stratum A	315	61 (19.4)	Not reached [-; -]	325	10 (3.1)	Not reached [-; -]	7.56 [3.87; 14.75]	< 0.001	0.629
Rest of the World	173	42 (24.3)	Not reached [-; -]	171	8 (4.7)	Not reached [-; -]	5.87 [2.75; 12.49]	< 0.001	
SOC: Gastrointestinal disorders - PT[g]: Dry mouth									
Sex									
Female	148	9 (6.1)	Not reached [-; -]	139	2 (1.4)	Not reached [-; -]	4.40 [0.95; 20.35]	0.058	0.478
Male	340	24 (7.1)	Not reached [-; -]	357	3 (0.8)	Not reached [-; -]	9.26 [2.79; 30.75]	< 0.001	
Age									
<65	333	26 (7.8)	Not reached [-; -]	324	4 (1.2)	Not reached [-; -]	6.75 [2.36; 19.35]	< 0.001	0.824
≥65	155	7 (4.5)	Not reached [-; -]	172	1 (0.6)	Not reached [-; -]	8.56 [1.05; 69.61]	0.045	
Region									
WHO Stratum A	315	27 (8.6)	Not reached [-; -]	325	4 (1.2)	Not reached [-; -]	7.78 [2.72; 22.24]	< 0.001	0.830
Rest of the World	173	6 (3.5)	Not reached [-; -]	171	1 (0.6)	Not reached [-; -]	5.93 [0.71; 49.21]	0.099	
SOC: Gastrointestinal disorders - PT[g]: Nausea									
Sex									
Female	148	30 (20.3)	Not reached [-; -]	139	19 (13.7)	Not reached [-; -]	1.59 [0.90; 2.83]	0.112	0.553
Male	340	50 (14.7)	Not reached [-; -]	357	29 (8.1)	Not reached [-; -]	1.96 [1.24; 3.09]	0.004	
Age									
<65	333	60 (18.0)	Not reached [-; -]	324	33 (10.2)	Not reached [-; -]	1.89 [1.24; 2.90]	0.003	0.713
≥65	155	20 (12.9)	Not reached [-; -]	172	15 (8.7)	Not reached [-; -]	1.64 [0.84; 3.21]	0.147	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
ECOG Performance Status									
0	416	65 (15.6)	Not reached [-; -]	424	41 (9.7)	Not reached [-; -]	1.73 [1.17; 2.55]	0.006	0.461
1	72	15 (20.8)	Not reached [-; -]	72	7 (9.7)	Not reached [-; -]	2.50 [1.02; 6.14]	0.046	
Region									
WHO Stratum A	315	65 (20.6)	Not reached [-; -]	325	40 (12.3)	Not reached [-; -]	1.86 [1.25; 2.76]	0.002	0.981
Rest of the World	173	15 (8.7)	Not reached [-; -]	171	8 (4.7)	Not reached [-; -]	1.92 [0.81; 4.52]	0.138	
SOC: General disorders and administration site conditions - PT[g]: Fatigue									
Sex									
Female	148	49 (33.1)	Not reached [-; -]	139	33 (23.7)	Not reached [-; -]	1.50 [0.96; 2.33]	0.073	0.451
Male	340	96 (28.2)	Not reached [-; -]	357	87 (24.4)	Not reached [-; -]	1.23 [0.92; 1.65]	0.159	
Age									
<65	333	107 (32.1)	Not reached [-; -]	324	82 (25.3)	Not reached [-; -]	1.33 [1.00; 1.77]	0.054	0.740
≥65	155	38 (24.5)	Not reached [-; -]	172	38 (22.1)	Not reached [-; -]	1.22 [0.78; 1.91]	0.387	
ECOG Performance Status									
0	416	125 (30.0)	Not reached [-; -]	424	99 (23.3)	Not reached [-; -]	1.37 [1.05; 1.79]	0.019	0.343
1	72	20 (27.8)	Not reached [-; -]	72	21 (29.2)	Not reached [-; -]	1.00 [0.54; 1.85]	0.999	
Region									
WHO Stratum A	315	116 (36.8)	Not reached [-; -]	325	98 (30.2)	Not reached [-; -]	1.33 [1.02; 1.74]	0.037	0.995
Rest of the World	173	29 (16.8)	Not reached [-; -]	171	22 (12.9)	Not reached [-; -]	1.33 [0.76; 2.31]	0.314	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC: General disorders and administration site conditions - PT[g]: Oedema									
Sex									
Female	148	7 (4.7)	n.c.	139	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Male	340	4 (1.2)	n.c.	357	1 (0.3)	n.c.	n.c.	n.c.	
Age									
<65	333	6 (1.8)	n.c.	324	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥65	155	5 (3.2)	n.c.	172	1 (0.6)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	416	10 (2.4)	Not reached [-; -]	424	1 (0.2)	Not reached [-; -]	10.51 [1.34; 82.07]	0.025	0.666
1	72	1 (1.4)	Not reached [-; -]	72	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.297	
