Dokumentvorlage, Version vom 21.02.2019

Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD SHARP & DOHME GM

Modul 4 A

Neoadjuvante und adjuvante Be lokal fortgeschrittenen oder früh ativen Mammakarzinoms mit vrisiko

Medizini und
mediz nutzen,
Patienter herapeutisch
be usatznutzen

Stand: 16.06.2022

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Anhang 4-G1: Rücklaufquoten des EORTC QLQ-C30, EORTC QLQ-BR23 und EQ-5D VAS

Im Folgenden werden die Rücklaufquoten des EORTC QLQ-C30, die Rücklaufquoten des EORTC QLQ-BR23 und die Rücklaufquoten des EQ-5D VAS dargestellt.

Alle Ergebnisse beziehen sich auf den vierten Datenschnitt (23.März 2021).

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

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

Study: KEYNOTE 522[a]		**Pembrolizumab + Chemotherapy[b]**	**Placebo + Chemotherapy[c]**
Visit	**EORTC QLQ-C30**	**N[d] = 762 n (%)**	**N[d] = 383 n (%)**
Neoadjuvant Baseline	Expected to Complete Questionnaires[e]	762 (100.0)	382 (99.7)
	Completed	701 (92.0)	366 (95.6)
	Compliance (% in those expected to complete questionnaires)[f]	701 (92.0)	366 (95.8)
	Not completed	61 (8.0)	16 (4.2)
	Not completed due to site staff error	17 (2.2)	6 (1.6)
	Other	15 (2.0)	6 (1.6)
	Subject refused for other reasons	2 (0.3)	0 (0.0)
	Subject was physically unable to complete	1 (0.1)	0 (0.0)
	With visit, no record	26 (3.4)	4 (1.0)
	Missing by Design	0 (0.0)	1 (0.3)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
Neoadjuvant Week 12	Expected to Complete Questionnaires[e]	711 (93.3)	363 (94.8)
	Completed	648 (85.0)	329 (85.9)
	Compliance (% in those expected to complete questionnaires)[f]	648 (91.1)	329 (90.6)
	Not completed	63 (8.3)	34 (8.9)
	Not completed due to site staff error	20 (2.6)	11 (2.9)
	Other	18 (2.4)	7 (1.8)
	Subject did not complete due to disease under study	1 (0.1)	0 (0.0)
	Subject did not complete due to side effect of treatment	3 (0.4)	0 (0.0)
	Subject lost to follow-up/unable to contact	1 (0.1)	0 (0.0)
	Subject refused for other reasons	2 (0.3)	5 (1.3)
	Subject was physically unable to complete	2 (0.3)	1 (0.3)
	With visit, no record	16 (2.1)	10 (2.6)
	Missing by Design	51 (6.7)	20 (5.2)
	No visit scheduled	50 (6.6)	19 (5.0)
	Subject died	1 (0.1)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
Neoadjuvant Week 21	Expected to Complete Questionnaires[e]	688 (90.3)	349 (91.1)
	Completed	615 (80.7)	309 (80.7)
	Compliance (% in those expected to complete questionnaires)[f]	615 (89.4)	309 (88.5)
	Not completed	73 (9.6)	40 (10.4)
	Not completed due to site staff error	25 (3.3)	18 (4.7)
	Other	25 (3.3)	10 (2.6)
	Subject did not complete due to disease under study	1 (0.1)	0 (0.0)
	Subject did not complete due to side effect of treatment	2 (0.3)	1 (0.3)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.3)
	Subject refused for other reasons	9 (1.2)	3 (0.8)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)

Study: KEYNOTE 522[a]		Pembrolizumab + Chemotherapy[b]	Placebo + Chemotherapy[c]
Visit	EORTC QLQ-C30	N[d] = 762 n (%)	N[d] = 383 n (%)
	With visit, no record	10 (1.3)	6 (1.6)
	Missing by Design	74 (9.7)	34 (8.9)
	Discontinued due to adverse event	6 (0.8)	2 (0.5)
	Discontinued due to clinical progression	0 (0.0)	2 (0.5)
	Discontinued due to physician decision	2 (0.3)	0 (0.0)
	Discontinued due to progressive disease	1 (0.1)	1 (0.3)
	Discontinued due to withdrawal by subject	2 (0.3)	0 (0.0)
	No visit scheduled	60 (7.9)	29 (7.6)
	Subject died	3 (0.4)	0 (0.0)

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants: full-analysis-set population over neoadjuvant phase

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

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

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Tabelle 4G-2: Gründe für das Fehlen von Werten im EORTC QLQ-C30 in der adjuvanten Phase

Study: KEYNOTE 522[a]		Pembrolizumab[b]	Placebo[c]
Visit	EORTC QLQ-C30	N[d] = 539 n (%)	N[d] = 308 n (%)
Adjuvant Baseline	Expected to Complete Questionnaires[e]	539 (100.0)	308 (100.0)
	Completed	489 (90.7)	283 (91.9)
	Compliance (% in those expected to complete questionnaires)[f]	489 (90.7)	283 (91.9)
	Not completed	50 (9.3)	25 (8.1)
	Not completed due to site staff error	23 (4.3)	10 (3.2)
	Other	6 (1.1)	6 (1.9)
	Subject refused for other reasons	3 (0.6)	1 (0.3)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	With visit, no record	18 (3.3)	7 (2.3)
	Missing by Design	0 (0.0)	0 (0.0)
Adjuvant Week 12	Expected to Complete Questionnaires[e]	527 (97.8)	302 (98.1)
	Completed	485 (90.0)	269 (87.3)
	Compliance (% in those expected to complete questionnaires)[f]	485 (92.0)	269 (89.1)
	Not completed	42 (7.8)	33 (10.7)
	Not completed due to site staff error	25 (4.6)	15 (4.9)
	Other	6 (1.1)	10 (3.2)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.6)
	Subject in hospital or hospice	1 (0.2)	0 (0.0)
	Subject refused for other reasons	6 (1.1)	1 (0.3)
	Subject was physically unable to complete	1 (0.2)	1 (0.3)
	With visit, no record	3 (0.6)	4 (1.3)
	Missing by Design	12 (2.2)	6 (1.9)
	No visit scheduled	12 (2.2)	6 (1.9)
Adjuvant Week 24	Expected to Complete Questionnaires[e]	484 (89.8)	282 (91.6)
	Completed	444 (82.4)	249 (80.8)

Study: KEYNOTE 522[a]		Pembrolizumab[b]	Placebo[c]
Visit	EORTC QLQ-C30	N[d] = 539 n (%)	N[d] = 308 n (%)
	Compliance (% in those expected to complete questionnaires)[f]	444 (91.7)	249 (88.3)
	Not completed	40 (7.4)	33 (10.7)
	Not completed due to site staff error	16 (3.0)	12 (3.9)
	Other	11 (2.0)	8 (2.6)
	Subject refused for other reasons	2 (0.4)	5 (1.6)
	With visit, no record	11 (2.0)	8 (2.6)
	Missing by Design	55 (10.2)	26 (8.4)
	Discontinued due to adverse event	17 (3.2)	2 (0.6)
	Discontinued due to physician decision	7 (1.3)	1 (0.3)
	Discontinued due to relapse/recurrence	9 (1.7)	7 (2.3)
	Discontinued due to withdrawal by subject	9 (1.7)	8 (2.6)
	No visit scheduled	12 (2.2)	8 (2.6)
	Subject died	1 (0.2)	0 (0.0)

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants: full-analysis-set population over adjuvant phase

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

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

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Anhang 4-G1.2: Rücklaufquoten des EORTC QLQ-BR23

Tabelle 4G-3: Gründe für das Fehlen von Werten im EORTC QLQ-BR23 in der neoadjuvanten Phase

Study: KEYNOTE 522[a]		Pembrolizumab + Chemotherapy[b]	Placebo + Chemotherapy[c]
Visit	EORTC QLQ-BR23	N[d] = 759 n (%)	N[d] = 382 n (%)
Neoadjuvant Baseline	Expected to Complete Questionnaires[e]	759 (100.0)	381 (99.7)
	Completed	695 (91.6)	361 (94.5)
	Compliance (% in those expected to complete questionnaires)[f]	695 (91.6)	361 (94.8)
	Not completed	64 (8.4)	20 (5.2)
	Not completed due to site staff error	19 (2.5)	9 (2.4)
	Other	16 (2.1)	7 (1.8)
	Subject refused for other reasons	2 (0.3)	0 (0.0)
	Subject was physically unable to complete	1 (0.1)	0 (0.0)
	With visit, no record	26 (3.4)	4 (1.0)
	Missing by Design	0 (0.0)	1 (0.3)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
Neoadjuvant Week 12	Expected to Complete Questionnaires[e]	709 (93.4)	362 (94.8)
	Completed	644 (84.8)	328 (85.9)
	Compliance (% in those expected to complete questionnaires)[f]	644 (90.8)	328 (90.6)
	Not completed	65 (8.6)	34 (8.9)
	Not completed due to site staff error	22 (2.9)	11 (2.9)
	Other	18 (2.4)	7 (1.8)
	Subject did not complete due to disease under study	1 (0.1)	0 (0.0)
	Subject did not complete due to side effect of treatment	3 (0.4)	0 (0.0)

Study: KEYNOTE 522[a]		Pembrolizumab + Chemotherapy[b]	Placebo + Chemotherapy[c]
		N[d] = 759	N[d] = 382
Visit	EORTC QLQ-BR23	n (%)	n (%)
	Subject lost to follow-up/unable to contact	1 (0.1)	0 (0.0)
	Subject refused for other reasons	2 (0.3)	5 (1.3)
	Subject was physically unable to complete	2 (0.3)	1 (0.3)
	With visit, no record	16 (2.1)	10 (2.6)
	Missing by Design	50 (6.6)	20 (5.2)
	No visit scheduled	49 (6.5)	19 (5.0)
	Subject died	1 (0.1)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
Neoadjuvant Week 21	Expected to Complete Questionnaires[e]	686 (90.4)	348 (91.1)
	Completed	611 (80.5)	307 (80.4)
	Compliance (% in those expected to complete questionnaires)[f]	611 (89.1)	307 (88.2)
	Not completed	75 (9.9)	41 (10.7)
	Not completed due to site staff error	27 (3.6)	19 (5.0)
	Other	25 (3.3)	10 (2.6)
	Subject did not complete due to disease under study	1 (0.1)	0 (0.0)
	Subject did not complete due to side effect of treatment	2 (0.3)	1 (0.3)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.3)
	Subject refused for other reasons	9 (1.2)	3 (0.8)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	With visit, no record	10 (1.3)	6 (1.6)
	Missing by Design	73 (9.6)	34 (8.9)
	Discontinued due to adverse event	6 (0.8)	2 (0.5)
	Discontinued due to clinical progression	0 (0.0)	2 (0.5)
	Discontinued due to physician decision	2 (0.3)	0 (0.0)
	Discontinued due to progressive disease	1 (0.1)	1 (0.3)
	Discontinued due to withdrawal by subject	2 (0.3)	0 (0.0)
	No visit scheduled	59 (7.8)	29 (7.6)
	Subject died	3 (0.4)	0 (0.0)

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants: full-analysis-set population over neoadjuvant phase

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

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

EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items

Tabelle 4G-4: Gründe für das Fehlen von Werten im EORTC QLQ-BR23 in der adjuvanten Phase

Study: KEYNOTE 522[a]		Pembrolizumab[b]	Placebo[c]
		N[d] = 538	N[d] = 306
Visit	EORTC QLQ-BR23	n (%)	n (%)
Adjuvant Baseline	Expected to Complete Questionnaires[e]	538 (100.0)	306 (100.0)
	Completed	487 (90.5)	282 (92.2)
	Compliance (% in those expected to complete questionnaires)[f]	487 (90.5)	282 (92.2)
	Not completed	51 (9.5)	24 (7.8)
	Not completed due to site staff error	22 (4.1)	9 (2.9)
	Other	6 (1.1)	6 (2.0)

Study: KEYNOTE 522[a]		Pembrolizumab[b]	Placebo[c]
Visit	EORTC QLQ-BR23	N[d] = 538 n (%)	N[d] = 306 n (%)
	Subject refused for other reasons	3 (0.6)	1 (0.3)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	With visit, no record	20 (3.7)	7 (2.3)
	Missing by Design	0 (0.0)	0 (0.0)
Adjuvant Week 12	Expected to Complete Questionnaires[e]	526 (97.8)	300 (98.0)
	Completed	483 (89.8)	267 (87.3)
	Compliance (% in those expected to complete questionnaires)[f]	483 (91.8)	267 (89.0)
	Not completed	43 (8.0)	33 (10.8)
	Not completed due to site staff error	25 (4.6)	14 (4.6)
	Other	6 (1.1)	11 (3.6)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.7)
	Subject in hospital or hospice	1 (0.2)	0 (0.0)
	Subject refused for other reasons	6 (1.1)	1 (0.3)
	Subject was physically unable to complete	1 (0.2)	1 (0.3)
	With visit, no record	4 (0.7)	4 (1.3)
	Missing by Design	12 (2.2)	6 (2.0)
	No visit scheduled	12 (2.2)	6 (2.0)
Adjuvant Week 24	Expected to Complete Questionnaires[e]	483 (89.8)	280 (91.5)
	Completed	442 (82.2)	247 (80.7)
	Compliance (% in those expected to complete questionnaires)[f]	442 (91.5)	247 (88.2)
	Not completed	41 (7.6)	33 (10.8)
	Not completed due to site staff error	17 (3.2)	12 (3.9)
	Other	11 (2.0)	8 (2.6)
	Subject refused for other reasons	2 (0.4)	5 (1.6)
	With visit, no record	11 (2.0)	8 (2.6)
	Missing by Design	55 (10.2)	26 (8.5)
	Discontinued due to adverse event	17 (3.2)	2 (0.7)
	Discontinued due to physician decision	7 (1.3)	1 (0.3)
	Discontinued due to relapse/recurrence	9 (1.7)	7 (2.3)
	Discontinued due to withdrawal by subject	9 (1.7)	8 (2.6)
	No visit scheduled	12 (2.2)	8 (2.6)
	Subject died	1 (0.2)	0 (0.0)

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants: full-analysis-set population over adjuvant phase

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

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

EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items

Anhang 4-G1.3: Rücklaufquoten des EQ-5D VAS

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

Study: KEYNOTE 522[a]		**Pembrolizumab + Chemotherapy[b]**	**Placebo + Chemotherapy[c]**
Visit	**EQ-5D**	**N[d] = 762 n (%)**	**N[d] = 384 n (%)**
Neoadjuvant Baseline	Expected to Complete Questionnaires[e]	762 (100.0)	383 (99.7)
	Completed	707 (92.8)	369 (96.1)
	Compliance (% in those expected to complete questionnaires)[f]	707 (92.8)	369 (96.3)
	Not completed	55 (7.2)	14 (3.6)
	Not completed due to site staff error	15 (2.0)	5 (1.3)
	Other	11 (1.4)	5 (1.3)
	Subject refused for other reasons	1 (0.1)	0 (0.0)
	With visit, no record	28 (3.7)	4 (1.0)
	Missing by Design	0 (0.0)	1 (0.3)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
Neoadjuvant Week 12	Expected to Complete Questionnaires[e]	711 (93.3)	365 (95.1)
	Completed	657 (86.2)	336 (87.5)
	Compliance (% in those expected to complete questionnaires)[f]	657 (92.4)	336 (92.1)
	Not completed	54 (7.1)	29 (7.6)
	Not completed due to site staff error	17 (2.2)	8 (2.1)
	Other	14 (1.8)	6 (1.6)
	Subject did not complete due to disease under study	1 (0.1)	0 (0.0)
	Subject did not complete due to side effect of treatment	2 (0.3)	0 (0.0)
	Subject lost to follow-up/unable to contact	1 (0.1)	0 (0.0)
	Subject refused for other reasons	1 (0.1)	4 (1.0)
	Subject was physically unable to complete	2 (0.3)	1 (0.3)
	With visit, no record	16 (2.1)	10 (2.6)
	Missing by Design	51 (6.7)	19 (4.9)
	No visit scheduled	50 (6.6)	18 (4.7)
	Subject died	1 (0.1)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
Neoadjuvant Week 21	Expected to Complete Questionnaires[e]	688 (90.3)	350 (91.1)
	Completed	616 (80.8)	311 (81.0)
	Compliance (% in those expected to complete questionnaires)[f]	616 (89.5)	311 (88.9)
	Not completed	72 (9.4)	39 (10.2)
	Not completed due to site staff error	26 (3.4)	17 (4.4)
	Other	25 (3.3)	10 (2.6)
	Subject did not complete due to disease under study	1 (0.1)	0 (0.0)
	Subject did not complete due to side effect of treatment	2 (0.3)	1 (0.3)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.3)
	Subject refused for other reasons	8 (1.0)	3 (0.8)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	With visit, no record	9 (1.2)	6 (1.6)
	Missing by Design	74 (9.7)	34 (8.9)
	Discontinued due to adverse event	6 (0.8)	2 (0.5)
	Discontinued due to clinical progression	0 (0.0)	2 (0.5)
	Discontinued due to physician decision	2 (0.3)	0 (0.0)
	Discontinued due to progressive disease	1 (0.1)	1 (0.3)
	Discontinued due to withdrawal by subject	2 (0.3)	0 (0.0)
	No visit scheduled	60 (7.9)	29 (7.6)
	Subject died	3 (0.4)	0 (0.0)

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

Study: KEYNOTE 522[a]		Pembrolizumab + Chemotherapy[b]	Placebo + Chemotherapy[c]
Visit	EQ-5D	N[d] = 762 n (%)	N[d] = 384 n (%)
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles			
d: Number of participants: full-analysis-set population over neoadjuvant phase			
e: Expected to complete questionnaire includes all subjects who do not have missing data due to a missing by design reason			
f: Compliance is the proportion of participants who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design. All the other categories are defined as the proportion of participants in the analysis population (N)			
EQ-5D: European Quality of Life 5 Dimensions			

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

Study: KEYNOTE 522[a]		Pembrolizumab[b]	Placebo[c]
Visit	EQ-5D	N[d] = 540 n (%)	N[d] = 310 n (%)
Adjuvant Baseline	Expected to Complete Questionnaires[e]	540 (100.0)	310 (100.0)
	Completed	495 (91.7)	285 (91.9)
	Compliance (% in those expected to complete questionnaires)[f]	495 (91.7)	285 (91.9)
	Not completed	45 (8.3)	25 (8.1)
	Not completed due to site staff error	21 (3.9)	10 (3.2)
	Other	4 (0.7)	6 (1.9)
	Subject refused for other reasons	2 (0.4)	1 (0.3)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	With visit, no record	18 (3.3)	7 (2.3)
	Missing by Design	0 (0.0)	0 (0.0)
Adjuvant Week 12	Expected to Complete Questionnaires[e]	528 (97.8)	304 (98.1)
	Completed	485 (89.8)	274 (88.4)
	Compliance (% in those expected to complete questionnaires)[f]	485 (91.9)	274 (90.1)
	Not completed	43 (8.0)	30 (9.7)
	Not completed due to site staff error	26 (4.8)	12 (3.9)
	Other	6 (1.1)	10 (3.2)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.6)
	Subject in hospital or hospice	1 (0.2)	0 (0.0)
	Subject refused for other reasons	6 (1.1)	1 (0.3)
	Subject was physically unable to complete	1 (0.2)	1 (0.3)
	With visit, no record	3 (0.6)	4 (1.3)
	Missing by Design	12 (2.2)	6 (1.9)
	No visit scheduled	12 (2.2)	6 (1.9)
Adjuvant Week 24	Expected to Complete Questionnaires[e]	485 (89.8)	284 (91.6)
	Completed	444 (82.2)	249 (80.3)
	Compliance (% in those expected to complete questionnaires)[f]	444 (91.5)	249 (87.7)
	Not completed	41 (7.6)	35 (11.3)
	Not completed due to site staff error	17 (3.1)	13 (4.2)
	Other	11 (2.0)	9 (2.9)
	Subject refused for other reasons	2 (0.4)	5 (1.6)
	With visit, no record	11 (2.0)	8 (2.6)
	Missing by Design	55 (10.2)	26 (8.4)
	Discontinued due to adverse event	17 (3.1)	2 (0.6)
	Discontinued due to physician decision	7 (1.3)	1 (0.3)
	Discontinued due to relapse/recurrence	9 (1.7)	7 (2.3)
	Discontinued due to withdrawal by subject	9 (1.7)	8 (2.6)
	No visit scheduled	12 (2.2)	8 (2.6)
	Subject died	1 (0.2)	0 (0.0)

Study: KEYNOTE 522[a]		**Pembrolizumab[b]**	**Placebo[c]**
		N[d] = 540	**N[d] = 310**
Visit	**EQ-5D**	**n (%)**	**n (%)**
a: Database Cutoff Date: 23MAR2021			
b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles			
c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles			
d: Number of participants: full-analysis-set population over adjuvant phase			
e: Expected to complete questionnaire includes all subjects who do not have missing data due to a missing by design reason			
f: Compliance is the proportion of participants who completed the questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design. All the other categories are defined as the proportion of participants in the analysis population (N)			
EQ-5D: European Quality of Life 5 Dimensions			

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

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

Alle Ergebnisse beziehen sich auf den vierten Datenschnitt (23. März 2021).

Anhang 4-G2.1: Mortalität

Gesamtüberleben

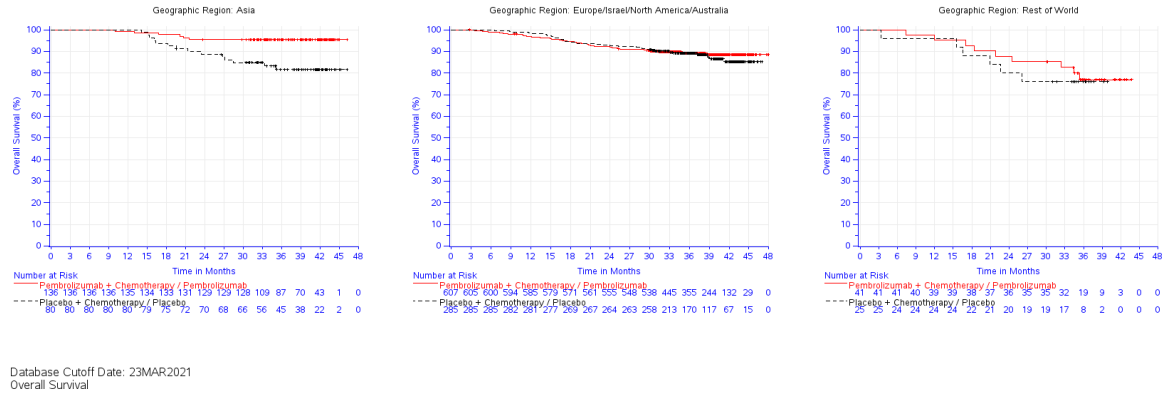

Abbildung 4G-1: Kaplan-Meier-Kurven für den Endpunkt Gesamtüberleben in der Subgruppenanalyse Region

Anhang 4-G2.2: Nebenwirkungen

Schwerwiegende unerwünschte Ereignisse

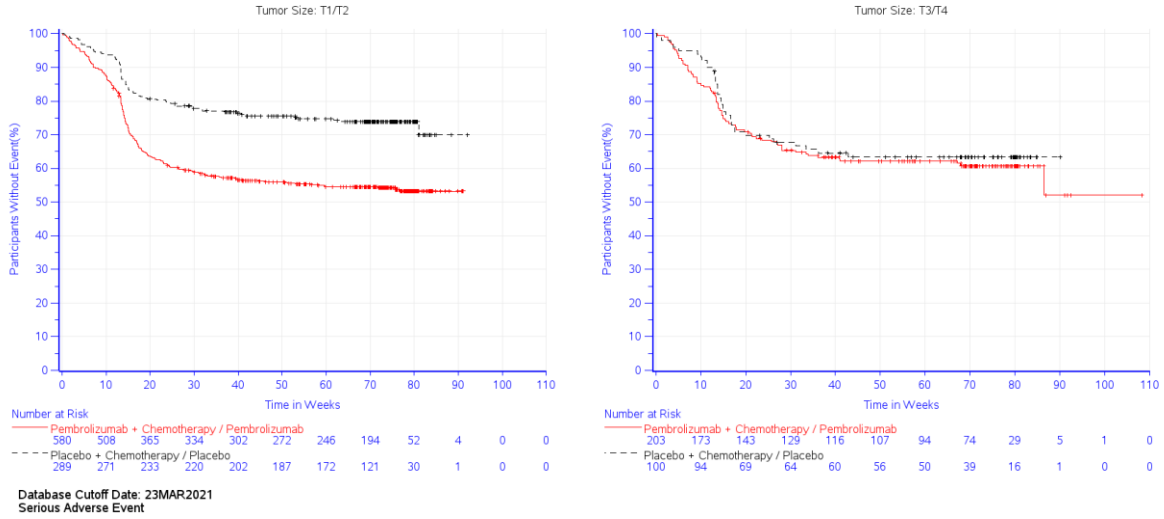

Abbildung 4G-2: Kaplan-Meier-Kurven für den Endpunkt schwerwiegende unerwünschte Ereignisse in der Subgruppenanalyse Tumorgröße

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

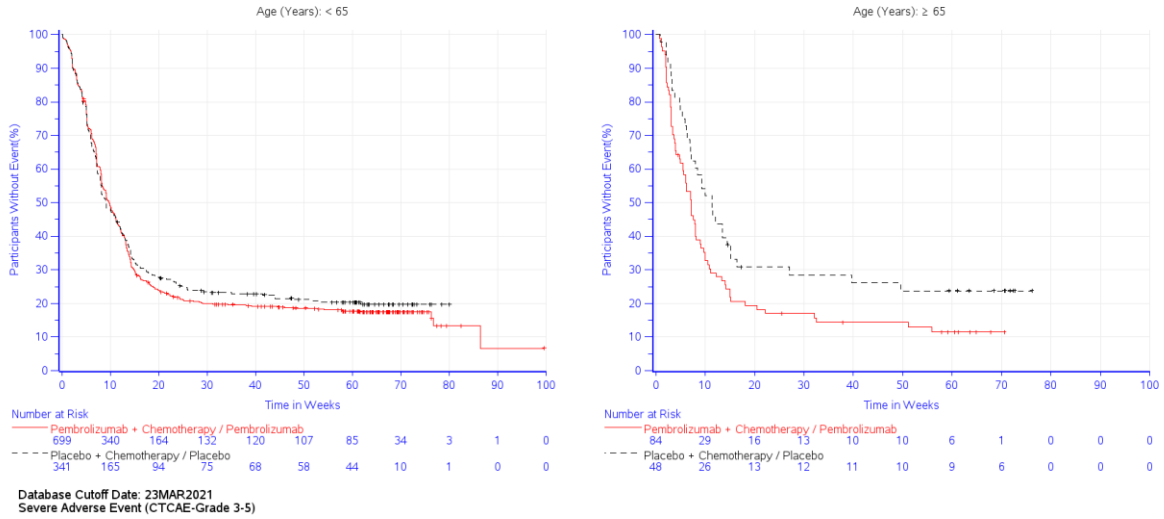

Abbildung 4G-3: Kaplan-Meier-Kurven für den Endpunkt schwere unerwünschte Ereignisse in der Subgruppenanalyse Alter (Jahre)

Unerwünschte Ereignisse nach SOC und PT

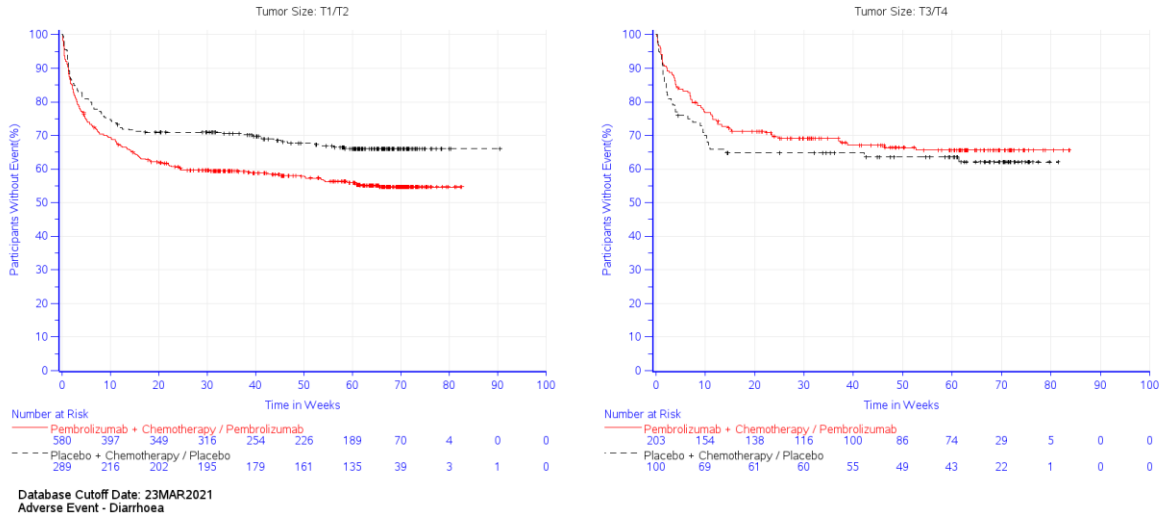

Abbildung 4G-4: Kaplan-Meier-Kurven für den Endpunkt unerwünschte Ereignisse nach SOC und PT im Endpunkt Diarrhoe in der Subgruppe Tumorgröße

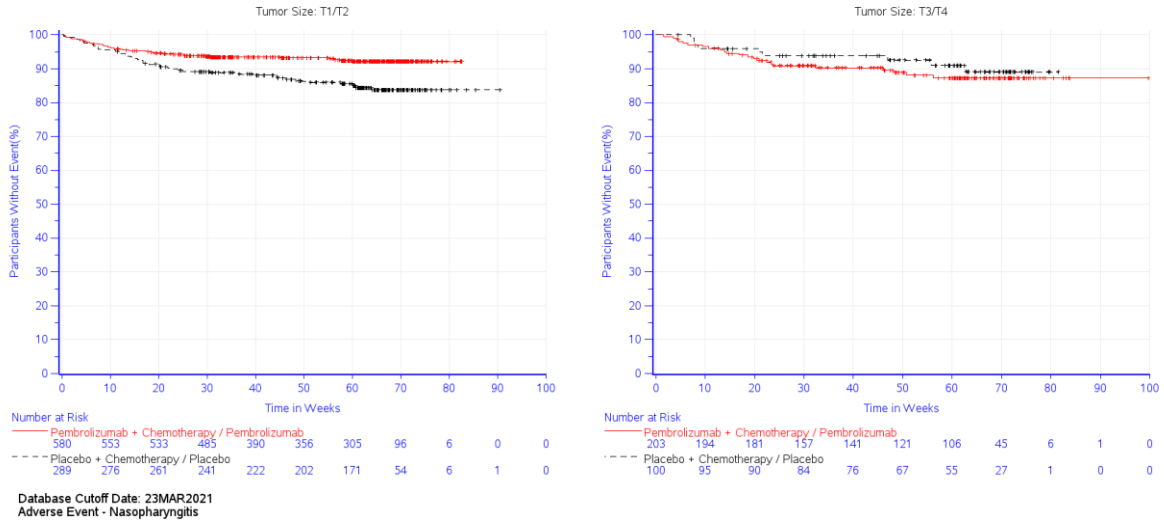

Abbildung 4G-5: Kaplan-Meier-Kurven für den Endpunkt unerwünschte Ereignisse nach SOC und PT im Endpunkt Nasopharyngitis in der Subgruppe Tumorgröße

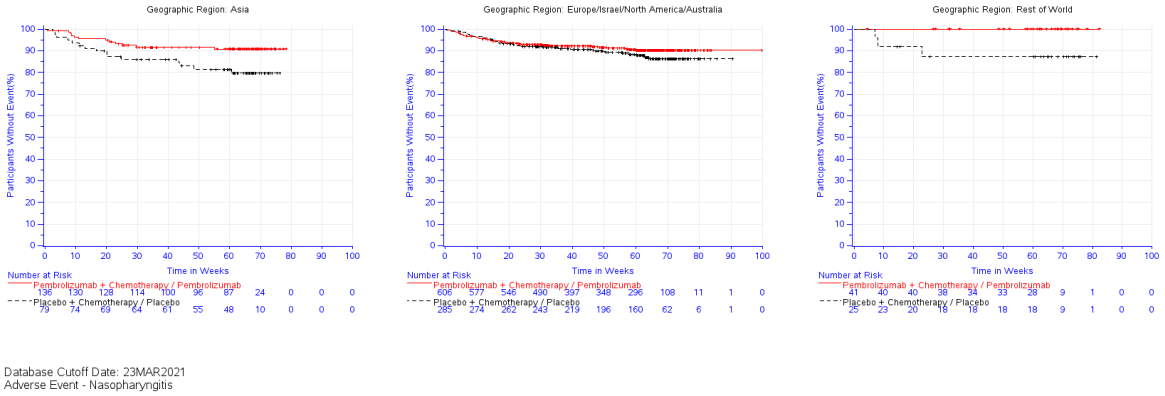

Abbildung 4G-6: Kaplan-Meier-Kurven für den Endpunkt unerwünschte Ereignisse nach SOC und PT im Endpunkt Nasopharyngitis in der Subgruppe Region

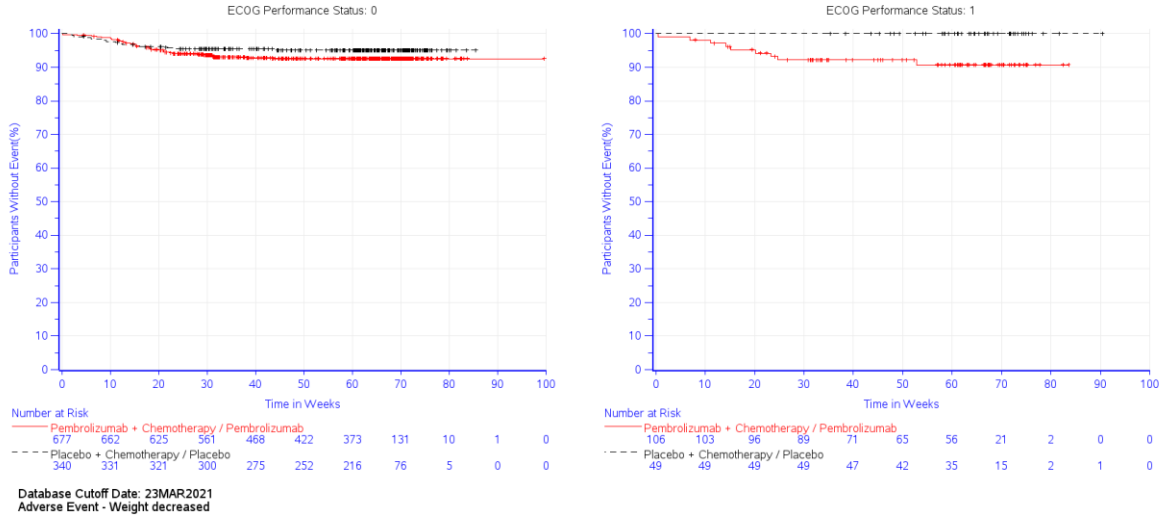

Abbildung 4G-7: Kaplan-Meier-Kurven für den Endpunkt unerwünschte Ereignisse nach SOC und PT im Endpunkt Gewicht erniedrigt in der Subgruppe ECOG Leistungsstatus

Schwerwiegende unerwünschte Ereignisse nach SOC und PT

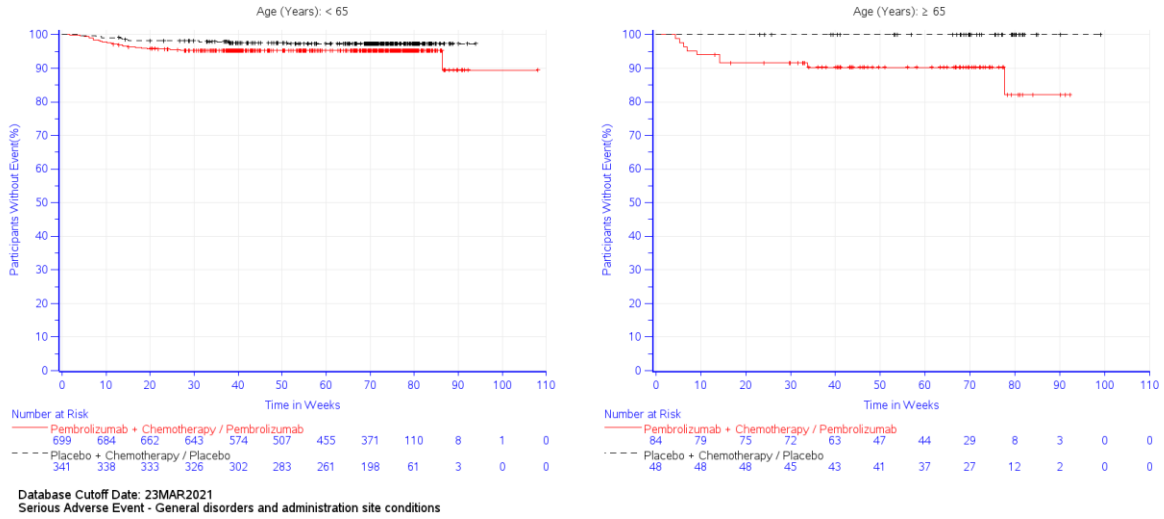

Abbildung 4G-8: Kaplan-Meier-Kurven für den Endpunkt schwerwiegende unerwünschte Ereignisse nach SOC und PT im Endpunkt Allgemeine Erkrankungen und Beschwerden am Verabreichungsort in der Subgruppe Alter (Jahre)

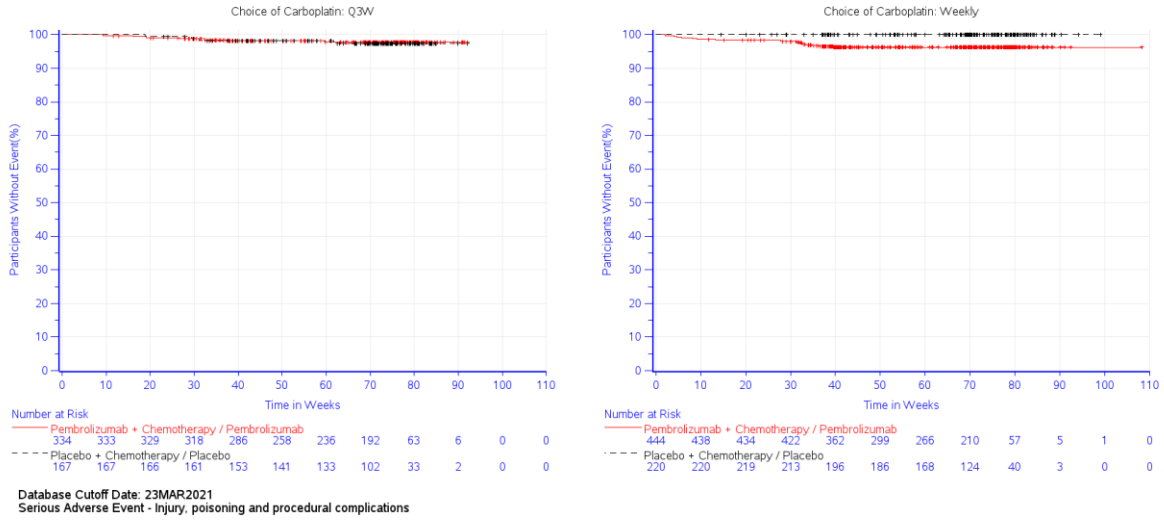

Abbildung 4G-9: Kaplan-Meier-Kurven für den Endpunkt schwerwiegende unerwünschte Ereignisse nach SOC und PT im Endpunkt Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen in der Subgruppe Wahl von Carboplatin

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

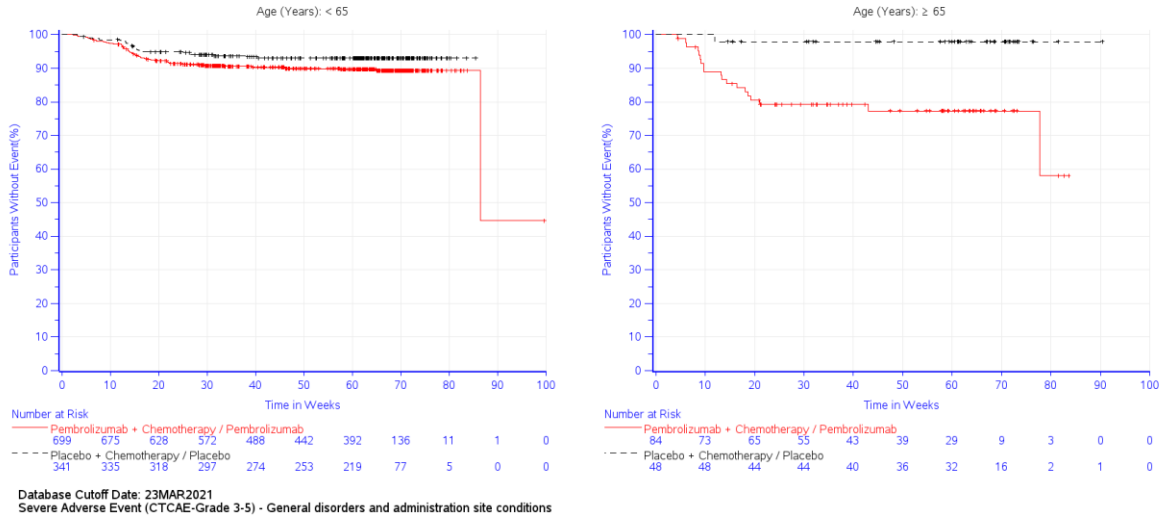

Abbildung 4G-10: Kaplan-Meier-Kurven für den Endpunkt schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) nach SOC und PT im Endpunkt Allgemeine Erkrankungen und Beschwerden am Verabreichungsort in der Subgruppe Alter (Jahre)