Region									
WHO Stratum A	315	8 (2.5)	n.c.	325	1 (0.3)	n.c.	n.c.	n.c.	n.c.
Rest of the World	173	3 (1.7)	n.c.	171	0 (0.0)	n.c.	n.c.	n.c.	
SOC: Infections and infestations - PT[g]: Sinusitis									
Sex									
Female	148	4 (2.7)	Not reached [-; -]	139	2 (1.4)	Not reached [-; -]	1.98 [0.36; 10.84]	0.429	0.608
Male	340	12 (3.5)	Not reached [-; -]	357	4 (1.1)	Not reached [-; -]	3.48 [1.12; 10.81]	0.031	
Age									
<65	333	11 (3.3)	Not reached [-; -]	324	2 (0.6)	Not reached [-; -]	5.70 [1.26; 25.72]	0.024	0.192
≥65	155	5 (3.2)	Not reached [-; -]	172	4 (2.3)	Not reached [-; -]	1.60 [0.43; 5.96]	0.483	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
ECOG Performance Status									
0	416	14 (3.4)	Not reached [-; -]	424	5 (1.2)	Not reached [-; -]	3.06 [1.10; 8.49]	0.032	0.854
1	72	2 (2.8)	Not reached [-; -]	72	1 (1.4)	Not reached [-; -]	2.54 [0.23; 28.08]	0.446	
Region									
WHO Stratum A	315	15 (4.8)	Not reached [-; -]	325	6 (1.8)	Not reached [-; -]	2.93 [1.14; 7.55]	0.026	0.449
Rest of the World	173	1 (0.6)	Not reached [-; -]	171	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.317	
SOC: Investigations - PT[g]: Alanine aminotransferase increased									
Sex									
Female	148	11 (7.4)	Not reached [-; -]	139	2 (1.4)	Not reached [-; -]	5.78 [1.28; 26.11]	0.022	0.147
Male	340	24 (7.1)	Not reached [-; -]	357	15 (4.2)	Not reached [-; -]	1.83 [0.96; 3.49]	0.066	
Age									
<65	333	23 (6.9)	Not reached [-; -]	324	14 (4.3)	Not reached [-; -]	1.71 [0.88; 3.32]	0.114	0.106
≥65	155	12 (7.7)	Not reached [-; -]	172	3 (1.7)	Not reached [-; -]	5.10 [1.44; 18.07]	0.012	
SOC: Investigations - PT[g]: Aspartate aminotransferase increased									
Sex									
Female	148	12 (8.1)	Not reached [-; -]	139	3 (2.2)	Not reached [-; -]	4.39 [1.24; 15.60]	0.022	0.945
Male	340	24 (7.1)	Not reached [-; -]	357	7 (2.0)	Not reached [-; -]	3.95 [1.70; 9.18]	0.001	
Age									
<65	333	24 (7.2)	Not reached [-; -]	324	6 (1.9)	Not reached [-; -]	4.19 [1.71; 10.27]	0.002	0.947
≥65	155	12 (7.7)	Not reached [-; -]	172	4 (2.3)	Not reached [-; -]	3.78 [1.22; 11.72]	0.021	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
ECOG Performance Status									
0	416	31 (7.5)	Not reached [-; -]	424	10 (2.4)	Not reached [-; -]	3.48 [1.70; 7.09]	< 0.001	0.098
1	72	5 (6.9)	Not reached [-; -]	72	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.019	
Region									
WHO Stratum A	315	19 (6.0)	Not reached [-; -]	325	8 (2.5)	Not reached [-; -]	2.78 [1.22; 6.35]	0.015	0.146
Rest of the World	173	17 (9.8)	Not reached [-; -]	171	2 (1.2)	Not reached [-; -]	8.91 [2.06; 38.56]	0.003	
SOC: Investigations - PT[g]: Blood alkaline phosphatase increased									
Sex									
Female	148	4 (2.7)	Not reached [-; -]	139	1 (0.7)	Not reached [-; -]	4.26 [0.48; 38.17]	0.195	0.863
Male	340	9 (2.6)	Not reached [-; -]	357	2 (0.6)	Not reached [-; -]	4.99 [1.08; 23.12]	0.040	
Age									
<65	333	6 (1.8)	n.c.	324	3 (0.9)	n.c.	n.c.	n.c.	n.c.
≥65	155	7 (4.5)	n.c.	172	0 (0.0)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	416	10 (2.4)	Not reached [-; -]	424	3 (0.7)	Not reached [-; -]	3.60 [0.99; 13.07]	0.052	0.231
1	72	3 (4.2)	Not reached [-; -]	72	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.060	
Region									
WHO Stratum A	315	8 (2.5)	Not reached [-; -]	325	2 (0.6)	Not reached [-; -]	4.59 [0.97; 21.64]	0.054	0.932
Rest of the World	173	5 (2.9)	Not reached [-; -]	171	1 (0.6)	Not reached [-; -]	5.06 [0.59; 43.29]	0.139	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC: Investigations - PT[g]: Weight decreased									
Sex									
Female	148	3 (2.0)	Not reached [-; -]	139	1 (0.7)	Not reached [-; -]	2.96 [0.31; 28.43]	0.348	0.989
Male	340	13 (3.8)	Not reached [-; -]	357	5 (1.4)	Not reached [-; -]	3.01 [1.07; 8.43]	0.037	
Age									
<65	333	11 (3.3)	Not reached [-; -]	324	5 (1.5)	Not reached [-; -]	2.27 [0.79; 6.55]	0.128	0.367
≥65	155	5 (3.2)	Not reached [-; -]	172	1 (0.6)	Not reached [-; -]	6.44 [0.75; 55.16]	0.089	
ECOG Performance Status									
0	416	14 (3.4)	Not reached [-; -]	424	6 (1.4)	Not reached [-; -]	2.56 [0.98; 6.67]	0.054	0.236
1	72	2 (2.8)	Not reached [-; -]	72	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.135	
Region									
WHO Stratum A	315	10 (3.2)	Not reached [-; -]	325	5 (1.5)	Not reached [-; -]	2.36 [0.81; 6.90]	0.118	0.407
Rest of the World	173	6 (3.5)	Not reached [-; -]	171	1 (0.6)	Not reached [-; -]	6.02 [0.72; 49.99]	0.097	
SOC: Metabolism and nutrition disorders - PT[g]: Decreased appetite									
Age									
<65	333	26 (7.8)	Not reached [-; -]	324	5 (1.5)	Not reached [-; -]	5.34 [2.05; 13.91]	< 0.001	0.235
≥65	155	9 (5.8)	Not reached [-; -]	172	5 (2.9)	Not reached [-; -]	2.13 [0.71; 6.37]	0.174	
ECOG Performance Status									
0	416	28 (6.7)	Not reached [-; -]	424	8 (1.9)	Not reached [-; -]	3.76 [1.71; 8.24]	< 0.001	0.961
1	72	7 (9.7)	Not reached [-; -]	72	2 (2.8)	Not reached [-; -]	3.84 [0.80; 18.50]	0.093	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Region									
WHO Stratum A	315	23 (7.3)	Not reached [-; -]	325	9 (2.8)	Not reached [-; -]	2.84 [1.31; 6.13]	0.008	0.135
Rest of the World	173	12 (6.9)	Not reached [-; -]	171	1 (0.6)	Not reached [-; -]	12.16 [1.58; 93.53]	0.016	
SOC: Metabolism and nutrition disorders - PT[g]: Hyperglycaemia									
Sex									
Female	148	9 (6.1)	Not reached [-; -]	139	2 (1.4)	Not reached [-; -]	4.79 [1.03; 22.19]	0.045	0.146
Male	340	19 (5.6)	Not reached [-; -]	357	15 (4.2)	Not reached [-; -]	1.45 [0.73; 2.85]	0.285	
Age									
<65	333	21 (6.3)	Not reached [-; -]	324	13 (4.0)	Not reached [-; -]	1.69 [0.84; 3.37]	0.139	0.683
≥65	155	7 (4.5)	Not reached [-; -]	172	4 (2.3)	Not reached [-; -]	2.22 [0.65; 7.58]	0.205	
ECOG Performance Status									
0	416	23 (5.5)	Not reached [-; -]	424	11 (2.6)	Not reached [-; -]	2.32 [1.13; 4.76]	0.022	0.200
1	72	5 (6.9)	Not reached [-; -]	72	6 (8.3)	Not reached [-; -]	0.96 [0.29; 3.16]	0.949	
Region									
WHO Stratum A	315	17 (5.4)	Not reached [-; -]	325	9 (2.8)	Not reached [-; -]	2.20 [0.98; 4.94]	0.056	0.442
Rest of the World	173	11 (6.4)	Not reached [-; -]	171	8 (4.7)	Not reached [-; -]	1.38 [0.56; 3.44]	0.484	
SOC: Musculoskeletal and connective tissue disorders - PT[g]: Neck pain									
Sex									
Female	148	1 (0.7)	Not reached [-; -]	139	4 (2.9)	Not reached [-; -]	0.24 [0.03; 2.19]	0.208	0.617
Male	340	2 (0.6)	Not reached [-; -]	357	18 (5.0)	Not reached [-; -]	0.13 [0.03; 0.54]	0.005	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age									
<65	333	1 (0.3)	Not reached [-; -]	324	18 (5.6)	Not reached [-; -]	0.06 [0.01; 0.42]	0.005	0.061
≥65	155	2 (1.3)	Not reached [-; -]	172	4 (2.3)	Not reached [-; -]	0.64 [0.12; 3.49]	0.606	
ECOG Performance Status									
0	416	2 (0.5)	Not reached [-; -]	424	20 (4.7)	Not reached [-; -]	0.11 [0.02; 0.46]	0.003	0.263
1	72	1 (1.4)	Not reached [-; -]	72	2 (2.8)	Not reached [-; -]	0.61 [0.06; 6.70]	0.684	
Region									