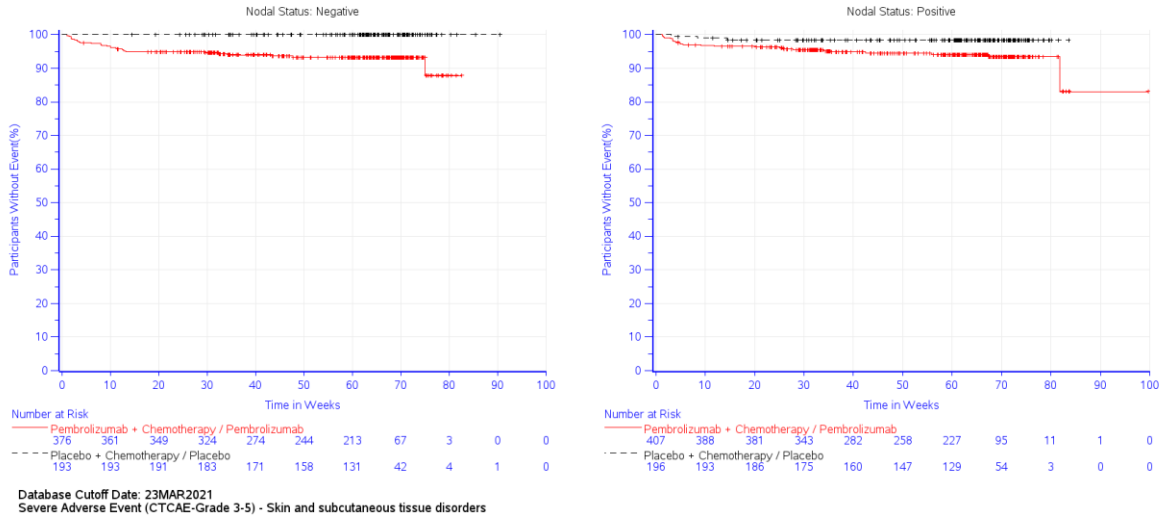

Abbildung 4G-11: Kaplan-Meier-Kurven für den Endpunkt schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) nach SOC und PT im Endpunkt Erkrankungen der Haut und des Unterhautzellgewebes in der Subgruppe Nodalstatus

Anhang 4-G3: Auswertungen über den Studienverlauf (tabellarische Darstellung)

Anhang 4-G3.1: Morbidität

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30

EORTC QLQ-C30: Symptomskala Erschöpfung (Fatigue)

Tabelle 4G-7: Auswertung über den Studienverlauf der Symptomskala Erschöpfung (Fatigue) des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Fatigue	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	701	366
Mean (SD)	19.0 (20.0)	19.2 (19.5)
Median (Q1; Q3)	11.1 (0.0; 33.3)	11.1 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	648	329
Mean (SD)	42.4 (24.7)	38.1 (22.7)
Median (Q1; Q3)	33.3 (33.3; 55.6)	33.3 (22.2; 44.4)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	615	309
Mean (SD)	39.8 (23.5)	36.7 (24.8)
Median (Q1; Q3)	33.3 (22.2; 55.6)	33.3 (22.2; 44.4)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	489	283
Mean (SD)	27.6 (20.2)	29.0 (22.5)
Median (Q1; Q3)	33.3 (11.1; 33.3)	33.3 (11.1; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	485	269
Mean (SD)	26.3 (20.5)	27.3 (21.2)
Median (Q1; Q3)	33.3 (11.1; 33.3)	33.3 (11.1; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	444	249
Mean (SD)	26.0 (22.0)	26.7 (22.4)
Median (Q1; Q3)	22.2 (11.1; 33.3)	22.2 (11.1; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	454	221
Mean (SD)	23.3 (21.1)	24.6 (22.3)
Median (Q1; Q3)	22.2 (0.0; 33.3)	22.2 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
a: Database Cutoff Date: 23MAR2021		

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants: full-analysis-set population
e: Number of observations at each time point
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-8: Auswertung über den Studienverlauf der Symptomskala Übelkeit und Erbrechen des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Nausea And Vomiting	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	701	366
Mean (SD)	2.8 (9.8)	3.1 (10.1)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	648	329
Mean (SD)	13.3 (18.9)	11.4 (18.7)
Median (Q1; Q3)	0.0 (0.0; 16.7)	0.0 (0.0; 16.7)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	615	309
Mean (SD)	14.3 (19.2)	13.1 (17.6)
Median (Q1; Q3)	0.0 (0.0; 16.7)	0.0 (0.0; 16.7)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	489	283
Mean (SD)	3.9 (10.0)	3.4 (9.8)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 66.7	0.0; 66.7
Adjuvant Week 12		
N[e]	485	269
Mean (SD)	4.3 (12.8)	4.1 (11.6)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	444	249
Mean (SD)	4.1 (10.6)	2.9 (8.7)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 66.7
Year 2		
N[e]	454	221
Mean (SD)	3.4 (9.3)	3.7 (11.4)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)

EORTC QLQ-C30 Nausea And Vomiting	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Min; Max	0.0; 66.7	0.0; 100.0

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

e: Number of observations at each time point

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Schmerzen

Tabelle 4G-9: Auswertung über den Studienverlauf der Symptomskala Schmerzen des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Pain	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	701	366
Mean (SD)	16.1 (20.1)	16.2 (18.4)
Median (Q1; Q3)	16.7 (0.0; 16.7)	16.7 (0.0; 16.7)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	648	329
Mean (SD)	22.1 (24.2)	20.2 (22.1)
Median (Q1; Q3)	16.7 (0.0; 33.3)	16.7 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	615	309
Mean (SD)	20.4 (23.1)	19.1 (22.1)
Median (Q1; Q3)	16.7 (0.0; 33.3)	16.7 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	489	283
Mean (SD)	20.9 (20.2)	24.9 (24.5)
Median (Q1; Q3)	16.7 (0.0; 33.3)	16.7 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	485	269
Mean (SD)	20.3 (20.4)	21.4 (22.1)
Median (Q1; Q3)	16.7 (0.0; 33.3)	16.7 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	444	249
Mean (SD)	18.7 (20.3)	20.1 (22.2)
Median (Q1; Q3)	16.7 (0.0; 33.3)	16.7 (0.0; 33.3)

EORTC QLQ-C30 Pain	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	454	221
Mean (SD)	18.1 (21.4)	18.7 (20.0)
Median (Q1; Q3)	16.7 (0.0; 33.3)	16.7 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants: full-analysis-set population
e: Number of observations at each time point
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Atemnot (Dyspnoe)

Tabelle 4G-10: Auswertung über den Studienverlauf der Symptomskala Atemnot (Dyspnoe) des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Dyspnoea	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	701	366
Mean (SD)	5.8 (14.8)	6.0 (16.0)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	648	329
Mean (SD)	22.3 (27.4)	22.6 (26.3)
Median (Q1; Q3)	0.0 (0.0; 33.3)	33.3 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	615	309
Mean (SD)	20.0 (25.4)	21.0 (24.8)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	489	283
Mean (SD)	11.5 (18.7)	13.1 (21.0)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	485	269
Mean (SD)	11.8 (20.3)	13.0 (21.4)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)

EORTC QLQ-C30 Dyspnoea	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	444	249
Mean (SD)	11.6 (19.3)	12.7 (20.8)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	454	221
Mean (SD)	11.5 (20.0)	11.8 (19.1)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants: full-analysis-set population
e: Number of observations at each time point
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

Tabelle 4G-11: Auswertung über den Studienverlauf der Symptomskala Schlaflosigkeit des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Insomnia	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	701	366
Mean (SD)	24.3 (27.0)	25.2 (27.2)
Median (Q1; Q3)	33.3 (0.0; 33.3)	33.3 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	648	329
Mean (SD)	31.5 (28.1)	29.2 (28.7)
Median (Q1; Q3)	33.3 (0.0; 33.3)	33.3 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	615	309
Mean (SD)	29.3 (27.6)	27.1 (27.3)
Median (Q1; Q3)	33.3 (0.0; 33.3)	33.3 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	489	283
Mean (SD)	28.2 (26.5)	29.6 (29.2)
Median (Q1; Q3)	33.3 (0.0; 33.3)	33.3 (0.0; 33.3)

EORTC QLQ-C30 Insomnia	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab	Placebo + Chemotherapy[c] / Placebo
	N[d]=772	N[d]=385
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	485	269
Mean (SD)	27.1 (26.0)	27.0 (28.6)
Median (Q1; Q3)	33.3 (0.0; 33.3)	33.3 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	444	249
Mean (SD)	25.5 (26.4)	25.4 (28.5)
Median (Q1; Q3)	33.3 (0.0; 33.3)	33.3 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	454	221
Mean (SD)	23.7 (26.5)	26.4 (30.8)
Median (Q1; Q3)	33.3 (0.0; 33.3)	33.3 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

e: Number of observations at each time point

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Appetitverlust

Tabelle 4G-12: Auswertung über den Studienverlauf der Symptomskala Appetitverlust des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Appetite Loss	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab	Placebo + Chemotherapy[c] / Placebo
	N[d]=772	N[d]=385
Neoadjuvant Baseline		
N[e]	701	366
Mean (SD)	8.3 (17.2)	8.8 (18.2)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 66.7
Neoadjuvant Week 12		
N[e]	648	329
Mean (SD)	23.4 (27.1)	16.8 (23.3)
Median (Q1; Q3)	33.3 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	615	309
Mean (SD)	24.0 (27.2)	18.9 (24.2)
Median (Q1; Q3)	33.3 (0.0; 33.3)	0.0 (0.0; 33.3)

EORTC QLQ-C30 Appetite Loss	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	489	283
Mean (SD)	10.1 (19.3)	9.0 (18.1)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	485	269
Mean (SD)	9.2 (18.1)	7.2 (17.0)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	444	249
Mean (SD)	7.7 (17.0)	5.5 (14.1)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 66.7
Year 2		
N[e]	454	221
Mean (SD)	6.2 (14.8)	6.9 (17.2)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants: full-analysis-set population
e: Number of observations at each time point
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Verstopfung

Tabelle 4G-13: Auswertung über den Studienverlauf der Symptomskala Verstopfung des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Constipation	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	701	366
Mean (SD)	7.0 (17.1)	9.7 (18.9)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	648	329
Mean (SD)	19.4 (27.2)	18.3 (25.7)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)

EORTC QLQ-C30 Constipation	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	615	309
Mean (SD)	21.3 (26.9)	19.2 (27.4)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	489	283
Mean (SD)	11.5 (21.2)	11.9 (21.3)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	485	269
Mean (SD)	12.4 (22.2)	11.3 (21.6)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	444	249
Mean (SD)	12.7 (21.8)	11.4 (21.2)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	454	221
Mean (SD)	11.5 (22.2)	10.7 (20.6)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

e: Number of observations at each time point

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Diarrhoe

Tabelle 4G-14: Auswertung über den Studienverlauf der Symptomskala Diarrhoe des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Diarrhea	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	701	366
Mean (SD)	5.3 (13.5)	4.9 (13.1)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)

EORTC QLQ-C30 Diarrhea	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Min; Max	0.0; 100.0	0.0; 66.7
Neoadjuvant Week 12		
N[e]	648	329
Mean (SD)	13.1 (22.4)	9.9 (17.9)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	615	309
Mean (SD)	9.2 (18.6)	6.8 (16.1)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	489	283
Mean (SD)	5.4 (14.8)	4.4 (12.6)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 66.7
Adjuvant Week 12		
N[e]	485	269
Mean (SD)	5.5 (13.8)	4.6 (12.5)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 66.7
Adjuvant Week 24		
N[e]	444	249
Mean (SD)	6.1 (15.0)	4.6 (12.9)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 66.7
Year 2		
N[e]	454	221
Mean (SD)	4.8 (13.3)	2.4 (8.7)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 66.7	0.0; 33.3

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

e: Number of observations at each time point

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-BR23

EORTC QLQ-BR23: Symptomskala Nebenwirkungen der systemischen Therapie

Tabelle 4G-15: Auswertung über den Studienverlauf der Symptomskala Nebenwirkungen der systemischen Therapie des EORTC QLQ-BR23 mit dem zu bewertenden Arzneimittel

EORTC QLQ-BR23 Systemic Therapy Side Effects	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	695	361
Mean (SD)	8.1 (10.7)	8.0 (10.7)
Median (Q1; Q3)	4.8 (0.0; 9.5)	4.8 (0.0; 14.3)
Min; Max	0.0; 76.2	0.0; 81.0
Neoadjuvant Week 12		
N[e]	644	328
Mean (SD)	35.0 (18.4)	32.4 (18.5)
Median (Q1; Q3)	33.3 (19.0; 47.6)	33.3 (19.0; 42.9)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	611	307
Mean (SD)	32.2 (18.7)	30.4 (19.6)
Median (Q1; Q3)	28.6 (19.0; 42.9)	28.6 (14.3; 42.9)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	487	282
Mean (SD)	16.4 (13.9)	16.0 (14.9)
Median (Q1; Q3)	14.3 (4.8; 23.8)	14.3 (4.8; 23.8)
Min; Max	0.0; 81.0	0.0; 85.7
Adjuvant Week 12		
N[e]	483	267
Mean (SD)	16.5 (13.8)	16.4 (15.4)
Median (Q1; Q3)	14.3 (4.8; 23.8)	14.3 (4.8; 23.8)
Min; Max	0.0; 71.4	0.0; 100.0
Adjuvant Week 24		
N[e]	442	247
Mean (SD)	15.7 (13.9)	14.4 (14.5)
Median (Q1; Q3)	14.3 (4.8; 23.8)	9.5 (4.8; 19.0)
Min; Max	0.0; 76.2	0.0; 81.0
Year 2		
N[e]	452	221
Mean (SD)	13.0 (13.0)	13.1 (13.8)
Median (Q1; Q3)	9.5 (4.8; 19.0)	9.5 (4.8; 19.0)
Min; Max	0.0; 71.4	0.0; 100.0

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

e: Number of observations at each time point

EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items;

EORTC QLQ-BR23 Systemic Therapy Side Effects	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	Placebo + Chemotherapy[c] / Placebo N[d]=385
Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation		

EORTC QLQ-BR23: Symptomskala Symptome im Brustbereich

Tabelle 4G-16: Auswertung über den Studienverlauf der Symptomskala Symptome im Brustbereich des EORTC QLQ-BR23 mit dem zu bewertenden Arzneimittel

EORTC QLQ-BR23 Breast Symptoms	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	695	361
Mean (SD)	18.7 (20.4)	18.5 (19.3)
Median (Q1; Q3)	16.7 (0.0; 25.0)	16.7 (0.0; 25.0)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	644	328
Mean (SD)	8.2 (12.0)	7.7 (13.2)
Median (Q1; Q3)	0.0 (0.0; 16.7)	0.0 (0.0; 8.3)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	611	307
Mean (SD)	8.8 (12.9)	8.5 (14.0)
Median (Q1; Q3)	0.0 (0.0; 16.7)	8.3 (0.0; 8.3)
Min; Max	0.0; 83.3	0.0; 100.0
Adjuvant Baseline		
N[e]	487	282
Mean (SD)	22.2 (18.7)	23.0 (20.2)
Median (Q1; Q3)	16.7 (8.3; 33.3)	16.7 (8.3; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	483	267
Mean (SD)	18.6 (18.0)	18.4 (18.8)
Median (Q1; Q3)	16.7 (8.3; 25.0)	16.7 (0.0; 25.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	442	247
Mean (SD)	16.8 (17.2)	16.7 (18.1)
Median (Q1; Q3)	16.7 (0.0; 25.0)	16.7 (0.0; 25.0)
Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	452	221
Mean (SD)	14.0 (16.2)	14.0 (17.6)
Median (Q1; Q3)	8.3 (0.0; 25.0)	8.3 (0.0; 25.0)
Min; Max	0.0; 100.0	0.0; 100.0

EORTC QLQ-BR23 Breast Symptoms	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	Placebo + Chemotherapy[c] / Placebo N[d]=385
a: Database Cutoff Date: 23MAR2021		
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles		
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles		
d: Number of participants: full-analysis-set population		
e: Number of observations at each time point		
EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation		

EORTC QLQ-BR23: Symptomskala Symptome im Armbereich

Tabelle 4G-17: Auswertung über den Studienverlauf der Symptomskala Symptome im Armbereich des EORTC QLQ-BR23 mit dem zu bewertenden Arzneimittel

EORTC QLQ-BR23 Arm Symptoms	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	695	361
Mean (SD)	10.5 (16.4)	10.0 (15.1)
Median (Q1; Q3)	0.0 (0.0; 11.1)	0.0 (0.0; 11.1)
Min; Max	0.0; 100.0	0.0; 77.8
Neoadjuvant Week 12		
N[e]	644	328
Mean (SD)	11.5 (17.2)	10.9 (17.3)
Median (Q1; Q3)	0.0 (0.0; 22.2)	0.0 (0.0; 11.1)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	611	307
Mean (SD)	10.6 (16.5)	11.6 (16.7)
Median (Q1; Q3)	0.0 (0.0; 11.1)	0.0 (0.0; 22.2)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	487	282
Mean (SD)	19.9 (19.5)	21.6 (20.5)
Median (Q1; Q3)	11.1 (0.0; 33.3)	22.2 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	483	267
Mean (SD)	19.4 (20.5)	20.3 (19.6)
Median (Q1; Q3)	11.1 (0.0; 33.3)	22.2 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 77.8
Adjuvant Week 24		
N[e]	442	247
Mean (SD)	20.1 (20.9)	18.7 (19.2)
Median (Q1; Q3)	11.1 (0.0; 33.3)	11.1 (0.0; 22.2)

EORTC QLQ-BR23 Arm Symptoms	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	Placebo + Chemotherapy[c] / Placebo N[d]=385
Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	452	221
Mean (SD)	16.8 (20.4)	15.4 (20.1)
Median (Q1; Q3)	11.1 (0.0; 22.2)	11.1 (0.0; 22.2)
Min; Max	0.0; 88.9	0.0; 100.0

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants: full-analysis-set population
e: Number of observations at each time point
EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-BR23: Symptomskala Belastung durch Haarausfall

Tabelle 4G-18: Auswertung über den Studienverlauf der Symptomskala Belastung durch Haarausfall des EORTC QLQ-BR23 mit dem zu bewertenden Arzneimittel

EORTC QLQ-BR23 Upset by Hair Loss (Imputed)[f]	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	695	361
Mean (SD)	2.2 (11.0)	2.5 (12.5)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	644	328
Mean (SD)	32.5 (36.8)	30.0 (34.4)
Median (Q1; Q3)	33.3 (0.0; 66.7)	33.3 (0.0; 66.7)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	611	307
Mean (SD)	22.4 (32.9)	24.0 (33.2)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	487	282
Mean (SD)	4.5 (18.6)	7.1 (23.0)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	483	267
Mean (SD)	2.4 (14.3)	4.6 (18.0)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)

EORTC QLQ-BR23 Upset by Hair Loss (Imputed)[f]	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	Placebo + Chemotherapy[c] / Placebo N[d]=385
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	442	247
Mean (SD)	2.9 (13.7)	3.4 (16.0)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	452	221
Mean (SD)	4.3 (17.5)	3.8 (13.9)
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants: full-analysis-set population
e: Number of observations at each time point
f: For participants who did not lose any hair, the score was imputed as not upset at all by the loss of hair
EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EQ-5D VAS

EQ-5D VAS

Tabelle 4G-19: Auswertung über den Studienverlauf des EQ-5D VAS mit dem zu bewertenden Arzneimittel

EQ-5D VAS	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	707	369
Mean (SD)	81.1 (18.1)	82.6 (17.0)
Median (Q1; Q3)	88.0 (74.0; 93.0)	89.0 (78.0; 94.0)
Min; Max	9.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	657	336
Mean (SD)	73.0 (17.5)	74.3 (17.8)
Median (Q1; Q3)	77.0 (61.0; 88.0)	79.0 (66.0; 88.0)
Min; Max	10.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	616	311
Mean (SD)	72.8 (18.1)	75.0 (16.4)
Median (Q1; Q3)	78.0 (60.0; 88.0)	79.0 (65.0; 89.0)
Min; Max	0.0; 100.0	9.0; 100.0
Adjuvant Baseline		

EQ-5D VAS	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
N[e]	495	285
Mean (SD)	78.4 (14.6)	78.8 (14.5)
Median (Q1; Q3)	80.0 (70.0; 90.0)	80.0 (70.0; 90.0)
Min; Max	30.0; 100.0	35.0; 100.0
Adjuvant Week 12		
N[e]	485	274
Mean (SD)	79.9 (14.6)	79.6 (15.5)
Median (Q1; Q3)	81.0 (71.0; 90.0)	81.0 (70.0; 90.0)
Min; Max	8.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	444	249
Mean (SD)	80.6 (14.9)	81.2 (13.3)
Median (Q1; Q3)	82.0 (71.0; 90.0)	81.0 (71.0; 91.0)
Min; Max	11.0; 100.0	35.0; 100.0
Year 2		
N[e]	454	221
Mean (SD)	80.9 (14.3)	81.6 (14.5)
Median (Q1; Q3)	81.5 (73.0; 91.0)	84.0 (75.0; 91.0)
Min; Max	13.0; 100.0	5.0; 100.0

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants: full-analysis-set population
e: Number of observations at each time point
EQ-5D VAS: European Quality of Life 5 Dimensions Visual Analog Scale; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

Anhang 4-G3.2: Gesundheitsbezogene Lebensqualität

Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-20: Auswertung über den Studienverlauf der Funktionsskala Körperliche Funktion des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Physical Functioning	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	701	366
Mean (SD)	91.9 (12.8)	91.5 (13.1)
Median (Q1; Q3)	100.0 (86.7; 100.0)	100.0 (86.7; 100.0)
Min; Max	6.7; 100.0	33.3; 100.0
Neoadjuvant Week 12		

EORTC QLQ-C30 Physical Functioning	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
N[e]	648	329
Mean (SD)	76.5 (19.4)	78.8 (18.2)
Median (Q1; Q3)	80.0 (66.7; 93.3)	86.7 (66.7; 93.3)
Min; Max	0.0; 100.0	6.7; 100.0
Neoadjuvant Week 21		
N[e]	615	309
Mean (SD)	77.0 (19.0)	79.2 (17.1)
Median (Q1; Q3)	80.0 (66.7; 93.3)	80.0 (73.3; 93.3)
Min; Max	0.0; 100.0	13.3; 100.0
Adjuvant Baseline		
N[e]	489	283
Mean (SD)	83.3 (15.3)	81.6 (16.6)
Median (Q1; Q3)	86.7 (80.0; 93.3)	86.7 (73.3; 93.3)
Min; Max	20.0; 100.0	26.7; 100.0
Adjuvant Week 12		
N[e]	485	269
Mean (SD)	84.8 (15.1)	84.1 (15.4)
Median (Q1; Q3)	86.7 (80.0; 100.0)	86.7 (80.0; 93.3)
Min; Max	20.0; 100.0	6.7; 100.0
Adjuvant Week 24		
N[e]	444	249
Mean (SD)	84.8 (15.7)	85.4 (15.0)
Median (Q1; Q3)	86.7 (80.0; 100.0)	86.7 (80.0; 100.0)
Min; Max	13.3; 100.0	33.3; 100.0
Year 2		
N[e]	454	221
Mean (SD)	86.3 (16.4)	86.9 (16.9)
Median (Q1; Q3)	93.3 (80.0; 100.0)	93.3 (80.0; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants: full-analysis-set population
e: Number of observations at each time point
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-21: Auswertung über den Studienverlauf der Funktionsskala Rollenfunktion des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Role Functioning	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		

EORTC QLQ-C30 Role Functioning	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
N[e]	701	366
Mean (SD)	90.9 (18.4)	89.1 (19.8)
Median (Q1; Q3)	100.0 (83.3; 100.0)	100.0 (83.3; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	648	329
Mean (SD)	70.1 (27.0)	75.2 (24.6)
Median (Q1; Q3)	66.7 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	615	309
Mean (SD)	71.4 (26.7)	75.3 (24.9)
Median (Q1; Q3)	66.7 (66.7; 100.0)	66.7 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	489	283
Mean (SD)	79.9 (21.7)	78.1 (23.0)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	485	269
Mean (SD)	82.6 (21.3)	82.0 (22.0)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	444	249
Mean (SD)	83.7 (20.5)	82.3 (21.9)
Median (Q1; Q3)	100.0 (66.7; 100.0)	100.0 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	454	221
Mean (SD)	84.9 (22.5)	87.1 (21.0)
Median (Q1; Q3)	100.0 (66.7; 100.0)	100.0 (83.3; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

e: Number of observations at each time point

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-22: Auswertung über den Studienverlauf der Funktionsskala Emotionale Funktion des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Emotional Functioning	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	701	366
Mean (SD)	76.1 (19.5)	75.2 (20.7)
Median (Q1; Q3)	75.0 (66.7; 91.7)	75.0 (66.7; 91.7)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	648	329
Mean (SD)	75.9 (21.1)	74.9 (22.1)
Median (Q1; Q3)	75.0 (66.7; 91.7)	75.0 (66.7; 91.7)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	615	309
Mean (SD)	74.6 (20.8)	74.9 (21.6)
Median (Q1; Q3)	75.0 (66.7; 91.7)	75.0 (66.7; 91.7)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	489	283
Mean (SD)	81.7 (17.7)	79.0 (20.8)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	8.3; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	485	269
Mean (SD)	80.6 (18.8)	79.4 (19.8)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	16.7; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	444	249
Mean (SD)	79.6 (19.6)	78.4 (20.4)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	8.3; 100.0
Year 2		
N[e]	454	221
Mean (SD)	80.3 (19.3)	78.8 (21.4)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	8.3; 100.0	8.3; 100.0

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

e: Number of observations at each time point

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-23: Auswertung über den Studienverlauf der Funktionsskala Kognitive Funktion des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Cognitive Functioning	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	701	366
Mean (SD)	88.3 (17.7)	88.6 (18.0)
Median (Q1; Q3)	100.0 (83.3; 100.0)	100.0 (83.3; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	648	329
Mean (SD)	79.4 (20.6)	80.7 (23.4)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	615	309
Mean (SD)	78.4 (21.7)	78.1 (23.7)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	489	283
Mean (SD)	82.4 (19.6)	82.0 (20.4)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	485	269
Mean (SD)	81.9 (19.2)	80.7 (20.6)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	444	249
Mean (SD)	80.8 (20.3)	80.3 (21.6)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	454	221
Mean (SD)	82.6 (20.2)	82.5 (20.0)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

e: Number of observations at each time point

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-24: Auswertung über den Studienverlauf der Funktionsskala Soziale Funktion des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Social Functioning	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=772	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	701	366
Mean (SD)	87.4 (20.0)	87.0 (20.7)
Median (Q1; Q3)	100.0 (83.3; 100.0)	100.0 (83.3; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	648	329
Mean (SD)	71.4 (26.8)	74.0 (23.3)
Median (Q1; Q3)	66.7 (66.7; 100.0)	66.7 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	615	309
Mean (SD)	71.4 (26.0)	75.3 (24.2)
Median (Q1; Q3)	66.7 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	489	283
Mean (SD)	80.2 (22.6)	77.5 (26.3)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	485	269
Mean (SD)	84.7 (19.1)	83.1 (22.4)
Median (Q1; Q3)	100.0 (66.7; 100.0)	100.0 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	444	249
Mean (SD)	83.6 (22.8)	83.3 (22.4)
Median (Q1; Q3)	100.0 (66.7; 100.0)	100.0 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	454	221
Mean (SD)	87.6 (20.9)	85.7 (22.7)
Median (Q1; Q3)	100.0 (83.3; 100.0)	100.0 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

e: Number of observations at each time point

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-BR23

EORTC QLQ-BR23: Funktionsskala Körperbild

Tabelle 4G-25: Auswertung über den Studienverlauf der Funktionsskala Körperbild des EORTC QLQ-BR23 mit dem zu bewertenden Arzneimittel

EORTC QLQ-BR23 Body Image	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	695	361
Mean (SD)	90.8 (16.1)	90.9 (16.2)
Median (Q1; Q3)	100.0 (83.3; 100.0)	100.0 (83.3; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	644	328
Mean (SD)	68.3 (27.5)	69.7 (27.2)
Median (Q1; Q3)	75.0 (50.0; 91.7)	75.0 (50.0; 91.7)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	611	307
Mean (SD)	68.5 (27.2)	68.8 (28.6)
Median (Q1; Q3)	75.0 (50.0; 91.7)	75.0 (50.0; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	487	282
Mean (SD)	75.6 (25.4)	75.1 (26.1)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	483	267
Mean (SD)	78.8 (22.2)	78.7 (24.0)
Median (Q1; Q3)	83.3 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	442	247
Mean (SD)	81.1 (22.3)	78.0 (24.0)
Median (Q1; Q3)	91.7 (66.7; 100.0)	83.3 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	452	221
Mean (SD)	83.3 (22.1)	80.8 (23.6)
Median (Q1; Q3)	91.7 (66.7; 100.0)	91.7 (66.7; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

e: Number of observations at each time point

EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items;

EORTC QLQ-BR23 Body Image	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	Placebo + Chemotherapy[c] / Placebo N[d]=385
Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation		

EORTC QLQ-BR23: Funktionsskala Sexuelle Aktivität

Tabelle 4G-26: Auswertung über den Studienverlauf der Funktionsskala Sexuelle Aktivität des EORTC QLQ-BR23 mit dem zu bewertenden Arzneimittel

EORTC QLQ-BR23 Sexual Functioning	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	678	352
Mean (SD)	21.8 (24.1)	21.8 (25.2)
Median (Q1; Q3)	16.7 (0.0; 33.3)	16.7 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	631	319
Mean (SD)	15.2 (21.0)	14.7 (20.9)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	599	302
Mean (SD)	13.9 (19.9)	12.2 (18.9)
Median (Q1; Q3)	0.0 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 83.3
Adjuvant Baseline		
N[e]	479	279
Mean (SD)	17.0 (20.8)	16.6 (21.3)
Median (Q1; Q3)	16.7 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	478	262
Mean (SD)	19.9 (22.3)	19.3 (22.9)
Median (Q1; Q3)	16.7 (0.0; 33.3)	16.7 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	433	241
Mean (SD)	20.3 (23.5)	21.2 (22.1)
Median (Q1; Q3)	16.7 (0.0; 33.3)	16.7 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	447	220
Mean (SD)	22.1 (25.4)	20.7 (24.7)
Median (Q1; Q3)	16.7 (0.0; 33.3)	0.0 (0.0; 33.3)
Min; Max	0.0; 100.0	0.0; 100.0

EORTC QLQ-BR23 Sexual Functioning	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	Placebo + Chemotherapy[c] / Placebo N[d]=385
a: Database Cutoff Date: 23MAR2021		
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles		
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles		
d: Number of participants: full-analysis-set population		
e: Number of observations at each time point		
EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation		

EORTC QLQ-BR23: Funktionsskala Sexueller Genuss

Tabelle 4G-27: Auswertung über den Studienverlauf der Funktionsskala Sexueller Genuss des EORTC QLQ-BR23 mit dem zu bewertenden Arzneimittel

EORTC QLQ-BR23 Sexual Enjoyment[f]	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	Placebo + Chemotherapy[c] / Placebo N[d]=385
Neoadjuvant Baseline		
N[e]	321	160
Mean (SD)	57.0 (28.3)	57.9 (32.0)
Median (Q1; Q3)	66.7 (33.3; 66.7)	66.7 (33.3; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	228	112
Mean (SD)	47.4 (28.8)	48.5 (26.8)
Median (Q1; Q3)	33.3 (33.3; 66.7)	33.3 (33.3; 66.7)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	202	89
Mean (SD)	43.1 (25.9)	45.3 (26.7)
Median (Q1; Q3)	33.3 (33.3; 66.7)	33.3 (33.3; 66.7)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	178	104
Mean (SD)	44.4 (26.0)	47.1 (26.1)
Median (Q1; Q3)	33.3 (33.3; 66.7)	33.3 (33.3; 66.7)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	218	114
Mean (SD)	45.7 (25.7)	48.0 (27.0)
Median (Q1; Q3)	33.3 (33.3; 66.7)	33.3 (33.3; 66.7)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		
N[e]	197	117
Mean (SD)	48.6 (26.6)	44.7 (24.8)
Median (Q1; Q3)	33.3 (33.3; 66.7)	33.3 (33.3; 66.7)

Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	224	99
Mean (SD)	50.3 (26.0)	48.8 (27.9)
Median (Q1; Q3)	33.3 (33.3; 66.7)	33.3 (33.3; 66.7)
Min; Max	0.0; 100.0	0.0; 100.0

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants: full-analysis-set population
e: Number of observations at each time point
f: For participants who were not sexually active, no answer was given to sexual enjoyment item
EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

EORTC QLQ-BR23: Funktionsskala Zukunftsperspektive

Tabelle 4G-28: Auswertung über den Studienverlauf der Funktionsskala Zukunftsperspektive des EORTC QLQ-BR23 mit dem zu bewertenden Arzneimittel

EORTC QLQ-BR23 Future Perspective	**Study: KEYNOTE 522[a]**	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	**Placebo + Chemotherapy[c] / Placebo** N[d]=385
Neoadjuvant Baseline		
N[e]	695	361
Mean (SD)	53.7 (31.3)	54.4 (31.6)
Median (Q1; Q3)	66.7 (33.3; 66.7)	66.7 (33.3; 66.7)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 12		
N[e]	644	328
Mean (SD)	52.3 (31.0)	50.3 (32.6)
Median (Q1; Q3)	66.7 (33.3; 66.7)	66.7 (33.3; 66.7)
Min; Max	0.0; 100.0	0.0; 100.0
Neoadjuvant Week 21		
N[e]	611	307
Mean (SD)	50.0 (31.7)	50.7 (32.5)
Median (Q1; Q3)	66.7 (33.3; 66.7)	66.7 (33.3; 66.7)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Baseline		
N[e]	487	282
Mean (SD)	59.5 (29.3)	58.2 (31.9)
Median (Q1; Q3)	66.7 (33.3; 66.7)	66.7 (33.3; 66.7)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 12		
N[e]	483	267
Mean (SD)	60.1 (30.0)	58.6 (31.2)
Median (Q1; Q3)	66.7 (33.3; 66.7)	66.7 (33.3; 66.7)
Min; Max	0.0; 100.0	0.0; 100.0
Adjuvant Week 24		

EORTC QLQ-BR23 Future Perspective	Study: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapy[b] / Pembrolizumab N[d]=770	Placebo + Chemotherapy[c] / Placebo N[d]=385
N[e]	442	247
Mean (SD)	59.1 (30.3)	57.1 (32.1)
Median (Q1; Q3)	66.7 (33.3; 66.7)	66.7 (33.3; 66.7)
Min; Max	0.0; 100.0	0.0; 100.0
Year 2		
N[e]	452	221
Mean (SD)	61.2 (30.9)	61.4 (30.9)
Median (Q1; Q3)	66.7 (33.3; 100.0)	66.7 (33.3; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

e: Number of observations at each time point

EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

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.

Alle Ergebnisse beziehen sich auf den vierten Datenschnitt (23.März.2021).

Anhang 4-G4.1: Mortalität

Gesamtüberleben

Tabelle 4G-29: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Overall Survival	N[d]	Participants with Event n (%)	Median Time[e] in Months [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age (Years)									
< 65	700	65 (9.3)	Not reached [-; -]	342	45 (13.2)	Not reached [-; -]	0.71 [0.48; 1.03]	0.073	0.708
≥ 65	84	15 (17.9)	Not reached [-; -]	48	10 (20.8)	Not reached [-; -]	0.83 [0.37; 1.85]	0.654	
ECOG Performance Status									
0	678	64 (9.4)	Not reached [-; -]	341	49 (14.4)	Not reached [-; -]	0.65 [0.45; 0.94]	0.022	0.152
1	106	16 (15.1)	Not reached [-; -]	49	6 (12.2)	Not reached [-; -]	1.32 [0.51; 3.36]	0.567	
Nodal Status									
Negative	376	24 (6.4)	Not reached [-; -]	194	15 (7.7)	Not reached [-; -]	0.82 [0.43; 1.57]	0.558	0.587
Positive	408	56 (13.7)	Not reached [-; -]	196	40 (20.4)	Not reached [-; -]	0.67 [0.45; 1.00]	0.052	
Tumor Size									
T1/T2	581	36 (6.2)	Not reached [-; -]	290	28 (9.7)	Not reached [-; -]	0.63 [0.39; 1.04]	0.069	0.447
T3/T4	203	44 (21.7)	Not reached [-; -]	100	27 (27.0)	Not reached [-; -]	0.83 [0.51; 1.34]	0.439	
Choice of Carboplatin									
Q3W	334	31 (9.3)	Not reached [-; -]	167	24 (14.4)	Not reached [-; -]	0.65 [0.38; 1.11]	0.112	0.654
Weekly	444	48 (10.8)	Not reached [-; -]	220	31 (14.1)	Not reached [-; -]	0.76 [0.49; 1.20]	0.239	

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants: intention-to-treat population
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Overall Survival	N[d]	Participants with Event n (%)	Median Time[e] in Months [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
g: Two-sided p-value based on Wald test									
h: Based on Cox regression model with subgroup and treatment as a covariate, as well as treatment by subgroup interaction (p-value of likelihood ratio test for interaction term)									
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; Q3W: Every 3 Weeks									

Anhang 4-G4.2: Morbidität

Ereignisfreies Überleben

Tabelle 4G-30: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Ereignisfreies Überleben aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Event-Free Survival	N[d]	Participants with Event n (%)	Median Time[e] in Months [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age (Years)									
< 65	700	103 (14.7)	Not reached [-; -]	342	79 (23.1)	Not reached [-; -]	0.61 [0.45; 0.82]	< 0.001	0.503
≥ 65	84	20 (23.8)	Not reached [-; -]	48	14 (29.2)	Not reached [41.9; -]	0.79 [0.40; 1.56]	0.498	
ECOG Performance Status									
0	678	101 (14.9)	Not reached [-; -]	341	80 (23.5)	Not reached [-; -]	0.60 [0.45; 0.80]	< 0.001	0.407
1	106	22 (20.8)	Not reached [-; -]	49	13 (26.5)	Not reached [-; -]	0.81 [0.41; 1.62]	0.556	
Geographic Region									
Asia	136	13 (9.6)	Not reached [-; -]	80	20 (25.0)	Not reached [-; -]	0.35 [0.17; 0.71]	0.003	0.177
Europe/Israel/North America/Australia	607	98 (16.1)	Not reached [-; -]	285	65 (22.8)	Not reached [-; -]	0.69 [0.50; 0.94]	0.019	
Rest of World	41	12 (29.3)	Not reached [36.8; -]	25	8 (32.0)	Not reached [23.6; -]	0.81 [0.33; 1.98]	0.640	
Nodal Status									
Negative	376	43 (11.4)	Not reached [-; -]	194	36 (18.6)	Not reached [-; -]	0.58 [0.37; 0.91]	0.017	0.713
Positive	408	80 (19.6)	Not reached [-; -]	196	57 (29.1)	Not reached [-; -]	0.65 [0.46; 0.91]	0.013	
Tumor Size									
T1/T2	581	64 (11.0)	Not reached [-; -]	290	59 (20.3)	Not reached [-; -]	0.51 [0.36; 0.73]	< 0.001	0.079
T3/T4	203	59 (29.1)	Not reached [-; -]	100	34 (34.0)	Not reached [-; -]	0.84 [0.55; 1.28]	0.413	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Event-Free Survival	N[d]	Participants with Event n (%)	Median Time[e] in Months [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Choice of Carboplatin									
Q3W	334	50 (15.0)	Not reached [-; -]	167	37 (22.2)	Not reached [-; -]	0.65 [0.42; 0.99]	0.044	0.804
Weekly	444	71 (16.0)	Not reached [-; -]	220	56 (25.5)	Not reached [-; -]	0.60 [0.42; 0.86]	0.005	
PD-L1 CPS 1 Cutoff									
PD-L1 CPS ≥ 1	656	98 (14.9)	Not reached [-; -]	317	68 (21.5)	Not reached [-; -]	0.67 [0.49; 0.92]	0.012	0.269
PD-L1 CPS < 1	128	25 (19.5)	Not reached [-; -]	69	25 (36.2)	Not reached [-; -]	0.48 [0.28; 0.85]	0.011	
PD-L1 CPS 10 Cutoff									
PD-L1 CPS ≥ 10	393	38 (9.7)	Not reached [-; -]	177	30 (16.9)	Not reached [-; -]	0.56 [0.35; 0.90]	0.017	0.496
PD-L1 CPS < 10	391	85 (21.7)	Not reached [-; -]	209	63 (30.1)	Not reached [-; -]	0.68 [0.49; 0.94]	0.020	
PD-L1 CPS 20 Cutoff									
PD-L1 CPS ≥ 20	247	17 (6.9)	Not reached [-; -]	121	19 (15.7)	Not reached [-; -]	0.42 [0.22; 0.81]	0.009	0.193
PD-L1 CPS < 20	537	106 (19.7)	Not reached [-; -]	265	74 (27.9)	Not reached [-; -]	0.68 [0.50; 0.91]	0.010	
Menopausal Status									
Pre-menopausal	438	60 (13.7)	Not reached [-; -]	221	47 (21.3)	Not reached [-; -]	0.62 [0.42; 0.91]	0.014	0.888
Post-menopausal	345	63 (18.3)	Not reached [-; -]	169	46 (27.2)	Not reached [-; -]	0.64 [0.44; 0.93]	0.020	
Ethnic Origin									
Hispanic or Latino	86	24 (27.9)	Not reached [-; -]	39	13 (33.3)	Not reached [28.9; -]	0.74 [0.38; 1.45]	0.377	0.520
Not Hispanic or Latino	615	83 (13.5)	Not reached [-; -]	307	69 (22.5)	Not reached [-; -]	0.58 [0.42; 0.80]	< 0.001	
HER2 Status									
0-1+ by IHC	595	91 (15.3)	Not reached [-; -]	286	69 (24.1)	Not reached [-; -]	0.60 [0.44; 0.82]	0.001	0.537
2+ by IHC (but FISH-)	188	32 (17.0)	Not reached [-; -]	104	24 (23.1)	Not reached [-; -]	0.73 [0.43; 1.24]	0.241	
Baseline Lactate Dehydrogenase (LDH)									
≤ ULN	631	93 (14.7)	Not reached [-; -]	309	69 (22.3)	Not reached [-; -]	0.63 [0.46; 0.86]	0.004	0.966
> ULN	149	29 (19.5)	Not reached [-; -]	80	23 (28.8)	Not reached [43.5; -]	0.65 [0.37; 1.12]	0.119	

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

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

f: For PD-L1 CPS 1 Cutoff subgroup, based on Cox regression model with treatment as a covariate stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Q3W vs. Weekly); for all other subgroups, unstratified Cox regression model is used

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Event-Free Survival	N[d]	Participants with Event n (%)	Median Time[e] in Months [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Months [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
g: Two-sided p-value based on Wald test									
h: For PD-L1 CPS 1 Cutoff subgroup, based on Cox regression model with subgroup,treatment and stratification factors (nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4) and choice of carboplatin (Q3W vs Weekly)) as a covariate, as well as treatment by subgroup interaction; for all other subgroups, stratification factors are not used in the model (p-value of likelihood ratio test for interaction term)									
CI: Confidence Interval; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; FISH: Fluorescence In Situ Hybridization; HER2: Human Epidermal Growth Factor Receptor 2; IHC: Immunohistochemistry; PD-L1: Programmed Cell Death - Ligand 1; Q3W: Every 3 Weeks; ULN: Upper Limit of Normal									

Pathologische Komplettremission

Tabelle 4G-31: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Pathologische Komplettremission aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b]		Placebo + Chemotherapy[c]		Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]		p-Value for Interaction[g]
Pathological Complete Response (ypT0/Tis ypN0)	N[d]	Participants with Event n (%)	N[d]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[e] [95 %-CI]	p-Value[f]	Test
Age (Years)							
< 65	700	450 (64.3)	342	196 (57.3)	1.12 [1.01; 1.25]	0.035	0.891
≥ 65	84	44 (52.4)	48	21 (43.8)	1.20 [0.82; 1.75]	0.353	
ECOG Performance Status							
0	678	430 (63.4)	341	184 (54.0)	1.18 [1.05; 1.32]	0.005	0.070
1	106	64 (60.4)	49	33 (67.3)	0.90 [0.70; 1.15]	0.389	
Geographic Region							
Asia	136	82 (60.3)	80	36 (45.0)	1.34 [1.01; 1.77]	0.039	0.403
Europe/Israel/North America/Australia	607	388 (63.9)	285	169 (59.3)	1.08 [0.96; 1.21]	0.194	
Rest of World	41	24 (58.5)	25	12 (48.0)	1.22 [0.75; 1.98]	0.420	
Nodal Status							
Negative	376	239 (63.6)	194	118 (60.8)	1.05 [0.91; 1.20]	0.527	0.139
Positive	408	255 (62.5)	196	99 (50.5)	1.24 [1.06; 1.45]	0.008	
Tumor Size							
T1/T2	581	393 (67.6)	290	175 (60.3)	1.12 [1.01; 1.25]	0.040	0.987
T3/T4	203	101 (49.8)	100	42 (42.0)	1.18 [0.91; 1.55]	0.216	
Choice of Carboplatin							
Q3W	334	214 (64.1)	167	100 (59.9)	1.07 [0.92; 1.24]	0.370	0.371
Weekly	444	280 (63.1)	220	117 (53.2)	1.19 [1.03; 1.37]	0.019	
PD-L1 CPS 1 Cutoff							
PD-L1 CPS ≥ 1	656	436 (66.5)	317	187 (59.0)	1.13 [1.02; 1.26]	0.022	0.842
PD-L1 CPS < 1	128	58 (45.3)	69	27 (39.1)	1.18 [0.83; 1.68]	0.366	
PD-L1 CPS 10 Cutoff							
PD-L1 CPS ≥ 10	393	298 (75.8)	177	119 (67.2)	1.13 [1.00; 1.27]	0.044	0.368

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b]		Placebo + Chemotherapy[c]		Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]		
Pathological Complete Response (ypT0/Tis ypN0)	N[d]	Participants with Event n (%)	N[d]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[e] [95 %-CI]	p-Value[f]	p-Value for Interaction[g] Test
PD-L1 CPS < 10	391	196 (50.1)	209	95 (45.5)	1.10 [0.92; 1.32]	0.282	
PD-L1 CPS 20 Cutoff							
PD-L1 CPS ≥ 20	247	197 (79.8)	121	89 (73.6)	1.08 [0.96; 1.23]	0.200	0.942
PD-L1 CPS < 20	537	297 (55.3)	265	125 (47.2)	1.17 [1.01; 1.36]	0.036	
Menopausal Status							
Pre-menopausal	438	290 (66.2)	221	141 (63.8)	1.04 [0.92; 1.17]	0.544	0.069
Post-menopausal	345	204 (59.1)	169	76 (45.0)	1.31 [1.09; 1.59]	0.004	
Ethnic Origin							
Hispanic or Latino	86	50 (58.1)	39	19 (48.7)	1.19 [0.83; 1.73]	0.347	0.912
Not Hispanic or Latino	615	390 (63.4)	307	170 (55.4)	1.15 [1.02; 1.29]	0.023	
HER2 Status							
0-1+ by IHC	595	384 (64.5)	286	155 (54.2)	1.19 [1.05; 1.35]	0.005	0.098
2+ by IHC (but FISH-)	188	110 (58.5)	104	62 (59.6)	0.98 [0.80; 1.20]	0.854	
Baseline Lactate Dehydrogenase (LDH)							
≤ ULN	631	398 (63.1)	309	174 (56.3)	1.12 [1.00; 1.26]	0.053	0.741
> ULN	149	94 (63.1)	80	43 (53.8)	1.17 [0.93; 1.49]	0.186	

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

e: For PD-L1 CPS 1 Cutoff subgroup, Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is ≤ 1 % or ≥ 99 % in at least one cell of the stratum defined by stratification factors nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4) and choice of carboplatin (Q3W vs Weekly); for all other subgroups, unstratified analysis is used

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

g: For PD-L1 CPS 1 Cutoff subgroup, based on generalized linear model with subgroup, treatment and stratification factors (nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4) and choice of carboplatin (Q3W vs Weekly)) as covariates as well as treatment by subgroup interaction, considering a binomial distribution with log link function; for all other subgroups, stratification factors are not used in the model (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; FISH: Fluorescence In Situ Hybridization; HER2: Human Epidermal Growth Factor Receptor 2; IHC: Immunohistochemistry; PD-L1: Programmed Cell Death - Ligand 1; Q3W: Every 3 Weeks; ULN: Upper Limit of Normal

Brusterhaltende Operationen

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

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b]		Placebo + Chemotherapy[c]		Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]		
Breast Conserving Surgery	N[d]	Participants with Event n (%)	N[d]	Participants with Event n (%)	Risk Ratio/ Peto-Odds Ratio[e] [95 %-CI]	p-Value[f]	p-Value for Interaction[g] Test
Age (Years)							
< 65	700	325 (46.4)	342	154 (45.0)	1.03 [0.89; 1.19]	0.672	0.074
≥ 65	84	29 (34.5)	48	24 (50.0)	0.69 [0.46; 1.04]	0.075	
ECOG Performance Status							
0	678	318 (46.9)	341	157 (46.0)	1.02 [0.89; 1.17]	0.795	0.275

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b]		Placebo + Chemotherapy[c]		Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]		
Breast Conserving Surgery	**Participants with Event**		**Participants with Event**		**Risk Ratio/ Peto-Odds Ratio[e]**		**p-Value for Interaction[g]**
	N[d]	**n (%)**	**N[d]**	**n (%)**	**[95 %-CI]**	**p-Value[f]**	**Test**
1	106	36 (34.0)	49	21 (42.9)	0.79 [0.52; 1.20]	0.276	
Nodal Status							
Negative	376	189 (50.3)	194	94 (48.5)	1.04 [0.87; 1.24]	0.684	0.487
Positive	408	165 (40.4)	196	84 (42.9)	0.94 [0.77; 1.15]	0.570	
Tumor Size							
T1/T2	581	300 (51.6)	290	145 (50.0)	1.03 [0.90; 1.19]	0.651	0.216
T3/T4	203	54 (26.6)	100	33 (33.0)	0.81 [0.56; 1.16]	0.242	
Choice of Carboplatin							
Q3W	334	147 (44.0)	167	76 (45.5)	0.97 [0.79; 1.19]	0.750	0.776
Weekly	444	205 (46.2)	220	101 (45.9)	1.01 [0.84; 1.20]	0.949	

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; Q3W: Every 3 Weeks

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30 in der neoadjuvanten Phase

EORTC QLQ-C30: Symptomskala Erschöpfung

Tabelle 4G-33: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Erschöpfung in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Fatigue	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	628	19.04 (19.96)	564	39.38 (23.23)	681	20.52 [18.55; 22.50]	3.67	0.024	0.16	0.633
Placebo + Chemotherapy[c]	324	19.27 (19.79)	274	36.29 (24.89)	336	16.85 [14.14; 19.56]	[0.49; 6.85]		[0.02; 0.31]	
≥ 65										
Pembrolizumab + Chemotherapy[b]	73	19.03 (20.16)	51	44.23 (25.87)	81	26.70 [20.16; 33.24]	6.86	0.179	-	
Placebo + Chemotherapy[c]	42	18.78 (17.44)	35	39.68 (24.00)	47	19.84 [11.87; 27.82]	[-3.19; 16.91]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	602	18.66 (19.69)	534	39.43 (23.27)	657	21.07 [19.04; 23.09]	3.53	0.033	0.16	0.760
Placebo + Chemotherapy[c]	317	18.33 (18.77)	270	36.30 (24.64)	334	17.54 [14.79; 20.28]	[0.29; 6.77]		[0.01; 0.30]	
1										
Pembrolizumab + Chemotherapy[b]	99	21.32 (21.51)	81	42.11 (24.83)	105	21.12 [15.84; 26.40]	6.01	0.174	-	
Placebo + Chemotherapy[c]	49	24.94 (23.19)	39	39.32 (25.85)	49	15.11 [7.79; 22.43]	[-2.69; 14.71]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	132	22.81 (17.38)	127	37.10 (18.79)	135	15.29 [11.52; 19.06]	4.74	0.096	-	0.583
Placebo + Chemotherapy[c]	79	19.27 (17.94)	73	31.51 (22.38)	79	10.54 [5.79; 15.29]	[-0.85; 10.34]			
Europe/Israel/North										

America/Australia											
Pembrolizumab + Chemotherapy[b]	533	18.43 (20.52)	451	41.27 (24.71)	588	22.83 [20.59; 25.07]	4.10	0.030	0.18	
Placebo + Chemotherapy[c]	262	19.93 (20.32)	215	38.76 (25.10)	279	18.73 [15.60; 21.87]	[0.40; 7.79]		[0.02; 0.34]	
Rest of World										
Pembrolizumab + Chemotherapy[b]	36	14.20 (18.90)	37	30.93 (19.97)	39	18.24 [10.03; 26.45]	-3.37	0.594	-	
Placebo + Chemotherapy[c]	25	11.56 (13.79)	21	33.33 (27.44)	25	21.61 [11.20; 32.01]	[-15.93; 9.20]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	336	17.69 (19.89)	295	41.92 (24.54)	368	24.52 [21.71; 27.33]	4.01	0.083	-	0.835
Placebo + Chemotherapy[c]	181	18.78 (19.57)	151	39.51 (25.87)	191	20.51 [16.71; 24.31]	[-0.52; 8.54]			
Positive										
Pembrolizumab + Chemotherapy[b]	365	20.27 (19.98)	320	37.81 (22.32)	394	17.87 [15.36; 20.37]	3.93	0.054	-	
Placebo + Chemotherapy[c]	185	19.64 (19.50)	158	33.97 (23.44)	192	13.94 [10.53; 17.35]	[-0.07; 7.93]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	520	17.93 (18.57)	453	40.18 (23.75)	564	22.45 [20.25; 24.66]	4.78	0.008	0.21	0.525
Placebo + Chemotherapy[c]	274	19.83 (19.52)	233	37.48 (24.76)	287	17.67 [14.69; 20.65]	[1.23; 8.33]		[0.05; 0.37]	
T3/T4										
Pembrolizumab + Chemotherapy[b]	181	22.22 (23.28)	162	38.68 (22.74)	198	17.06 [13.42; 20.70]	1.34	0.651	-	
Placebo + Chemotherapy[c]	92	17.39 (19.51)	76	34.21 (24.80)	96	15.73 [10.72; 20.73]	[-4.47; 7.14]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	293	20.82 (20.46)	259	41.87 (24.50)	325	21.51 [18.55; 24.47]	5.33	0.026	0.23	0.369
Placebo + Chemotherapy[c]	158	18.14 (19.96)	138	35.19 (25.06)	163	16.18 [12.25; 20.10]	[0.64; 10.03]		[0.03; 0.44]	
Weekly										
Pembrolizumab + Chemotherapy[b]	408	17.76 (19.52)	356	38.26 (22.62)	437	20.64 [18.18; 23.09]	2.48	0.220	-	
Placebo + Chemotherapy[c]	206	19.90 (19.20)	171	37.88 (24.54)	218	18.16 [14.76; 21.55]	[-1.49; 6.45]			

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-34: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Übelkeit und Erbrechen in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Nausea And Vomiting	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	628	2.73 (9.46)	564	14.54 (19.37)	681	11.67 [10.08; 13.27]	1.51	0.265	-	0.271
Placebo + Chemotherapy[c]	324	3.19 (10.50)	274	13.02 (17.32)	336	10.16 [7.93; 12.39]	[-1.15; 4.17]			
≥ 65										
Pembrolizumab + Chemotherapy[b]	73	3.20 (12.63)	51	12.09 (16.69)	81	9.66 [4.16; 15.15]	-1.99	0.630	-	
Placebo + Chemotherapy[c]	42	2.38 (6.96)	35	13.33 (19.72)	47	11.64 [5.07; 18.21]	[-10.16; 6.19]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	602	2.85 (9.74)	534	14.33 (19.16)	657	11.45 [9.82; 13.09]	1.38	0.312	-	0.646
Placebo + Chemotherapy[c]	317	2.79 (9.48)	270	12.53 (17.08)	334	10.07 [7.83; 12.32]	[-1.30; 4.07]			
1										
Pembrolizumab + Chemotherapy[b]	99	2.36 (10.38)	81	14.40 (19.32)	105	11.47 [7.09; 15.86]	-0.50	0.894	-	
Placebo + Chemotherapy[c]	49	5.10 (13.69)	39	16.67 (20.59)	49	11.97 [5.81; 18.13]	[-7.87; 6.88]			

Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	132	3.91 (12.67)	127	12.07 (17.15)	135	8.52 [5.24; 11.80]	-3.71	0.155	-	0.109
Placebo + Chemotherapy[c]	79	2.32 (6.39)	73	15.30 (18.99)	79	12.23 [8.01; 16.44]	[-8.82; 1.41]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	533	2.38 (8.15)	451	14.49 (19.30)	588	11.83 [10.11; 13.55]	2.89	0.053	-	
Placebo + Chemotherapy[c]	262	3.56 (11.40)	215	11.71 (16.15)	279	8.95 [6.50; 11.39]	[-0.04; 5.81]			
Rest of World										
Pembrolizumab + Chemotherapy[b]	36	4.63 (17.64)	37	20.27 (22.95)	39	18.40 [9.52; 27.28]	1.14	0.864	-	
Placebo + Chemotherapy[c]	25	0.67 (3.33)	21	19.05 (24.32)	25	17.26 [6.05; 28.47]	[-12.15; 14.43]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	336	2.23 (6.75)	295	14.58 (19.45)	368	12.33 [10.21; 14.45]	1.94	0.290	-	0.710
Placebo + Chemotherapy[c]	181	2.30 (7.20)	151	12.69 (16.86)	191	10.39 [7.46; 13.33]	[-1.66; 5.53]			
Positive										
Pembrolizumab + Chemotherapy[b]	365	3.29 (11.97)	320	14.11 (18.93)	394	10.63 [8.43; 12.84]	0.40	0.824	-	
Placebo + Chemotherapy[c]	185	3.87 (12.35)	158	13.40 (18.28)	192	10.23 [7.21; 13.25]	[-3.14; 3.94]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	520	2.60 (8.73)	453	14.53 (19.21)	564	11.90 [10.13; 13.67]	1.58	0.290	-	0.811
Placebo + Chemotherapy[c]	274	3.41 (10.89)	233	13.38 (18.01)	287	10.32 [7.89; 12.75]	[-1.35; 4.51]			
T3/T4										
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Pembrolizumab + Chemotherapy[b]	181	3.31 (12.47)	162	13.79 (19.09)	198	10.42 [7.39; 13.45]	0.30	0.907	-	
Placebo + Chemotherapy[c]	92	2.17 (7.50)	76	12.06 (16.24)	96	10.12 [5.87; 14.37]	[-4.68; 5.27]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	293	2.84 (10.11)	259	14.74 (19.76)	325	11.96 [9.59; 14.33]	2.68	0.175	-	0.302
Placebo + Chemotherapy[c]	158	2.64 (7.87)	138	12.08 (17.18)	163	9.28 [6.09; 12.48]	[-1.20; 6.55]			

Weekly									
Pembrolizumab + Chemotherapy[b]	408	2.74 (9.63)	356	14.04 (18.75)	437	11.12 [9.12; 13.12]	0.08	0.961	-	
Placebo + Chemotherapy[c]	206	3.32 (11.46)	171	13.84 (17.90)	218	11.04 [8.23; 13.85]	[-3.25; 3.42]			

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Schmerzen

Tabelle 4G-35: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Schmerzen in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Pain	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	628	16.00 (19.99)	564	20.45 (22.79)	681	4.41 [2.46; 6.36]	1.79	0.254	-	0.875
Placebo + Chemotherapy[c]	324	16.46 (18.22)	274	19.10 (22.24)	336	2.62 [-0.03; 5.27]	[-1.29; 4.87]			
≥ 65										
Pembrolizumab + Chemotherapy[b]	73	16.89 (21.06)	51	20.26 (26.73)	81	6.24 [-1.34; 13.82]	3.91	0.469	-	
Placebo + Chemotherapy[c]	42	13.89 (19.79)	35	19.52 (21.57)	47	2.33 [-6.70; 11.36]	[-6.75; 14.57]			
ECOG Performance Status										
0										

Pembrolizumab + Chemotherapy[b]	602	16.00 (20.09)	534	20.16 (23.08)	657	4.42 [2.37; 6.46]	1.16	0.474	-	0.338
Placebo + Chemotherapy[c]	317	15.51 (18.00)	270	19.07 (22.02)	334	3.26 [0.52; 5.99]	[-2.02; 4.33]			
1										
Pembrolizumab + Chemotherapy[b]	99	16.67 (20.20)	81	22.22 (23.42)	105	5.68 [0.55; 10.81]	6.45	0.126	-	
Placebo + Chemotherapy[c]	49	20.41 (20.49)	39	19.66 (23.22)	49	-0.77 [-7.82; 6.27]	[-1.84; 14.75]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	132	17.30 (17.03)	127	21.26 (20.21)	135	5.07 [1.37; 8.76]	2.06	0.468	-	0.349
Placebo + Chemotherapy[c]	79	13.71 (14.80)	73	18.04 (19.79)	79	3.00 [-1.70; 7.70]	[-3.54; 7.66]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	533	15.23 (20.31)	451	20.29 (24.10)	588	4.95 [2.68; 7.23]	2.66	0.151	-	
Placebo + Chemotherapy[c]	262	16.73 (19.38)	215	18.99 (22.78)	279	2.30 [-0.84; 5.43]	[-0.97; 6.29]			
Rest of World										
Pembrolizumab + Chemotherapy[b]	36	24.54 (25.04)	37	19.37 (20.61)	39	-2.06 [-10.58; 6.47]	-6.41	0.286	-	
Placebo + Chemotherapy[c]	25	18.00 (17.95)	21	24.60 (23.34)	25	4.36 [-6.07; 14.79]	[-18.35; 5.52]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	336	14.78 (19.22)	295	20.06 (23.65)	368	5.81 [3.17; 8.46]	0.93	0.664	-	0.609
Placebo + Chemotherapy[c]	181	13.90 (16.90)	151	19.54 (20.88)	191	4.88 [1.33; 8.43]	[-3.27; 5.12]			
Positive										
Pembrolizumab + Chemotherapy[b]	365	17.31 (20.81)	320	20.78 (22.66)	394	3.33 [0.60; 6.05]	2.59	0.226	-	
Placebo + Chemotherapy[c]	185	18.38 (19.55)	158	18.78 (23.32)	192	0.74 [-2.92; 4.40]	[-1.61; 6.78]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	520	13.91 (17.71)	453	20.68 (23.53)	564	6.84 [4.70; 8.97]	2.16	0.217	-	0.922
Placebo + Chemotherapy[c]	274	15.33 (18.66)	233	20.03 (22.89)	287	4.68 [1.79; 7.57]	[-1.27; 5.60]			
T3/T4										
Pembrolizumab + Chemotherapy[b]	181	22.38 (24.74)	162	19.75 (22.00)	198	-1.71 [-5.66; 2.25]	2.04	0.480	-	
Placebo + Chemotherapy[c]	92	18.66 (17.44)	76	16.45 (19.53)	96	-3.75 [-8.95; 1.46]	[-3.63; 7.71]			

Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	293	16.67 (21.46)	259	20.66 (24.40)	325	4.55 [1.42; 7.69]	1.09	0.652	-	0.554
Placebo + Chemotherapy[c]	158	14.77 (16.50)	138	19.32 (22.26)	163	3.46 [-0.63; 7.55]	[-3.67; 5.85]			
Weekly										
Pembrolizumab + Chemotherapy[b]	408	15.69 (19.07)	356	20.27 (22.17)	437	4.61 [2.25; 6.98]	2.69	0.161	-	
Placebo + Chemotherapy[c]	206	17.15 (19.75)	171	19.01 (22.09)	218	1.92 [-1.32; 5.17]	[-1.08; 6.45]			

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Dyspnoe

Tabelle 4G-36: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Dyspnoe in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Dyspnoea	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	628	5.47 (14.47)	564	19.98 (25.27)	681	15.09 [13.09; 17.08]	-0.13	0.940	-	0.615
Placebo + Chemotherapy[c]	324	5.76 (15.77)	274	21.17 (24.83)	336	15.22 [12.39; 18.04]	[-3.53; 3.27]			
≥ 65										
Pembrolizumab + Chemotherapy[b]	73	9.13 (16.91)	51	20.26 (27.55)	81	10.12 [2.59; 17.65]	-1.27	0.822	-	

Placebo + Chemotherapy[c]	42	7.94 (17.74)	35	20.00 (24.52)	47	11.40 [2.38; 20.41]	[-12.47; 9.92]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	602	5.87 (14.60)	534	20.16 (25.49)	657	14.81 [12.71; 16.90]	-0.57	0.749	-	0.707
Placebo + Chemotherapy[c]	317	5.05 (14.61)	270	20.99 (24.13)	334	15.38 [12.48; 18.27]	[-4.07; 2.93]			
1										
Pembrolizumab + Chemotherapy[b]	99	5.72 (15.82)	81	18.93 (25.24)	105	13.67 [8.52; 18.83]	3.09	0.494	-	
Placebo + Chemotherapy[c]	49	12.24 (22.25)	39	21.37 (29.11)	49	10.58 [3.26; 17.90]	[-5.82; 12.01]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	336	4.46 (13.50)	295	19.77 (25.88)	368	15.64 [12.81; 18.47]	-0.64	0.793	-	0.526
Placebo + Chemotherapy[c]	181	5.89 (14.56)	151	22.08 (25.21)	191	16.28 [12.37; 20.19]	[-5.40; 4.13]			
Positive										
Pembrolizumab + Chemotherapy[b]	365	7.12 (15.76)	320	20.21 (25.07)	394	13.56 [10.89; 16.24]	0.19	0.933	-	
Placebo + Chemotherapy[c]	185	6.13 (17.33)	158	20.04 (24.36)	192	13.37 [9.64; 17.10]	[-4.28; 4.66]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	520	5.26 (13.17)	453	19.50 (24.59)	564	14.46 [12.23; 16.69]	-0.60	0.752	-	0.815
Placebo + Chemotherapy[c]	274	6.45 (16.23)	233	21.17 (24.56)	287	15.06 [12.00; 18.12]	[-4.31; 3.11]			
T3/T4										
Pembrolizumab + Chemotherapy[b]	181	7.55 (18.54)	162	21.40 (27.71)	198	14.61 [10.67; 18.56]	0.03	0.994	-	
Placebo + Chemotherapy[c]	92	4.71 (15.30)	76	20.61 (25.51)	96	14.59 [8.94; 20.24]	[-6.76; 6.81]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	293	6.60 (15.91)	259	21.24 (26.08)	325	14.81 [11.74; 17.87]	-1.94	0.451	-	0.315
Placebo + Chemotherapy[c]	158	5.27 (15.29)	138	22.22 (25.89)	163	16.75 [12.61; 20.89]	[-7.00; 3.12]			
Weekly										
Pembrolizumab + Chemotherapy[b]	408	5.31 (13.89)	356	19.10 (24.96)	437	14.38 [11.87; 16.89]	0.90	0.680	-	
Placebo + Chemotherapy[c]	206	6.31 (16.06)	171	20.08 (23.84)	218	13.48 [9.92; 17.04]	[-3.38; 5.17]			
a: Database Cutoff Date: 23MAR2021										

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

Tabelle 4G-37: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Schlaflosigkeit in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Insomnia	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	628	23.73 (26.72)	564	29.49 (27.73)	681	5.94 [3.62; 8.25]	3.00	0.106	-	0.174
Placebo + Chemotherapy[c]	324	24.59 (27.18)	274	26.76 (27.02)	336	2.94 [-0.19; 6.08]	[-0.63; 6.63]			
≥ 65										
Pembrolizumab + Chemotherapy[b]	73	28.77 (29.04)	51	26.80 (25.84)	81	-3.53 [-11.16; 4.10]	-3.28	0.550	-	
Placebo + Chemotherapy[c]	42	30.16 (27.36)	35	29.52 (30.00)	47	-0.25 [-9.29; 8.78]	[-14.14; 7.58]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	602	24.47 (27.24)	534	29.03 (27.70)	657	4.42 [2.02; 6.82]	2.19	0.246	-	0.739
Placebo + Chemotherapy[c]	317	25.34 (27.29)	270	26.54 (27.10)	334	2.23 [-0.96; 5.43]	[-1.51; 5.89]			
1										
Pembrolizumab + Chemotherapy[b]	99	22.90 (25.49)	81	30.86 (26.76)	105	9.08 [3.31; 14.85]	3.61	0.447	-	

Placebo + Chemotherapy[c]	49	24.49 (27.02)	39	30.77 (29.00)	49	5.47 [-2.49; 13.42]	[-5.77; 13.00]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	336	24.90 (27.95)	295	30.96 (28.00)	368	5.86 [2.57; 9.14]	1.63	0.525	-	0.713
Placebo + Chemotherapy[c]	181	27.44 (27.48)	151	30.02 (27.69)	191	4.23 [-0.11; 8.57]	[-3.41; 6.67]			
Positive										
Pembrolizumab + Chemotherapy[b]	365	23.65 (26.10)	320	27.71 (27.10)	394	4.26 [1.26; 7.25]	3.09	0.196	-	
Placebo + Chemotherapy[c]	185	23.06 (26.86)	158	24.26 (26.77)	192	1.17 [-2.87; 5.21]	[-1.60; 7.78]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	520	23.91 (26.80)	453	29.43 (27.46)	564	5.48 [2.90; 8.07]	2.49	0.217	-	0.729
Placebo + Chemotherapy[c]	274	25.18 (28.57)	233	27.75 (27.37)	287	2.99 [-0.43; 6.41]	[-1.47; 6.46]			
T3/T4										
Pembrolizumab + Chemotherapy[b]	181	25.23 (27.59)	162	28.81 (27.93)	198	3.62 [-0.69; 7.94]	2.17	0.539	-	
Placebo + Chemotherapy[c]	92	25.36 (22.84)	76	25.00 (27.28)	96	1.45 [-4.52; 7.42]	[-4.78; 9.12]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	293	26.73 (27.76)	259	29.86 (27.70)	325	3.99 [0.53; 7.44]	1.72	0.518	-	0.596
Placebo + Chemotherapy[c]	158	25.11 (28.57)	138	27.29 (27.97)	163	2.26 [-2.21; 6.74]	[-3.51; 6.95]			
Weekly										
Pembrolizumab + Chemotherapy[b]	408	22.47 (26.31)	356	28.84 (27.49)	437	5.75 [2.85; 8.64]	2.95	0.206	-	
Placebo + Chemotherapy[c]	206	25.40 (26.27)	171	26.90 (26.89)	218	2.79 [-1.18; 6.76]	[-1.63; 7.54]			

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Appetitverlust

Tabelle 4G-38: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Appetitverlust in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Appetite Loss	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	628	8.28 (17.42)	564	23.35 (26.82)	681	15.10 [12.83; 17.37]	5.76	0.002	0.23	0.994
Placebo + Chemotherapy[c]	324	8.85 (18.09)	274	17.76 (23.20)	336	9.34 [6.22; 12.46]	[2.11; 9.41]		[0.08; 0.37]	
≥ 65										
Pembrolizumab + Chemotherapy[b]	73	8.22 (15.50)	51	31.37 (30.85)	81	23.98 [15.18; 32.79]	4.84	0.472	-	
Placebo + Chemotherapy[c]	42	8.73 (19.56)	35	27.62 (29.69)	47	19.14 [8.63; 29.65]	[-8.48; 18.16]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	602	8.03 (16.55)	534	23.47 (27.14)	657	15.64 [13.31; 17.97]	5.69	0.003	0.22	0.640
Placebo + Chemotherapy[c]	317	8.31 (17.52)	270	17.90 (23.97)	334	9.95 [6.78; 13.13]	[1.93; 9.46]		[0.07; 0.37]	
1										
Pembrolizumab + Chemotherapy[b]	99	9.76 (20.89)	81	27.57 (27.78)	105	17.66 [10.95; 24.37]	3.38	0.518	-	
Placebo + Chemotherapy[c]	49	12.24 (22.25)	39	25.64 (24.73)	49	14.27 [5.21; 23.33]	[-6.96; 13.73]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	132	9.85 (18.76)	127	24.41 (25.70)	135	15.35 [10.71; 20.00]	2.62	0.474	-	0.516
Placebo + Chemotherapy[c]	79	7.59 (16.84)	73	21.46 (25.07)	79	12.74 [6.79; 18.69]	[-4.57; 9.80]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	533	8.01 (16.93)	451	24.09 (27.50)	588	16.11 [13.51; 18.70]	6.92	0.001	0.27	
Placebo + Chemotherapy[c]	262	9.41 (18.81)	215	17.67 (23.41)	279	9.18 [5.57; 12.80]	[2.70; 11.15]		[0.10; 0.43]	

Rest of World									
Pembrolizumab + Chemotherapy[b]	36	6.48 (15.57)	37	21.62 (29.62)	39	15.19 [5.22; 25.16]	-1.11	0.891	-	
Placebo + Chemotherapy[c]	25	6.67 (16.67)	21	22.22 (28.54)	25	16.30 [3.30; 29.30]	[-17.12; 14.91]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	336	7.54 (15.96)	295	27.01 (27.99)	368	19.73 [16.53; 22.92]	7.67	0.004	0.29	0.241
Placebo + Chemotherapy[c]	181	8.47 (17.97)	151	20.09 (23.75)	191	12.06 [7.73; 16.39]	[2.50; 12.83]		[0.09; 0.49]	
Positive										
Pembrolizumab + Chemotherapy[b]	365	8.95 (18.30)	320	21.25 (26.26)	394	12.44 [9.41; 15.47]	3.51	0.155	-	
Placebo + Chemotherapy[c]	185	9.19 (18.54)	158	17.72 (24.58)	192	8.93 [4.79; 13.06]	[-1.33; 8.35]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	520	8.27 (17.25)	453	24.06 (27.29)	564	15.91 [13.30; 18.53]	5.36	0.011	0.20	0.930
Placebo + Chemotherapy[c]	274	9.37 (18.86)	233	19.46 (24.43)	287	10.56 [7.05; 14.06]	[1.23; 9.49]		[0.05; 0.36]	
T3/T4										
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Pembrolizumab + Chemotherapy[b]	181	8.29 (17.18)	162	23.87 (27.17)	198	15.77 [11.66; 19.88]	5.27	0.135	-	
Placebo + Chemotherapy[c]	92	7.25 (16.26)	76	17.11 (23.41)	96	10.50 [4.66; 16.33]	[-1.65; 12.20]			

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Verstopfung

Tabelle 4G-39: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Verstopfung in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Constipation	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	628	6.63 (16.31)	564	21.28 (26.74)	681	14.05 [11.78; 16.31]	3.05	0.111	-	0.997
Placebo + Chemotherapy[c]	324	9.77 (19.20)	274	19.59 (27.40)	336	11.00 [7.84; 14.16]	[-0.71; 6.80]			
≥ 65										
Pembrolizumab + Chemotherapy[b]	73	10.50 (22.82)	51	21.57 (28.92)	81	10.64 [3.15; 18.12]	4.38	0.446	-	
Placebo + Chemotherapy[c]	42	8.73 (16.56)	35	16.19 (27.26)	47	6.26 [-2.80; 15.32]	[-6.99; 15.74]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	602	7.14 (17.27)	534	21.66 (26.92)	657	13.88 [11.57; 16.19]	3.89	0.043	0.15	0.470
Placebo + Chemotherapy[c]	317	9.57 (18.83)	270	18.64 (26.54)	334	10.00 [6.83; 13.16]	[0.12; 7.66]		[0.00; 0.30]	
1										
Pembrolizumab + Chemotherapy[b]	99	6.40 (16.27)	81	18.93 (26.84)	105	13.07 [6.81; 19.33]	-0.21	0.970	-	
Placebo + Chemotherapy[c]	49	10.20 (19.49)	39	23.08 (32.58)	49	13.28 [4.41; 22.14]	[-10.91; 10.50]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	132	9.85 (18.30)	127	21.78 (26.02)	135	10.35 [5.65; 15.04]	4.26	0.242	-	0.097
Placebo + Chemotherapy[c]	79	15.61 (23.17)	73	19.63 (24.74)	79	6.09 [0.12; 12.07]	[-2.89; 11.40]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	533	6.44 (16.92)	451	20.47 (26.80)	588	13.84 [11.32; 16.35]	1.99	0.357	-	
Placebo + Chemotherapy[c]	262	8.14 (17.31)	215	19.38 (28.67)	279	11.84 [8.28; 15.41]	[-2.26; 6.24]			

Rest of World										
Pembrolizumab + Chemotherapy[b]	36	5.56 (14.91)	37	29.73 (30.21)	39	24.58 [14.87; 34.29]	14.66	0.062	-	
Placebo + Chemotherapy[c]	25	6.67 (16.67)	21	15.87 (22.65)	25	9.92 [-2.67; 22.52]	[-0.74; 30.06]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	336	6.45 (15.28)	295	23.95 (28.68)	368	17.06 [13.85; 20.27]	5.17	0.059	-	0.222
Placebo + Chemotherapy[c]	181	10.68 (18.16)	151	21.41 (29.65)	191	11.89 [7.47; 16.31]	[-0.21; 10.54]			
Positive										
Pembrolizumab + Chemotherapy[b]	365	7.58 (18.66)	320	18.85 (24.94)	394	10.95 [8.05; 13.85]	2.23	0.345	-	
Placebo + Chemotherapy[c]	185	8.65 (19.59)	158	17.09 (24.88)	192	8.73 [4.77; 12.68]	[-2.40; 6.85]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	520	6.86 (16.87)	453	22.30 (27.35)	564	14.97 [12.45; 17.49]	4.06	0.055	-	0.591
Placebo + Chemotherapy[c]	274	9.85 (18.61)	233	20.03 (28.02)	287	10.91 [7.47; 14.35]	[-0.09; 8.20]			
T3/T4										
Pembrolizumab + Chemotherapy[b]	181	7.55 (17.87)	162	18.52 (25.47)	198	10.51 [6.28; 14.73]	1.72	0.621	-	
Placebo + Chemotherapy[c]	92	9.06 (19.83)	76	16.67 (25.24)	96	8.79 [2.90; 14.68]	[-5.13; 8.57]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	293	6.94 (17.70)	259	19.56 (26.64)	325	12.60 [9.28; 15.91]	2.49	0.355	-	0.946
Placebo + Chemotherapy[c]	158	8.44 (18.41)	138	17.63 (25.53)	163	10.11 [5.70; 14.52]	[-2.80; 7.78]			
Weekly										
Pembrolizumab + Chemotherapy[b]	408	7.11 (16.72)	356	22.57 (27.05)	437	14.65 [11.78; 17.52]	3.81	0.120	-	
Placebo + Chemotherapy[c]	206	10.36 (19.21)	171	20.47 (28.76)	218	10.84 [6.80; 14.88]	[-1.00; 8.62]			

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit

interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Diarrhoe

Tabelle 4G-40: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Diarrhoe in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Diarrhea	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	628	5.41 (13.54)	564	9.34 (18.73)	681	4.30 [2.66; 5.93]	2.71	0.039	0.15	0.759
Placebo + Chemotherapy[c]	324	5.14 (13.41)	274	6.93 (16.28)	336	1.59 [-0.64; 3.81]	[0.14; 5.28]		[0.01; 0.30]	
≥ 65										
Pembrolizumab + Chemotherapy[b]	73	4.57 (12.81)	51	7.19 (16.75)	81	3.35 [-1.33; 8.03]	1.16	0.743	-	
Placebo + Chemotherapy[c]	42	3.17 (9.90)	35	5.71 (15.09)	47	2.19 [-3.39; 7.77]	[-5.87; 8.19]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	602	5.43 (13.19)	534	9.24 (18.99)	657	4.32 [2.64; 6.00]	2.41	0.073	-	0.513
Placebo + Chemotherapy[c]	317	4.84 (12.90)	270	7.04 (16.38)	334	1.91 [-0.35; 4.17]	[-0.23; 5.05]			
1										
Pembrolizumab + Chemotherapy[b]	99	4.71 (15.07)	81	8.64 (15.61)	105	3.93 [0.06; 7.80]	4.30	0.148	-	
Placebo + Chemotherapy[c]	49	5.44 (14.19)	39	5.13 (14.38)	49	-0.38 [-5.55; 4.80]	[-1.55; 10.16]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	132	8.08 (14.92)	127	10.76 (18.73)	135	2.73 [-0.57; 6.04]	3.14	0.211	-	0.920
Placebo + Chemotherapy[c]	79	8.02 (15.30)	73	7.76 (15.24)	79	-0.40 [-4.58; 3.77]	[-1.79; 8.07]			

Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	533	4.88 (13.29)	451	8.94 (18.89)	588	4.65 [2.80; 6.50]	2.80	0.062	-	
Placebo + Chemotherapy[c]	262	4.20 (12.52)	215	6.51 (16.40)	279	1.85 [-0.69; 4.39]	[-0.14; 5.73]			
Rest of World										
Pembrolizumab + Chemotherapy[b]	36	1.85 (7.74)	37	6.31 (13.24)	39	4.25 [-0.66; 9.15]	-0.06	0.989	-	
Placebo + Chemotherapy[c]	25	2.67 (9.23)	21	6.35 (17.06)	25	4.30 [-2.13; 10.73]	[-8.03; 7.92]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	336	6.05 (15.01)	295	10.85 (21.19)	368	5.23 [2.76; 7.70]	3.41	0.083	-	0.787
Placebo + Chemotherapy[c]	181	5.52 (13.84)	151	7.51 (16.85)	191	1.82 [-1.48; 5.12]	[-0.45; 7.27]			
Positive										
Pembrolizumab + Chemotherapy[b]	365	4.66 (11.83)	320	7.60 (15.65)	394	3.31 [1.42; 5.19]	1.88	0.212	-	
Placebo + Chemotherapy[c]	185	4.32 (12.26)	158	6.12 (15.44)	192	1.43 [-1.12; 3.98]	[-1.07; 4.83]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	520	5.13 (13.06)	453	9.86 (19.35)	564	4.90 [3.04; 6.76]	2.75	0.064	-	> 0.999
Placebo + Chemotherapy[c]	274	5.60 (14.02)	233	7.58 (17.08)	287	2.15 [-0.34; 4.64]	[-0.16; 5.67]			
T3/T4										
Pembrolizumab + Chemotherapy[b]	181	5.89 (14.56)	162	7.20 (16.07)	198	2.45 [-0.22; 5.11]	2.63	0.209	-	
Placebo + Chemotherapy[c]	92	2.90 (9.44)	76	4.39 (12.58)	96	-0.18 [-3.80; 3.44]	[-1.48; 6.73]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	293	5.23 (12.76)	259	8.11 (17.57)	325	3.18 [1.00; 5.37]	3.28	0.053	-	0.582
Placebo + Chemotherapy[c]	158	4.43 (12.54)	138	4.83 (13.08)	163	-0.09 [-2.94; 2.76]	[-0.04; 6.60]			
Weekly										
Pembrolizumab + Chemotherapy[b]	408	5.39 (13.95)	356	9.93 (19.25)	437	5.08 [2.94; 7.22]	2.12	0.224	-	
Placebo + Chemotherapy[c]	206	5.18 (13.38)	171	8.38 (18.11)	218	2.96 [0.01; 5.91]	[-1.30; 5.54]			