WHO Stratum A	315	3 (1.0)	Not reached [-; -]	325	20 (6.2)	Not reached [-; -]	0.17 [0.05; 0.57]	0.004	0.438
Rest of the World	173	0 (0.0)	Not reached [-; -]	171	2 (1.2)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.158	
SOC: Nervous system disorders - PT[g]: Paraesthesia									
Sex									
Female	148	8 (5.4)	Not reached [-; -]	139	3 (2.2)	Not reached [-; -]	2.73 [0.72; 10.31]	0.138	0.736
Male	340	9 (2.6)	Not reached [-; -]	357	5 (1.4)	Not reached [-; -]	2.01 [0.67; 5.99]	0.212	
Age									
<65	333	15 (4.5)	Not reached [-; -]	324	6 (1.9)	Not reached [-; -]	2.60 [1.01; 6.71]	0.048	0.507
≥65	155	2 (1.3)	Not reached [-; -]	172	2 (1.2)	Not reached [-; -]	1.16 [0.16; 8.23]	0.883	
ECOG Performance Status									
0	416	16 (3.8)	Not reached [-; -]	424	6 (1.4)	Not reached [-; -]	2.88 [1.13; 7.37]	0.027	0.199
1	72	1 (1.4)	Not reached [-; -]	72	2 (2.8)	Not reached [-; -]	0.60 [0.05; 6.63]	0.676	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Region									
WHO Stratum A	315	14 (4.4)	Not reached [-; -]	325	8 (2.5)	Not reached [-; -]	1.99 [0.84; 4.75]	0.120	0.132
Rest of the World	173	3 (1.7)	Not reached [-; -]	171	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.077	
SOC: Respiratory, thoracic and mediastinal disorders - PT[g]: Cough									
Sex									
Female	148	28 (18.9)	Not reached [-; -]	139	11 (7.9)	Not reached [-; -]	2.66 [1.33; 5.35]	0.006	0.111
Male	340	48 (14.1)	Not reached [-; -]	357	39 (10.9)	Not reached [-; -]	1.42 [0.93; 2.17]	0.105	
Age									
<65	333	55 (16.5)	Not reached [-; -]	324	29 (9.0)	Not reached [-; -]	2.01 [1.28; 3.16]	0.002	0.231
≥65	155	21 (13.5)	Not reached [-; -]	172	21 (12.2)	Not reached [-; -]	1.25 [0.68; 2.29]	0.466	
ECOG Performance Status									
0	416	68 (16.3)	Not reached [-; -]	424	41 (9.7)	Not reached [-; -]	1.84 [1.25; 2.72]	0.002	0.273
1	72	8 (11.1)	Not reached [-; -]	72	9 (12.5)	Not reached [-; -]	1.08 [0.42; 2.81]	0.871	
Region									
WHO Stratum A	315	62 (19.7)	Not reached [-; -]	325	41 (12.6)	Not reached [-; -]	1.80 [1.21; 2.67]	0.004	0.781
Rest of the World	173	14 (8.1)	Not reached [-; -]	171	9 (5.3)	Not reached [-; -]	1.58 [0.68; 3.64]	0.287	
SOC: Skin and subcutaneous tissue disorders - PT[g]: Pruritus									
Sex									
Female	148	30 (20.3)	Not reached [-; -]	139	21 (15.1)	Not reached [-; -]	1.44 [0.82; 2.52]	0.201	0.219
Male	340	81 (23.8)	Not reached [-; -]	357	44 (12.3)	Not reached [-; -]	2.18 [1.51; 3.15]	< 0.001	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age									
<65	333	76 (22.8)	Not reached [-; -]	324	39 (12.0)	Not reached [-; -]	2.11 [1.43; 3.10]	< 0.001	0.471
≥65	155	35 (22.6)	Not reached [-; -]	172	26 (15.1)	Not reached [-; -]	1.67 [1.00; 2.77]	0.048	
ECOG Performance Status									
0	416	97 (23.3)	Not reached [-; -]	424	53 (12.5)	Not reached [-; -]	2.08 [1.48; 2.90]	< 0.001	0.292
1	72	14 (19.4)	Not reached [-; -]	72	12 (16.7)	Not reached [-; -]	1.31 [0.61; 2.84]	0.489	
Region									
WHO Stratum A	315	80 (25.4)	Not reached [-; -]	325	49 (15.1)	Not reached [-; -]	1.94 [1.36; 2.78]	< 0.001	0.933
Rest of the World	173	31 (17.9)	Not reached [-; -]	171	16 (9.4)	Not reached [-; -]	1.99 [1.09; 3.64]	0.025	
SOC: Skin and subcutaneous tissue disorders - PT[g]: Rash									
Sex									
Female	148	36 (24.3)	Not reached [-; -]	139	19 (13.7)	Not reached [-; -]	1.92 [1.10; 3.35]	0.021	0.824
Male	340	62 (18.2)	Not reached [-; -]	357	34 (9.5)	Not reached [60.4; -]	2.11 [1.39; 3.21]	< 0.001	
Age									
<65	333	70 (21.0)	Not reached [-; -]	324	36 (11.1)	Not reached [60.4; -]	2.04 [1.36; 3.05]	< 0.001	0.988