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-BR23 neoadjuvanten Phase

EORTC QLQ-BR23: Symptomskala Nebenwirkungen der systemischen Therapie

Tabelle 4G-41: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Nebenwirkungen der systemischen Therapie in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Systemic Therapy Side Effects	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	624	8.02 (10.65)	560	32.16 (19.03)	679	24.24 [22.73; 25.76]	2.21	0.095	-	0.241
Placebo + Chemotherapy[c]	320	8.07 (11.00)	272	29.73 (19.78)	335	22.03 [19.89; 24.18]	[-0.39; 4.81]			
≥ 65										
Pembrolizumab + Chemotherapy[b]	71	8.92 (11.49)	51	32.31 (14.70)	80	24.68 [20.37; 28.98]	-2.72	0.417	-	
Placebo + Chemotherapy[c]	41	7.08 (8.46)	35	35.65 (17.49)	47	27.39 [22.15; 32.64]	[-9.33; 3.90]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	597	7.98 (10.70)	530	32.43 (18.73)	655	24.58 [23.04; 26.12]	1.69	0.202	-	0.845
Placebo + Chemotherapy[c]	313	7.55 (10.76)	268	30.22 (18.97)	333	22.89 [20.75; 25.03]	[-0.91; 4.28]			
1										
Pembrolizumab +	98	8.94 (10.97)	81	30.51 (18.55)	104	22.55 [18.56; 26.53]	2.06	0.558	-	

Chemotherapy[b]											
Placebo + Chemotherapy[c]	48	10.62 (10.27)	39	31.62 (23.67)	49	20.49 [14.81; 26.16]	[-4.88; 9.01]				
Geographic Region											
Asia											
Pembrolizumab + Chemotherapy[b]	131	10.47 (10.65)	126	30.01 (16.63)	134	19.63 [16.81; 22.46]	2.50	0.284	-	0.868	
Placebo + Chemotherapy[c]	79	9.64 (11.74)	73	27.14 (19.27)	79	17.13 [13.45; 20.81]	[-2.09; 7.10]				
Europe/Israel/North America/Australia											
Pembrolizumab + Chemotherapy[b]	528	7.37 (10.47)	448	32.42 (19.44)	586	25.29 [23.60; 26.99]	1.22	0.416	-		
Placebo + Chemotherapy[c]	257	7.19 (10.07)	213	30.99 (19.36)	278	24.07 [21.64; 26.51]	[-1.72; 4.16]				
Rest of World											
Pembrolizumab + Chemotherapy[b]	36	10.45 (13.36)	37	36.55 (15.39)	39	26.60 [19.99; 33.21]	0.84	0.868	-		
Placebo + Chemotherapy[c]	25	10.48 (13.33)	21	35.83 (22.16)	25	25.76 [17.39; 34.13]	[-9.32; 11.01]				
Nodal Status											
Negative											
Pembrolizumab + Chemotherapy[b]	333	7.35 (10.01)	293	34.29 (18.92)	366	27.29 [25.22; 29.35]	1.93	0.280	-	0.902	
Placebo + Chemotherapy[c]	178	6.55 (8.74)	151	31.88 (19.70)	191	25.36 [22.50; 28.22]	[-1.58; 5.43]				
Positive											
Pembrolizumab + Chemotherapy[b]	362	8.81 (11.33)	318	30.22 (18.30)	393	21.45 [19.49; 23.41]	1.36	0.420	-		
Placebo + Chemotherapy[c]	183	9.32 (12.25)	156	28.97 (19.45)	191	20.08 [17.33; 22.84]	[-1.96; 4.69]				
Tumor Size											
T1/T2											
Pembrolizumab + Chemotherapy[b]	516	7.50 (9.89)	450	32.58 (18.69)	562	25.23 [23.56; 26.89]	3.02	0.036	0.17	0.078	
Placebo + Chemotherapy[c]	270	8.41 (11.37)	232	30.40 (20.16)	286	22.21 [19.90; 24.52]	[0.20; 5.84]		[0.01; 0.32]		
T3/T4											
Pembrolizumab + Chemotherapy[b]	179	9.87 (12.73)	161	31.03 (18.75)	197	21.73 [18.93; 24.52]	-1.94	0.423	-		
Placebo + Chemotherapy[c]	91	6.59 (8.48)	75	30.41 (17.85)	96	23.67 [19.68; 27.66]	[-6.72; 2.83]				
Choice of Carboplatin											
Q3W											
Pembrolizumab + Chemotherapy[b]	292	8.50 (11.60)	258	31.84 (18.49)	324	23.38 [21.17; 25.60]	0.58	0.755	-	0.511	
Placebo + Chemotherapy[c]	155	7.04 (8.48)	138	29.61 (19.64)	163	22.80 [19.79; 25.80]	[-3.10; 4.27]				

Weekly									
Pembrolizumab + Chemotherapy[b]	403	7.83 (10.07)	353	32.42 (18.87)	435	24.94 [23.05; 26.82]	2.40	0.148	-	
Placebo + Chemotherapy[c]	204	8.40 (11.90)	169	31.05 (19.59)	217	22.54 [19.85; 25.23]	[-0.85; 5.64]			

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-BR23: Symptomskala Symptome im Brustbereich

Tabelle 4G-42: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Symptome im Brustbereich in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Breast Symptoms	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	624	18.87 (20.67)	560	8.59 (12.49)	679	-10.16 [-11.64; -8.68]	-0.18	0.843	-	0.651
Placebo + Chemotherapy[c]	320	18.12 (18.64)	272	8.43 (14.36)	335	-9.97 [-11.80; -8.15]	[-2.02; 1.65]			
≥ 65										
Pembrolizumab + Chemotherapy[b]	71	16.90 (17.42)	51	11.44 (16.83)	80	-7.41 [-12.48; -2.34]	0.98	0.768	-	
Placebo + Chemotherapy[c]	41	21.14 (24.09)	35	9.05 (11.32)	47	-8.39 [-14.33; -2.46]	[-5.61; 7.57]			

ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	597	18.27 (19.98)	530	8.85 (12.99)	655	-9.38 [-10.91; -7.84]	-0.18	0.855	-	0.714
Placebo + Chemotherapy[c]	313	17.63 (19.14)	268	8.46 (14.46)	333	-9.20 [-11.09; -7.30]	[-2.11; 1.75]			
1										
Pembrolizumab + Chemotherapy[b]	98	21.09 (22.46)	81	8.64 (12.53)	104	-13.02 [-16.67; -9.37]	0.79	0.716	-	
Placebo + Chemotherapy[c]	48	23.96 (19.80)	39	8.76 (10.81)	49	-13.81 [-18.22; -9.41]	[-3.49; 5.07]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	131	19.34 (18.93)	126	9.99 (10.65)	134	-8.61 [-11.45; -5.77]	-1.47	0.409	-	0.695
Placebo + Chemotherapy[c]	79	16.56 (14.03)	73	10.62 (15.29)	79	-7.14 [-10.50; -3.79]	[-4.96; 2.03]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	528	17.80 (19.69)	448	8.52 (13.70)	586	-9.42 [-11.04; -7.79]	0.51	0.645	-	
Placebo + Chemotherapy[c]	257	17.77 (18.05)	213	7.82 (13.76)	278	-9.92 [-11.99; -7.85]	[-1.65; 2.66]			
Rest of World										
Pembrolizumab + Chemotherapy[b]	36	28.94 (30.44)	37	8.56 (9.92)	39	-20.45 [-28.72; -12.19]	-0.32	0.921	-	
Placebo + Chemotherapy[c]	25	31.67 (35.84)	21	7.94 (11.92)	25	-20.13 [-28.91; -11.35]	[-6.84; 6.20]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	333	15.39 (17.19)	293	9.07 (12.56)	366	-6.67 [-8.41; -4.93]	1.23	0.296	-	0.084
Placebo + Chemotherapy[c]	178	15.54 (16.32)	151	7.78 (12.83)	191	-7.90 [-10.08; -5.73]	[-1.08; 3.55]			
Positive										
Pembrolizumab + Chemotherapy[b]	362	21.69 (22.49)	318	8.60 (13.25)	393	-12.93 [-15.11; -10.74]	-1.16	0.384	-	
Placebo + Chemotherapy[c]	183	21.31 (21.51)	156	9.19 (15.12)	191	-11.76 [-14.43; -9.10]	[-3.79; 1.46]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	516	14.28 (15.46)	450	8.37 (12.04)	562	-6.23 [-7.62; -4.84]	0.35	0.714	-	0.121
Placebo + Chemotherapy[c]	270	15.49 (15.93)	232	8.37 (13.42)	286	-6.58 [-8.33; -4.83]	[-1.54; 2.25]			
T3/T4										
Pembrolizumab +	179	31.33 (26.59)	161	10.09 (15.06)	197	-20.43 [-23.93; -16.92]	-0.80	0.703	-	

Chemotherapy[b]										
Placebo + Chemotherapy[c]	91	27.29 (25.09)	75	8.89 (15.88)	96	-19.63 [-23.91; -15.34]	[-4.94; 3.34]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	292	19.01 (20.29)	258	8.88 (12.65)	324	-9.90 [-12.05; -7.75]	-0.92	0.503	-	0.179
Placebo + Chemotherapy[c]	155	16.67 (18.46)	138	8.33 (15.24)	163	-8.98 [-11.58; -6.38]	[-3.61; 1.78]			
Weekly										
Pembrolizumab + Chemotherapy[b]	403	18.42 (20.43)	353	8.78 (13.13)	435	-9.90 [-11.79; -8.01]	0.62	0.606	-	
Placebo + Chemotherapy[c]	204	19.69 (19.91)	169	8.63 (13.01)	217	-10.52 [-12.86; -8.17]	[-1.73; 2.96]			

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-BR23: Symptomskala Symptome im Armbereich

Tabelle 4G-43: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Symptome im Armbereich in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Arm Symptoms	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab +	624	10.65 (16.52)	560	10.62 (16.63)	679	0.01 [-1.53; 1.54]	-1.25	0.290	-	0.877

Chemotherapy[b]										
Placebo + Chemotherapy[c]	320	10.69 (15.56)	272	11.85 (17.01)	335	1.26 [-0.79; 3.31]	[-3.58; 1.07]			
≥ 65										
Pembrolizumab + Chemotherapy[b]	71	9.39 (15.33)	51	10.02 (14.78)	80	0.92 [-2.90; 4.73]	-2.73	0.335	-	
Placebo + Chemotherapy[c]	41	4.88 (9.31)	35	9.52 (14.04)	47	3.64 [-0.92; 8.21]	[-8.31; 2.86]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	597	10.55 (16.54)	530	10.48 (16.57)	655	0.10 [-1.45; 1.65]	-0.95	0.423	-	0.472
Placebo + Chemotherapy[c]	313	9.90 (14.86)	268	11.03 (16.35)	333	1.05 [-0.99; 3.09]	[-3.28; 1.38]			
1										
Pembrolizumab + Chemotherapy[b]	98	10.32 (15.57)	81	11.11 (15.91)	104	0.52 [-3.43; 4.48]	-2.78	0.365	-	
Placebo + Chemotherapy[c]	48	10.88 (16.61)	39	15.38 (18.66)	49	3.31 [-1.98; 8.60]	[-8.83; 3.27]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	131	12.38 (13.76)	126	14.11 (14.70)	134	2.72 [-0.35; 5.80]	-2.83	0.230	-	0.424
Placebo + Chemotherapy[c]	79	8.58 (11.25)	73	15.98 (19.06)	79	5.55 [1.67; 9.44]	[-7.47; 1.80]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	528	9.81 (16.59)	448	9.00 (16.41)	586	-0.87 [-2.54; 0.80]	-0.84	0.513	-	
Placebo + Chemotherapy[c]	257	10.25 (15.84)	213	9.86 (15.74)	278	-0.03 [-2.28; 2.21]	[-3.36; 1.68]			
Rest of World										
Pembrolizumab + Chemotherapy[b]	36	14.20 (21.18)	37	17.42 (19.52)	39	4.50 [-1.78; 10.78]	2.60	0.572	-	
Placebo + Chemotherapy[c]	25	12.44 (17.66)	21	13.76 (14.87)	25	1.90 [-5.91; 9.72]	[-6.56; 11.77]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	516	9.26 (14.51)	450	10.57 (16.56)	562	1.22 [-0.40; 2.85]	-1.25	0.327	-	0.914
Placebo + Chemotherapy[c]	270	9.92 (15.57)	232	12.21 (16.65)	286	2.47 [0.32; 4.63]	[-3.75; 1.25]			
T3/T4										
Pembrolizumab + Chemotherapy[b]	179	14.15 (20.53)	161	10.56 (16.28)	197	-2.69 [-5.69; 0.31]	-0.77	0.727	-	
Placebo + Chemotherapy[c]	91	10.38 (13.64)	75	9.63 (16.77)	96	-1.92 [-5.89; 2.06]	[-5.13; 3.59]			

Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	292	10.24 (16.05)	258	11.28 (17.34)	324	1.06 [-1.22; 3.35]	-0.72	0.690	-	0.586
Placebo + Chemotherapy[c]	155	10.25 (13.84)	138	11.59 (18.25)	163	1.78 [-1.22; 4.77]	[-4.24; 2.81]			
Weekly										
Pembrolizumab + Chemotherapy[b]	403	10.73 (16.66)	353	10.04 (15.81)	435	-0.43 [-2.27; 1.42]	-1.56	0.262	-	
Placebo + Chemotherapy[c]	204	9.75 (15.98)	169	11.57 (15.35)	217	1.13 [-1.32; 3.59]	[-4.29; 1.17]			

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-BR23: Symptomskala Belastung durch Haarausfall

Tabelle 4G-44: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Belastung durch Haarausfall in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Upset by Hair Loss (Imputed)[i]	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	624	2.35 (11.40)	560	22.02 (32.69)	679	19.43 [16.73; 22.14]	-0.63	0.791	-	0.228
Placebo + Chemotherapy[c]	320	2.40 (12.57)	272	22.06 (32.83)	335	20.06 [16.22; 23.90]	[-5.27; 4.02]			
≥ 65										

Pembrolizumab + Chemotherapy[b]	71	0.94 (5.55)	51	26.14 (34.84)	80	25.18 [16.28; 34.08]	-9.66	0.179	-	
Placebo + Chemotherapy[c]	41	3.25 (12.48)	35	39.05 (32.83)	47	34.84 [23.85; 45.82]	[-23.83; 4.52]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	597	2.12 (11.06)	530	22.39 (33.08)	655	19.80 [16.99; 22.61]	-2.78	0.255	-	0.186
Placebo + Chemotherapy[c]	313	2.77 (13.32)	268	24.88 (33.81)	333	22.58 [18.65; 26.50]	[-7.56; 2.00]			
1										
Pembrolizumab + Chemotherapy[b]	98	2.72 (10.35)	81	22.22 (31.62)	104	20.52 [13.76; 27.29]	4.08	0.490	-	
Placebo + Chemotherapy[c]	48	0.69 (4.81)	39	17.95 (28.46)	49	16.44 [6.80; 26.08]	[-7.60; 15.76]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	131	3.82 (14.11)	126	20.63 (29.77)	134	16.92 [11.68; 22.16]	-0.22	0.959	-	0.777
Placebo + Chemotherapy[c]	79	3.38 (16.53)	73	21.00 (29.66)	79	17.14 [10.33; 23.94]	[-8.65; 8.21]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	528	1.58 (9.61)	448	22.92 (33.75)	586	21.01 [17.91; 24.10]	-2.86	0.299	-	
Placebo + Chemotherapy[c]	257	2.20 (11.39)	213	25.35 (34.63)	278	23.87 [19.40; 28.35]	[-8.28; 2.55]			
Rest of World										
Pembrolizumab + Chemotherapy[b]	36	5.56 (14.91)	37	21.62 (32.60)	39	16.70 [5.60; 27.79]	1.03	0.907	-	
Placebo + Chemotherapy[c]	25	2.67 (9.23)	21	20.63 (30.69)	25	15.67 [1.33; 30.01]	[-16.56; 18.62]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	333	1.90 (9.31)	293	21.84 (32.54)	366	20.35 [16.68; 24.02]	2.16	0.490	-	0.135
Placebo + Chemotherapy[c]	178	1.31 (8.21)	151	19.65 (29.63)	191	18.19 [13.13; 23.24]	[-3.99; 8.32]			
Positive										
Pembrolizumab + Chemotherapy[b]	362	2.49 (12.28)	318	22.85 (33.20)	393	19.69 [16.04; 23.35]	-5.53	0.086	-	
Placebo + Chemotherapy[c]	183	3.64 (15.59)	156	28.21 (35.95)	191	25.22 [20.02; 30.42]	[-11.84; 0.78]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	516	2.00 (10.50)	450	21.41 (32.29)	562	19.14 [16.16; 22.13]	-1.38	0.592	-	0.642

Placebo + Chemotherapy[c] T3/T4	270	2.72 (13.82)	232	22.99 (32.95)	286	20.52 [16.39; 24.65]	[-6.42; 3.67]		
Pembrolizumab + Chemotherapy[b]	179	2.79 (12.17)	161	25.05 (34.37)	197	21.91 [16.66; 27.16]	-4.13	0.378	-
Placebo + Chemotherapy[c]	91	1.83 (7.64)	75	27.11 (34.09)	96	26.04 [18.41; 33.67]	[-13.35; 5.08]		
Choice of Carboplatin									
Q3W									
Pembrolizumab + Chemotherapy[b]	292	1.94 (9.17)	258	22.35 (31.87)	324	20.51 [16.55; 24.47]	-3.01	0.378	-	0.860
Placebo + Chemotherapy[c]	155	0.65 (4.61)	138	23.91 (34.17)	163	23.52 [18.09; 28.94]	[-9.71; 3.69]		
Weekly									
Pembrolizumab + Chemotherapy[b]	403	2.40 (12.09)	353	22.38 (33.61)	435	19.46 [16.02; 22.90]	-1.36	0.653	-
Placebo + Chemotherapy[c]	204	3.76 (15.94)	169	24.06 (32.52)	217	20.82 [15.90; 25.73]	[-7.28; 4.57]		

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

i: For participants who did not lose any hair, the score was imputed as not upset at all by the loss of hair

CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EQ-5D VAS in der neoadjuvanten Phase

Tabelle 4G-45: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EQ-5D VAS	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	608	81.08 (18.17)	535	72.69 (18.05)	657	-9.06 [-10.69; -7.43]	-1.73	0.160	-	0.673
Placebo + Chemotherapy[c]	320	82.96 (17.50)	272	75.47 (16.55)	335	-7.33 [-9.46; -5.20]	[-4.15; 0.68]			
1										
Pembrolizumab + Chemotherapy[b]	99	81.19 (17.49)	81	73.19 (18.86)	105	-8.73 [-12.69; -4.76]	-0.62	0.847	-	
Placebo + Chemotherapy[c]	49	80.24 (13.03)	39	71.67 (14.77)	49	-8.10 [-13.55; -2.65]	[-7.01; 5.76]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	132	80.69 (15.13)	127	75.78 (16.04)	135	-5.57 [-8.66; -2.47]	-0.05	0.984	-	0.785
Placebo + Chemotherapy[c]	79	81.95 (13.46)	73	75.75 (16.45)	79	-5.52 [-9.40; -1.63]	[-4.59; 4.50]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	539	81.05 (18.61)	452	71.40 (18.65)	588	-10.21 [-12.00; -8.42]	-2.09	0.130	-	
Placebo + Chemotherapy[c]	265	82.45 (17.94)	217	74.06 (16.31)	280	-8.12 [-10.52; -5.72]	[-4.80; 0.62]			
Rest of World										
Pembrolizumab + Chemotherapy[b]	36	83.33 (19.94)	37	78.97 (16.34)	39	-5.20 [-11.03; 0.64]	-0.19	0.963	-	
Placebo + Chemotherapy[c]	25	86.24 (16.70)	21	82.00 (15.54)	25	-5.00 [-12.13; 2.12]	[-8.39; 8.00]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	341	80.95 (18.18)	296	71.66 (18.17)	368	-10.34 [-12.56; -8.13]	-2.74	0.098	-	0.428
Placebo + Chemotherapy[c]	182	83.42 (17.15)	153	75.25 (15.97)	191	-7.61 [-10.47; -4.74]	[-5.98; 0.50]			

Positive										
Pembrolizumab + Chemotherapy[b]	366	81.23 (17.99)	320	73.78 (18.09)	394	-7.76 [-9.83; -5.70]	-0.66	0.680	-	
Placebo + Chemotherapy[c]	187	81.81 (16.82)	158	74.75 (16.78)	193	-7.10 [-9.85; -4.36]	[-3.80; 2.48]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	526	81.78 (17.87)	454	72.88 (18.13)	564	-9.76 [-11.52; -8.00]	-1.36	0.308	-	0.691
Placebo + Chemotherapy[c]	276	83.35 (15.80)	235	74.34 (16.49)	287	-8.40 [-10.70; -6.10]	[-3.99; 1.26]			
T3/T4										
Pembrolizumab + Chemotherapy[b]	181	79.10 (18.54)	162	72.42 (18.21)	198	-6.71 [-9.63; -3.79]	-2.52	0.263	-	
Placebo + Chemotherapy[c]	93	80.39 (20.02)	76	77.01 (15.92)	97	-4.19 [-8.12; -0.26]	[-6.95; 1.91]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	296	81.50 (16.72)	259	71.43 (17.68)	325	-10.32 [-12.51; -8.14]	-2.37	0.159	-	0.984
Placebo + Chemotherapy[c]	159	82.97 (17.17)	139	75.35 (16.51)	163	-7.95 [-10.79; -5.12]	[-5.68; 0.94]			
Weekly										
Pembrolizumab + Chemotherapy[b]	411	80.80 (18.99)	357	73.72 (18.43)	437	-7.98 [-10.04; -5.91]	-0.97	0.536	-	
Placebo + Chemotherapy[c]	208	82.46 (16.80)	172	74.70 (16.29)	219	-7.01 [-9.75; -4.26]	[-4.04; 2.10]			

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EQ-5D: European Quality of Life 5 Dimensions; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation; VAS: Visual Analog Scale

EORTC QLQ-C30 in der adjuvanten Phase

EORTC QLQ-C30: Symptomskala Erschöpfung

Tabelle 4G-46: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Erschöpfung in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Fatigue	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
ECOG Performance Status										
0										
Pembrolizumab[b]	418	27.83 (20.51)	385	25.57 (21.95)	466	-2.30 [-4.19; -0.42]	0.47	0.756	-	0.755
Placebo[c]	247	28.97 (22.26)	215	26.10 (22.23)	268	-2.77 [-5.21; -0.32]	[-2.49; 3.43]			
1										
Pembrolizumab[b]	71	26.29 (18.33)	59	28.44 (22.34)	73	1.22 [-3.62; 6.06]	-0.74	0.850	-	
Placebo[c]	36	29.01 (24.09)	34	30.72 (23.38)	40	1.96 [-4.39; 8.31]	[-8.51; 7.02]			
Geographic Region										
Asia										
Pembrolizumab[b]	107	29.39 (17.01)	95	25.73 (17.63)	109	-2.61 [-6.04; 0.82]	1.44	0.579	-	0.911
Placebo[c]	67	26.87 (19.74)	56	24.21 (16.56)	67	-4.05 [-8.32; 0.22]	[-3.66; 6.53]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	352	27.78 (21.09)	321	26.69 (23.58)	398	-1.55 [-3.71; 0.62]	0.08	0.963	-	
Placebo[c]	198	30.19 (23.22)	178	28.09 (23.57)	221	-1.63 [-4.47; 1.21]	[-3.36; 3.52]			
Rest of World										
Pembrolizumab[b]	30	19.26 (18.44)	28	18.25 (14.25)	32	-1.44 [-7.19; 4.30]	0.09	0.984	-	
Placebo[c]	18	23.46 (23.15)	15	20.00 (26.29)	20	-1.53 [-9.14; 6.07]	[-9.06; 9.24]			
Nodal Status										
Negative										
Pembrolizumab[b]	238	28.99 (20.52)	219	27.75 (22.38)	263	-1.48 [-4.05; 1.08]	1.38	0.496	-	0.528
Placebo[c]	150	31.56 (22.85)	133	28.07 (23.43)	162	-2.86 [-6.10; 0.37]	[-2.60; 5.35]			
Positive										
Pembrolizumab[b]	251	26.29 (19.83)	225	24.20 (21.53)	276	-2.09 [-4.50; 0.32]	-0.67	0.734	-	
Placebo[c]	133	26.07 (21.71)	116	25.19 (21.15)	146	-1.42 [-4.65; 1.81]	[-4.52; 3.19]			

Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	215	28.68 (20.30)	198	27.55 (23.58)	240	-0.86 [-3.42; 1.71]	1.91	0.376	-	0.343
Placebo[c]	118	29.28 (22.25)	101	26.95 (22.19)	127	-2.76 [-6.25; 0.72]	[-2.33; 6.14]			
Weekly										
Pembrolizumab[b]	274	26.76 (20.11)	246	24.66 (20.60)	299	-2.63 [-5.03; -0.23]	-1.24	0.503	-	
Placebo[c]	164	28.79 (22.72)	147	26.76 (22.59)	180	-1.39 [-4.41; 1.64]	[-4.87; 2.39]			

a: Database Cutoff Date: 23MAR2021
b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-47: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Übelkeit und Erbrechen in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Nausea And Vomiting	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab[b]	448	3.94 (10.12)	403	4.30 (10.94)	492	0.64 [-0.42; 1.71]	1.23	0.128	-	0.126
Placebo[c]	250	3.20 (9.61)	219	2.82 (8.04)	271	-0.59 [-1.96; 0.78]	[-0.36; 2.81]			
≥ 65										
Pembrolizumab[b]	41	3.25 (8.51)	41	2.44 (7.03)	47	-1.68 [-4.70; 1.34]	-1.14	0.593	-	
Placebo[c]	33	4.55 (11.24)	30	3.89 (12.90)	37	-0.54 [-3.95; 2.87]	[-5.39; 3.10]			

ECOG Performance Status									
0									
Pembrolizumab[b]	418	3.75 (9.76)	385	4.24 (10.52)	466	0.76 [-0.31; 1.83]	0.84	0.302	-	0.833
Placebo[c]	247	2.90 (9.11)	215	3.02 (9.11)	268	-0.09 [-1.45; 1.28]	[-0.76; 2.45]			
1										
Pembrolizumab[b]	71	4.69 (11.33)	59	3.39 (11.49)	73	-1.64 [-4.42; 1.14]	1.76	0.363	-	
Placebo[c]	36	6.48 (13.38)	34	2.45 (5.99)	40	-3.40 [-6.83; 0.04]	[-2.05; 5.56]			
Geographic Region									
Asia									
Pembrolizumab[b]	107	2.65 (6.54)	95	3.51 (12.61)	109	1.37 [-1.00; 3.75]	1.17	0.527	-	0.911
Placebo[c]	67	1.99 (6.82)	56	2.08 (5.56)	67	0.21 [-2.80; 3.21]	[-2.48; 4.81]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	352	4.07 (10.64)	321	4.10 (9.84)	398	0.05 [-1.06; 1.16]	0.80	0.334	-	
Placebo[c]	198	3.79 (10.40)	178	3.18 (9.66)	221	-0.75 [-2.16; 0.66]	[-0.83; 2.43]			
Rest of World										
Pembrolizumab[b]	30	6.11 (11.97)	28	6.55 (12.29)	32	1.01 [-3.99; 6.00]	2.95	0.396	-	
Placebo[c]	18	3.70 (12.20)	15	3.33 (6.90)	20	-1.95 [-8.22; 4.33]	[-4.00; 9.91]			
Nodal Status									
Negative									
Pembrolizumab[b]	238	4.62 (10.59)	219	4.03 (9.59)	263	-0.10 [-1.53; 1.33]	0.89	0.376	-	0.568
Placebo[c]	150	3.78 (11.28)	133	3.13 (9.21)	162	-1.00 [-2.73; 0.74]	[-1.09; 2.88]			
Positive										
Pembrolizumab[b]	251	3.19 (9.36)	225	4.22 (11.60)	276	1.09 [-0.32; 2.50]	1.20	0.295	-	
Placebo[c]	133	2.88 (7.82)	116	2.73 (8.21)	146	-0.11 [-2.00; 1.79]	[-1.05; 3.44]			
Tumor Size									
T1/T2									
Pembrolizumab[b]	358	3.21 (8.35)	333	3.10 (9.53)	393	-0.06 [-1.20; 1.08]	0.21	0.806	-	0.101
Placebo[c]	215	3.64 (10.49)	190	2.98 (8.90)	237	-0.26 [-1.69; 1.16]	[-1.44; 1.85]			
T3/T4										
Pembrolizumab[b]	131	5.73 (13.36)	111	7.21 (13.03)	146	2.02 [-0.11; 4.16]	3.10	0.063	-	
Placebo[c]	68	2.45 (7.21)	59	2.82 (8.28)	71	-1.08 [-3.87; 1.70]	[-0.17; 6.38]			

a: Database Cutoff Date: 23MAR2021
b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates

g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Schmerzen

Tabelle 4G-48: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schmerzen in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Pain	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab[b]	448	20.94 (20.18)	403	18.69 (20.51)	492	-2.75 [-4.76; -0.74]	0.55	0.721	-	0.481
Placebo[c]	250	25.73 (24.27)	219	20.47 (22.14)	271	-3.31 [-5.91; -0.70]	[-2.49; 3.59]			
≥ 65										
Pembrolizumab[b]	41	19.92 (20.49)	41	19.11 (18.47)	47	-0.77 [-6.40; 4.87]	-1.25	0.750	-	
Placebo[c]	33	18.18 (25.81)	30	17.78 (22.71)	37	0.48 [-5.84; 6.80]	[-9.03; 6.53]			
ECOG Performance Status										
0										
Pembrolizumab[b]	418	21.05 (20.27)	385	19.09 (20.73)	466	-2.35 [-4.43; -0.27]	0.88	0.579	-	0.317
Placebo[c]	247	24.56 (24.59)	215	19.84 (22.42)	268	-3.23 [-5.88; -0.58]	[-2.23; 3.99]			
1										
Pembrolizumab[b]	71	19.72 (19.78)	59	16.38 (17.37)	73	-3.62 [-8.04; 0.80]	-2.47	0.458	-	
Placebo[c]	36	26.85 (24.33)	34	22.06 (20.81)	40	-1.15 [-6.78; 4.48]	[-9.06; 4.12]			
Geographic Region										
Asia										
Pembrolizumab[b]	107	22.12 (17.99)	95	17.89 (15.80)	109	-4.04 [-7.45; -0.64]	2.06	0.402	-	0.775
Placebo[c]	67	23.63 (20.95)	56	16.37 (17.55)	67	-6.11 [-10.29; -1.92]	[-2.78; 6.91]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	352	20.55 (20.92)	321	18.69 (21.58)	398	-2.43 [-4.80; -0.05]	-0.35	0.846	-	

Placebo[c]	198	25.67 (26.05)	178	21.44 (23.72)	221	-2.07 [-5.12; 0.97]	[-3.93; 3.22]		
Rest of World									
Pembrolizumab[b]	30	20.00 (19.28)	28	22.02 (19.27)	32	1.19 [-5.46; 7.83]	1.54	0.766	-
Placebo[c]	18	20.37 (19.43)	15	18.89 (17.67)	20	-0.35 [-9.14; 8.43]	[-8.90; 11.98]		
Nodal Status									
Negative									
Pembrolizumab[b]	238	20.94 (19.59)	219	19.56 (20.92)	263	-1.66 [-4.48; 1.15]	2.72	0.193	-
Placebo[c]	150	26.11 (26.01)	133	19.92 (21.85)	162	-4.39 [-7.86; -0.91]	[-1.38; 6.82]		
Positive									
Pembrolizumab[b]	251	20.78 (20.78)	225	17.93 (19.72)	276	-3.35 [-5.90; -0.80]	-1.98	0.322	-
Placebo[c]	133	23.43 (22.76)	116	20.40 (22.64)	146	-1.36 [-4.73; 2.01]	[-5.92; 1.95]		
Tumor Size									
T1/T2									
Pembrolizumab[b]	358	19.93 (19.57)	333	18.77 (19.72)	393	-1.80 [-3.98; 0.38]	0.99	0.549	-
Placebo[c]	215	25.27 (24.32)	190	20.35 (22.96)	237	-2.79 [-5.55; -0.04]	[-2.26; 4.25]		
T3/T4									
Pembrolizumab[b]	131	23.41 (21.66)	111	18.62 (22.10)	146	-4.73 [-8.58; -0.88]	-1.41	0.634	-
Placebo[c]	68	23.53 (25.31)	59	19.49 (19.61)	71	-3.32 [-8.35; 1.71]	[-7.26; 4.43]		
Choice of Carboplatin									
Q3W									
Pembrolizumab[b]	215	20.47 (19.46)	198	19.36 (21.20)	240	-0.97 [-3.94; 2.01]	1.76	0.444	-
Placebo[c]	118	22.88 (23.35)	101	19.31 (19.82)	127	-2.73 [-6.64; 1.19]	[-2.77; 6.29]		
Weekly									
Pembrolizumab[b]	274	21.17 (20.77)	246	18.22 (19.60)	299	-3.73 [-6.18; -1.27]	-0.60	0.748	-
Placebo[c]	164	26.42 (25.31)	147	20.86 (23.72)	180	-3.13 [-6.20; -0.06]	[-4.24; 3.04]		

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Dyspnoe

Tabelle 4G-49: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Dyspnoe in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Dyspnoea	Adjuvant Baseline		Adjuvant Week 24		Change from Adjuvant Baseline to Adjuvant Week 24		Pembrolizumab[b] vs. Placebo[c]			p-Value for Interaction Test[h]
							Mean Difference at Adjuvant Week 24		Standardized Mean Difference at Adjuvant Week 24	
	N[d]	Mean (SD)	N[d]	Mean (SD)	N[e]	Mean [95 %-CI][f]	[95 %-CI][f]	p-Value	[95 %-CI][g]	
ECOG Performance Status										
0										
Pembrolizumab[b]	418	11.32 (18.74)	385	11.43 (19.45)	466	0.15 [-1.71; 2.01]	0.20	0.889	-	0.755
Placebo[c]	247	12.15 (19.85)	215	11.78 (20.01)	268	-0.05 [-2.43; 2.33]	[-2.63; 3.03]			
1										
Pembrolizumab[b]	71	12.21 (18.89)	59	12.43 (18.46)	73	-1.88 [-6.88; 3.12]	-1.51	0.690	-	
Placebo[c]	36	19.44 (26.87)	34	18.63 (24.88)	40	-0.37 [-6.77; 6.03]	[-9.01; 5.99]			
Nodal Status										
Negative										
Pembrolizumab[b]	238	12.04 (19.95)	219	11.57 (19.89)	263	-0.53 [-3.10; 2.05]	-0.51	0.796	-	0.500
Placebo[c]	150	12.22 (22.32)	133	12.28 (22.65)	162	-0.02 [-3.23; 3.19]	[-4.36; 3.35]			
Positive										
Pembrolizumab[b]	251	10.89 (17.54)	225	11.56 (18.76)	276	0.26 [-2.11; 2.63]	0.38	0.838	-	
Placebo[c]	133	14.04 (19.34)	116	13.22 (18.59)	146	-0.12 [-3.25; 3.01]	[-3.28; 4.04]			
Tumor Size										
T1/T2										
Pembrolizumab[b]	358	11.08 (17.94)	333	11.11 (18.48)	393	-0.32 [-2.33; 1.69]	-0.18	0.908	-	0.731
Placebo[c]	215	12.87 (21.25)	190	12.28 (20.32)	237	-0.14 [-2.69; 2.40]	[-3.18; 2.82]			
T3/T4										
Pembrolizumab[b]	131	12.47 (20.81)	111	12.91 (21.64)	146	0.43 [-3.07; 3.94]	0.27	0.925	-	
Placebo[c]	68	13.73 (20.14)	59	14.12 (22.49)	71	0.17 [-4.54; 4.87]	[-5.35; 5.89]			
Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	215	12.25 (18.51)	198	11.95 (20.09)	240	0.02 [-2.71; 2.75]	-0.96	0.665	-	0.507
Placebo[c]	118	12.71 (19.45)	101	14.19 (22.28)	127	0.98 [-2.68; 4.63]	[-5.29; 3.38]			
Weekly										
Pembrolizumab[b]	274	10.83 (18.93)	246	11.25 (18.69)	299	-0.30 [-2.56; 1.96]	0.59	0.726	-	

Placebo[c]	164	13.41 (22.07)	147	11.79 (19.82)	180	-0.89 [-3.71; 1.93]	[-2.73; 3.92]		

a: Database Cutoff Date: 23MAR2021
b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

Tabelle 4G-50: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Schlaflosigkeit in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Insomnia	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab[b]	448	28.65 (26.86)	403	25.72 (26.65)	492	-3.10 [-5.70; -0.51]	0.93	0.643	-	0.793
Placebo[c]	250	30.53 (29.82)	219	26.03 (28.69)	271	-4.03 [-7.40; -0.67]	[-3.01; 4.87]			
≥ 65										
Pembrolizumab[b]	41	22.76 (21.65)	41	22.76 (24.08)	47	-0.22 [-7.48; 7.05]	1.83	0.732	-	
Placebo[c]	33	22.22 (23.07)	30	21.11 (26.96)	37	-2.04 [-10.30; 6.21]	[-8.77; 12.42]			
ECOG Performance Status										
0										
Pembrolizumab[b]	418	29.11 (26.84)	385	25.28 (26.05)	466	-4.05 [-6.64; -1.46]	1.38	0.486	-	0.581
Placebo[c]	247	30.09 (29.27)	215	24.50 (27.90)	268	-5.43 [-8.73; -2.13]	[-2.50; 5.26]			
1										
Pembrolizumab[b]	71	22.54 (23.75)	59	26.55 (28.89)	73	4.65 [-2.29; 11.58]	-0.91	0.870	-	
Placebo[c]	36	25.93 (28.85)	34	31.37 (31.72)	40	5.56 [-3.50; 14.62]	[-11.97; 10.14]			

Geographic Region									
Asia									
Pembrolizumab[b]	107	27.73 (24.00)	95	23.16 (23.36)	109	-3.13 [-7.64; 1.38]	4.12	0.229	-	0.229
Placebo[c]	67	22.39 (24.88)	56	17.86 (22.89)	67	-7.25 [-12.89; -1.60]	[-2.62; 10.86]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	352	28.50 (27.08)	321	25.96 (27.21)	398	-3.08 [-6.07; -0.08]	-1.07	0.641	-	
Placebo[c]	198	32.49 (30.12)	178	29.03 (29.44)	221	-2.01 [-5.85; 1.84]	[-5.59; 3.44]			
Rest of World										
Pembrolizumab[b]	30	25.56 (28.61)	28	27.38 (27.30)	32	0.56 [-9.53; 10.65]	13.39	0.085	-	
Placebo[c]	18	24.07 (29.83)	15	11.11 (27.22)	20	-12.83 [-25.88; 0.22]	[-1.91; 28.70]			
Nodal Status										
Negative										
Pembrolizumab[b]	238	28.29 (27.09)	219	26.33 (26.55)	263	-2.91 [-6.24; 0.42]	1.48	0.554	-	0.761
Placebo[c]	150	33.33 (30.16)	133	27.32 (27.78)	162	-4.39 [-8.51; -0.27]	[-3.43; 6.39]			
Positive										
Pembrolizumab[b]	251	28.02 (25.96)	225	24.59 (26.31)	276	-2.60 [-6.18; 0.98]	1.03	0.714	-	
Placebo[c]	133	25.31 (27.57)	116	23.28 (29.23)	146	-3.63 [-8.37; 1.11]	[-4.50; 6.57]			
Tumor Size										
T1/T2										
Pembrolizumab[b]	358	27.84 (26.60)	333	24.72 (25.60)	393	-3.48 [-6.23; -0.74]	-0.67	0.749	-	0.098
Placebo[c]	215	29.92 (29.34)	190	26.67 (29.54)	237	-2.81 [-6.30; 0.68]	[-4.81; 3.46]			
T3/T4										
Pembrolizumab[b]	131	29.01 (26.28)	111	27.63 (28.74)	146	-0.86 [-6.13; 4.41]	6.72	0.099	-	
Placebo[c]	68	28.43 (28.95)	59	21.47 (24.58)	71	-7.58 [-14.46; -0.70]	[-1.28; 14.71]			
Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	215	28.68 (26.75)	198	27.10 (28.70)	240	-0.99 [-4.91; 2.93]	3.89	0.206	-	0.230
Placebo[c]	118	28.25 (28.12)	101	24.09 (26.30)	127	-4.88 [-10.07; 0.31]	[-2.15; 9.93]			
Weekly										
Pembrolizumab[b]	274	27.74 (26.33)	246	24.12 (24.39)	299	-4.38 [-7.46; -1.29]	-1.00	0.670	-	
Placebo[c]	164	30.69 (29.99)	147	26.53 (29.95)	180	-3.38 [-7.24; 0.48]	[-5.59; 3.60]			

a: Database Cutoff Date: 23MAR2021
b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates

g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Appetitverlust

Tabelle 4G-51: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Appetitverlust in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Appetite Loss	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab[b]	448	9.30 (17.85)	403	7.20 (16.48)	492	-1.76 [-3.42; -0.09]	2.39	0.046	0.17	0.339
Placebo[c]	250	8.40 (17.56)	219	4.72 (12.89)	271	-4.15 [-6.24; -2.05]	[0.04; 4.74]		[0.00; 0.33]	
≥ 65										
Pembrolizumab[b]	41	18.70 (29.86)	41	12.20 (20.76)	47	-5.06 [-12.40; 2.28]	-1.12	0.804	-	
Placebo[c]	33	13.13 (21.95)	30	11.11 (20.22)	37	-3.94 [-11.97; 4.09]	[-10.11; 7.86]			
ECOG Performance Status										
0										
Pembrolizumab[b]	418	9.89 (18.84)	385	7.45 (16.39)	466	-1.95 [-3.75; -0.15]	1.92	0.127	-	0.800
Placebo[c]	247	8.77 (18.27)	215	5.43 (14.29)	268	-3.87 [-6.09; -1.64]	[-0.55; 4.39]			
1										
Pembrolizumab[b]	71	11.27 (21.78)	59	9.04 (20.37)	73	-2.85 [-7.18; 1.48]	1.85	0.566	-	
Placebo[c]	36	10.19 (17.49)	34	5.88 (12.90)	40	-4.70 [-10.21; 0.81]	[-4.52; 8.23]			
Geographic Region										
Asia										
Pembrolizumab[b]	107	10.59 (18.08)	95	7.72 (14.95)	109	-2.72 [-5.99; 0.55]	3.01	0.172	-	0.563
Placebo[c]	67	10.45 (16.63)	56	4.17 (11.12)	67	-5.73 [-9.67; -1.80]	[-1.33; 7.36]			
Europe/Israel/North America/Australia										

Pembrolizumab[b]	352	10.04 (19.98)	321	7.27 (17.35)	398	-2.25 [-4.24; -0.27]	1.19	0.399	-	
Placebo[c]	198	8.25 (18.53)	178	5.99 (15.08)	221	-3.44 [-5.92; -0.97]	[-1.58; 3.97]			
Rest of World										
Pembrolizumab[b]	30	8.89 (14.99)	28	11.90 (18.62)	32	2.31 [-5.15; 9.77]	8.04	0.143	-	
Placebo[c]	18	11.11 (19.80)	15	4.44 (11.73)	20	-5.72 [-15.28; 3.83]	[-2.84; 18.91]			
Nodal Status										
Negative										
Pembrolizumab[b]	238	10.36 (20.65)	219	8.68 (18.36)	263	-1.12 [-3.58; 1.34]	3.55	0.037	0.23	0.091
Placebo[c]	150	9.11 (19.27)	133	5.26 (13.51)	162	-4.67 [-7.64; -1.71]	[0.22; 6.89]		[0.01; 0.45]	
Positive										
Pembrolizumab[b]	251	9.83 (17.91)	225	6.67 (15.43)	276	-2.92 [-5.15; -0.69]	0.40	0.804	-	
Placebo[c]	133	8.77 (16.86)	116	5.75 (14.76)	146	-3.32 [-6.18; -0.46]	[-2.79; 3.59]			
Tumor Size										
T1/T2										
Pembrolizumab[b]	358	9.59 (18.78)	333	7.71 (17.28)	393	-1.47 [-3.37; 0.42]	2.06	0.131	-	0.993
Placebo[c]	215	8.53 (17.19)	190	5.44 (13.70)	237	-3.53 [-5.88; -1.18]	[-0.61; 4.72]			
T3/T4										
Pembrolizumab[b]	131	11.45 (20.58)	111	7.51 (16.01)	146	-3.66 [-7.11; -0.20]	1.71	0.469	-	
Placebo[c]	68	10.29 (20.97)	59	5.65 (15.35)	71	-5.37 [-9.66; -1.08]	[-2.95; 6.37]			
Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	215	10.23 (18.75)	198	8.25 (17.59)	240	-1.55 [-4.11; 1.02]	4.71	0.010	0.32	0.079
Placebo[c]	118	9.04 (18.83)	101	3.96 (10.84)	127	-6.26 [-9.51; -3.00]	[1.15; 8.27]		[0.08; 0.56]	
Weekly										
Pembrolizumab[b]	274	9.98 (19.71)	246	7.18 (16.44)	299	-2.51 [-4.68; -0.34]	-0.30	0.845	-	
Placebo[c]	164	8.94 (17.75)	147	6.58 (15.91)	180	-2.20 [-4.86; 0.45]	[-3.34; 2.73]			

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Verstopfung

Tabelle 4G-52: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Verstopfung in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Constipation	Adjuvant Baseline		Adjuvant Week 24		Change from Adjuvant Baseline to Adjuvant Week 24		Pembrolizumab[b] vs. Placebo[c]			p-Value for Interaction Test[h]
							Mean Difference at Adjuvant Week 24		Standardized Mean Difference at Adjuvant Week 24	
	N[d]	Mean (SD)	N[d]	Mean (SD)	N[e]	Mean [95 %-CI][f]	[95 %-CI][f]	p-Value	[95 %-CI][g]	
Age (Years)										
< 65										
Pembrolizumab[b]	448	11.16 (20.90)	403	12.32 (21.92)	492	1.16 [-0.89; 3.20]	2.03	0.204	-	0.681
Placebo[c]	250	11.73 (21.23)	219	10.65 (20.65)	271	-0.87 [-3.53; 1.79]	[-1.10; 5.16]			
≥ 65										
Pembrolizumab[b]	41	15.45 (23.68)	41	16.26 (19.89)	47	1.90 [-4.91; 8.70]	0.34	0.941	-	
Placebo[c]	33	13.13 (21.95)	30	16.67 (24.37)	37	1.56 [-6.06; 9.17]	[-8.92; 9.60]			
ECOG Performance Status										
0										
Pembrolizumab[b]	418	11.24 (20.48)	385	12.81 (21.86)	466	1.60 [-0.44; 3.64]	1.11	0.488	-	0.425
Placebo[c]	247	11.47 (21.01)	215	11.94 (21.79)	268	0.49 [-2.14; 3.12]	[-2.03; 4.25]			
1										
Pembrolizumab[b]	71	13.15 (24.87)	59	11.86 (21.23)	73	-1.64 [-7.72; 4.44]	4.40	0.286	-	
Placebo[c]	36	14.81 (23.16)	34	7.84 (16.53)	40	-6.04 [-13.47; 1.39]	[-3.75; 12.55]			
Geographic Region										
Asia										
Pembrolizumab[b]	107	13.08 (20.35)	95	13.68 (20.34)	109	0.90 [-3.13; 4.93]	3.91	0.209	-	0.173
Placebo[c]	67	12.94 (19.21)	56	10.12 (21.00)	67	-3.02 [-8.08; 2.05]	[-2.21; 10.04]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	352	10.80 (21.13)	321	11.84 (21.85)	398	1.07 [-1.23; 3.37]	1.61	0.361	-	
Placebo[c]	198	11.28 (21.55)	178	10.67 (20.47)	221	-0.54 [-3.49; 2.42]	[-1.85; 5.07]			
Rest of World										
Pembrolizumab[b]	30	14.44 (24.26)	28	19.05 (24.73)	32	3.66 [-5.28; 12.59]	-6.75	0.330	-	
Placebo[c]	18	14.81 (26.13)	15	24.44 (26.63)	20	10.40 [-1.24; 22.04]	[-20.60; 7.11]			
Tumor Size										
T1/T2										

Pembrolizumab[b]	358	11.73 (21.14)	333	13.01 (22.20)	393	1.30 [-0.98; 3.59]	1.98	0.262	-	> 0.999
Placebo[c]	215	12.40 (22.12)	190	11.75 (22.40)	237	-0.67 [-3.58; 2.23]	[-1.48; 5.44]			
T3/T4										
Pembrolizumab[b]	131	10.94 (21.26)	111	11.71 (20.42)	146	1.09 [-2.77; 4.95]	1.25	0.666	-	
Placebo[c]	68	10.29 (18.44)	59	10.17 (16.67)	71	-0.16 [-5.14; 4.81]	[-4.46; 6.96]			
Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	215	11.94 (21.79)	198	13.13 (22.19)	240	0.95 [-1.88; 3.78]	1.18	0.600	-	0.757
Placebo[c]	118	11.58 (20.62)	101	11.88 (20.86)	127	-0.23 [-4.00; 3.54]	[-3.25; 5.61]			
Weekly										
Pembrolizumab[b]	274	11.19 (20.68)	246	12.33 (21.44)	299	1.36 [-1.35; 4.06]	1.92	0.346	-	
Placebo[c]	164	12.20 (21.85)	147	11.11 (21.49)	180	-0.56 [-3.94; 2.81]	[-2.08; 5.92]			

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Diarrhoe

Tabelle 4G-53: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Diarrhoe in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Diarrhea	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab[b]	448	5.51 (15.10)	403	6.29 (15.39)	492	0.98 [-0.65; 2.61]	1.62	0.179	-	0.353
Placebo[c]	250	4.53 (12.56)	219	4.57 (13.14)	271	-0.63 [-2.71; 1.44]	[-0.74; 3.97]			

≥ 65									
Pembrolizumab[b]	41	4.07 (11.04)	41	4.07 (11.04)	47	0.38 [-3.46; 4.22]	-0.47	0.857	-	
Placebo[c]	33	3.03 (12.81)	30	4.44 (11.52)	37	0.85 [-3.46; 5.16]	[-5.60; 4.67]			
ECOG Performance Status										
0										
Pembrolizumab[b]	418	5.74 (14.92)	385	6.58 (15.68)	466	1.29 [-0.38; 2.96]	1.54	0.211	-	0.363
Placebo[c]	247	3.91 (11.95)	215	4.65 (13.25)	268	-0.25 [-2.36; 1.85]	[-0.88; 3.96]			
1										
Pembrolizumab[b]	71	3.29 (13.98)	59	2.82 (9.36)	73	-1.70 [-5.19; 1.78]	-0.27	0.899	-	
Placebo[c]	36	7.41 (16.16)	34	3.92 (10.90)	40	-1.44 [-5.55; 2.68]	[-4.46; 3.92]			
Geographic Region										
Asia										
Pembrolizumab[b]	107	6.85 (14.29)	95	5.61 (14.30)	109	-0.11 [-3.09; 2.87]	1.59	0.463	-	0.853
Placebo[c]	67	3.48 (10.27)	56	3.57 (10.40)	67	-1.69 [-5.37; 1.98]	[-2.68; 5.85]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	352	5.02 (14.99)	321	6.33 (15.52)	398	1.22 [-0.63; 3.08]	1.43	0.290	-	
Placebo[c]	198	4.88 (13.59)	178	4.87 (13.77)	221	-0.21 [-2.55; 2.13]	[-1.22; 4.09]			
Rest of World										
Pembrolizumab[b]	30	4.44 (14.47)	28	4.76 (11.88)	32	1.07 [-4.63; 6.78]	0.28	0.943	-	
Placebo[c]	18	1.85 (7.86)	15	4.44 (11.73)	20	0.80 [-6.33; 7.92]	[-7.54; 8.09]			
Nodal Status										
Negative										
Pembrolizumab[b]	238	6.16 (14.01)	219	6.85 (15.60)	263	1.12 [-1.01; 3.24]	1.63	0.297	-	0.680
Placebo[c]	150	4.44 (13.19)	133	4.76 (13.07)	162	-0.52 [-3.13; 2.10]	[-1.44; 4.70]			
Positive										
Pembrolizumab[b]	251	4.65 (15.51)	225	5.33 (14.47)	276	0.74 [-1.43; 2.91]	1.17	0.453	-	
Placebo[c]	133	4.26 (11.90)	116	4.31 (12.84)	146	-0.43 [-3.20; 2.34]	[-1.89; 4.23]			
Tumor Size										
T1/T2										
Pembrolizumab[b]	358	5.40 (13.73)	333	6.61 (15.83)	393	1.12 [-0.69; 2.93]	2.08	0.119	-	0.236
Placebo[c]	215	5.58 (14.04)	190	4.74 (13.54)	237	-0.96 [-3.22; 1.30]	[-0.54; 4.70]			
T3/T4										
Pembrolizumab[b]	131	5.34 (17.45)	111	4.50 (12.30)	146	0.45 [-2.31; 3.20]	-0.25	0.895	-	
Placebo[c]	68	0.49 (4.04)	59	3.95 (10.87)	71	0.69 [-2.72; 4.11]	[-3.92; 3.43]			
Choice of Carboplatin										
Q3W										

Pembrolizumab[b]	215	3.88 (13.30)	198	6.06 (15.66)	240	2.09 [-0.32; 4.50]	2.37	0.187	-	0.316
Placebo[c]	118	4.24 (11.97)	101	3.96 (12.73)	127	-0.28 [-3.41; 2.85]	[-1.15; 5.89]			
Weekly										
Pembrolizumab[b]	274	6.57 (15.80)	246	6.10 (14.56)	299	-0.02 [-1.97; 1.94]	0.46	0.739	-	
Placebo[c]	164	4.47 (13.07)	147	4.99 (13.15)	180	-0.48 [-2.87; 1.91]	[-2.28; 3.21]			

a: Database Cutoff Date: 23MAR2021
b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

<u>EORTC QLQ-BR23 adjuvanten Phase</u>

EORTC QLQ-BR23: Symptomskala Nebenwirkungen der systemischen Therapie

Tabelle 4G-54: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Nebenwirkungen der systemischen Therapie in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Systemic Therapy Side Effects	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab[b]	447	16.25 (14.03)	402	15.86 (14.04)	492	-0.48 [-1.63; 0.68]	1.16	0.216	-	0.480
Placebo[c]	249	16.16 (14.76)	217	14.53 (14.40)	269	-1.63 [-3.16; -0.10]	[-0.68; 2.99]			
≥ 65										
Pembrolizumab[b]	40	17.74 (12.25)	40	14.17 (12.46)	46	-2.88 [-6.33; 0.56]	-1.64	0.508	-	
Placebo[c]	33	14.72 (15.72)	30	13.17 (15.65)	37	-1.24 [-5.04; 2.55]	[-6.54; 3.27]			

ECOG Performance Status									
0									
Pembrolizumab[b]	417	16.50 (14.12)	384	16.08 (14.08)	466	-0.40 [-1.60; 0.79]	1.38	0.145	-	0.188
Placebo[c]	246	15.95 (15.08)	213	14.22 (14.64)	266	-1.78 [-3.33; -0.24]	[-0.48; 3.24]			
1									
Pembrolizumab[b]	70	15.58 (12.43)	58	13.22 (12.46)	72	-2.52 [-5.36; 0.33]	-1.87	0.408	-	
Placebo[c]	36	16.27 (13.44)	34	15.27 (14.01)	40	-0.65 [-4.33; 3.03]	[-6.33; 2.59]			
Geographic Region									
Asia									
Pembrolizumab[b]	106	15.50 (12.24)	95	12.78 (11.29)	109	-2.48 [-4.52; -0.44]	-1.06	0.503	-	0.192
Placebo[c]	67	15.42 (14.62)	56	14.29 (13.16)	67	-1.43 [-3.99; 1.13]	[-4.17; 2.05]			
Europe/Israel/North America/Australia									
Pembrolizumab[b]	351	16.55 (14.22)	319	16.38 (14.39)	397	-0.11 [-1.46; 1.23]	1.86	0.084	-	
Placebo[c]	197	16.10 (15.05)	176	14.34 (15.21)	219	-1.98 [-3.74; -0.22]	[-0.25; 3.98]			
Rest of World									
Pembrolizumab[b]	30	17.30 (15.59)	28	18.03 (15.24)	32	-1.05 [-5.37; 3.28]	-2.00	0.563	-	
Placebo[c]	18	16.93 (14.26)	15	14.92 (11.65)	20	0.95 [-4.84; 6.74]	[-8.96; 4.97]			
Nodal Status									
Negative									
Pembrolizumab[b]	237	17.72 (14.56)	218	16.89 (14.14)	263	-0.39 [-2.06; 1.27]	1.42	0.264	-	0.496
Placebo[c]	150	16.10 (15.08)	132	15.04 (14.14)	161	-1.81 [-3.88; 0.26]	[-1.07; 3.91]			
Positive									
Pembrolizumab[b]	250	15.09 (13.11)	224	14.56 (13.60)	275	-0.94 [-2.37; 0.50]	0.55	0.645	-	
Placebo[c]	132	15.87 (14.66)	115	13.58 (14.98)	145	-1.49 [-3.43; 0.46]	[-1.80; 2.90]			
Tumor Size									
T1/T2									
Pembrolizumab[b]	357	15.87 (13.66)	332	15.35 (13.57)	393	-0.39 [-1.69; 0.92]	0.83	0.421	-	0.854
Placebo[c]	214	16.18 (15.39)	188	14.94 (15.12)	235	-1.21 [-2.89; 0.46]	[-1.19; 2.85]			
T3/T4									
Pembrolizumab[b]	130	17.73 (14.45)	110	16.80 (14.87)	145	-1.64 [-3.66; 0.38]	1.16	0.484	-	
Placebo[c]	68	15.41 (13.12)	59	12.51 (12.41)	71	-2.79 [-5.49; -0.09]	[-2.09; 4.41]			
Choice of Carboplatin									
Q3W									
Pembrolizumab[b]	214	16.36 (13.67)	197	16.17 (14.10)	239	-0.30 [-2.05; 1.45]	1.65	0.238	-	0.505
Placebo[c]	118	15.50 (14.67)	100	14.24 (13.94)	126	-1.95 [-4.28; 0.37]	[-1.10; 4.40]			
Weekly									

Pembrolizumab[b]	273	16.38 (14.08)	245	15.34 (13.76)	299	-0.99 [-2.40; 0.41]	0.38	0.732	-	
Placebo[c]	163	16.42 (15.04)	146	14.55 (14.96)	179	-1.37 [-3.17; 0.42]	[-1.81; 2.57]			

a: Database Cutoff Date: 23MAR2021
b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-BR23: Symptomskala Symptome im Brustbereich

Tabelle 4G-55: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Symptome im Brustbereich in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Breast Symptoms	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab[b]	447	21.92 (18.30)	402	16.94 (17.32)	492	-5.39 [-7.06; -3.72]	-0.07	0.956	-	0.684
Placebo[c]	249	23.49 (20.49)	217	17.59 (18.24)	269	-5.32 [-7.48; -3.16]	[-2.58; 2.44]			
≥ 65										
Pembrolizumab[b]	40	25.63 (22.83)	40	15.83 (15.99)	46	-9.61 [-14.73; -4.50]	1.87	0.565	-	
Placebo[c]	33	19.44 (18.12)	30	10.28 (16.18)	37	-11.48 [-17.07; -5.89]	[-4.58; 8.32]			
ECOG Performance Status										
0										
Pembrolizumab[b]	417	22.70 (18.71)	384	16.93 (17.42)	466	-6.03 [-7.76; -4.30]	-0.03	0.981	-	0.698
Placebo[c]	246	22.43 (19.38)	213	16.63 (18.36)	266	-6.00 [-8.20; -3.80]	[-2.59; 2.53]			
1										
Pembrolizumab[b]	70	19.40 (18.59)	58	16.24 (15.72)	72	-3.89 [-7.89; 0.10]	2.08	0.466	-	

Placebo[c]	36	27.08 (25.31)	34	17.16 (16.91)	40	-5.97 [-10.96; -0.98]	[-3.56; 7.72]		
Tumor Size									
T1/T2									
Pembrolizumab[b]	357	21.71 (17.79)	332	16.87 (17.27)	393	-5.57 [-7.42; -3.72]	0.83	0.546	-	0.266
Placebo[c]	214	23.71 (20.92)	188	16.58 (17.32)	235	-6.40 [-8.72; -4.08]	[-1.87; 3.52]		
T3/T4									
Pembrolizumab[b]	130	23.65 (21.03)	110	16.74 (17.03)	145	-6.34 [-9.44; -3.23]	-1.91	0.429	-	
Placebo[c]	68	20.83 (17.90)	59	17.09 (20.67)	71	-4.43 [-8.47; -0.38]	[-6.66; 2.84]		
Choice of Carboplatin									
Q3W									
Pembrolizumab[b]	214	21.18 (18.07)	197	16.50 (17.88)	239	-4.45 [-6.70; -2.20]	-0.68	0.706	-	0.407
Placebo[c]	118	19.77 (17.83)	100	16.75 (18.21)	126	-3.78 [-6.77; -0.79]	[-4.20; 2.85]		
Weekly									
Pembrolizumab[b]	273	23.05 (19.19)	245	17.11 (16.65)	299	-6.75 [-8.96; -4.54]	0.59	0.712	-	
Placebo[c]	163	25.31 (21.61)	146	16.78 (18.15)	179	-7.34 [-10.06; -4.62]	[-2.54; 3.71]		

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-BR23: Symptomskala Symptome im Armbereich

Tabelle 4G-56: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Symptome im Armbereich in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Arm Symptoms	Adjuvant Baseline		Adjuvant Week 24		Change from Adjuvant Baseline to Adjuvant Week 24		Pembrolizumab[b] vs. Placebo[c]			p-Value for Interaction Test[h]
							Mean Difference at Adjuvant Week 24		Standardized Mean Difference at Adjuvant Week 24	
	N[d]	Mean (SD)	N[d]	Mean (SD)	N[e]	Mean [95 %-CI][f]	[95 %-CI][f]	p-Value	[95 %-CI][g]	
Age (Years)										
< 65										
Pembrolizumab[b]	447	20.21 (19.84)	402	20.51 (21.23)	492	-0.59 [-2.46; 1.28]	2.07	0.159	-	0.319
Placebo[c]	249	22.98 (20.71)	217	19.25 (19.58)	269	-2.66 [-5.11; -0.22]	[-0.81; 4.96]			
≥ 65										
Pembrolizumab[b]	40	16.67 (15.71)	40	15.83 (16.28)	46	-0.67 [-4.52; 3.18]	-4.20	0.143	-	
Placebo[c]	33	10.77 (14.83)	30	14.81 (16.07)	37	3.53 [-0.78; 7.84]	[-9.85; 1.46]			
ECOG Performance Status										
0										
Pembrolizumab[b]	417	19.88 (19.86)	384	19.79 (20.75)	466	-0.58 [-2.48; 1.32]	1.97	0.179	-	0.512
Placebo[c]	246	20.87 (20.33)	213	17.89 (18.76)	266	-2.55 [-4.98; -0.11]	[-0.90; 4.84]			
1										
Pembrolizumab[b]	70	20.16 (17.67)	58	22.03 (21.68)	72	0.61 [-3.45; 4.66]	0.84	0.802	-	
Placebo[c]	36	26.23 (21.11)	34	23.86 (21.39)	40	-0.24 [-5.60; 5.13]	[-5.82; 7.51]			
Geographic Region										
Asia										
Pembrolizumab[b]	106	25.16 (21.10)	95	23.74 (19.96)	109	-0.41 [-4.02; 3.20]	3.89	0.148	-	0.474
Placebo[c]	67	23.71 (19.90)	56	19.84 (16.78)	67	-4.30 [-8.75; 0.16]	[-1.39; 9.17]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	351	17.89 (18.51)	319	18.63 (20.53)	397	-0.39 [-2.42; 1.64]	1.27	0.427	-	
Placebo[c]	197	20.81 (20.69)	176	18.06 (19.93)	219	-1.66 [-4.30; 0.98]	[-1.87; 4.42]			
Rest of World										
Pembrolizumab[b]	30	25.19 (21.82)	28	24.21 (25.85)	32	-2.03 [-10.54; 6.47]	-2.18	0.742	-	
Placebo[c]	18	21.60 (20.69)	15	22.22 (19.70)	20	0.15 [-10.94; 11.24]	[-15.47; 11.10]			
Nodal Status										
Negative										

Pembrolizumab[b]	237	19.69 (20.61)	218	17.43 (19.86)	263	-2.93 [-5.41; -0.45]	0.64	0.727	-	0.792
Placebo[c]	150	21.70 (20.08)	132	17.51 (19.32)	161	-3.57 [-6.64; -0.51]	[-2.98; 4.27]			
Positive										
Pembrolizumab[b]	250	20.13 (18.53)	224	22.67 (21.52)	275	1.82 [-0.58; 4.23]	2.33	0.234	-	
Placebo[c]	132	21.38 (20.98)	115	20.10 (19.07)	145	-0.51 [-3.74; 2.72]	[-1.52; 6.18]			
Tumor Size										
T1/T2										
Pembrolizumab[b]	357	18.30 (18.71)	332	19.34 (20.29)	393	0.11 [-1.88; 2.11]	2.88	0.062	-	0.056
Placebo[c]	214	21.96 (20.69)	188	17.67 (19.29)	235	-2.76 [-5.30; -0.23]	[-0.14; 5.90]			
T3/T4										
Pembrolizumab[b]	130	24.36 (21.12)	110	22.32 (22.45)	145	-2.64 [-6.19; 0.90]	-2.76	0.332	-	
Placebo[c]	68	20.26 (19.85)	59	22.03 (18.74)	71	0.12 [-4.58; 4.81]	[-8.36; 2.84]			
Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	214	19.73 (18.88)	197	19.85 (21.19)	239	-0.10 [-2.62; 2.41]	2.38	0.251	-	0.801
Placebo[c]	118	19.30 (17.58)	100	17.22 (19.37)	126	-2.48 [-5.88; 0.92]	[-1.70; 6.46]			
Weekly										
Pembrolizumab[b]	273	20.07 (20.08)	245	20.27 (20.63)	299	-0.93 [-3.32; 1.45]	0.75	0.673	-	
Placebo[c]	163	23.18 (22.30)	146	19.86 (19.10)	179	-1.69 [-4.66; 1.29]	[-2.75; 4.26]			

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-BR23: Symptomskala Belastung durch Haarausfall

Tabelle 4G-57: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Belastung durch Haarausfall in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Upset by Hair Loss (Imputed)[i]	Adjuvant Baseline		Adjuvant Week 24		Change from Adjuvant Baseline to Adjuvant Week 24		Pembrolizumab[b] vs. Placebo[c]			p-Value for Interaction Test[h]
							Mean Difference at Adjuvant Week 24		Standardized Mean Difference at Adjuvant Week 24	
	N[d]	Mean (SD)	N[d]	Mean (SD)	N[e]	Mean [95 %-CI][f]	[95 %-CI][f]	p-Value	[95 %-CI][g]	
Age (Years)										
< 65										
Pembrolizumab[b]	447	4.47 (18.54)	402	2.65 (13.26)	492	-2.53 [-4.28; -0.77]	-0.18	0.873	-	0.729
Placebo[c]	249	7.36 (23.65)	217	3.23 (15.54)	269	-2.35 [-4.48; -0.22]	[-2.38; 2.03]			
≥ 65										
Pembrolizumab[b]	40	5.00 (19.32)	40	5.00 (17.78)	46	-0.03 [-4.20; 4.15]	0.87	0.772	-	
Placebo[c]	33	5.05 (16.92)	30	4.44 (19.04)	37	-0.89 [-5.50; 3.71]	[-5.08; 6.81]			
ECOG Performance Status										
0										
Pembrolizumab[b]	417	5.20 (19.94)	384	2.78 (13.55)	466	-3.01 [-4.83; -1.19]	-0.51	0.661	-	0.289
Placebo[c]	246	7.72 (24.07)	213	3.76 (17.02)	266	-2.50 [-4.68; -0.31]	[-2.80; 1.78]			
1										
Pembrolizumab[b]	70	0.48 (3.98)	58	3.45 (14.89)	72	2.19 [-1.41; 5.78]	2.44	0.370	-	
Placebo[c]	36	2.78 (12.28)	34	0.98 (5.72)	40	-0.25 [-4.77; 4.27]	[-2.94; 7.82]			
Geographic Region										
Asia										
Pembrolizumab[b]	106	2.52 (12.76)	95	2.11 (9.49)	109	-3.36 [-6.82; 0.09]	-1.61	0.451	-	0.732
Placebo[c]	67	11.94 (28.25)	56	5.95 (19.18)	67	-1.75 [-5.77; 2.27]	[-5.83; 2.61]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	351	5.13 (19.98)	319	2.93 (14.18)	397	-2.19 [-4.20; -0.17]	0.42	0.746	-	
Placebo[c]	197	5.75 (21.31)	176	2.84 (15.48)	219	-2.61 [-5.04; -0.17]	[-2.12; 2.96]			
Rest of World										
Pembrolizumab[b]	30	4.44 (19.04)	28	4.76 (19.70)	32	-2.62 [-7.39; 2.15]	-5.83	0.114	-	
Placebo[c]	18	3.70 (15.71)	15	0.00 (0.00)	20	3.21 [-2.97; 9.40]	[-13.28; 1.62]			
Nodal Status										
Negative										

Pembrolizumab[b]	237	6.89 (23.26)	218	3.67 (15.90)	263	-2.58 [-4.86; -0.29]	0.58	0.695	-	0.479
Placebo[c]	150	5.11 (19.21)	132	2.78 (14.29)	161	-3.15 [-5.84; -0.46]	[-2.32; 3.47]			
Positive										
Pembrolizumab[b]	250	2.27 (12.29)	224	2.08 (11.19)	275	-2.17 [-4.55; 0.20]	-1.71	0.276	-	
Placebo[c]	132	9.34 (26.47)	115	4.06 (17.74)	145	-0.46 [-3.40; 2.47]	[-4.79; 1.37]			
Tumor Size										
T1/T2										
Pembrolizumab[b]	357	4.11 (17.36)	332	2.31 (11.21)	393	-2.31 [-4.16; -0.45]	-0.93	0.446	-	0.076
Placebo[c]	214	7.63 (23.49)	188	4.26 (18.07)	235	-1.38 [-3.61; 0.85]	[-3.33; 1.47]			
T3/T4										
Pembrolizumab[b]	130	5.64 (21.62)	110	4.55 (19.41)	145	-1.60 [-5.16; 1.96]	3.32	0.160	-	
Placebo[c]	68	5.39 (21.25)	59	0.56 (4.34)	71	-4.92 [-9.29; -0.55]	[-1.32; 7.97]			
Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	214	3.89 (16.16)	197	1.69 (8.07)	239	-3.00 [-5.49; -0.51]	-2.49	0.109	-	0.132
Placebo[c]	118	7.63 (24.43)	100	4.33 (18.75)	126	-0.51 [-3.53; 2.51]	[-5.54; 0.56]			
Weekly										
Pembrolizumab[b]	273	5.01 (20.30)	245	3.81 (16.91)	299	-1.71 [-3.91; 0.49]	1.49	0.310	-	
Placebo[c]	163	6.75 (21.96)	146	2.74 (13.84)	179	-3.21 [-5.85; -0.57]	[-1.40; 4.38]			

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

i: For participants who did not lose any hair, the score was imputed as not upset at all by the loss of hair

CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EQ-5D VAS

Tabelle 4G-58: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EQ-5D VAS	Adjuvant Baseline		Adjuvant Week 24		Change from Adjuvant Baseline to Adjuvant Week 24		Pembrolizumab[b] vs. Placebo[c]			p-Value for Interaction Test[h]
							Mean Difference at Adjuvant Week 24		Standardized Mean Difference at Adjuvant Week 24	
	N[d]	Mean (SD)	N[d]	Mean (SD)	N[e]	Mean [95 %-CI][f]	[95 %-CI][f]	p-Value	[95 %-CI][g]	
Age (Years)										
< 65										
Pembrolizumab[b]	452	79.00 (14.43)	403	80.90 (14.78)	492	1.54 [0.35; 2.73]	-0.68	0.475	-	0.623
Placebo[c]	252	78.96 (13.87)	219	81.16 (13.12)	273	2.22 [0.66; 3.79]	[-2.55; 1.19]			
≥ 65										
Pembrolizumab[b]	43	72.42 (14.97)	41	77.41 (15.42)	48	4.11 [-0.82; 9.05]	-1.20	0.724	-	
Placebo[c]	33	77.48 (19.12)	30	81.53 (15.12)	37	5.31 [-0.26; 10.88]	[-7.93; 5.53]			
ECOG Performance Status										
0										
Pembrolizumab[b]	424	78.93 (14.70)	385	80.79 (15.16)	467	1.55 [0.29; 2.81]	-1.14	0.254	-	0.110
Placebo[c]	249	79.04 (14.46)	215	81.78 (13.02)	269	2.69 [1.06; 4.32]	[-3.09; 0.82]			
1										
Pembrolizumab[b]	71	75.45 (13.55)	59	79.17 (12.73)	73	3.64 [0.47; 6.80]	2.96	0.229	-	
Placebo[c]	36	77.11 (15.20)	34	77.56 (14.92)	41	0.68 [-3.40; 4.76]	[-1.89; 7.81]			
Geographic Region										
Asia										
Pembrolizumab[b]	107	79.39 (11.81)	95	81.87 (10.10)	109	2.27 [0.24; 4.30]	0.82	0.594	-	0.147
Placebo[c]	67	78.37 (14.77)	56	80.07 (13.44)	67	1.45 [-1.09; 3.98]	[-2.21; 3.86]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	358	77.99 (15.26)	321	80.39 (15.54)	399	2.27 [0.93; 3.62]	-0.23	0.833	-	
Placebo[c]	200	78.37 (14.60)	178	80.89 (13.13)	223	2.50 [0.75; 4.26]	[-2.33; 1.88]			
Rest of World										
Pembrolizumab[b]	30	80.23 (15.37)	28	78.39 (19.83)	32	-5.46 [-13.49; 2.58]	-12.43	0.048	-0.65	
Placebo[c]	18	85.06 (12.04)	15	89.07 (13.86)	20	6.97 [-3.48; 17.43]	[-24.75; -0.11]		[-1.30; -0.01]	
Nodal Status										
Negative										
Pembrolizumab[b]	241	77.65 (14.34)	219	80.05 (14.35)	263	2.30 [0.75; 3.84]	-1.43	0.230	-	0.280

Placebo[c]	152	78.16 (14.29)	133	81.80 (12.30)	163	3.73 [1.80; 5.66]	[-3.77; 0.91]		
Positive									
Pembrolizumab[b]	254	79.17 (14.79)	225	81.09 (15.35)	277	1.37 [-0.40; 3.13]	0.38	0.788	-
Placebo[c]	133	79.52 (14.84)	116	80.52 (14.48)	147	0.98 [-1.38; 3.34]	[-2.42; 3.19]		
Tumor Size									
T1/T2									
Pembrolizumab[b]	364	78.62 (14.52)	333	80.76 (14.57)	394	2.07 [0.74; 3.39]	-0.86	0.407	-
Placebo[c]	217	78.45 (14.50)	190	81.41 (12.91)	239	2.92 [1.23; 4.62]	[-2.89; 1.17]		
T3/T4									
Pembrolizumab[b]	131	77.89 (14.80)	111	80.05 (15.74)	146	1.23 [-1.27; 3.72]	0.39	0.846	-
Placebo[c]	68	79.88 (14.73)	59	80.53 (14.77)	71	0.83 [-2.50; 4.16]	[-3.61; 4.40]		
Choice of Carboplatin									
Q3W									
Pembrolizumab[b]	218	77.39 (15.34)	198	80.57 (14.58)	241	1.97 [0.09; 3.86]	-0.43	0.774	-
Placebo[c]	120	79.53 (15.23)	101	81.39 (13.80)	129	2.40 [-0.09; 4.89]	[-3.34; 2.49]		
Weekly									
Pembrolizumab[b]	277	79.25 (13.92)	246	80.59 (15.10)	299	1.66 [0.17; 3.14]	-0.72	0.542	-
Placebo[c]	164	78.24 (14.09)	147	80.99 (13.08)	180	2.38 [0.48; 4.27]	[-3.03; 1.59]		

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EQ-5D: European Quality of Life 5 Dimensions; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation; VAS: Visual Analog Scale

Anhang 4-G4.3: Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30 in der neoadjuvanten Phase

Tabelle 4G-59: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den globalen Gesundheitsstatus in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Global Health Status/QoL	Neoadjuvant Baseline		Neoadjuvant Week 21		Change from Neoadjuvant Baseline to Neoadjuvant Week 21		Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]			p-Value for Interaction Test[h]
							Mean Difference at Neoadjuvant Week 21		Standardized Mean Difference at Neoadjuvant Week 21	
	N[d]	Mean (SD)	N[d]	Mean (SD)	N[e]	Mean [95 %-CI][f]	[95 %-CI][f]	p-Value	[95 %-CI][g]	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	628	77.34 (18.44)	564	67.01 (19.17)	681	-11.20 [-12.85; -9.55]	-1.03	0.424	-	0.788
Placebo + Chemotherapy[c]	324	79.32 (16.80)	274	68.70 (17.64)	336	-10.17 [-12.38; -7.95]	[-3.57; 1.51]			
≥ 65										
Pembrolizumab + Chemotherapy[b]	73	74.89 (18.97)	51	64.38 (21.74)	81	-11.64 [-17.06; -6.22]	-1.67	0.679	-	
Placebo + Chemotherapy[c]	42	76.19 (19.44)	35	64.76 (19.08)	47	-9.98 [-16.49; -3.46]	[-9.64; 6.31]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	602	77.24 (18.51)	534	67.10 (19.43)	657	-11.22 [-12.90; -9.53]	-0.69	0.602	-	0.642
Placebo + Chemotherapy[c]	317	80.13 (16.82)	270	68.83 (18.01)	334	-10.53 [-12.77; -8.29]	[-3.27; 1.90]			
1										
Pembrolizumab + Chemotherapy[b]	99	76.09 (18.43)	81	64.71 (19.06)	105	-10.96 [-15.51; -6.41]	-2.11	0.545	-	
Placebo + Chemotherapy[c]	49	71.43 (17.35)	39	64.32 (16.10)	49	-8.85 [-14.93; -2.77]	[-9.00; 4.78]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	132	73.17 (18.37)	127	66.21 (19.31)	135	-8.08 [-11.64; -4.52]	-1.54	0.558	-	0.894
Placebo + Chemotherapy[c]	79	76.16 (17.44)	73	68.38 (17.40)	79	-6.55 [-11.00; -2.10]	[-6.69; 3.62]			
Europe/Israel/North America/Australia										

Pembrolizumab + Chemotherapy[b]	533	77.74 (18.03)	451	66.48 (19.59)	588	-12.14 [-13.95; -10.32]	-0.80	0.586	-	
Placebo + Chemotherapy[c]	262	79.04 (16.93)	215	67.36 (17.89)	279	-11.34 [-13.83; -8.85]	[-3.67; 2.08]			
Rest of World										
Pembrolizumab + Chemotherapy[b]	36	81.71 (23.39)	37	72.52 (16.53)	39	-11.35 [-18.34; -4.36]	-1.87	0.681	-	
Placebo + Chemotherapy[c]	25	87.00 (16.15)	21	76.98 (16.85)	25	-9.48 [-17.83; -1.12]	[-10.95; 7.20]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	336	77.53 (17.85)	295	66.64 (18.65)	368	-11.85 [-14.03; -9.68]	-0.16	0.926	-	0.505
Placebo + Chemotherapy[c]	181	80.76 (15.77)	151	68.10 (17.53)	191	-11.70 [-14.57; -8.82]	[-3.50; 3.18]			
Positive										
Pembrolizumab + Chemotherapy[b]	365	76.67 (19.08)	320	66.93 (20.07)	394	-10.64 [-12.92; -8.36]	-1.86	0.298	-	
Placebo + Chemotherapy[c]	185	77.21 (18.22)	158	68.41 (18.14)	192	-8.78 [-11.84; -5.73]	[-5.35; 1.64]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	520	78.14 (17.75)	453	66.69 (19.57)	564	-12.21 [-14.06; -10.36]	-1.80	0.214	-	0.581
Placebo + Chemotherapy[c]	274	78.86 (17.47)	233	68.17 (17.98)	287	-10.41 [-12.86; -7.96]	[-4.64; 1.04]			
T3/T4										
Pembrolizumab + Chemotherapy[b]	181	74.03 (20.23)	162	67.08 (18.92)	198	-8.42 [-11.43; -5.40]	1.25	0.594	-	
Placebo + Chemotherapy[c]	92	79.26 (16.13)	76	68.53 (17.41)	96	-9.67 [-13.75; -5.59]	[-3.38; 5.88]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	293	76.59 (17.66)	259	64.83 (19.77)	325	-12.72 [-15.14; -10.31]	-2.78	0.139	-	0.449
Placebo + Chemotherapy[c]	158	79.54 (16.12)	138	69.26 (17.02)	163	-9.94 [-13.09; -6.80]	[-6.46; 0.91]			
Weekly										
Pembrolizumab + Chemotherapy[b]	408	77.43 (19.08)	356	68.21 (19.00)	437	-10.17 [-12.27; -8.08]	0.31	0.850	-	
Placebo + Chemotherapy[c]	206	78.64 (17.93)	171	67.45 (18.44)	218	-10.48 [-13.31; -7.65]	[-2.91; 3.53]			

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase

f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-60: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Körperliche Funktion in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Physical Functioning	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	628	92.41 (12.23)	564	77.53 (18.59)	681	-15.14 [-16.51; -13.77]	-2.44	0.039	-0.15	0.288
Placebo + Chemotherapy[c]	324	92.12 (12.54)	274	79.46 (16.75)	336	-12.70 [-14.62; -10.77]	[-4.77; -0.12]		[-0.29; -0.01]	
≥ 65										
Pembrolizumab + Chemotherapy[b]	73	87.40 (16.35)	51	71.24 (22.33)	81	-17.36 [-22.93; -11.78]	-6.83	0.116	-	
Placebo + Chemotherapy[c]	42	86.83 (16.49)	35	76.95 (19.96)	47	-10.53 [-17.37; -3.68]	[-15.36; 1.71]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	602	92.49 (12.15)	534	77.79 (18.79)	657	-15.19 [-16.61; -13.78]	-2.11	0.082	-	0.120
Placebo + Chemotherapy[c]	317	93.06 (11.18)	270	79.93 (16.29)	334	-13.08 [-15.05; -11.12]	[-4.49; 0.27]			
1										
Pembrolizumab + Chemotherapy[b]	99	88.22 (15.76)	81	71.85 (19.61)	105	-16.82 [-20.91; -12.74]	-7.84	0.026	-0.43	
Placebo + Chemotherapy[c]	49	81.50 (19.26)	39	74.02 (21.62)	49	-8.99 [-14.69; -3.28]	[-14.71; -0.97]		[-0.81; -0.05]	

Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	132	91.46 (11.42)	127	76.17 (20.18)	135	-15.46 [-18.46; -12.47]	-4.68	0.060	-	0.474
Placebo + Chemotherapy[c]	79	91.98 (10.85)	73	80.82 (15.59)	79	-10.78 [-14.70; -6.86]	[-9.57; 0.20]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	533	91.94 (13.18)	451	76.78 (18.90)	588	-15.76 [-17.32; -14.19]	-2.63	0.053	-	
Placebo + Chemotherapy[c]	262	91.53 (13.62)	215	78.57 (17.31)	279	-13.13 [-15.35; -10.90]	[-5.30; 0.04]			
Rest of World										
Pembrolizumab + Chemotherapy[b]	36	92.59 (12.01)	37	82.70 (14.78)	39	-9.45 [-14.98; -3.92]	2.21	0.611	-	
Placebo + Chemotherapy[c]	25	89.87 (14.80)	21	79.68 (20.60)	25	-11.66 [-18.69; -4.62]	[-6.46; 10.87]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	336	92.84 (11.63)	295	76.11 (19.24)	368	-17.41 [-19.36; -15.45]	-2.74	0.102	-	0.850
Placebo + Chemotherapy[c]	181	92.89 (12.22)	151	78.68 (16.35)	191	-14.66 [-17.36; -11.97]	[-6.03; 0.54]			
Positive										
Pembrolizumab + Chemotherapy[b]	365	91.01 (13.74)	320	77.83 (18.74)	394	-13.51 [-15.34; -11.67]	-3.02	0.055	-	
Placebo + Chemotherapy[c]	185	90.16 (13.87)	158	79.66 (17.88)	192	-10.49 [-13.05; -7.92]	[-6.11; 0.06]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	520	92.92 (11.30)	453	77.17 (19.19)	564	-16.24 [-17.78; -14.71]	-3.76	0.005	-0.22	0.263
Placebo + Chemotherapy[c]	274	91.56 (13.31)	233	79.31 (16.86)	287	-12.49 [-14.61; -10.36]	[-6.34; -1.17]		[-0.38; -0.07]	
T3/T4										
Pembrolizumab + Chemotherapy[b]	181	88.91 (16.01)	162	76.54 (18.45)	198	-13.03 [-15.79; -10.27]	-0.76	0.741	-	
Placebo + Chemotherapy[c]	92	91.38 (12.68)	76	78.77 (18.04)	96	-12.27 [-16.12; -8.41]	[-5.31; 3.79]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	293	90.99 (13.18)	259	74.95 (19.99)	325	-16.52 [-18.64; -14.40]	-4.25	0.018	-0.25	0.307
Placebo + Chemotherapy[c]	158	92.45 (12.09)	138	80.14 (16.75)	163	-12.27 [-15.14; -9.39]	[-7.78; -0.73]		[-0.45; -0.04]	
Weekly										
Pembrolizumab +	408	92.53 (12.49)	356	78.50 (18.10)	437	-14.46 [-16.19; -12.73]	-1.64	0.271	-	

Chemotherapy[b]									
Placebo + Chemotherapy[c]	206	90.78 (13.91)	171	78.40 (17.44)	218	-12.82 [-15.27; -10.37]	[-4.57; 1.29]		

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-61: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Rollenfunktion in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Role Functioning	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	628	90.95 (18.35)	564	72.10 (26.39)	681	-19.00 [-21.12; -16.88]	-4.84	0.007	-0.20	0.443
Placebo + Chemotherapy[c]	324	88.73 (20.21)	274	75.55 (25.24)	336	-14.16 [-17.11; -11.21]	[-8.35; -1.33]		[-0.34; -0.05]	
≥ 65										
Pembrolizumab + Chemotherapy[b]	73	90.64 (18.63)	51	63.07 (29.31)	81	-29.11 [-36.55; -21.67]	-11.16	0.049	-0.42	
Placebo + Chemotherapy[c]	42	92.06 (16.56)	35	73.33 (21.84)	47	-17.95 [-27.00; -8.89]	[-22.28; -0.04]		[-0.84; -0.00]	
ECOG Performance Status										
0										
Pembrolizumab +	602	91.14 (18.16)	534	71.41 (26.81)	657	-20.17 [-22.37; -17.97]	-4.74	0.010	-0.19	0.470

Chemotherapy[b]										
Placebo + Chemotherapy[c]	317	90.17 (19.37)	270	75.31 (25.09)	334	-15.43 [-18.45; -12.41]	[-8.35; -1.12]		[-0.33; -0.04]	
1										
Pembrolizumab + Chemotherapy[b]	99	89.56 (19.57)	81	70.99 (26.45)	105	-17.83 [-23.55; -12.10]	-8.46	0.074	-	
Placebo + Chemotherapy[c]	49	82.31 (21.63)	39	75.21 (23.53)	49	-9.37 [-17.24; -1.49]	[-17.74; 0.82]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	132	91.41 (17.41)	127	74.28 (25.00)	135	-17.34 [-21.42; -13.26]	-4.32	0.194	-	0.322
Placebo + Chemotherapy[c]	79	93.67 (13.42)	73	79.68 (22.78)	79	-13.02 [-18.32; -7.72]	[-10.85; 2.22]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	533	90.87 (18.51)	451	69.77 (27.60)	588	-21.29 [-23.73; -18.84]	-6.24	0.003	-0.24	
Placebo + Chemotherapy[c]	262	87.53 (21.28)	215	73.64 (25.12)	279	-15.05 [-18.49; -11.60]	[-10.33; -2.16]		[-0.40; -0.08]	
Rest of World										
Pembrolizumab + Chemotherapy[b]	36	89.81 (20.03)	37	80.63 (18.22)	39	-10.15 [-18.66; -1.65]	4.83	0.438	-	
Placebo + Chemotherapy[c]	25	91.33 (19.32)	21	76.98 (28.12)	25	-14.98 [-25.55; -4.41]	[-7.55; 17.20]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	336	91.82 (17.47)	295	70.00 (27.44)	368	-22.02 [-25.06; -18.97]	-4.64	0.068	-	0.983
Placebo + Chemotherapy[c]	181	89.41 (20.33)	151	72.96 (25.44)	191	-17.38 [-21.52; -13.23]	[-9.63; 0.35]			
Positive										
Pembrolizumab + Chemotherapy[b]	365	90.09 (19.14)	320	72.60 (26.05)	394	-17.93 [-20.69; -15.18]	-6.00	0.009	-0.25	
Placebo + Chemotherapy[c]	185	88.83 (19.38)	158	77.53 (24.16)	192	-11.94 [-15.75; -8.13]	[-10.52; -1.47]		[-0.43; -0.06]	
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	520	92.08 (17.09)	453	71.23 (26.93)	564	-21.18 [-23.57; -18.78]	-5.70	0.005	-0.23	0.768
Placebo + Chemotherapy[c]	274	88.99 (19.91)	233	74.46 (25.76)	287	-15.47 [-18.75; -12.20]	[-9.65; -1.76]		[-0.38; -0.07]	
T3/T4										
Pembrolizumab + Chemotherapy[b]	181	87.57 (21.31)	162	71.71 (26.28)	198	-16.28 [-20.24; -12.32]	-4.54	0.166	-	
Placebo + Chemotherapy[c]	92	89.49 (19.72)	76	77.85 (21.84)	96	-11.74 [-17.25; -6.23]	[-10.98; 1.89]			

Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	293	90.73 (18.72)	259	71.30 (26.29)	325	-19.55 [-22.62; -16.47]	-6.55	0.010	-0.27	0.436
Placebo + Chemotherapy[c]	158	89.56 (20.73)	138	77.17 (26.03)	163	-13.00 [-17.12; -8.88]	[-11.53; -1.56]		[-0.47; -0.06]	
Weekly										
Pembrolizumab + Chemotherapy[b]	408	91.05 (18.13)	356	71.40 (27.10)	437	-20.13 [-22.87; -17.38]	-4.23	0.068	-	
Placebo + Chemotherapy[c]	206	89.08 (18.86)	171	73.78 (23.84)	218	-15.89 [-19.74; -12.05]	[-8.78; 0.31]			

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-62: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Emotionale Funktion in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Emotional Functioning	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	628	76.02 (19.50)	564	74.66 (20.84)	681	-1.23 [-2.83; 0.37]	-0.29	0.826	-	0.463
Placebo + Chemotherapy[c]	324	75.13 (20.83)	274	74.54 (21.79)	336	-0.94 [-3.14; 1.26]	[-2.89; 2.30]			
≥ 65										

Pembrolizumab + Chemotherapy[b]		73	77.17 (19.59)	51	74.02 (20.32)	81	-1.40 [-6.07; 3.27]	-3.58	0.318	-	
Placebo + Chemotherapy[c]		42	75.79 (19.81)	35	78.10 (20.42)	47	2.18 [-3.52; 7.88]	[-10.66; 3.50]			
ECOG Performance Status											
0											
Pembrolizumab + Chemotherapy[b]		602	76.16 (19.16)	534	74.34 (20.55)	657	-1.45 [-3.04; 0.14]	-0.52	0.694	-	0.732
Placebo + Chemotherapy[c]		317	75.63 (20.38)	270	75.09 (21.76)	334	-0.94 [-3.10; 1.22]	[-3.09; 2.06]			
1											
Pembrolizumab + Chemotherapy[b]		99	76.01 (21.54)	81	76.34 (22.34)	105	-0.01 [-4.75; 4.73]	-1.25	0.743	-	
Placebo + Chemotherapy[c]		49	72.45 (22.64)	39	73.93 (20.96)	49	1.24 [-5.21; 7.70]	[-8.81; 6.30]			
Geographic Region											
Asia											
Pembrolizumab + Chemotherapy[b]		132	78.03 (15.66)	127	77.23 (18.47)	135	-0.60 [-3.67; 2.47]	-3.07	0.204	-	0.205
Placebo + Chemotherapy[c]		79	76.27 (19.39)	73	79.68 (19.39)	79	2.47 [-1.45; 6.40]	[-7.82; 1.68]			
Europe/Israel/North America/Australia											
Pembrolizumab + Chemotherapy[b]		533	75.48 (20.06)	451	73.60 (21.54)	588	-1.39 [-3.15; 0.37]	-0.50	0.737	-	
Placebo + Chemotherapy[c]		262	74.27 (21.31)	215	73.57 (21.38)	279	-0.89 [-3.35; 1.57]	[-3.40; 2.40]			
Rest of World											
Pembrolizumab + Chemotherapy[b]		36	78.94 (23.19)	37	77.93 (18.03)	39	-2.47 [-10.46; 5.53]	6.84	0.258	-	
Placebo + Chemotherapy[c]		25	81.67 (17.18)	21	72.62 (29.24)	25	-9.30 [-19.24; 0.63]	[-5.15; 18.83]			
Nodal Status											
Negative											
Pembrolizumab + Chemotherapy[b]		336	76.17 (19.37)	295	73.02 (21.17)	368	-2.55 [-4.73; -0.36]	-2.58	0.154	-	0.092
Placebo + Chemotherapy[c]		181	75.28 (19.42)	151	75.22 (22.09)	191	0.03 [-2.93; 2.99]	[-6.13; 0.97]			
Positive											
Pembrolizumab + Chemotherapy[b]		365	76.12 (19.63)	320	76.07 (20.35)	394	-0.03 [-2.13; 2.06]	1.20	0.483	-	
Placebo + Chemotherapy[c]		185	75.14 (21.92)	158	74.68 (21.26)	192	-1.23 [-4.08; 1.62]	[-2.15; 4.55]			
Tumor Size											
T1/T2											
Pembrolizumab + Chemotherapy[b]		520	76.44 (18.93)	453	74.30 (20.98)	564	-1.95 [-3.75; -0.16]	-1.56	0.290	-	0.356

Placebo + Chemotherapy[c] T3/T4	274	74.15 (21.69)	233	74.11 (22.09)	287	-0.39 [-2.82; 2.03]	[-4.44; 1.33]			
Pembrolizumab + Chemotherapy[b]	181	75.28 (21.06)	162	75.46 (20.27)	198	0.54 [-2.22; 3.30]	1.87	0.415	-	
Placebo + Chemotherapy[c]	92	78.35 (17.12)	76	77.52 (20.09)	96	-1.33 [-5.17; 2.51]	[-2.64; 6.38]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	293	75.51 (20.18)	259	73.42 (21.23)	325	-1.75 [-4.21; 0.71]	-0.38	0.849	-	0.896
Placebo + Chemotherapy[c]	158	74.37 (20.36)	138	74.28 (22.95)	163	-1.37 [-4.62; 1.87]	[-4.27; 3.52]			
Weekly										
Pembrolizumab + Chemotherapy[b]	408	76.59 (19.00)	356	75.47 (20.45)	437	-0.96 [-2.87; 0.95]	-0.90	0.574	-	
Placebo + Chemotherapy[c]	206	75.97 (20.93)	171	75.49 (20.57)	218	-0.06 [-2.72; 2.60]	[-4.03; 2.23]			

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-63: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Kognitive Funktion in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Cognitive Functioning	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	628	88.38 (17.52)	564	78.61 (21.86)	681	-10.15 [-11.92; -8.39]	0.19	0.898	-	0.851
Placebo + Chemotherapy[c]	324	88.27 (18.35)	274	78.04 (23.69)	336	-10.34 [-12.79; -7.90]	[-2.72; 3.10]			
≥ 65										
Pembrolizumab + Chemotherapy[b]	73	87.44 (19.60)	51	75.82 (19.81)	81	-13.25 [-18.65; -7.85]	-2.61	0.530	-	
Placebo + Chemotherapy[c]	42	90.87 (15.27)	35	78.57 (24.45)	47	-10.64 [-17.23; -4.04]	[-10.84; 5.62]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	602	88.46 (17.49)	534	78.09 (21.57)	657	-10.68 [-12.45; -8.92]	-0.59	0.690	-	0.218
Placebo + Chemotherapy[c]	317	88.59 (17.85)	270	78.58 (23.06)	334	-10.10 [-12.51; -7.68]	[-3.48; 2.30]			
1										
Pembrolizumab + Chemotherapy[b]	99	87.21 (19.17)	81	80.25 (22.53)	105	-8.68 [-13.83; -3.53]	3.51	0.418	-	
Placebo + Chemotherapy[c]	49	88.44 (19.31)	39	74.79 (28.06)	49	-12.19 [-19.35; -5.03]	[-5.04; 12.06]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	132	90.91 (14.32)	127	77.82 (20.69)	135	-13.27 [-16.68; -9.86]	-4.81	0.081	-	0.136
Placebo + Chemotherapy[c]	79	89.66 (15.17)	73	81.28 (19.23)	79	-8.46 [-12.87; -4.06]	[-10.21; 0.59]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	533	87.62 (18.36)	451	78.12 (22.04)	588	-9.93 [-11.91; -7.95]	1.52	0.367	-	
Placebo + Chemotherapy[c]	262	88.36 (18.66)	215	76.67 (25.26)	279	-11.46 [-14.24; -8.67]	[-1.79; 4.84]			

Rest of World										
Pembrolizumab + Chemotherapy[b]	36	88.43 (19.03)	37	83.33 (20.79)	39	-6.37 [-14.17; 1.42]	-0.16	0.979	-	
Placebo + Chemotherapy[c]	25	87.33 (20.00)	21	81.75 (21.02)	25	-6.21 [-15.91; 3.48]	[-11.85; 11.53]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	336	89.43 (17.61)	295	75.65 (23.15)	368	-13.77 [-16.23; -11.31]	-1.92	0.358	-	0.247
Placebo + Chemotherapy[c]	181	88.49 (16.79)	151	76.71 (25.02)	191	-11.85 [-15.22; -8.49]	[-6.00; 2.17]			
Positive										
Pembrolizumab + Chemotherapy[b]	365	87.21 (17.80)	320	80.89 (19.97)	394	-7.36 [-9.62; -5.10]	1.48	0.424	-	
Placebo + Chemotherapy[c]	185	88.65 (19.20)	158	79.43 (22.43)	192	-8.84 [-11.93; -5.75]	[-2.15; 5.10]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	520	88.69 (17.30)	453	77.70 (22.41)	564	-11.52 [-13.51; -9.53]	-0.59	0.724	-	0.753
Placebo + Chemotherapy[c]	274	88.20 (18.23)	233	77.18 (24.52)	287	-10.93 [-13.65; -8.21]	[-3.86; 2.69]			
T3/T4										
Pembrolizumab + Chemotherapy[b]	181	87.11 (18.91)	162	80.25 (19.50)	198	-7.39 [-10.38; -4.39]	1.29	0.598	-	
Placebo + Chemotherapy[c]	92	89.67 (17.44)	76	80.92 (21.03)	96	-8.68 [-12.82; -4.54]	[-3.53; 6.12]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	293	88.62 (17.81)	259	78.64 (22.07)	325	-10.43 [-12.99; -7.87]	-2.22	0.292	-	0.213
Placebo + Chemotherapy[c]	158	88.82 (18.47)	138	80.92 (22.83)	163	-8.21 [-11.62; -4.79]	[-6.35; 1.91]			
Weekly										
Pembrolizumab + Chemotherapy[b]	408	88.03 (17.69)	356	78.18 (21.45)	437	-10.43 [-12.65; -8.22]	1.56	0.405	-	
Placebo + Chemotherapy[c]	206	88.35 (17.78)	171	75.83 (24.26)	218	-11.99 [-15.09; -8.89]	[-2.11; 5.23]			

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit

interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-64: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Soziale Funktion in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Social Functioning	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	628	87.23 (20.11)	564	71.84 (25.76)	681	-15.49 [-17.52; -13.46]	-4.10	0.016	-0.18	0.928
Placebo + Chemotherapy[c]	324	86.21 (21.07)	274	75.49 (24.26)	336	-11.39 [-14.20; -8.58]	[-7.43; -0.77]		[-0.32; -0.03]	
≥ 65										
Pembrolizumab + Chemotherapy[b]	73	89.04 (19.09)	51	66.01 (27.88)	81	-24.49 [-31.26; -17.72]	-7.05	0.186	-	
Placebo + Chemotherapy[c]	42	93.25 (16.07)	35	73.81 (23.67)	47	-17.44 [-25.77; -9.12]	[-17.57; 3.47]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	602	87.21 (19.88)	534	71.38 (25.95)	657	-16.10 [-18.15; -14.05]	-4.42	0.010	-0.19	0.737
Placebo + Chemotherapy[c]	317	87.17 (20.76)	270	75.80 (23.50)	334	-11.68 [-14.48; -8.87]	[-7.77; -1.07]		[-0.34; -0.05]	
1										
Pembrolizumab + Chemotherapy[b]	99	88.72 (20.73)	81	71.19 (26.22)	105	-17.28 [-23.19; -11.37]	-2.85	0.565	-	
Placebo + Chemotherapy[c]	49	86.05 (20.23)	39	71.79 (28.40)	49	-14.43 [-22.64; -6.22]	[-12.61; 6.91]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	132	81.94 (21.70)	127	70.21 (24.81)	135	-13.38 [-17.55; -9.21]	-6.95	0.031	-0.32	0.541

Placebo + Chemotherapy[c]	79	88.82 (20.10)	73	79.91 (21.69)	79	-6.43 [-11.72; -1.14]	[-13.27; -0.63]		[-0.60; -0.03]	
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	533	88.62 (19.25)	451	71.06 (26.78)	588	-17.49 [-19.78; -15.20]	-3.38	0.085	-	
Placebo + Chemotherapy[c]	262	86.20 (20.97)	215	72.87 (24.81)	279	-14.10 [-17.34; -10.87]	[-7.24; 0.47]			
Rest of World										
Pembrolizumab + Chemotherapy[b]	36	89.81 (21.56)	37	78.83 (17.85)	39	-11.50 [-19.30; -3.70]	-4.49	0.397	-	
Placebo + Chemotherapy[c]	25	90.00 (19.25)	21	84.13 (22.03)	25	-7.01 [-16.41; 2.40]	[-15.02; 6.04]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	336	88.19 (18.91)	295	69.60 (24.99)	368	-18.52 [-21.31; -15.73]	-2.93	0.204	-	0.377
Placebo + Chemotherapy[c]	181	87.85 (20.10)	151	72.74 (24.61)	191	-15.59 [-19.37; -11.80]	[-7.47; 1.60]			
Positive										
Pembrolizumab + Chemotherapy[b]	365	86.71 (20.95)	320	72.97 (26.77)	394	-14.20 [-16.89; -11.51]	-5.60	0.013	-0.24	
Placebo + Chemotherapy[c]	185	86.22 (21.23)	158	77.74 (23.54)	192	-8.60 [-12.32; -4.89]	[-10.02; -1.18]		[-0.43; -0.05]	
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	520	88.11 (18.86)	453	70.46 (26.02)	564	-18.09 [-20.38; -15.80]	-4.97	0.009	-0.21	0.633
Placebo + Chemotherapy[c]	274	87.10 (21.06)	233	74.03 (24.94)	287	-13.12 [-16.23; -10.01]	[-8.70; -1.23]		[-0.36; -0.05]	
T3/T4										
Pembrolizumab + Chemotherapy[b]	181	85.45 (22.91)	162	73.87 (25.73)	198	-11.21 [-14.79; -7.62]	-2.17	0.469	-	
Placebo + Chemotherapy[c]	92	86.78 (19.54)	76	79.17 (21.28)	96	-9.03 [-14.04; -4.02]	[-8.08; 3.73]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	293	88.96 (19.05)	259	70.59 (25.97)	325	-17.99 [-21.01; -14.98]	-5.48	0.026	-0.23	0.539
Placebo + Chemotherapy[c]	158	87.55 (20.69)	138	76.45 (23.63)	163	-12.51 [-16.53; -8.50]	[-10.31; -0.65]		[-0.44; -0.03]	
Weekly										
Pembrolizumab + Chemotherapy[b]	408	86.32 (20.60)	356	71.91 (25.98)	437	-15.11 [-17.65; -12.57]	-3.37	0.119	-	
Placebo + Chemotherapy[c]	206	86.81 (20.69)	171	74.37 (24.60)	218	-11.74 [-15.31; -8.18]	[-7.60; 0.86]			

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-BR23 in der neoadjuvanten Phase

EORTC-QLQ-BR23: Funktionsskala Körperbild

Tabelle 4G-65: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Körperbild in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Body Image	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	624	90.41 (16.69)	560	68.62 (27.41)	679	-21.47 [-23.63; -19.31]	1.09	0.562	-	0.134
Placebo + Chemotherapy[c]	320	90.42 (16.81)	272	68.50 (28.73)	335	-22.56 [-25.61; -19.50]	[-2.60; 4.78]			
≥ 65										
Pembrolizumab + Chemotherapy[b]	71	94.60 (9.03)	51	67.32 (25.54)	80	-27.86 [-34.57; -21.16]	-6.45	0.232	-	
Placebo + Chemotherapy[c]	41	94.51 (9.97)	35	71.43 (27.81)	47	-21.41 [-29.64; -13.18]	[-17.11; 4.21]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	597	90.70 (16.71)	530	68.13 (27.14)	655	-22.30 [-24.54; -20.07]	0.25	0.896	-	0.903
Placebo + Chemotherapy[c]	313	91.43 (15.91)	268	69.25 (28.92)	333	-22.56 [-25.67; -19.44]	[-3.52; 4.03]			

1										
Pembrolizumab + Chemotherapy[b]	98	91.67 (11.91)	81	70.99 (27.89)	104	-20.59 [-25.57; -15.62]	0.44	0.921	-	
Placebo + Chemotherapy[c]	48	87.33 (17.95)	39	66.03 (26.45)	49	-21.03 [-28.13; -13.94]	[-8.26; 9.14]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	131	88.93 (14.30)	126	66.87 (22.15)	134	-21.68 [-25.76; -17.61]	-5.45	0.097	-	0.167
Placebo + Chemotherapy[c]	79	88.40 (19.86)	73	71.92 (26.11)	79	-16.23 [-21.48; -10.99]	[-11.88; 0.99]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	528	91.22 (16.15)	448	68.23 (28.75)	586	-22.67 [-25.13; -20.21]	2.63	0.228	-	
Placebo + Chemotherapy[c]	257	91.60 (15.13)	213	66.78 (29.19)	278	-25.30 [-28.84; -21.75]	[-1.65; 6.91]			
Rest of World										
Pembrolizumab + Chemotherapy[b]	36	92.13 (21.08)	37	77.48 (22.56)	39	-14.74 [-22.90; -6.58]	0.70	0.914	-	
Placebo + Chemotherapy[c]	25	91.33 (14.13)	21	78.97 (28.94)	25	-15.44 [-25.77; -5.11]	[-12.25; 13.65]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	333	91.17 (15.26)	293	67.43 (27.17)	366	-23.68 [-26.56; -20.81]	0.84	0.736	-	0.681
Placebo + Chemotherapy[c]	178	91.90 (14.59)	151	67.77 (27.50)	191	-24.52 [-28.50; -20.54]	[-4.04; 5.71]			
Positive										
Pembrolizumab + Chemotherapy[b]	362	90.54 (16.89)	318	69.50 (27.30)	393	-20.43 [-23.34; -17.52]	0.07	0.978	-	
Placebo + Chemotherapy[c]	183	89.89 (17.65)	156	69.87 (29.67)	191	-20.50 [-24.61; -16.39]	[-4.88; 5.02]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	516	92.12 (14.25)	450	68.07 (27.55)	562	-23.97 [-26.36; -21.58]	-0.50	0.808	-	0.358
Placebo + Chemotherapy[c]	270	91.08 (16.38)	232	67.56 (28.85)	286	-23.47 [-26.79; -20.15]	[-4.56; 3.56]			
T3/T4										
Pembrolizumab + Chemotherapy[b]	179	87.15 (20.17)	161	69.72 (26.40)	197	-16.71 [-20.66; -12.75]	2.32	0.498	-	
Placebo + Chemotherapy[c]	91	90.29 (15.82)	75	72.78 (27.62)	96	-19.03 [-24.67; -13.40]	[-4.41; 9.05]			

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; SD: Standard Deviation

EORTC-QLQ-BR23: Funktionsskala Sexuelle Aktivität

Tabelle 4G-66: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Sexuelle Aktivität in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Sexual Functioning	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	611	22.64 (24.28)	550	14.61 (20.16)	677	-8.37 [-10.08; -6.65]	1.25	0.323	-	0.340
Placebo + Chemotherapy[c]	311	23.69 (25.68)	267	12.98 (19.50)	333	-9.61 [-11.86; -7.37]	[-1.23; 3.73]			
≥ 65										
Pembrolizumab + Chemotherapy[b]	67	14.18 (21.37)	49	5.78 (14.25)	77	-6.36 [-10.64; -2.09]	-1.92	0.475	-	
Placebo + Chemotherapy[c]	41	7.72 (15.85)	35	6.19 (12.18)	47	-4.44 [-9.26; 0.38]	[-7.26; 3.41]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	584	22.52 (24.08)	518	14.41 (19.81)	650	-8.57 [-10.33; -6.82]	1.11	0.380	-	0.963
Placebo + Chemotherapy[c]	304	22.97 (25.90)	264	12.63 (19.35)	331	-9.68 [-11.93; -7.43]	[-1.37; 3.59]			
1										
Pembrolizumab + Chemotherapy[b]	94	17.38 (24.06)	81	10.49 (20.15)	104	-4.62 [-8.66; -0.58]	0.38	0.905	-	
Placebo + Chemotherapy[c]	48	14.58 (19.33)	38	9.21 (15.35)	49	-5.00 [-10.41; 0.41]	[-5.87; 6.63]			

Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	128	12.50 (19.17)	125	8.40 (15.50)	134	-3.15 [-5.60; -0.69]	0.01	0.998	-	0.569
Placebo + Chemotherapy[c]	78	6.84 (14.32)	72	4.86 (14.11)	78	-3.15 [-6.20; -0.10]	[-3.55; 3.56]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	515	23.62 (24.51)	437	15.06 (20.78)	581	-9.12 [-11.10; -7.14]	1.36	0.354	-	
Placebo + Chemotherapy[c]	250	25.40 (25.84)	209	13.64 (18.96)	277	-10.48 [-13.10; -7.87]	[-1.52; 4.25]			
Rest of World										
Pembrolizumab + Chemotherapy[b]	35	29.05 (26.61)	37	18.47 (19.16)	39	-11.83 [-19.84; -3.83]	-2.09	0.691	-	
Placebo + Chemotherapy[c]	24	33.33 (27.80)	21	23.02 (24.42)	25	-9.74 [-19.25; -0.22]	[-12.59; 8.40]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	323	22.39 (23.66)	283	15.08 (19.71)	363	-8.30 [-10.68; -5.93]	2.43	0.147	-	0.163
Placebo + Chemotherapy[c]	174	24.81 (27.69)	148	12.39 (19.16)	190	-10.74 [-13.73; -7.74]	[-0.86; 5.72]			
Positive										
Pembrolizumab + Chemotherapy[b]	355	21.27 (24.56)	316	12.82 (20.01)	391	-7.84 [-10.03; -5.66]	-0.35	0.832	-	
Placebo + Chemotherapy[c]	178	18.91 (22.30)	154	12.01 (18.72)	190	-7.49 [-10.37; -4.61]	[-3.57; 2.87]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	505	22.31 (24.36)	444	13.74 (20.35)	560	-8.41 [-10.25; -6.56]	1.59	0.238	-	0.689
Placebo + Chemotherapy[c]	263	21.55 (25.15)	227	11.31 (18.34)	284	-10.00 [-12.38; -7.62]	[-1.05; 4.23]			
T3/T4										
Pembrolizumab + Chemotherapy[b]	173	20.33 (23.42)	155	14.30 (18.56)	194	-7.11 [-10.41; -3.81]	-0.62	0.796	-	
Placebo + Chemotherapy[c]	89	22.66 (25.65)	75	14.89 (20.43)	96	-6.50 [-10.77; -2.23]	[-5.29; 4.06]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b]	285	21.52 (24.20)	251	13.75 (20.39)	322	-7.18 [-9.74; -4.62]	0.29	0.875	-	0.578
Placebo + Chemotherapy[c]	152	20.18 (24.16)	136	12.87 (19.66)	162	-7.47 [-10.70; -4.25]	[-3.36; 3.94]			
Weekly										
Pembrolizumab +	393	22.01 (24.10)	348	13.98 (19.54)	432	-8.73 [-10.80; -6.66]	1.67	0.270	-	

Chemotherapy[b]									
Placebo + Chemotherapy[c]	198	22.98 (26.09)	166	11.65 (18.30)	216	-10.40 [-13.12; -7.68]	[-1.30; 4.63]		

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-BR23: Funktionsskala Sexueller Genuss

Tabelle 4G-67: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Sexueller Genuss in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Sexual Enjoyment[i]	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	300	57.22 (28.39)	195	43.25 (25.86)	387	-14.56 [-18.58; -10.54]	-0.27	0.933	-	0.165
Placebo + Chemotherapy[c]	153	58.39 (32.05)	83	45.38 (26.84)	188	-14.29 [-19.92; -8.66]	[-6.52; 5.99]			
≥ 65										
Pembrolizumab + Chemotherapy[b]	21	53.97 (26.82)	7	38.10 (29.99)	24	-12.36 [-35.37; 10.65]	0.54	0.974	-	
Placebo + Chemotherapy[c]	7	47.62 (32.53)	6	44.44 (27.22)	11	-12.90 [-41.72; 15.91]	[-33.48; 34.56]			
ECOG Performance Status										
0										
Pembrolizumab +	287	57.26 (28.16)	184	43.48 (25.96)	367	-14.51 [-18.73; -10.30]	-0.54	0.871	-	0.944

Chemotherapy[b]										
Placebo + Chemotherapy[c]	145	58.16 (32.82)	80	45.42 (27.68)	178	-13.97 [-19.83; -8.11]	[-7.06; 5.98]			
1										
Pembrolizumab + Chemotherapy[b]	34	54.90 (29.45)	18	38.89 (26.20)	44	-14.24 [-26.33; -2.15]	-2.87	0.754	-	
Placebo + Chemotherapy[c]	15	55.56 (24.12)	9	44.44 (16.67)	21	-11.37 [-27.64; 4.89]	[-21.45; 15.71]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	37	43.24 (24.68)	24	30.56 (16.79)	46	-10.03 [-19.78; -0.27]	-7.36	0.345	-	0.618
Placebo + Chemotherapy[c]	16	31.25 (22.67)	8	37.50 (27.82)	21	-2.67 [-17.21; 11.88]	[-22.96; 8.24]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	263	59.70 (28.35)	160	45.21 (26.79)	338	-15.86 [-20.36; -11.36]	0.04	0.991	-	
Placebo + Chemotherapy[c]	130	62.31 (30.04)	70	46.19 (26.19)	158	-15.90 [-22.21; -9.60]	[-7.04; 7.12]			
Rest of World										
Pembrolizumab + Chemotherapy[b]	21	47.62 (24.88)	18	40.74 (24.40)	27	-5.12 [-20.29; 10.06]	3.70	0.718	-	
Placebo + Chemotherapy[c]	14	47.62 (42.80)	11	45.45 (30.81)	20	-8.82 [-27.38; 9.74]	[-17.09; 24.50]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	160	57.08 (27.06)	106	42.45 (21.84)	203	-18.38 [-23.57; -13.19]	-0.67	0.868	-	0.643
Placebo + Chemotherapy[c]	83	66.27 (30.13)	46	44.93 (28.30)	102	-17.71 [-24.87; -10.56]	[-8.55; 7.22]			
Positive										
Pembrolizumab + Chemotherapy[b]	161	56.94 (29.50)	96	43.75 (29.94)	208	-10.71 [-16.72; -4.70]	-0.98	0.840	-	
Placebo + Chemotherapy[c]	77	48.92 (31.80)	43	45.74 (25.22)	97	-9.73 [-18.16; -1.31]	[-10.51; 8.56]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b]	243	57.61 (28.59)	148	43.24 (26.50)	311	-15.52 [-20.19; -10.85]	-1.69	0.650	-	0.766
Placebo + Chemotherapy[c]	120	58.61 (31.75)	65	45.13 (28.52)	147	-13.83 [-20.36; -7.30]	[-9.02; 5.64]			
T3/T4										
Pembrolizumab + Chemotherapy[b]	78	55.13 (27.30)	54	42.59 (24.59)	100	-11.80 [-19.13; -4.47]	1.66	0.767	-	
Placebo + Chemotherapy[c]	40	55.83 (33.24)	24	45.83 (21.56)	52	-13.46 [-23.58; -3.34]	[-9.46; 12.78]			

Choice of Carboplatin											
Q3W											
Pembrolizumab + Chemotherapy[b]	129	61.24 (27.89)	84	44.44 (28.02)	169	-14.87 [-21.30; -8.45]	0.05	0.992	-	0.802
Placebo + Chemotherapy[c]	60	57.78 (34.10)	41	44.72 (26.47)	81	-14.92 [-23.47; -6.37]	[-9.53; 9.62]			
Weekly										
Pembrolizumab + Chemotherapy[b]	192	54.17 (28.23)	118	42.09 (24.43)	242	-14.37 [-19.43; -9.32]	-1.29	0.753	-	
Placebo + Chemotherapy[c]	98	58.84 (30.57)	48	45.83 (27.18)	116	-13.09 [-20.34; -5.84]	[-9.34; 6.77]			

a: Database Cutoff Date: 23MAR2021
b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
i: For participants who were not sexually active, no answer was given to sexual enjoyment item
CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-BR23: Funktionsskala Zukunftsperspektive

Tabelle 4G-68: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Zukunftsperspektive in der neoadjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Future Perspective	**Neoadjuvant Baseline**		**Neoadjuvant Week 21**		**Change from Neoadjuvant Baseline to Neoadjuvant Week 21**		**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Neoadjuvant Week 21		**Standardized Mean Difference at Neoadjuvant Week 21**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab + Chemotherapy[b]	624	53.21 (31.15)	560	50.00 (31.40)	679	-3.10 [-5.64; -0.55]	0.51	0.805	-	0.794
Placebo + Chemotherapy[c]	320	54.06 (30.96)	272	50.25 (32.52)	335	-3.60 [-7.07; -0.14]	[-3.52; 4.54]			

≥ 65											
Pembrolizumab + Chemotherapy[b]	71	57.75 (32.83)	51	49.67 (34.88)	80	-5.49 [-13.44; 2.46]	-2.89	0.631	-	
Placebo + Chemotherapy[c]	41	56.91 (36.70)	35	54.29 (32.42)	47	-2.60 [-12.19; 6.98]	[-14.78; 9.01]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b]	597	53.88 (31.17)	530	50.25 (31.17)	655	-3.19 [-5.82; -0.56]	-0.42	0.842	-	0.441
Placebo + Chemotherapy[c]	313	54.21 (31.65)	268	51.49 (32.67)	333	-2.77 [-6.29; 0.74]	[-4.51; 3.68]			
1										
Pembrolizumab + Chemotherapy[b]	98	52.38 (32.46)	81	48.15 (34.96)	104	-4.71 [-10.86; 1.44]	3.61	0.487	-	
Placebo + Chemotherapy[c]	48	55.56 (31.76)	39	45.30 (31.05)	49	-8.32 [-16.86; 0.22]	[-6.64; 13.85]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b]	131	55.47 (27.61)	126	52.38 (29.04)	134	-4.18 [-9.00; 0.64]	-4.19	0.259	-	0.307
Placebo + Chemotherapy[c]	79	58.23 (27.97)	73	57.53 (27.92)	79	0.01 [-6.09; 6.11]	[-11.49; 3.11]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b]	528	53.09 (32.25)	448	48.74 (32.59)	586	-3.44 [-6.33; -0.55]	2.16	0.361	-	
Placebo + Chemotherapy[c]	257	52.53 (32.19)	213	46.79 (33.28)	278	-5.60 [-9.59; -1.61]	[-2.48; 6.79]			
Rest of World										
Pembrolizumab + Chemotherapy[b]	36	55.56 (30.86)	37	56.76 (28.18)	39	-0.98 [-11.66; 9.70]	-7.01	0.361	-	
Placebo + Chemotherapy[c]	25	61.33 (35.59)	21	66.67 (31.62)	25	6.02 [-7.06; 19.10]	[-22.25; 8.24]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b]	333	55.16 (31.12)	293	49.15 (30.91)	366	-4.91 [-8.37; -1.45]	0.26	0.924	-	0.927
Placebo + Chemotherapy[c]	178	53.00 (31.00)	151	48.79 (33.51)	191	-5.17 [-9.78; -0.57]	[-5.15; 5.68]			
Positive										
Pembrolizumab + Chemotherapy[b]	362	52.30 (31.52)	318	50.73 (32.39)	393	-2.02 [-5.41; 1.37]	-0.19	0.945	-	
Placebo + Chemotherapy[c]	183	55.74 (32.25)	156	52.56 (31.46)	191	-1.83 [-6.43; 2.77]	[-5.55; 5.17]			
Tumor Size										
T1/T2										
Pembrolizumab +	516	55.23 (29.82)	450	50.37 (31.00)	562	-4.84 [-7.61; -2.06]	0.38	0.863	-	0.571

Chemotherapy[b]									
Placebo + Chemotherapy[c]	270	55.68 (31.07)	232	50.00 (32.08)	286	-5.22 [-8.92; -1.52]	[-3.96; 4.73]		
T3/T4									
Pembrolizumab + Chemotherapy[b]	179	49.16 (35.03)	161	48.86 (33.55)	197	0.67 [-4.29; 5.62]	-0.97	0.810	-
Placebo + Chemotherapy[c]	91	50.55 (33.10)	75	52.89 (33.82)	96	1.64 [-5.20; 8.47]	[-8.91; 6.97]		
Choice of Carboplatin									
Q3W									
Pembrolizumab + Chemotherapy[b]	292	53.31 (30.78)	258	47.93 (33.24)	324	-4.56 [-8.40; -0.72]	-1.77	0.564	-
Placebo + Chemotherapy[c]	155	54.84 (30.33)	138	51.93 (33.46)	163	-2.80 [-7.85; 2.26]	[-7.79; 4.26]		
Weekly									
Pembrolizumab + Chemotherapy[b]	403	53.93 (31.77)	353	51.46 (30.44)	435	-2.53 [-5.64; 0.59]	1.46	0.560	-
Placebo + Chemotherapy[c]	204	53.92 (32.77)	169	49.70 (31.73)	217	-3.98 [-8.25; 0.28]	[-3.45; 6.36]		

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective neoadjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in neoadjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30 in der adjuvanten Phase

Tabelle 4G-69: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den globalen Gesundheitsstatus in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Global Health Status/QoL	Adjuvant Baseline		Adjuvant Week 24		Change from Adjuvant Baseline to Adjuvant Week 24		Pembrolizumab[b] vs. Placebo[c]			p-Value for Interaction Test[h]
							Mean Difference at Adjuvant Week 24		Standardized Mean Difference at Adjuvant Week 24	
	N[d]	Mean (SD)	N[d]	Mean (SD)	N[e]	Mean [95 %-CI][f]	[95 %-CI][f]	p-Value	[95 %-CI][g]	
Age (Years)										
< 65										
Pembrolizumab[b]	448	74.26 (15.63)	403	76.39 (16.73)	492	2.16 [0.70; 3.62]	-1.03	0.376	-	0.109
Placebo[c]	250	73.07 (18.21)	219	76.52 (16.09)	271	3.19 [1.27; 5.11]	[-3.32; 1.25]			
≥ 65										
Pembrolizumab[b]	41	69.11 (15.62)	41	75.00 (16.24)	47	5.15 [-0.23; 10.52]	3.78	0.327	-	
Placebo[c]	33	73.74 (17.94)	30	74.17 (19.86)	37	1.37 [-4.72; 7.45]	[-3.87; 11.44]			
ECOG Performance Status										
0										
Pembrolizumab[b]	418	74.02 (15.92)	385	76.67 (16.77)	466	2.50 [0.96; 4.04]	-0.72	0.552	-	0.768
Placebo[c]	247	73.89 (18.01)	215	77.13 (16.54)	268	3.22 [1.24; 5.20]	[-3.09; 1.65]			
1										
Pembrolizumab[b]	71	72.65 (14.24)	59	73.59 (15.87)	73	1.93 [-1.82; 5.68]	1.02	0.727	-	
Placebo[c]	36	68.06 (18.53)	34	70.59 (15.79)	40	0.91 [-3.94; 5.76]	[-4.77; 6.81]			
Geographic Region										
Asia										
Pembrolizumab[b]	107	70.79 (16.60)	95	75.35 (14.93)	109	3.60 [0.56; 6.64]	-1.13	0.617	-	0.698
Placebo[c]	67	70.90 (18.08)	56	75.60 (15.31)	67	4.73 [0.97; 8.48]	[-5.58; 3.33]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	352	74.46 (15.19)	321	76.14 (17.38)	398	2.19 [0.51; 3.87]	-0.03	0.981	-	
Placebo[c]	198	73.02 (17.21)	178	75.51 (16.69)	221	2.22 [0.03; 4.41]	[-2.67; 2.61]			
Rest of World										
Pembrolizumab[b]	30	77.22 (16.94)	28	80.65 (13.43)	32	0.83 [-5.02; 6.68]	-3.79	0.376	-	
Placebo[c]	18	82.87 (25.32)	15	87.22 (16.63)	20	4.62 [-2.86; 12.10]	[-12.40; 4.82]			
Nodal Status										
Negative										