≥65	155	28 (18.1)	Not reached [-; -]	172	17 (9.9)	Not reached [-; -]	2.07 [1.13; 3.79]	0.018	
ECOG Performance Status									
0	416	88 (21.2)	Not reached [-; -]	424	44 (10.4)	Not reached [-; -]	2.23 [1.55; 3.20]	< 0.001	0.249
1	72	10 (13.9)	Not reached [-; -]	72	9 (12.5)	Not reached [-; -]	1.26 [0.51; 3.10]	0.618	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Region									
WHO Stratum A	315	70 (22.2)	Not reached [-; -]	325	36 (11.1)	Not reached [-; -]	2.28 [1.53; 3.42]	< 0.001	0.418
Rest of the World	173	28 (16.2)	Not reached [-; -]	171	17 (9.9)	Not reached [-; -]	1.70 [0.93; 3.10]	0.086	
SOC: Skin and subcutaneous tissue disorders - PT[g]: Rash maculo-papular									
Sex									
Female	148	3 (2.0)	Not reached [-; -]	139	1 (0.7)	Not reached [-; -]	2.86 [0.30; 27.50]	0.363	0.852
Male	340	17 (5.0)	Not reached [-; -]	357	8 (2.2)	Not reached [-; -]	2.35 [1.01; 5.44]	0.047	
Age									
<65	333	13 (3.9)	Not reached [-; -]	324	6 (1.9)	Not reached [-; -]	2.18 [0.83; 5.72]	0.115	0.768
≥65	155	7 (4.5)	Not reached [-; -]	172	3 (1.7)	Not reached [-; -]	2.80 [0.72; 10.83]	0.136	
ECOG Performance Status									
0	416	17 (4.1)	Not reached [-; -]	424	8 (1.9)	Not reached [-; -]	2.23 [0.96; 5.18]	0.061	0.755
1	72	3 (4.2)	Not reached [-; -]	72	1 (1.4)	Not reached [-; -]	3.60 [0.37; 34.62]	0.268	
Region									
WHO Stratum A	315	18 (5.7)	Not reached [-; -]	325	8 (2.5)	Not reached [-; -]	2.48 [1.08; 5.71]	0.032	0.866
Rest of the World	173	2 (1.2)	Not reached [-; -]	171	1 (0.6)	Not reached [-; -]	1.98 [0.18; 21.83]	0.577	
SOC: Skin and subcutaneous tissue disorders - PT[g]: Rash pruritic									
Sex									
Female	148	3 (2.0)	Not reached [-; -]	139	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.089	0.486
Male	340	10 (2.9)	Not reached [-; -]	357	1 (0.3)	Not reached [-; -]	10.76 [1.38; 84.19]	0.024	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age									
<65	333	9 (2.7)	n.c.	324	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥65	155	4 (2.6)	n.c.	172	1 (0.6)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	416	9 (2.2)	Not reached [-; -]	424	1 (0.2)	Not reached [-; -]	9.35 [1.18; 73.84]	0.034	0.381
1	72	4 (5.6)	Not reached [-; -]	72	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.031	
Region									
WHO Stratum A	315	10 (3.2)	Not reached [-; -]	325	1 (0.3)	Not reached [-; -]	11.13 [1.42; 86.95]	0.022	0.497
Rest of the World	173	3 (1.7)	Not reached [57.1; -]	171	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.086	
SOC: Vascular disorders - PTs[g]: Hot flush									
Sex									
Female	148	7 (4.7)	Not reached [-; -]	139	3 (2.2)	Not reached [-; -]	2.34 [0.61; 9.07]	0.218	0.113
Male	340	4 (1.2)	Not reached [-; -]	357	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.036	
Age									
<65	333	8 (2.4)	Not reached [-; -]	324	2 (0.6)	Not reached [-; -]	4.08 [0.87; 19.22]	0.075	0.938
≥65	155	3 (1.9)	Not reached [-; -]	172	1 (0.6)	Not reached [-; -]	3.63 [0.38; 34.95]	0.264	
ECOG Performance Status									
0	416	10 (2.4)	Not reached [-; -]	424	2 (0.5)	Not reached [-; -]	5.37 [1.18; 24.52]	0.030	0.331
1	72	1 (1.4)	Not reached [-; -]	72	1 (1.4)	Not reached [-; -]	1.11 [0.07; 17.77]	0.941	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Region									
WHO Stratum A	315	9 (2.9)	Not reached [-; -]	325	3 (0.9)	Not reached [-; -]	3.35 [0.91; 12.40]	0.070	0.326
Rest of the World	173	2 (1.2)	Not reached [-; -]	171	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.152	