Pembrolizumab[b]	238	73.39 (15.15)	219	75.91 (15.76)	263	2.71 [0.74; 4.69]	-1.50	0.325	-	0.324
Placebo[c]	150	72.39 (17.06)	133	76.63 (16.52)	162	4.21 [1.74; 6.68]	[-4.48; 1.49]			
Positive										
Pembrolizumab[b]	251	74.24 (16.18)	225	76.59 (17.54)	276	2.20 [0.15; 4.24]	0.72	0.662	-	
Placebo[c]	133	74.00 (19.33)	116	75.79 (16.67)	146	1.48 [-1.25; 4.21]	[-2.51; 3.95]			
Tumor Size										
T1/T2										
Pembrolizumab[b]	358	74.19 (15.76)	333	76.63 (16.66)	393	2.73 [1.12; 4.35]	0.08	0.946	-	0.443
Placebo[c]	215	72.98 (17.77)	190	76.05 (16.59)	237	2.65 [0.59; 4.71]	[-2.40; 2.57]			
T3/T4										
Pembrolizumab[b]	131	72.84 (15.46)	111	75.15 (16.74)	146	1.75 [-1.22; 4.72]	-1.83	0.436	-	
Placebo[c]	68	73.65 (19.40)	59	76.84 (16.60)	71	3.58 [-0.34; 7.50]	[-6.47; 2.80]			
Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	215	72.75 (15.54)	198	76.26 (16.91)	240	2.66 [0.51; 4.80]	-0.18	0.918	-	0.933
Placebo[c]	118	73.52 (19.48)	101	76.16 (15.81)	127	2.83 [-0.03; 5.69]	[-3.55; 3.20]			
Weekly										
Pembrolizumab[b]	274	74.67 (15.76)	246	76.25 (16.51)	299	2.31 [0.41; 4.21]	-0.60	0.684	-	
Placebo[c]	164	72.82 (17.22)	147	76.25 (17.15)	180	2.91 [0.51; 5.31]	[-3.50; 2.30]			

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-70: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Körperliche Funktion in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Physical Functioning	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
ECOG Performance Status										
0										
Pembrolizumab[b]	418	84.02 (15.07)	385	85.49 (15.12)	466	1.54 [0.33; 2.75]	-2.09	0.028	-0.19	0.262
Placebo[c]	247	82.16 (16.60)	215	86.45 (14.16)	268	3.63 [2.07; 5.18]	[-3.95; -0.23]		[-0.35; -0.02]	
1										
Pembrolizumab[b]	71	79.06 (16.19)	59	80.45 (18.48)	73	1.75 [-1.76; 5.26]	1.18	0.684	-	
Placebo[c]	36	77.96 (16.39)	34	78.63 (18.55)	40	0.57 [-4.09; 5.23]	[-4.57; 6.93]			
Geographic Region										
Asia										
Pembrolizumab[b]	107	81.56 (13.10)	95	86.53 (11.21)	109	4.74 [2.59; 6.89]	0.13	0.933	-	0.625
Placebo[c]	67	81.39 (17.16)	56	86.31 (14.07)	67	4.61 [1.95; 7.27]	[-3.01; 3.28]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	352	83.77 (15.63)	321	84.09 (16.98)	398	0.52 [-0.87; 1.90]	-2.25	0.046	-0.19	
Placebo[c]	198	81.14 (16.52)	178	84.64 (15.21)	221	2.77 [0.94; 4.59]	[-4.46; -0.04]		[-0.37; -0.00]	
Rest of World										
Pembrolizumab[b]	30	84.00 (18.74)	28	87.38 (12.35)	32	2.23 [-2.55; 7.02]	-1.08	0.755	-	
Placebo[c]	18	87.78 (15.04)	15	90.67 (16.09)	20	3.31 [-2.76; 9.38]	[-7.99; 5.84]			
Nodal Status										
Negative										
Pembrolizumab[b]	238	83.73 (14.41)	219	84.84 (14.71)	263	1.27 [-0.33; 2.87]	-2.58	0.039	-0.23	0.453
Placebo[c]	150	80.71 (16.62)	133	85.31 (15.78)	162	3.85 [1.84; 5.86]	[-5.03; -0.13]		[-0.44; -0.01]	
Positive										
Pembrolizumab[b]	251	82.90 (16.15)	225	84.80 (16.59)	276	1.92 [0.28; 3.57]	-0.67	0.616	-	
Placebo[c]	133	82.66 (16.59)	116	85.46 (14.19)	146	2.59 [0.39; 4.80]	[-3.30; 1.96]			
Tumor Size										
T1/T2										

Pembrolizumab[b]	358	84.47 (14.68)	333	85.79 (14.50)	393	1.65 [0.36; 2.95]	-1.46	0.151	-	0.758
Placebo[c]	215	81.77 (16.79)	190	85.86 (15.61)	237	3.12 [1.46; 4.77]	[-3.46; 0.54]			
T3/T4										
Pembrolizumab[b]	131	80.10 (16.58)	111	81.92 (18.54)	146	1.55 [-0.89; 3.99]	-1.88	0.346	-	
Placebo[c]	68	81.18 (16.12)	59	83.84 (13.00)	71	3.44 [0.15; 6.72]	[-5.82; 2.05]			
Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	215	81.98 (15.96)	198	83.80 (16.68)	240	1.15 [-0.51; 2.82]	-2.60	0.062	-	0.263
Placebo[c]	118	82.94 (14.04)	101	85.87 (13.99)	127	3.76 [1.50; 6.01]	[-5.33; 0.13]			
Weekly										
Pembrolizumab[b]	274	84.33 (14.74)	246	85.64 (14.80)	299	2.01 [0.44; 3.58]	-0.62	0.611	-	
Placebo[c]	164	80.65 (18.26)	147	84.94 (15.74)	180	2.63 [0.65; 4.61]	[-2.99; 1.76]			

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-71: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Rollenfunktion in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Role Functioning	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab[b]	448	80.58 (21.38)	403	83.79 (20.51)	492	3.16 [1.29; 5.04]	-0.54	0.713	-	0.083
Placebo[c]	250	77.47 (23.36)	219	82.19 (22.00)	271	3.70 [1.26; 6.14]	[-3.41; 2.33]			

≥ 65										
Pembrolizumab[b]	41	71.95 (24.28)	41	83.33 (21.08)	47	8.18 [1.48; 14.87]	5.31	0.248	-	
Placebo[c]	33	82.83 (20.19)	30	83.33 (21.88)	37	2.86 [-4.58; 10.31]	[-3.79; 14.41]			
ECOG Performance Status										
0										
Pembrolizumab[b]	418	79.55 (22.04)	385	83.94 (20.72)	466	3.91 [1.92; 5.89]	0.26	0.864	-	0.949
Placebo[c]	247	78.61 (22.94)	215	82.87 (21.73)	268	3.65 [1.11; 6.18]	[-2.72; 3.24]			
1										
Pembrolizumab[b]	71	81.69 (19.95)	59	82.49 (19.43)	73	1.49 [-2.84; 5.81]	-1.07	0.755	-	
Placebo[c]	36	74.54 (23.73)	34	78.92 (23.32)	40	2.56 [-3.08; 8.20]	[-7.88; 5.74]			
Geographic Region										
Asia										
Pembrolizumab[b]	107	81.15 (19.44)	95	85.61 (17.29)	109	3.33 [-0.13; 6.78]	-0.42	0.870	-	0.931
Placebo[c]	67	82.84 (18.80)	56	86.31 (18.01)	67	3.75 [-0.54; 8.04]	[-5.53; 4.68]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	352	79.21 (22.60)	321	82.81 (21.80)	398	3.69 [1.44; 5.95]	0.34	0.845	-	
Placebo[c]	198	75.67 (24.08)	178	80.43 (22.88)	221	3.35 [0.45; 6.25]	[-3.07; 3.75]			
Rest of World										
Pembrolizumab[b]	30	82.78 (19.32)	28	88.10 (14.24)	32	4.64 [-0.69; 9.97]	0.31	0.939	-	
Placebo[c]	18	87.04 (21.81)	15	90.00 (21.64)	20	4.34 [-2.62; 11.29]	[-7.74; 8.35]			
Nodal Status										
Negative										
Pembrolizumab[b]	238	78.57 (21.40)	219	82.50 (20.89)	263	3.82 [1.23; 6.41]	-1.58	0.421	-	0.270
Placebo[c]	150	75.22 (24.71)	133	81.83 (22.89)	162	5.40 [2.18; 8.61]	[-5.43; 2.27]			
Positive										
Pembrolizumab[b]	251	81.08 (22.05)	225	84.96 (20.16)	276	3.41 [0.87; 5.95]	1.94	0.328	-	
Placebo[c]	133	81.33 (20.62)	116	82.90 (20.90)	146	1.47 [-1.87; 4.81]	[-1.95; 5.84]			
Tumor Size										
T1/T2										
Pembrolizumab[b]	358	79.52 (22.30)	333	84.43 (20.38)	393	4.51 [2.37; 6.65]	1.36	0.401	-	0.150
Placebo[c]	215	78.60 (22.66)	190	82.19 (22.36)	237	3.15 [0.44; 5.85]	[-1.82; 4.55]			
T3/T4										
Pembrolizumab[b]	131	80.79 (20.20)	111	81.68 (20.96)	146	1.22 [-2.18; 4.63]	-3.38	0.213	-	
Placebo[c]	68	76.47 (24.30)	59	82.77 (20.75)	71	4.60 [0.12; 9.08]	[-8.71; 1.96]			
Choice of Carboplatin										
Q3W										

Pembrolizumab[b]	215	79.53 (21.00)	198	83.16 (20.84)	240	3.42 [0.68; 6.16]	-1.76	0.411	-	0.196
Placebo[c]	118	75.71 (22.61)	101	81.68 (19.79)	127	5.18 [1.57; 8.79]	[-5.96; 2.44]			
Weekly										
Pembrolizumab[b]	274	80.11 (22.35)	246	84.21 (20.32)	299	3.94 [1.51; 6.37]	1.84	0.319	-	
Placebo[c]	164	79.67 (23.28)	147	82.65 (23.40)	180	2.10 [-0.94; 5.14]	[-1.79; 5.46]			

a: Database Cutoff Date: 23MAR2021
b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-72: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Emotionale Funktion in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Emotional Functioning	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab[b]	448	81.99 (17.79)	403	79.71 (19.35)	492	-1.61 [-3.17; -0.06]	-0.49	0.700	-	0.776
Placebo[c]	250	78.50 (21.00)	219	77.89 (20.28)	271	-1.13 [-3.19; 0.93]	[-2.98; 2.00]			
≥ 65										
Pembrolizumab[b]	41	79.07 (16.99)	41	78.66 (22.60)	47	-0.44 [-6.26; 5.38]	-0.98	0.823	-	
Placebo[c]	33	82.58 (19.25)	30	82.22 (21.52)	37	0.54 [-6.08; 7.16]	[-9.69; 7.73]			
ECOG Performance Status										
0										
Pembrolizumab[b]	418	81.68 (17.49)	385	79.83 (19.59)	466	-1.40 [-2.99; 0.19]	-0.29	0.825	-	0.358

Placebo[c]	247	79.32 (20.30)	215	78.60 (20.75)	268	-1.12 [-3.20; 0.97]	[-2.84; 2.27]		
1									
Pembrolizumab[b]	71	82.16 (19.17)	59	78.25 (20.12)	73	-2.19 [-6.61; 2.22]	-1.99	0.560	-
Placebo[c]	36	76.62 (24.22)	34	77.21 (18.61)	40	-0.20 [-5.89; 5.48]	[-8.73; 4.75]		
Geographic Region									
Asia									
Pembrolizumab[b]	107	81.78 (16.35)	95	82.63 (15.12)	109	0.56 [-2.16; 3.28]	0.17	0.938	-
Placebo[c]	67	81.84 (19.19)	56	81.10 (18.77)	67	0.40 [-3.05; 3.85]	[-4.06; 4.39]		
Europe/Israel/North America/Australia									
Pembrolizumab[b]	352	81.79 (18.31)	321	78.58 (21.05)	398	-2.41 [-4.26; -0.56]	-0.81	0.590	-
Placebo[c]	198	78.20 (20.54)	178	77.43 (19.84)	221	-1.60 [-4.03; 0.84]	[-3.77; 2.15]		
Rest of World									
Pembrolizumab[b]	30	81.11 (15.77)	28	81.25 (15.32)	32	1.26 [-5.01; 7.53]	-0.17	0.974	-
Placebo[c]	18	76.85 (28.66)	15	80.00 (31.62)	20	1.42 [-7.01; 9.86]	[-10.48; 10.15]		
Nodal Status									
Negative									
Pembrolizumab[b]	238	80.60 (18.80)	219	78.96 (19.77)	263	-1.17 [-3.19; 0.85]	-1.75	0.274	-
Placebo[c]	150	77.67 (20.87)	133	78.38 (20.02)	162	0.58 [-1.97; 3.14]	[-4.90; 1.39]		
Positive									
Pembrolizumab[b]	251	82.84 (16.60)	225	80.26 (19.55)	276	-1.88 [-4.10; 0.34]	0.72	0.697	-
Placebo[c]	133	80.45 (20.72)	116	78.45 (21.00)	146	-2.60 [-5.60; 0.41]	[-2.91; 4.35]		
Tumor Size									
T1/T2									
Pembrolizumab[b]	358	81.98 (18.22)	333	80.08 (19.10)	393	-1.28 [-2.92; 0.36]	-0.08	0.949	-
Placebo[c]	215	78.06 (21.41)	190	77.54 (21.11)	237	-1.20 [-3.32; 0.92]	[-2.68; 2.51]		
T3/T4									
Pembrolizumab[b]	131	81.11 (16.34)	111	78.23 (21.24)	146	-2.25 [-5.65; 1.16]	-2.51	0.377	-
Placebo[c]	68	81.86 (18.66)	59	81.21 (18.02)	71	0.26 [-4.36; 4.88]	[-8.09; 3.08]		
Choice of Carboplatin									
Q3W									
Pembrolizumab[b]	215	81.90 (16.90)	198	79.42 (19.56)	240	-2.44 [-4.82; -0.06]	-0.37	0.852	-
Placebo[c]	118	78.95 (22.56)	101	77.06 (21.49)	127	-2.07 [-5.29; 1.14]	[-4.23; 3.50]		
Weekly									
Pembrolizumab[b]	274	81.63 (18.37)	246	79.78 (19.75)	299	-0.72 [-2.64; 1.20]	-0.43	0.780	-
Placebo[c]	164	78.96 (19.59)	147	79.20 (19.71)	180	-0.29 [-2.74; 2.17]	[-3.46; 2.60]		

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint
e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase
f: Based on constrained longitudinal data analysis model with the PRO scores as the response variable, and treatment by timepoint interaction as covariates
g: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates
CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-73: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Kognitive Funktion in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Cognitive Functioning	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab[b]	448	82.63 (19.34)	403	80.60 (20.48)	492	-1.76 [-3.40; -0.13]	0.31	0.820	-	0.201
Placebo[c]	250	81.80 (20.29)	219	79.91 (21.94)	271	-2.07 [-4.24; 0.11]	[-2.34; 2.95]			
≥ 65										
Pembrolizumab[b]	41	79.67 (22.21)	41	82.52 (18.99)	47	3.92 [-0.94; 8.79]	2.89	0.373	-	
Placebo[c]	33	83.33 (21.65)	30	83.33 (19.08)	37	1.03 [-4.31; 6.38]	[-3.55; 9.34]			
Geographic Region										
Asia										
Pembrolizumab[b]	107	82.87 (16.10)	95	82.63 (17.18)	109	0.08 [-2.54; 2.71]	3.16	0.144	-	0.533
Placebo[c]	67	82.34 (17.62)	56	78.27 (22.00)	67	-3.08 [-6.46; 0.30]	[-1.09; 7.42]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	352	81.82 (20.73)	321	80.11 (21.00)	398	-1.54 [-3.47; 0.40]	-0.13	0.935	-	
Placebo[c]	198	81.99 (21.00)	178	80.81 (21.00)	221	-1.41 [-3.94; 1.12]	[-3.17; 2.92]			
Rest of World										

Pembrolizumab[b]	30	87.22 (16.77)	28	82.14 (22.65)	32	-3.84 [-11.00; 3.31]	-3.40	0.566	-	
Placebo[c]	18	80.56 (24.42)	15	82.22 (27.79)	20	-0.44 [-10.08; 9.19]	[-15.27; 8.47]			
Nodal Status										
Negative										
Pembrolizumab[b]	238	80.95 (20.29)	219	79.83 (21.66)	263	-0.82 [-2.97; 1.34]	-0.19	0.914	-	0.550
Placebo[c]	150	80.33 (21.33)	133	79.82 (22.20)	162	-0.63 [-3.37; 2.11]	[-3.59; 3.22]			
Positive										
Pembrolizumab[b]	251	83.73 (18.85)	225	81.70 (18.96)	276	-1.78 [-4.03; 0.46]	1.04	0.568	-	
Placebo[c]	133	83.83 (19.24)	116	80.89 (21.00)	146	-2.82 [-5.83; 0.19]	[-2.54; 4.62]			
Tumor Size										
T1/T2										
Pembrolizumab[b]	358	82.26 (19.83)	333	81.03 (20.32)	393	-1.16 [-2.99; 0.66]	1.36	0.354	-	0.209
Placebo[c]	215	83.18 (20.25)	190	80.26 (21.77)	237	-2.52 [-4.88; -0.16]	[-1.52; 4.24]			
T3/T4										
Pembrolizumab[b]	131	82.70 (18.99)	111	80.03 (20.45)	146	-1.71 [-4.69; 1.27]	-2.43	0.327	-	
Placebo[c]	68	78.19 (20.62)	59	80.51 (21.25)	71	0.72 [-3.28; 4.73]	[-7.30; 2.45]			
Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	215	83.72 (19.70)	198	82.07 (19.79)	240	-0.96 [-3.43; 1.51]	0.56	0.783	-	0.592
Placebo[c]	118	80.79 (22.08)	101	80.03 (23.45)	127	-1.52 [-4.85; 1.81]	[-3.43; 4.55]			
Weekly										
Pembrolizumab[b]	274	81.33 (19.48)	246	79.74 (20.75)	299	-1.50 [-3.51; 0.51]	0.51	0.751	-	
Placebo[c]	164	82.72 (19.18)	147	80.39 (20.34)	180	-2.01 [-4.57; 0.56]	[-2.65; 3.67]			

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-74: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Soziale Funktion in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Social Functioning	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab[b]	448	80.21 (22.58)	403	83.83 (22.55)	492	4.07 [1.95; 6.18]	-0.59	0.715	-	0.815
Placebo[c]	250	76.73 (26.92)	219	82.50 (22.76)	271	4.66 [1.93; 7.40]	[-3.79; 2.60]			
≥ 65										
Pembrolizumab[b]	41	80.08 (23.04)	41	81.71 (25.22)	47	3.10 [-3.19; 9.40]	-3.21	0.478	-	
Placebo[c]	33	83.33 (20.41)	30	89.44 (18.82)	37	6.31 [-0.80; 13.42]	[-12.18; 5.77]			
ECOG Performance Status										
0										
Pembrolizumab[b]	418	79.78 (22.80)	385	83.59 (22.82)	466	4.17 [2.00; 6.33]	-1.27	0.443	-	0.726
Placebo[c]	247	77.87 (25.42)	215	83.88 (22.29)	268	5.44 [2.67; 8.20]	[-4.52; 1.98]			
1										
Pembrolizumab[b]	71	82.63 (21.35)	59	83.90 (22.74)	73	2.52 [-2.63; 7.67]	0.79	0.841	-	
Placebo[c]	36	75.00 (32.00)	34	79.90 (23.13)	40	1.73 [-4.88; 8.34]	[-7.00; 8.58]			
Geographic Region										
Asia										
Pembrolizumab[b]	107	78.97 (23.16)	95	85.96 (18.72)	109	6.77 [2.91; 10.64]	3.44	0.241	-	0.285
Placebo[c]	67	78.61 (25.26)	56	80.95 (26.29)	67	3.33 [-1.49; 8.16]	[-2.33; 9.21]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	352	80.63 (22.08)	321	82.71 (24.11)	398	2.86 [0.45; 5.27]	-2.48	0.184	-	
Placebo[c]	198	76.35 (26.34)	178	83.33 (21.63)	221	5.35 [2.24; 8.46]	[-6.15; 1.19]			
Rest of World										
Pembrolizumab[b]	30	79.44 (26.87)	28	86.31 (19.27)	32	4.83 [-3.82; 13.48]	-3.96	0.471	-	
Placebo[c]	18	86.11 (29.29)	15	92.22 (12.39)	20	8.79 [-1.75; 19.32]	[-14.95; 7.04]			
Nodal Status										
Negative										

Pembrolizumab[b]	238	78.78 (22.43)	219	83.49 (22.46)	263	5.25 [2.42; 8.09]	-0.53	0.803	-	0.597
Placebo[c]	150	75.44 (26.10)	133	82.21 (23.59)	162	5.79 [2.27; 9.30]	[-4.74; 3.67]			
Positive										
Pembrolizumab[b]	251	81.54 (22.71)	225	83.78 (23.14)	276	2.47 [-0.36; 5.30]	-1.71	0.438	-	
Placebo[c]	133	79.82 (26.44)	116	84.63 (20.98)	146	4.18 [0.45; 7.91]	[-6.03; 2.61]			
Tumor Size										
T1/T2										
Pembrolizumab[b]	358	80.49 (21.55)	333	84.33 (22.20)	393	4.35 [2.13; 6.57]	0.15	0.931	-	0.172
Placebo[c]	215	77.21 (26.82)	190	82.11 (23.29)	237	4.20 [1.37; 7.03]	[-3.21; 3.50]			
T3/T4										
Pembrolizumab[b]	131	79.39 (25.30)	111	81.53 (24.45)	146	2.69 [-1.73; 7.11]	-5.04	0.129	-	
Placebo[c]	68	78.43 (24.78)	59	87.29 (18.91)	71	7.73 [2.03; 13.44]	[-11.57; 1.48]			
Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	215	79.61 (21.89)	198	82.32 (24.37)	240	2.68 [-0.36; 5.72]	-2.72	0.266	-	0.553
Placebo[c]	118	77.97 (26.23)	101	83.83 (21.92)	127	5.40 [1.34; 9.46]	[-7.52; 2.08]			
Weekly										
Pembrolizumab[b]	274	80.66 (23.16)	246	84.69 (21.41)	299	4.98 [2.32; 7.63]	0.54	0.784	-	
Placebo[c]	164	77.24 (26.50)	147	82.88 (22.83)	180	4.44 [1.15; 7.73]	[-3.30; 4.38]			

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-BR23 in der adjuvanten Phase

EORTC-QLQ-BR23: Funktionsskala Körperbild

Tabelle 4G-75: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Körperbild in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Body Image	Adjuvant Baseline		Adjuvant Week 24		Change from Adjuvant Baseline to Adjuvant Week 24		Pembrolizumab[b] vs. Placebo[c]			p-Value for Interaction Test[h]
							Mean Difference at Adjuvant Week 24		Standardized Mean Difference at Adjuvant Week 24	
	N[d]	Mean (SD)	N[d]	Mean (SD)	N[e]	Mean [95 %-CI][f]	[95 %-CI][f]	p-Value	[95 %-CI][g]	
Age (Years)										
< 65										
Pembrolizumab[b]	447	75.62 (25.81)	402	80.64 (22.71)	492	5.20 [3.34; 7.06]	0.98	0.500	-	0.148
Placebo[c]	249	74.73 (25.40)	217	77.76 (23.79)	269	4.22 [1.80; 6.65]	[-1.87; 3.82]			
≥ 65										
Pembrolizumab[b]	40	75.00 (20.06)	40	85.21 (16.93)	46	8.32 [2.80; 13.85]	6.73	0.075	-	
Placebo[c]	33	77.53 (31.28)	30	80.00 (25.48)	37	1.59 [-4.43; 7.62]	[-0.69; 14.15]			
ECOG Performance Status										
0										
Pembrolizumab[b]	417	75.38 (25.07)	384	81.03 (21.90)	466	5.79 [3.87; 7.71]	1.61	0.275	-	0.846
Placebo[c]	246	75.00 (26.01)	213	78.13 (24.71)	266	4.18 [1.73; 6.63]	[-1.28; 4.50]			
1										
Pembrolizumab[b]	70	76.67 (27.24)	58	81.18 (24.81)	72	3.58 [-1.06; 8.22]	0.68	0.842	-	
Placebo[c]	36	75.46 (27.16)	34	77.45 (18.86)	40	2.90 [-2.99; 8.79]	[-6.13; 7.50]			
Geographic Region										
Asia										
Pembrolizumab[b]	106	75.55 (21.59)	95	82.19 (19.24)	109	5.88 [2.36; 9.41]	1.49	0.585	-	0.993
Placebo[c]	67	74.25 (26.14)	56	77.38 (26.81)	67	4.39 [-0.02; 8.81]	[-3.90; 6.88]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	351	75.21 (26.39)	319	80.69 (22.90)	397	5.55 [3.37; 7.73]	1.54	0.354	-	
Placebo[c]	197	74.11 (26.53)	176	77.32 (23.41)	219	4.01 [1.21; 6.81]	[-1.72; 4.80]			
Rest of World										
Pembrolizumab[b]	30	79.72 (26.05)	28	81.25 (25.12)	32	3.82 [-1.42; 9.07]	-0.45	0.913	-	
Placebo[c]	18	88.43 (17.18)	15	88.89 (16.57)	20	4.27 [-2.73; 11.27]	[-8.73; 7.83]			

Nodal Status										
Negative										
Pembrolizumab[b]	237	74.19 (25.52)	218	81.31 (20.82)	263	7.12 [4.54; 9.70]	2.49	0.189	-	0.614
Placebo[c]	150	73.78 (25.44)	132	77.65 (23.10)	161	4.63 [1.47; 7.80]	[-1.23; 6.20]			
Positive										
Pembrolizumab[b]	250	76.87 (25.21)	224	80.80 (23.65)	275	3.87 [1.45; 6.30]	0.49	0.801	-	
Placebo[c]	132	76.52 (26.87)	115	78.48 (25.00)	145	3.39 [0.16; 6.62]	[-3.32; 4.30]			
Tumor Size										
T1/T2										
Pembrolizumab[b]	357	77.19 (24.50)	332	82.30 (21.42)	393	5.44 [3.46; 7.41]	2.27	0.134	-	0.310
Placebo[c]	214	74.10 (26.48)	188	76.77 (24.39)	235	3.17 [0.66; 5.68]	[-0.70; 5.23]			
T3/T4										
Pembrolizumab[b]	130	71.09 (27.22)	110	77.27 (24.39)	145	5.43 [1.55; 9.30]	-1.59	0.594	-	
Placebo[c]	68	78.06 (24.85)	59	82.06 (22.25)	71	7.02 [1.95; 12.09]	[-7.48; 4.30]			
Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	214	75.97 (26.12)	197	81.13 (23.48)	239	5.36 [2.59; 8.12]	0.66	0.760	-	0.822
Placebo[c]	118	76.13 (27.84)	100	78.67 (24.51)	126	4.70 [1.05; 8.35]	[-3.60; 4.92]			
Weekly										
Pembrolizumab[b]	273	75.24 (24.81)	245	80.99 (21.30)	299	5.51 [3.21; 7.81]	2.06	0.236	-	
Placebo[c]	163	74.13 (24.84)	146	77.45 (23.65)	179	3.45 [0.57; 6.33]	[-1.36; 5.48]			

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-BR23: Funktionsskala Sexuelle Aktivität

Tabelle 4G-76: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Sexuelle Aktivität in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Sexual Functioning	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab[b]	441	17.84 (21.12)	393	21.46 (23.88)	490	3.44 [1.56; 5.32]	-1.44	0.353	-	0.841
Placebo[c]	247	18.02 (21.79)	211	23.30 (22.08)	267	4.88 [2.37; 7.38]	[-4.48; 1.60]			
≥ 65										
Pembrolizumab[b]	38	7.02 (12.63)	40	8.75 (15.09)	46	1.03 [-2.27; 4.32]	0.26	0.916	-	
Placebo[c]	32	5.73 (12.42)	30	6.11 (15.46)	37	0.76 [-2.94; 4.46]	[-4.68; 5.21]			
ECOG Performance Status										
0										
Pembrolizumab[b]	409	17.89 (20.87)	376	21.23 (23.36)	464	3.51 [1.63; 5.39]	-1.06	0.492	-	0.887
Placebo[c]	243	17.08 (21.74)	207	22.14 (22.45)	264	4.57 [2.09; 7.04]	[-4.08; 1.96]			
1										
Pembrolizumab[b]	70	11.67 (19.53)	57	14.04 (23.53)	72	1.94 [-2.51; 6.39]	0.06	0.986	-	
Placebo[c]	36	13.43 (17.74)	34	15.20 (18.97)	40	1.88 [-3.97; 7.73]	[-7.12; 7.25]			
Geographic Region										
Asia										
Pembrolizumab[b]	104	9.29 (16.23)	93	11.11 (17.78)	109	2.25 [-0.43; 4.92]	0.20	0.927	-	0.638
Placebo[c]	66	6.31 (13.64)	55	9.39 (15.64)	67	2.05 [-1.35; 5.45]	[-4.03; 4.43]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	347	19.02 (21.36)	312	23.08 (24.46)	395	4.05 [1.89; 6.21]	-1.07	0.545	-	
Placebo[c]	195	18.97 (21.78)	171	23.88 (22.07)	217	5.12 [2.26; 7.98]	[-4.55; 2.41]			
Rest of World										
Pembrolizumab[b]	28	20.24 (22.39)	28	19.64 (21.78)	32	-3.05 [-11.57; 5.46]	-6.53	0.325	-	
Placebo[c]	18	28.70 (25.44)	15	33.33 (26.73)	20	3.47 [-7.59; 14.53]	[-19.74; 6.69]			
Nodal Status										
Negative										

Pembrolizumab[b]	236	18.79 (21.91)	214	22.04 (23.76)	262	3.68 [1.18; 6.18]	-1.05	0.597	-	0.978
Placebo[c]	149	17.79 (21.28)	130	23.21 (22.87)	160	4.74 [1.58; 7.89]	[-4.97; 2.86]			
Positive										
Pembrolizumab[b]	243	15.23 (19.50)	219	18.57 (23.14)	274	2.91 [0.49; 5.33]	-0.59	0.773	-	
Placebo[c]	130	15.26 (21.27)	111	18.77 (20.98)	144	3.50 [0.18; 6.81]	[-4.59; 3.41]			
Tumor Size										
T1/T2										
Pembrolizumab[b]	353	17.28 (20.50)	326	20.81 (23.98)	392	3.87 [1.82; 5.91]	-0.82	0.624	-	0.983
Placebo[c]	211	16.19 (21.45)	183	21.13 (22.30)	233	4.69 [2.01; 7.36]	[-4.10; 2.46]			
T3/T4										
Pembrolizumab[b]	126	16.14 (21.60)	107	18.69 (21.92)	144	1.64 [-1.63; 4.92]	-1.12	0.671	-	
Placebo[c]	68	17.89 (20.83)	58	21.26 (21.58)	71	2.76 [-1.52; 7.05]	[-6.32; 4.08]			
Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	213	15.41 (20.44)	193	20.03 (23.05)	239	4.65 [1.98; 7.32]	-0.38	0.866	-	0.657
Placebo[c]	118	15.54 (20.18)	97	21.48 (20.83)	126	5.03 [1.39; 8.66]	[-4.75; 4.00]			
Weekly										
Pembrolizumab[b]	266	18.23 (21.00)	240	20.49 (23.87)	297	2.19 [-0.09; 4.46]	-1.66	0.367	-	
Placebo[c]	160	17.29 (22.11)	143	21.10 (22.98)	177	3.85 [0.93; 6.77]	[-5.28; 1.95]			

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-BR23: Funktionsskala Sexueller Genuss

Tabelle 4G-77: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Sexueller Genuss in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Sexual Enjoyment[i]	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab[b]	172	44.57 (25.80)	190	48.60 (26.91)	275	4.13 [0.52; 7.73]	4.05	0.129	-	0.444
Placebo[c]	99	47.47 (26.55)	113	45.13 (24.77)	154	0.08 [-4.43; 4.59]	[-1.19; 9.29]			
≥ 65										
Pembrolizumab[b]	6	38.89 (32.77)	7	47.62 (17.82)	12	6.13 [-13.67; 25.94]	5.79	0.640	-	
Placebo[c]	5	40.00 (14.91)	4	33.33 (27.22)	6	0.34 [-22.06; 22.74]	[-23.22; 34.81]			
ECOG Performance Status										
0										
Pembrolizumab[b]	161	45.13 (25.66)	181	49.36 (26.20)	259	4.23 [0.54; 7.93]	4.74	0.085	-	> 0.999
Placebo[c]	90	48.52 (26.98)	104	44.87 (25.77)	143	-0.51 [-5.19; 4.18]	[-0.66; 10.13]			
1										
Pembrolizumab[b]	17	37.25 (28.58)	16	39.58 (30.35)	28	2.70 [-9.65; 15.04]	-0.53	0.951	-	
Placebo[c]	14	38.10 (17.82)	13	43.59 (16.01)	17	3.23 [-9.98; 16.43]	[-17.93; 16.87]			
Geographic Region										
Asia										
Pembrolizumab[b]	23	34.78 (18.74)	26	39.74 (18.90)	37	7.44 [-2.16; 17.05]	10.93	0.090	-	0.209
Placebo[c]	11	24.24 (21.56)	13	28.21 (18.49)	19	-3.48 [-15.54; 8.58]	[-1.78; 23.63]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	144	46.76 (25.34)	159	51.57 (26.97)	230	4.00 [0.13; 7.86]	4.99	0.085	-	
Placebo[c]	84	51.98 (23.91)	94	47.87 (23.73)	128	-0.99 [-5.84; 3.86]	[-0.70; 10.67]			
Rest of World										
Pembrolizumab[b]	11	33.33 (39.44)	12	27.78 (23.92)	20	1.41 [-16.20; 19.02]	-9.92	0.375	-	
Placebo[c]	9	29.63 (30.93)	10	36.67 (33.15)	13	11.33 [-7.34; 29.99]	[-32.65; 12.82]			
Nodal Status										
Negative										

Pembrolizumab[b]	93	44.44 (25.69)	103	50.49 (26.76)	144	4.94 [-0.05; 9.93]	4.26	0.234	-	0.607
Placebo[c]	60	50.00 (24.16)	69	48.31 (25.27)	89	0.68 [-5.22; 6.59]	[-2.77; 11.28]			
Positive										
Pembrolizumab[b]	85	44.31 (26.42)	94	46.45 (26.42)	143	3.77 [-1.15; 8.68]	3.88	0.306	-	
Placebo[c]	44	43.18 (28.38)	48	39.58 (23.48)	71	-0.12 [-6.71; 6.48]	[-3.59; 11.35]			
Tumor Size										
T1/T2										
Pembrolizumab[b]	135	44.20 (26.34)	152	49.78 (27.93)	219	5.17 [1.01; 9.33]	4.61	0.136	-	0.495
Placebo[c]	76	47.81 (26.29)	90	45.19 (25.14)	122	0.56 [-4.64; 5.76]	[-1.45; 10.68]			
T3/T4										
Pembrolizumab[b]	43	44.96 (25.08)	45	44.44 (21.32)	68	1.65 [-4.78; 8.07]	2.14	0.641	-	
Placebo[c]	28	45.24 (26.00)	27	43.21 (24.13)	38	-0.50 [-8.44; 7.44]	[-6.97; 11.26]			
Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	68	45.59 (27.56)	88	47.35 (29.35)	130	4.01 [-2.11; 10.12]	2.66	0.533	-	0.832
Placebo[c]	41	43.90 (26.29)	52	43.59 (23.37)	69	1.35 [-6.11; 8.80]	[-5.76; 11.07]			
Weekly										
Pembrolizumab[b]	110	43.64 (25.04)	109	49.54 (24.26)	157	4.19 [-0.02; 8.41]	4.99	0.123	-	
Placebo[c]	62	49.46 (26.13)	65	45.64 (26.07)	90	-0.79 [-6.16; 4.58]	[-1.36; 11.34]			

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

i: For participants who were not sexually active, no answer was given to sexual enjoyment item

CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-BR23: Funktionsskala Zukunftsperspektive

Tabelle 4G-78: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Zukunftsperspektive in der adjuvanten Phase aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Future Perspective	**Adjuvant Baseline**		**Adjuvant Week 24**		**Change from Adjuvant Baseline to Adjuvant Week 24**		**Pembrolizumab[b] vs. Placebo[c]**			**p-Value for Interaction Test[h]**
							Mean Difference at Adjuvant Week 24		**Standardized Mean Difference at Adjuvant Week 24**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Age (Years)										
< 65										
Pembrolizumab[b]	447	59.73 (29.26)	402	59.12 (30.26)	492	0.05 [-2.68; 2.78]	0.59	0.785	-	0.555
Placebo[c]	249	57.30 (31.98)	217	56.53 (32.07)	269	-0.55 [-4.13; 3.04]	[-3.67; 4.85]			
≥ 65										
Pembrolizumab[b]	40	56.67 (29.43)	40	59.17 (31.57)	46	2.06 [-7.23; 11.34]	2.73	0.683	-	
Placebo[c]	33	64.65 (31.11)	30	61.11 (32.85)	37	-0.68 [-11.05; 9.69]	[-10.55; 16.01]			
ECOG Performance Status										
0										
Pembrolizumab[b]	417	59.39 (28.64)	384	59.90 (29.70)	466	0.74 [-2.04; 3.52]	1.24	0.573	-	0.547
Placebo[c]	246	59.21 (31.35)	213	58.06 (32.44)	266	-0.50 [-4.09; 3.10]	[-3.07; 5.54]			
1										
Pembrolizumab[b]	70	60.00 (32.90)	58	54.02 (34.10)	72	-3.50 [-11.12; 4.11]	-3.11	0.598	-	
Placebo[c]	36	50.93 (35.17)	34	50.98 (29.85)	40	-0.40 [-10.16; 9.37]	[-14.76; 8.54]			
Geographic Region										
Asia										
Pembrolizumab[b]	106	58.49 (27.14)	95	61.75 (26.17)	109	1.11 [-3.67; 5.88]	0.66	0.861	-	0.922
Placebo[c]	67	62.19 (30.65)	56	60.12 (32.67)	67	0.45 [-5.59; 6.49]	[-6.77; 8.09]			
Europe/Israel/North America/Australia										
Pembrolizumab[b]	351	59.83 (29.56)	319	58.20 (31.52)	397	0.02 [-3.21; 3.24]	1.06	0.675	-	
Placebo[c]	197	55.16 (32.17)	176	54.92 (31.69)	219	-1.05 [-5.24; 3.14]	[-3.92; 6.04]			
Rest of World										
Pembrolizumab[b]	30	58.89 (33.54)	28	60.71 (30.16)	32	-1.02 [-12.36; 10.32]	-2.48	0.779	-	
Placebo[c]	18	75.93 (27.55)	15	71.11 (33.01)	20	1.46 [-13.52; 16.44]	[-20.15; 15.20]			
Nodal Status										
Negative										

Pembrolizumab[b]	237	58.23 (29.18)	218	58.87 (28.90)	263	0.61 [-2.81; 4.03]	0.50	0.847	-	0.933
Placebo[c]	150	57.78 (30.57)	132	58.08 (29.30)	161	0.11 [-4.15; 4.37]	[-4.61; 5.62]			
Positive										
Pembrolizumab[b]	250	60.67 (29.34)	224	59.37 (31.75)	275	-0.28 [-4.26; 3.70]	0.98	0.761	-	
Placebo[c]	132	58.59 (33.49)	115	55.94 (35.20)	145	-1.26 [-6.62; 4.09]	[-5.38; 7.35]			
Tumor Size										
T1/T2										
Pembrolizumab[b]	357	61.16 (27.78)	332	61.14 (29.42)	393	0.78 [-2.06; 3.63]	1.24	0.581	-	0.696
Placebo[c]	214	58.88 (31.01)	188	57.98 (31.05)	235	-0.45 [-4.11; 3.20]	[-3.16; 5.64]			
T3/T4										
Pembrolizumab[b]	130	54.87 (32.64)	110	53.03 (32.34)	145	-1.88 [-7.96; 4.20]	-0.86	0.857	-	
Placebo[c]	68	55.88 (34.77)	59	54.24 (35.50)	71	-1.02 [-9.02; 6.98]	[-10.28; 8.56]			
Choice of Carboplatin										
Q3W										
Pembrolizumab[b]	214	59.97 (29.10)	197	58.54 (31.07)	239	-1.40 [-5.58; 2.78]	-2.41	0.472	-	0.177
Placebo[c]	118	58.19 (33.24)	100	58.00 (32.69)	126	1.01 [-4.57; 6.59]	[-8.99; 4.17]			
Weekly										
Pembrolizumab[b]	273	59.10 (29.42)	245	59.59 (29.80)	299	1.37 [-1.95; 4.68]	3.45	0.182	-	
Placebo[c]	163	58.28 (31.06)	146	56.16 (31.74)	179	-2.09 [-6.29; 2.11]	[-1.63; 8.53]			

a: Database Cutoff Date: 23MAR2021

b: In the neoadjuvant phase, participant received: Pembrolizumab + paclitaxel + carboplatin x 4 cycles and pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: In the neoadjuvant phase, participant received: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

d: Number of participants in full-analysis-set population with data available at respective adjuvant timepoint

e: Number of participants in full-analysis-set population with data available for analysis in adjuvant phase