a: Database Cutoff Date: 14JUN2021

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

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

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

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

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

g: A 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 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 the rule of 10 is not met

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

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-36: 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 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Serious Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC[g]: Endocrine disorders									
Sex									
Female	148	2 (1.4)	Not reached [-; -]	139	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.164	0.997
Male	340	10 (2.9)	Not reached [-; -]	357	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Age									
<65	333	7 (2.1)	n.c.	324	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥65	155	5 (3.2)	n.c.	172	0 (0.0)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	416	10 (2.4)	Not reached [-; -]	424	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	0.997
1	72	2 (2.8)	Not reached [-; -]	72	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.137	
Region									
WHO Stratum A	315	9 (2.9)	n.c.	325	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Rest of the World	173	3 (1.7)	n.c.	171	0 (0.0)	n.c.	n.c.	n.c.	
SOC[g]: Metabolism and nutrition disorders									
Sex									
Female	148	3 (2.0)	Not reached [-; -]	139	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.078	0.386
Male	340	12 (3.5)	Not reached [-; -]	357	2 (0.6)	Not reached [-; -]	6.78 [1.52; 30.28]	0.012	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Serious Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age									
<65	333	9 (2.7)	Not reached [-; -]	324	1 (0.3)	Not reached [-; -]	9.23 [1.17; 72.85]	0.035	0.890
≥65	155	6 (3.9)	Not reached [-; -]	172	1 (0.6)	Not reached [-; -]	7.65 [0.92; 63.57]	0.060	
ECOG Performance Status									
0	416	14 (3.4)	Not reached [-; -]	424	2 (0.5)	Not reached [-; -]	7.64 [1.74; 33.61]	0.007	0.602
1	72	1 (1.4)	Not reached [-; -]	72	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.276	
Region									
WHO Stratum A	315	10 (3.2)	Not reached [-; -]	325	2 (0.6)	Not reached [-; -]	5.81 [1.27; 26.56]	0.023	0.246
Rest of the World	173	5 (2.9)	Not reached [-; -]	171	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.026	

a: Database Cutoff Date: 14JUN2021

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

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

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

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

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

g: A system organ class appears on this report only if its incidence ≥ 5% or (incidence ≥ 1% and in at least 10 participants) in one or more 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 the rule of 10 is not met

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

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

Tabelle 4G-37: 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 564[a]	**Pembrolizumab**			**Placebo**			**Pembrolizumab vs. Placebo**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
SOC[g]: Endocrine disorders									
Sex									
Female	148	3 (2.0)	Not reached [-; -]	139	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.088	0.473
Male	340	9 (2.6)	Not reached [-; -]	357	1 (0.3)	Not reached [-; -]	9.91 [1.25; 78.30]	0.030	
Age									
<65	333	7 (2.1)	n.c.	324	1 (0.3)	n.c.	n.c.	n.c.	n.c.
≥65	155	5 (3.2)	n.c.	172	0 (0.0)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	416	10 (2.4)	Not reached [-; -]	424	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	0.078
1	72	2 (2.8)	Not reached [-; -]	72	1 (1.4)	Not reached [-; -]	2.46 [0.22; 27.14]	0.462	
Region									
WHO Stratum A	315	9 (2.9)	Not reached [-; -]	325	1 (0.3)	Not reached [-; -]	10.11 [1.28; 79.86]	0.028	0.485
Rest of the World	173	3 (1.7)	Not reached [-; -]	171	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.085	
SOC[g]: Gastrointestinal disorders									
Sex									
Female	148	8 (5.4)	77.1 [-; -]	139	3 (2.2)	Not reached [-; -]	2.34 [0.61; 9.05]	0.218	0.776
Male	340	16	Not reached	357	6	Not reached	2.99	0.022	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
		(4.7)	[-; -]		(1.7)	[-; -]	[1.17; 7.64]		
Age									
<65	333	17 (5.1)	77.1 [-; -]	324	4 (1.2)	Not reached [-; -]	4.01 [1.34; 12.00]	0.013	0.310
≥65	155	7 (4.5)	Not reached [-; -]	172	5 (2.9)	Not reached [-; -]	1.76 [0.56; 5.55]	0.333	
ECOG Performance Status									
0	416	19 (4.6)	Not reached [-; -]	424	9 (2.1)	Not reached [-; -]	2.27 [1.03; 5.03]	0.042	0.081
1	72	5 (6.9)	77.1 [-; -]	72	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.029	
Region									
WHO Stratum A	315	21 (6.7)	77.1 [-; -]	325	6 (1.8)	Not reached [-; -]	3.87 [1.55; 9.65]	0.004	0.154
Rest of the World	173	3 (1.7)	Not reached [-; -]	171	3 (1.8)	Not reached [-; -]	0.99 [0.20; 4.90]	0.988	
SOC[g]: Investigations									
Sex									
Female	148	8 (5.4)	Not reached [-; -]	139	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.004	0.125
Male	340	19 (5.6)	Not reached [-; -]	357	4 (1.1)	Not reached [-; -]	5.32 [1.81; 15.63]	0.002	
Age									
<65	333	16 (4.8)	Not reached [-; -]	324	3 (0.9)	Not reached [-; -]	5.33 [1.55; 18.32]	0.008	0.402
≥65	155	11 (7.1)	Not reached [-; -]	172	1 (0.6)	Not reached [-; -]	13.47 [1.74; 104.34]	0.013	
ECOG Performance Status									
0	416	19 (4.6)	Not reached [-; -]	424	3 (0.7)	Not reached [-; -]	6.83 [2.02; 23.10]	0.002	0.812
1	72	8 (11.1)	Not reached [-; -]	72	1 (1.4)	Not reached [-; -]	8.98 [1.12; 71.85]	0.039	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Region									
WHO Stratum A	315	19 (6.0)	Not reached [-; -]	325	3 (0.9)	Not reached [-; -]	7.08 [2.10; 23.94]	0.002	0.929
Rest of the World	173	8 (4.6)	Not reached [-; -]	171	1 (0.6)	Not reached [-; -]	8.05 [1.01; 64.38]	0.049	
SOC[g]: Metabolism and nutrition disorders									
Sex									
Female	148	7 (4.7)	Not reached [-; -]	139	2 (1.4)	Not reached [-; -]	3.63 [0.75; 17.50]	0.108	0.426
Male	340	19 (5.6)	Not reached [-; -]	357	12 (3.4)	Not reached [-; -]	1.82 [0.88; 3.76]	0.104	
Age									
<65	333	20 (6.0)	Not reached [-; -]	324	7 (2.2)	Not reached [-; -]	2.98 [1.26; 7.06]	0.013	0.156
≥65	155	6 (3.9)	Not reached [-; -]	172	7 (4.1)	Not reached [-; -]	1.10 [0.37; 3.27]	0.868	
ECOG Performance Status									
0	416	22 (5.3)	Not reached [-; -]	424	9 (2.1)	Not reached [-; -]	2.72 [1.25; 5.90]	0.012	0.171
1	72	4 (5.6)	Not reached [-; -]	72	5 (6.9)	Not reached [-; -]	0.96 [0.26; 3.57]	0.950	
Region									
WHO Stratum A	315	19 (6.0)	Not reached [-; -]	325	8 (2.5)	Not reached [-; -]	2.88 [1.26; 6.58]	0.012	0.197
Rest of the World	173	7 (4.0)	Not reached [-; -]	171	6 (3.5)	Not reached [-; -]	1.16 [0.39; 3.46]	0.788	
SOC[g]: Skin and subcutaneous tissue disorders									
Sex									
Female	148	6 (4.1)	n.c.	139	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Male	340	4 (1.2)	n.c.	357	2 (0.6)	n.c.	n.c.	n.c.	

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age									
<65	333	7 (2.1)	n.c.	324	2 (0.6)	n.c.	n.c.	n.c.	n.c.
≥65	155	3 (1.9)	n.c.	172	0 (0.0)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	416	8 (1.9)	n.c.	424	1 (0.2)	n.c.	n.c.	n.c.	n.c.
1	72	2 (2.8)	n.c.	72	1 (1.4)	n.c.	n.c.	n.c.	
Region									
WHO Stratum A	315	7 (2.2)	n.c.	325	2 (0.6)	n.c.	n.c.	n.c.	n.c.
Rest of the World	173	3 (1.7)	n.c.	171	0 (0.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 14JUN2021

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

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

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

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

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

g: A system organ class appears on this report only if its incidence ≥ 5% or (incidence ≥ 1% and in at least 10 participants) in one or more 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 the rule of 10 is not met

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

Tabelle 4G-38: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für PT aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 564[a]	Pembrolizumab			Placebo			Pembrolizumab vs. Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC: Investigations - PT[g]: Alanine aminotransferase increased									
Sex									
Female	148	3 (2.0)	n.c.	139	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Male	340	8 (2.4)	n.c.	357	1 (0.3)	n.c.	n.c.	n.c.	
Age									
<65	333	7 (2.1)	n.c.	324	1 (0.3)	n.c.	n.c.	n.c.	n.c.
≥65	155	4 (2.6)	n.c.	172	0 (0.0)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	416	7 (1.7)	n.c.	424	1 (0.2)	n.c.	n.c.	n.c.	n.c.
1	72	4 (5.6)	n.c.	72	0 (0.0)	n.c.	n.c.	n.c.	
Region									
WHO Stratum A	315	6 (1.9)	n.c.	325	1 (0.3)	n.c.	n.c.	n.c.	n.c.
Rest of the World	173	5 (2.9)	n.c.	171	0 (0.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 14JUN2021

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

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

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

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

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

g: A 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 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 the rule of 10 is not met

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

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

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

Tabelle 4G-39: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT in der Studie KEYNOTE 564

AEOSI	Preferred Term	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

AEOSI	Preferred Term	Immune-mediated (yes/no)
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
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