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

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

h: Based on constrained longitudinal data analysis model with change as the response variable, baseline, treatment, subgroup, study visit, treatment by subgroup interaction, treatment by study visit interaction, subgroup by study visit interaction and treatment by study visit and by subgroup interaction as covariates

CI: Confidence Interval; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 items; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

Anhang 4-G4.4: Nebenwirkungen

Unerwünschte Ereignisse

Unerwünschte Ereignisse gesamt

Tabelle 4G-79: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**			**Placebo + Chemotherapy[c] / Placebo**			**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**		
Adverse Events	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Age (Years)									
< 65	699	694 (99.3)	0.4 [-; -]	341	341 (100.0)	0.4 [0.4; 0.6]	1.05 [0.92; 1.20]	0.448	0.346
≥ 65	84	83 (98.8)	0.8 [0.4; 1.0]	48	48 (100.0)	0.5 [0.3; 0.9]	0.84 [0.59; 1.21]	0.359	
ECOG Performance Status									
0	677	671 (99.1)	0.4 [-; -]	340	340 (100.0)	0.4 [0.4; 0.6]	1.02 [0.90; 1.16]	0.751	0.641
1	106	106 (100.0)	0.6 [0.4; 1.1]	49	49 (100.0)	0.3 [0.3; 0.7]	1.09 [0.77; 1.55]	0.631	
Geographic Region									
Asia	136	135 (99.3)	0.6 [0.4; 0.9]	79	79 (100.0)	0.4 [0.3; 0.7]	0.93 [0.70; 1.23]	0.606	0.578
Europe/Israel/North America/Australia	606	602 (99.3)	0.4 [-; -]	285	285 (100.0)	0.4 [0.3; 0.6]	1.04 [0.91; 1.20]	0.554	
Rest of World	41	40 (97.6)	0.4 [0.3; 0.9]	25	25 (100.0)	0.7 [0.3; 1.1]	1.29 [0.77; 2.15]	0.339	
Nodal Status									
Negative	376	374 (99.5)	0.4 [0.3; 0.4]	193	193 (100.0)	0.4 [0.3; 0.6]	0.98 [0.83; 1.17]	0.850	0.505
Positive	407	403 (99.0)	0.4 [0.4; 0.6]	196	196 (100.0)	0.4 [0.4; 0.7]	1.08 [0.91; 1.28]	0.395	
Tumor Size									
T1/T2	580	575 (99.1)	0.4 [0.4; 0.6]	289	289 (100.0)	0.4 [0.3; 0.6]	1.02 [0.89; 1.18]	0.765	0.838
T3/T4	203	202 (99.5)	0.4 [0.4; 0.7]	100	100 (100.0)	0.4 [0.4; 0.7]	1.06 [0.83; 1.35]	0.626	
Choice of Carboplatin									
Q3W	334	333 (99.7)	0.4 [0.3; 0.4]	167	167 (100.0)	0.4 [0.3; 0.4]	0.93 [0.77; 1.12]	0.467	0.099
Weekly	444	444 (100.0)	0.6 [0.4; 0.7]	220	220 (100.0)	0.6 [0.4; 0.9]	1.16 [0.98; 1.36]	0.082	

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants: all-participants-as-treated population
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate using Wald confidence interval
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
h: 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; Q3W: Every 3 Weeks									

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-80: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Serious Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age (Years)									
< 65	699	296 (42.3)	Not reached [86.4; -]	341	100 (29.3)	Not reached [-; -]	1.59 [1.27; 2.00]	< 0.001	0.051
≥ 65	84	45 (53.6)	32.6 [16.1; -]	48	11 (22.9)	Not reached [-; -]	3.11 [1.61; 6.03]	< 0.001	
ECOG Performance Status									
0	677	290 (42.8)	Not reached [86.4; -]	340	94 (27.6)	Not reached [-; -]	1.74 [1.38; 2.20]	< 0.001	0.708
1	106	51 (48.1)	Not reached [22.4; -]	49	17 (34.7)	Not reached [61.7; -]	1.58 [0.91; 2.73]	0.104	
Geographic Region									
Asia	136	54 (39.7)	Not reached [75.7; -]	79	16 (20.3)	Not reached [-; -]	2.30 [1.31; 4.01]	0.003	0.381
Europe/Israel/North America/Australia	606	268 (44.2)	86.4 [86.4; -]	285	85 (29.8)	Not reached [-; -]	1.65 [1.30; 2.11]	< 0.001	
Rest of World	41	19 (46.3)	Not reached [27.7; -]	25	10 (40.0)	Not reached [13.4; -]	1.21 [0.56; 2.61]	0.626	
Nodal Status									
Negative	376	170 (45.2)	86.4 [59.6; -]	193	56 (29.0)	Not reached [-; -]	1.78 [1.32; 2.41]	< 0.001	0.723
Positive	407	171 (42.0)	Not reached [-; -]	196	55 (28.1)	Not reached [-; -]	1.65 [1.22; 2.24]	0.001	
Choice of Carboplatin									
Q3W	334	143 (42.8)	Not reached [-; -]	167	50 (29.9)	Not reached [-; -]	1.55 [1.13; 2.14]	0.007	0.436
Weekly	444	198 (44.6)	86.4 [75.7; -]	220	61 (27.7)	Not reached [-; -]	1.84 [1.38; 2.45]	< 0.001	
a: Database Cutoff Date: 23MAR2021									
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles									
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles									

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Serious Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
d: Number of participants: all-participants-as-treated population									
e: From product-limit (Kaplan-Meier) method for censored data									
f: Based on Cox regression model with treatment as a covariate using Wald confidence interval									
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)									
h: 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; Q3W: Every 3 Weeks									

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

Tabelle 4G-81: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
ECOG Performance Status									
0	677	549 (81.1)	9.3 [8.3; 10.6]	340	266 (78.2)	10.0 [8.1; 11.4]	1.08 [0.94; 1.26]	0.280	0.711
1	106	96 (90.6)	8.2 [7.1; 10.1]	49	40 (81.6)	8.1 [5.9; 12.0]	1.18 [0.81; 1.71]	0.383	
Geographic Region									
Asia	136	112 (82.4)	8.1 [7.0; 9.7]	79	67 (84.8)	7.3 [5.9; 10.1]	0.94 [0.69; 1.27]	0.671	0.378
Europe/Israel/North America/Australia	606	501 (82.7)	9.7 [8.4; 10.9]	285	219 (76.8)	10.6 [8.1; 12.3]	1.16 [0.99; 1.36]	0.061	
Rest of World	41	32 (78.0)	11.0 [8.0; 12.1]	25	20 (80.0)	9.3 [6.9; 13.0]	0.93 [0.53; 1.62]	0.787	
Nodal Status									
Negative	376	319 (84.8)	9.0 [8.0; 10.1]	193	156 (80.8)	11.1 [8.1; 13.0]	1.19 [0.98; 1.44]	0.082	0.313
Positive	407	326 (80.1)	9.7 [8.3; 11.0]	196	150 (76.5)	8.4 [7.1; 10.7]	1.02 [0.84; 1.24]	0.814	
Tumor Size									
T1/T2	580	476 (82.1)	9.3 [8.3; 10.4]	289	224 (77.5)	10.0 [8.1; 12.1]	1.13 [0.96; 1.32]	0.131	0.450
T3/T4	203	169 (83.3)	9.1 [7.9; 10.9]	100	82 (82.0)	9.0 [7.0; 11.1]	1.01 [0.77; 1.31]	0.949	
Choice of Carboplatin									
Q3W	334	290 (86.8)	8.0 [7.1; 9.1]	167	133 (79.6)	9.0 [7.1; 11.1]	1.24 [1.01; 1.52]	0.042	0.122
Weekly	444	355 (80.0)	10.5 [9.1; 12.3]	220	171 (77.7)	9.6 [8.1; 13.4]	1.01 [0.84; 1.21]	0.920	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants: all-participants-as-treated population
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate using Wald confidence interval
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: 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; Q3W: Every 3 Weeks

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-82: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Event Leading to Treatment Discontinuation	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Age (Years)									
< 65	699	197 (28.2)	Not reached [-; -]	341	51 (15.0)	Not reached [-; -]	2.04 [1.50; 2.78]	< 0.001	0.508
≥ 65	84	37 (44.0)	77.7 [32.6; -]	48	9 (18.8)	Not reached [-; -]	2.60 [1.26; 5.40]	0.010	
ECOG Performance Status									
0	677	208 (30.7)	Not reached [-; -]	340	52 (15.3)	Not reached [-; -]	2.20 [1.62; 2.98]	< 0.001	0.462
1	106	26 (24.5)	Not reached [-; -]	49	8 (16.3)	Not reached [-; -]	1.56 [0.71; 3.45]	0.269	
Geographic Region									
Asia	136	23 (16.9)	77.7 [77.7; -]	79	7 (8.9)	Not reached [-; -]	1.87 [0.80; 4.37]	0.150	0.880
Europe/Israel/North America/Australia	606	204 (33.7)	Not reached [-; -]	285	50 (17.5)	Not reached [-; -]	2.12 [1.55; 2.89]	< 0.001	
Rest of World	41	7 (17.1)	Not reached [-; -]	25	3 (12.0)	Not reached [-; -]	1.57 [0.40; 6.06]	0.517	
Nodal Status									
Negative	376	124 (33.0)	Not reached [77.7; -]	193	28 (14.5)	Not reached [-; -]	2.52 [1.67; 3.80]	< 0.001	0.230
Positive	407	110 (27.0)	Not reached [-; -]	196	32 (16.3)	Not reached [-; -]	1.77 [1.19; 2.62]	0.005	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Event Leading to Treatment Discontinuation	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Tumor Size									
T1/T2	580	181 (31.2)	Not reached [77.7; -]	289	40 (13.8)	Not reached [-; -]	2.50 [1.77; 3.52]	< 0.001	0.063
T3/T4	203	53 (26.1)	Not reached [-; -]	100	20 (20.0)	Not reached [-; -]	1.37 [0.82; 2.29]	0.228	
Choice of Carboplatin									
Q3W	334	86 (25.7)	Not reached [-; -]	167	23 (13.8)	Not reached [-; -]	1.98 [1.25; 3.13]	0.004	0.572
Weekly	444	148 (33.3)	Not reached [77.7; -]	220	35 (15.9)	Not reached [-; -]	2.34 [1.62; 3.38]	< 0.001	

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants: all-participants-as-treated population
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate using Wald confidence interval
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: 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; Q3W: Every 3 Weeks

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-83: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
SOC[i]: Endocrine disorders									
Age (Years)									
< 65	699	169 (24.2)	Not reached [-; -]	341	28 (8.2)	Not reached [-; -]	3.44 [2.30; 5.13]	< 0.001	0.360
≥ 65	84	15 (17.9)	Not reached [-; -]	48	5 (10.4)	Not reached [-; -]	1.98 [0.72; 5.47]	0.186	
ECOG Performance Status									
0	677	163 (24.1)	Not reached [-; -]	340	30 (8.8)	Not reached [-; -]	3.15 [2.14; 4.66]	< 0.001	0.701
1	106	21	Not reached	49	3	Not reached	3.97	0.026	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(19.8)	[-; -]		(6.1)	[-; -]	[1.18; 13.34]		
Geographic Region									
Asia	136	29 (21.3)	Not reached [-; -]	79	6 (7.6)	Not reached [-; -]	3.18 [1.32; 7.67]	0.010	0.439
Europe/Israel/North America/Australia	606	149 (24.6)	Not reached [-; -]	285	24 (8.4)	Not reached [-; -]	3.44 [2.23; 5.29]	< 0.001	
Rest of World	41	6 (14.6)	Not reached [72.9; -]	25	3 (12.0)	Not reached [75.3; -]	1.49 [0.37; 6.05]	0.577	
Nodal Status									
Negative	376	90 (23.9)	Not reached [-; -]	193	17 (8.8)	Not reached [-; -]	3.17 [1.89; 5.32]	< 0.001	0.909
Positive	407	94 (23.1)	Not reached [-; -]	196	16 (8.2)	Not reached [-; -]	3.29 [1.94; 5.60]	< 0.001	
Tumor Size									
T1/T2	580	138 (23.8)	Not reached [-; -]	289	23 (8.0)	Not reached [-; -]	3.48 [2.23; 5.41]	< 0.001	0.452
T3/T4	203	46 (22.7)	Not reached [-; -]	100	10 (10.0)	Not reached [-; -]	2.64 [1.33; 5.24]	0.005	
Choice of Carboplatin									
Q3W	334	79 (23.7)	Not reached [-; -]	167	14 (8.4)	Not reached [-; -]	3.27 [1.85; 5.78]	< 0.001	0.999
Weekly	444	105 (23.6)	Not reached [-; -]	220	19 (8.6)	Not reached [-; -]	3.17 [1.95; 5.18]	< 0.001	
SOC[i]: Skin and subcutaneous tissue disorders									
Age (Years)									
< 65	699	597 (85.4)	3.1 [3.1; 3.3]	341	286 (83.9)	4.1 [3.4; 4.4]	1.20 [1.05; 1.39]	0.010	0.265
≥ 65	84	71 (84.5)	3.7 [2.9; 5.0]	48	42 (87.5)	3.2 [2.3; 5.3]	0.96 [0.66; 1.41]	0.839	
ECOG Performance Status									
0	677	578 (85.4)	3.1 [3.1; 3.3]	340	286 (84.1)	3.8 [3.3; 4.1]	1.16 [1.01; 1.34]	0.035	0.780
1	106	90 (84.9)	3.1 [2.6; 4.0]	49	42 (85.7)	5.6 [3.0; 7.0]	1.22 [0.84; 1.76]	0.290	
Geographic Region									
Asia	136	129 (94.9)	2.1 [2.1; 2.4]	79	76 (96.2)	2.6 [2.1; 2.9]	1.21 [0.91; 1.60]	0.197	0.992
Europe/Israel/North America/Australia	606	513 (84.7)	3.4 [3.1; 3.9]	285	237 (83.2)	4.4 [4.0; 5.9]	1.20 [1.03; 1.40]	0.020	
Rest of World	41	26 (63.4)	9.4 [2.6; -]	25	15 (60.0)	20.3 [3.4; -]	1.18 [0.63; 2.23]	0.605	
Nodal Status									
Negative	376	329 (87.5)	3.1 [3.1; 3.4]	193	173 (89.6)	3.6 [3.0; 4.1]	1.05 [0.87; 1.26]	0.615	0.088
Positive	407	339 (83.3)	3.1 [3.1; 3.4]	196	155 (79.1)	4.4 [3.4; 6.0]	1.31 [1.08; 1.58]	0.005	
Tumor Size									
T1/T2	580	496	3.1	289	253	4.0	1.13	0.102	0.360

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(85.5)	[3.1; 3.3]		(87.5)	[3.3; 4.3]	[0.98; 1.32]		
T3/T4	203	172 (84.7)	3.4 [3.1; 4.1]	100	75 (75.0)	4.1 [3.1; 6.6]	1.30 [0.99; 1.71]	0.055	
Choice of Carboplatin									
Q3W	334	284 (85.0)	3.3 [3.1; 3.9]	167	140 (83.8)	4.1 [3.3; 5.3]	1.16 [0.95; 1.43]	0.141	0.777
Weekly	444	384 (86.5)	3.1 [3.0; 3.3]	220	187 (85.0)	3.6 [3.1; 4.3]	1.20 [1.01; 1.43]	0.038	

a: Database Cutoff Date: 23MAR2021
b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles
d: Number of participants: all-participants-as-treated population
e: From product-limit (Kaplan-Meier) method for censored data
f: Based on Cox regression model with treatment as a covariate using Wald confidence interval
g: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
h: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
i: A system organ class appears on this report only if its incidence ≥ 10% or (incidence ≥ 1% and in at least 10 participants) in one or more treatment groups and p-value of main treatment effect is smaller than 0.05, and the interaction p-value is greater than 0.05 or not calculated
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; Q3W: Every 3 Weeks; SOC: System Organ Class

Tabelle 4G-84: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
SOC: Endocrine disorders, PT[i]: Adrenal insufficiency									
Age (Years)									
< 65	699	18 (2.6)	Not reached [-; -]	341	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	0.998
≥ 65	84	2 (2.4)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.267	
ECOG Performance Status									
0	677	19 (2.8)	Not reached [-; -]	340	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	0.998
1	106	1 (0.9)	Not reached [-; -]	49	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.488	
Geographic Region									
Asia	136	2 (1.5)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.283	> 0.999

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Europe/Israel/North America/Australia	606	18 (3.0)	Not reached [-; -]	285	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.003	
Rest of World	41	0 (0.0)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
Nodal Status									
Negative	376	11 (2.9)	Not reached [-; -]	193	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.015	0.998
Positive	407	9 (2.2)	Not reached [-; -]	196	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.033	
Tumor Size									
T1/T2	580	13 (2.2)	Not reached [-; -]	289	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.009	0.998
T3/T4	203	7 (3.4)	Not reached [-; -]	100	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.059	
Choice of Carboplatin									
Q3W	334	10 (3.0)	Not reached [-; -]	167	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.023	0.998
Weekly	444	10 (2.3)	Not reached [-; -]	220	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.022	
SOC: Endocrine disorders, PT[i]: Hyperthyroidism									
Age (Years)									
< 65	699	37 (5.3)	Not reached [-; -]	341	5 (1.5)	Not reached [-; -]	3.79 [1.49; 9.64]	0.005	0.293
≥ 65	84	4 (4.8)	Not reached [-; -]	48	2 (4.2)	Not reached [-; -]	1.29 [0.24; 7.07]	0.769	
ECOG Performance Status									
0	677	39 (5.8)	Not reached [-; -]	340	7 (2.1)	Not reached [-; -]	2.95 [1.32; 6.59]	0.009	0.432
1	106	2 (1.9)	Not reached [-; -]	49	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.315	
Geographic Region									
Asia	136	8 (5.9)	Not reached [-; -]	79	1 (1.3)	Not reached [-; -]	4.82 [0.60; 38.56]	0.138	0.717
Europe/Israel/North America/Australia	606	32 (5.3)	Not reached [-; -]	285	6 (2.1)	Not reached [-; -]	2.68 [1.12; 6.42]	0.026	
Rest of World	41	1 (2.4)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.457	
Nodal Status									
Negative	376	20 (5.3)	Not reached [-; -]	193	4 (2.1)	Not reached [-; -]	2.74 [0.94; 8.02]	0.066	0.754
Positive	407	21 (5.2)	Not reached [-; -]	196	3 (1.5)	Not reached [-; -]	3.52 [1.05; 11.80]	0.041	
Tumor Size									
T1/T2	580	35 (6.0)	Not reached [-; -]	289	6 (2.1)	Not reached [-; -]	3.09 [1.30; 7.34]	0.011	0.983
T3/T4	203	6 (3.0)	Not reached [-; -]	100	1 (1.0)	Not reached [-; -]	3.07 [0.37; 25.48]	0.299	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Choice of Carboplatin									
Q3W	334	11 (3.3)	Not reached [-; -]	167	2 (1.2)	Not reached [-; -]	2.90 [0.64; 13.08]	0.166	0.897
Weekly	444	30 (6.8)	Not reached [-; -]	220	5 (2.3)	Not reached [-; -]	3.14 [1.22; 8.10]	0.018	
SOC: Endocrine disorders, PT[i]: Hypophysitis									
Age (Years)									
< 65	699	9 (1.3)	n.c.	341	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	84	1 (1.2)	n.c.	48	0 (0.0)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	677	7 (1.0)	n.c.	340	0 (0.0)	n.c.	n.c.	n.c.	n.c.
1	106	3 (2.8)	n.c.	49	0 (0.0)	n.c.	n.c.	n.c.	
Geographic Region									
Asia	136	0 (0.0)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	> 0.999
Europe/Israel/North America/Australia	606	10 (1.7)	Not reached [-; -]	285	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.028	
Rest of World	41	0 (0.0)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
Nodal Status									
Negative	376	2 (0.5)	n.c.	193	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Positive	407	8 (2.0)	n.c.	196	0 (0.0)	n.c.	n.c.	n.c.	
Tumor Size									
T1/T2	580	9 (1.6)	n.c.	289	0 (0.0)	n.c.	n.c.	n.c.	n.c.
T3/T4	203	1 (0.5)	n.c.	100	0 (0.0)	n.c.	n.c.	n.c.	
Choice of Carboplatin									
Q3W	334	5 (1.5)	n.c.	167	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Weekly	444	5 (1.1)	n.c.	220	0 (0.0)	n.c.	n.c.	n.c.	
SOC: Endocrine disorders, PT[i]: Hypothyroidism									
Age (Years)									
< 65	699	110 (15.7)	Not reached [-; -]	341	19 (5.6)	Not reached [-; -]	3.21 [1.97; 5.22]	< 0.001	0.438
≥ 65	84	8 (9.5)	Not reached [-; -]	48	3 (6.3)	Not reached [-; -]	1.75 [0.46; 6.61]	0.411	
ECOG Performance Status									
0	677	103 (15.2)	Not reached [-; -]	340	19 (5.6)	Not reached [-; -]	3.07 [1.88; 5.01]	< 0.001	0.902

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
1	106	15 (14.2)	Not reached [-; -]	49	3 (6.1)	Not reached [-; -]	2.78 [0.80; 9.64]	0.106	
Geographic Region									
Asia	136	19 (14.0)	Not reached [-; -]	79	5 (6.3)	Not reached [-; -]	2.39 [0.89; 6.39]	0.084	0.385
Europe/Israel/North America/Australia	606	93 (15.3)	Not reached [-; -]	285	14 (4.9)	Not reached [-; -]	3.58 [2.04; 6.28]	< 0.001	
Rest of World	41	6 (14.6)	Not reached [72.9; -]	25	3 (12.0)	Not reached [75.3; -]	1.49 [0.37; 6.04]	0.578	
Nodal Status									
Negative	376	61 (16.2)	Not reached [-; -]	193	11 (5.7)	Not reached [-; -]	3.29 [1.73; 6.25]	< 0.001	0.755
Positive	407	57 (14.0)	Not reached [-; -]	196	11 (5.6)	Not reached [-; -]	2.79 [1.46; 5.32]	0.002	
Tumor Size									
T1/T2	580	90 (15.5)	Not reached [-; -]	289	14 (4.8)	Not reached [-; -]	3.63 [2.07; 6.38]	< 0.001	0.191
T3/T4	203	28 (13.8)	Not reached [-; -]	100	8 (8.0)	Not reached [-; -]	1.97 [0.90; 4.32]	0.092	
Choice of Carboplatin									
Q3W	334	49 (14.7)	Not reached [-; -]	167	10 (6.0)	Not reached [-; -]	2.78 [1.41; 5.49]	0.003	0.696
Weekly	444	69 (15.5)	Not reached [-; -]	220	12 (5.5)	Not reached [-; -]	3.22 [1.74; 5.94]	< 0.001	
SOC: Gastrointestinal disorders, PT[i]: Diarrhoea									
Age (Years)									
< 65	699	286 (40.9)	Not reached [-; -]	341	121 (35.5)	Not reached [-; -]	1.20 [0.97; 1.49]	0.086	0.342
≥ 65	84	32 (38.1)	Not reached [49.3; -]	48	12 (25.0)	Not reached [-; -]	1.69 [0.87; 3.29]	0.124	
ECOG Performance Status									
0	677	279 (41.2)	Not reached [-; -]	340	117 (34.4)	Not reached [-; -]	1.27 [1.02; 1.57]	0.031	0.700
1	106	39 (36.8)	Not reached [-; -]	49	16 (32.7)	Not reached [-; -]	1.15 [0.64; 2.06]	0.639	
Geographic Region									
Asia	136	46 (33.8)	Not reached [-; -]	79	15 (19.0)	Not reached [-; -]	1.98 [1.11; 3.55]	0.022	0.219
Europe/Israel/North America/Australia	606	252 (41.6)	Not reached [-; -]	285	108 (37.9)	Not reached [-; -]	1.13 [0.90; 1.42]	0.277	
Rest of World	41	20 (48.8)	54.3 [8.4; -]	25	10 (40.0)	Not reached [10.3; -]	1.29 [0.60; 2.75]	0.515	
Nodal Status									
Negative	376	173 (46.0)	Not reached [49.3; -]	193	69 (35.8)	Not reached [-; -]	1.40 [1.06; 1.85]	0.019	0.305
Positive	407	145 (35.6)	Not reached [-; -]	196	64 (32.7)	Not reached [-; -]	1.12 [0.83; 1.50]	0.466	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Choice of Carboplatin									
Q3W	334	129 (38.6)	Not reached [-; -]	167	59 (35.3)	Not reached [-; -]	1.14 [0.84; 1.56]	0.393	0.452
Weekly	444	189 (42.6)	Not reached [-; -]	220	74 (33.6)	Not reached [-; -]	1.33 [1.02; 1.74]	0.037	
SOC: Gastrointestinal disorders, PT[i]: Gastrooesophageal reflux disease									
Age (Years)									
< 65	699	52 (7.4)	Not reached [-; -]	341	39 (11.4)	Not reached [-; -]	0.65 [0.43; 0.99]	0.045	0.878
≥ 65	84	5 (6.0)	Not reached [-; -]	48	4 (8.3)	Not reached [-; -]	0.71 [0.19; 2.66]	0.615	
ECOG Performance Status									
0	677	51 (7.5)	Not reached [-; -]	340	41 (12.1)	Not reached [-; -]	0.63 [0.41; 0.94]	0.025	0.293
1	106	6 (5.7)	Not reached [-; -]	49	2 (4.1)	Not reached [-; -]	1.41 [0.28; 6.97]	0.675	
Geographic Region									
Asia	136	5 (3.7)	Not reached [-; -]	79	5 (6.3)	Not reached [-; -]	0.59 [0.17; 2.04]	0.404	0.461
Europe/Israel/North America/Australia	606	52 (8.6)	Not reached [-; -]	285	37 (13.0)	Not reached [-; -]	0.67 [0.44; 1.01]	0.058	
Rest of World	41	0 (0.0)	Not reached [-; -]	25	1 (4.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.200	
Nodal Status									
Negative	376	28 (7.4)	Not reached [-; -]	193	25 (13.0)	Not reached [-; -]	0.58 [0.34; 0.99]	0.046	0.437
Positive	407	29 (7.1)	Not reached [-; -]	196	18 (9.2)	Not reached [-; -]	0.78 [0.43; 1.41]	0.409	
Tumor Size									
T1/T2	580	45 (7.8)	Not reached [-; -]	289	31 (10.7)	Not reached [-; -]	0.74 [0.47; 1.17]	0.196	0.345
T3/T4	203	12 (5.9)	Not reached [-; -]	100	12 (12.0)	Not reached [-; -]	0.47 [0.21; 1.06]	0.068	
Choice of Carboplatin									
Q3W	334	29 (8.7)	Not reached [-; -]	167	19 (11.4)	Not reached [-; -]	0.77 [0.43; 1.38]	0.387	0.463
Weekly	444	28 (6.3)	Not reached [-; -]	220	24 (10.9)	Not reached [-; -]	0.57 [0.33; 0.99]	0.046	
SOC: General disorders and administration site conditions, PT[i]: Chills									
Age (Years)									
< 65	699	40 (5.7)	Not reached [-; -]	341	7 (2.1)	Not reached [-; -]	2.89 [1.29; 6.45]	0.010	0.520
≥ 65	84	2 (2.4)	Not reached [-; -]	48	1 (2.1)	Not reached [-; -]	1.15 [0.10; 12.68]	0.909	
ECOG Performance Status									
0	677	37 (5.5)	Not reached [-; -]	340	6 (1.8)	Not reached [-; -]	3.18 [1.34; 7.54]	0.009	0.328

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
1	106	5 (4.7)	Not reached [-; -]	49	2 (4.1)	Not reached [-; -]	1.28 [0.25; 6.62]	0.766	
Geographic Region									
Asia	136	3 (2.2)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.184	0.257
Europe/Israel/North America/Australia	606	36 (5.9)	Not reached [-; -]	285	8 (2.8)	Not reached [-; -]	2.21 [1.03; 4.75]	0.043	
Rest of World	41	3 (7.3)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.165	
Nodal Status									
Negative	376	24 (6.4)	Not reached [-; -]	193	4 (2.1)	Not reached [-; -]	3.17 [1.10; 9.14]	0.033	0.639
Positive	407	18 (4.4)	Not reached [-; -]	196	4 (2.0)	Not reached [-; -]	2.26 [0.76; 6.67]	0.141	
Tumor Size									
T1/T2	580	38 (6.6)	Not reached [-; -]	289	7 (2.4)	Not reached [-; -]	2.83 [1.26; 6.34]	0.011	0.776
T3/T4	203	4 (2.0)	Not reached [-; -]	100	1 (1.0)	Not reached [-; -]	1.98 [0.22; 17.68]	0.542	
Choice of Carboplatin									
Q3W	334	15 (4.5)	Not reached [-; -]	167	3 (1.8)	Not reached [-; -]	2.56 [0.74; 8.84]	0.137	0.926
Weekly	444	27 (6.1)	Not reached [-; -]	220	5 (2.3)	Not reached [-; -]	2.78 [1.07; 7.21]	0.036	
SOC: General disorders and administration site conditions, PT[i]: Pyrexia									
Age (Years)									
< 65	699	203 (29.0)	Not reached [-; -]	341	62 (18.2)	Not reached [-; -]	1.78 [1.34; 2.36]	< 0.001	0.251
≥ 65	84	18 (21.4)	Not reached [-; -]	48	10 (20.8)	Not reached [-; -]	1.06 [0.49; 2.29]	0.887	
ECOG Performance Status									
0	677	188 (27.8)	Not reached [-; -]	340	60 (17.6)	Not reached [-; -]	1.73 [1.30; 2.32]	< 0.001	0.557
1	106	33 (31.1)	Not reached [-; -]	49	12 (24.5)	Not reached [-; -]	1.43 [0.74; 2.78]	0.286	
Geographic Region									
Asia	136	56 (41.2)	Not reached [37.0; -]	79	21 (26.6)	Not reached [-; -]	1.79 [1.08; 2.95]	0.023	0.729
Europe/Israel/North America/Australia	606	154 (25.4)	Not reached [-; -]	285	45 (15.8)	Not reached [-; -]	1.76 [1.26; 2.46]	< 0.001	
Rest of World	41	11 (26.8)	Not reached [-; -]	25	6 (24.0)	Not reached [75.3; -]	1.23 [0.45; 3.34]	0.683	
Nodal Status									
Negative	376	119 (31.6)	Not reached [-; -]	193	39 (20.2)	Not reached [-; -]	1.76 [1.22; 2.53]	0.002	0.772
Positive	407	102 (25.1)	Not reached [-; -]	196	33 (16.8)	Not reached [-; -]	1.62 [1.09; 2.40]	0.016	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Tumor Size									
T1/T2	580	167 (28.8)	Not reached [-; -]	289	57 (19.7)	Not reached [-; -]	1.63 [1.21; 2.21]	0.001	0.688
T3/T4	203	54 (26.6)	Not reached [-; -]	100	15 (15.0)	Not reached [-; -]	1.89 [1.06; 3.34]	0.030	
Choice of Carboplatin									
Q3W	334	78 (23.4)	Not reached [-; -]	167	22 (13.2)	Not reached [-; -]	1.94 [1.21; 3.12]	0.006	0.511
Weekly	444	143 (32.2)	Not reached [-; -]	220	50 (22.7)	Not reached [-; -]	1.57 [1.14; 2.16]	0.006	
SOC: Immune system disorders, PT[i]: Hypersensitivity									
Age (Years)									
< 65	699	37 (5.3)	Not reached [-; -]	341	9 (2.6)	Not reached [-; -]	2.08 [1.00; 4.30]	0.049	0.918
≥ 65	84	3 (3.6)	Not reached [-; -]	48	1 (2.1)	Not reached [-; -]	1.73 [0.18; 16.66]	0.634	
ECOG Performance Status									
0	677	34 (5.0)	Not reached [-; -]	340	10 (2.9)	Not reached [-; -]	1.77 [0.87; 3.57]	0.114	0.095
1	106	6 (5.7)	Not reached [-; -]	49	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.091	
Geographic Region									
Asia	136	6 (4.4)	Not reached [-; -]	79	1 (1.3)	Not reached [-; -]	3.53 [0.43; 29.36]	0.242	0.461
Europe/Israel/North America/Australia	606	32 (5.3)	Not reached [-; -]	285	9 (3.2)	Not reached [-; -]	1.75 [0.84; 3.67]	0.137	
Rest of World	41	2 (4.9)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.266	
Nodal Status									
Negative	376	20 (5.3)	Not reached [-; -]	193	6 (3.1)	Not reached [-; -]	1.78 [0.71; 4.43]	0.217	0.636
Positive	407	20 (4.9)	Not reached [-; -]	196	4 (2.0)	Not reached [-; -]	2.50 [0.85; 7.30]	0.095	
Tumor Size									
T1/T2	580	30 (5.2)	Not reached [-; -]	289	8 (2.8)	Not reached [-; -]	1.94 [0.89; 4.24]	0.095	0.761
T3/T4	203	10 (4.9)	Not reached [-; -]	100	2 (2.0)	Not reached [-; -]	2.53 [0.55; 11.54]	0.231	
Choice of Carboplatin									
Q3W	334	12 (3.6)	Not reached [-; -]	167	2 (1.2)	Not reached [-; -]	3.09 [0.69; 13.79]	0.140	0.635
Weekly	444	28 (6.3)	Not reached [-; -]	220	7 (3.2)	Not reached [-; -]	2.07 [0.91; 4.75]	0.084	
SOC: Infections and infestations, PT[i]: Nasopharyngitis									
Age (Years)									
< 65	699	56 (8.0)	Not reached [-; -]	341	49 (14.4)	Not reached [-; -]	0.56 [0.38; 0.83]	0.003	0.061

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
≥ 65	84	9 (10.7)	Not reached [-; -]	48	3 (6.3)	Not reached [-; -]	2.02 [0.55; 7.50]	0.292	
ECOG Performance Status									
0	677	61 (9.0)	Not reached [-; -]	340	48 (14.1)	Not reached [-; -]	0.65 [0.44; 0.95]	0.025	0.701
1	106	4 (3.8)	Not reached [-; -]	49	4 (8.2)	Not reached [-; -]	0.48 [0.12; 1.92]	0.299	
Nodal Status									
Negative	376	23 (6.1)	Not reached [-; -]	193	26 (13.5)	Not reached [-; -]	0.46 [0.26; 0.80]	0.006	0.138
Positive	407	42 (10.3)	Not reached [-; -]	196	26 (13.3)	Not reached [-; -]	0.80 [0.49; 1.31]	0.378	
Choice of Carboplatin									
Q3W	334	26 (7.8)	Not reached [-; -]	167	23 (13.8)	Not reached [-; -]	0.57 [0.33; 1.00]	0.051	0.642
Weekly	444	39 (8.8)	Not reached [-; -]	220	29 (13.2)	Not reached [-; -]	0.68 [0.42; 1.11]	0.120	
SOC: Infections and infestations, PT[i]: Rhinitis									
Age (Years)									
< 65	699	27 (3.9)	Not reached [-; -]	341	8 (2.3)	Not reached [-; -]	1.74 [0.79; 3.82]	0.171	0.059
≥ 65	84	6 (7.1)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.059	
ECOG Performance Status									
0	677	28 (4.1)	Not reached [-; -]	340	7 (2.1)	Not reached [-; -]	2.12 [0.93; 4.85]	0.075	0.857
1	106	5 (4.7)	Not reached [-; -]	49	1 (2.0)	Not reached [-; -]	2.49 [0.29; 21.40]	0.404	
Geographic Region									
Asia	136	4 (2.9)	Not reached [-; -]	79	3 (3.8)	Not reached [-; -]	0.77 [0.17; 3.45]	0.735	0.184
Europe/Israel/North America/Australia	606	26 (4.3)	Not reached [-; -]	285	5 (1.8)	Not reached [-; -]	2.64 [1.01; 6.87]	0.047	
Rest of World	41	3 (7.3)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.166	
Nodal Status									
Negative	376	11 (2.9)	Not reached [-; -]	193	4 (2.1)	Not reached [-; -]	1.51 [0.48; 4.75]	0.478	0.426
Positive	407	22 (5.4)	Not reached [-; -]	196	4 (2.0)	Not reached [-; -]	2.81 [0.97; 8.16]	0.057	
Tumor Size									
T1/T2	580	21 (3.6)	Not reached [-; -]	289	5 (1.7)	Not reached [-; -]	2.26 [0.85; 6.00]	0.101	0.904
T3/T4	203	12 (5.9)	Not reached [-; -]	100	3 (3.0)	Not reached [-; -]	2.02 [0.57; 7.15]	0.276	
Choice of Carboplatin									
Q3W	334	22	Not reached	167	4	Not reached	2.91	0.050[j]	0.392

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(6.6)	[-; -]		(2.4)	[-; -]	[1.00; 8.44]		
Weekly	444	11 (2.5)	Not reached [-; -]	220	4 (1.8)	Not reached [-; -]	1.41 [0.45; 4.42]	0.558	
SOC: Investigations, PT[i]: Blood creatinine increased									
Age (Years)									
< 65	699	22 (3.1)	Not reached [-; -]	341	5 (1.5)	Not reached [-; -]	2.25 [0.85; 5.94]	0.102	0.304
≥ 65	84	10 (11.9)	Not reached [-; -]	48	1 (2.1)	Not reached [-; -]	7.23 [0.92; 56.71]	0.060	
ECOG Performance Status									
0	677	20 (3.0)	Not reached [-; -]	340	5 (1.5)	Not reached [-; -]	2.09 [0.78; 5.56]	0.142	0.296
1	106	12 (11.3)	Not reached [-; -]	49	1 (2.0)	Not reached [-; -]	6.87 [0.89; 52.88]	0.064	
Geographic Region									
Asia	136	0 (0.0)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	0.814
Europe/Israel/North America/Australia	606	31 (5.1)	Not reached [-; -]	285	6 (2.1)	Not reached [-; -]	2.62 [1.09; 6.29]	0.031	
Rest of World	41	1 (2.4)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.410	
Nodal Status									
Negative	376	16 (4.3)	Not reached [-; -]	193	1 (0.5)	Not reached [-; -]	8.78 [1.16; 66.20]	0.035	0.095
Positive	407	16 (3.9)	Not reached [-; -]	196	5 (2.6)	Not reached [-; -]	1.63 [0.60; 4.46]	0.338	
Tumor Size									
T1/T2	580	18 (3.1)	Not reached [-; -]	289	3 (1.0)	Not reached [-; -]	3.18 [0.94; 10.79]	0.064	0.743
T3/T4	203	14 (6.9)	Not reached [-; -]	100	3 (3.0)	Not reached [-; -]	2.41 [0.69; 8.40]	0.166	
Choice of Carboplatin									
Q3W	334	12 (3.6)	Not reached [-; -]	167	4 (2.4)	Not reached [-; -]	1.55 [0.50; 4.80]	0.449	0.175
Weekly	444	20 (4.5)	Not reached [-; -]	220	2 (0.9)	Not reached [-; -]	5.44 [1.27; 23.30]	0.022	
SOC: Investigations, PT[i]: Neutrophil count decreased									
Age (Years)									
< 65	699	171 (24.5)	Not reached [-; -]	341	98 (28.7)	Not reached [-; -]	0.80 [0.63; 1.03]	0.086	0.734
≥ 65	84	20 (23.8)	Not reached [-; -]	48	15 (31.3)	Not reached [-; -]	0.72 [0.37; 1.41]	0.341	
ECOG Performance Status									
0	677	176 (26.0)	Not reached [-; -]	340	99 (29.1)	Not reached [-; -]	0.85 [0.66; 1.08]	0.188	0.113
1	106	15 (14.2)	Not reached [-; -]	49	14 (28.6)	Not reached [-; -]	0.46 [0.22; 0.94]	0.034	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Geographic Region									
Asia	136	70 (51.5)	20.0 [9.1; -]	79	42 (53.2)	14.4 [7.1; -]	0.87 [0.59; 1.28]	0.475	0.846
Europe/Israel/North America/Australia	606	112 (18.5)	Not reached [-; -]	285	63 (22.1)	Not reached [-; -]	0.80 [0.59; 1.09]	0.160	
Rest of World	41	9 (22.0)	Not reached [-; -]	25	8 (32.0)	Not reached [25.1; -]	0.65 [0.25; 1.69]	0.380	
Nodal Status									
Negative	376	90 (23.9)	Not reached [-; -]	193	56 (29.0)	Not reached [-; -]	0.77 [0.55; 1.07]	0.117	0.776
Positive	407	101 (24.8)	Not reached [-; -]	196	57 (29.1)	Not reached [-; -]	0.82 [0.59; 1.13]	0.224	
Tumor Size									
T1/T2	580	148 (25.5)	Not reached [-; -]	289	86 (29.8)	Not reached [-; -]	0.82 [0.63; 1.07]	0.144	0.615
T3/T4	203	43 (21.2)	Not reached [-; -]	100	27 (27.0)	Not reached [-; -]	0.71 [0.44; 1.15]	0.169	
Choice of Carboplatin									
Q3W	334	65 (19.5)	Not reached [-; -]	167	41 (24.6)	Not reached [-; -]	0.75 [0.51; 1.11]	0.152	0.713
Weekly	444	126 (28.4)	Not reached [-; -]	220	72 (32.7)	Not reached [-; -]	0.81 [0.61; 1.09]	0.162	
SOC: Investigations, PT[i]: Weight decreased									
Age (Years)									
< 65	699	42 (6.0)	Not reached [-; -]	341	13 (3.8)	Not reached [-; -]	1.62 [0.87; 3.01]	0.130	0.308
≥ 65	84	15 (17.9)	Not reached [-; -]	48	3 (6.3)	Not reached [-; -]	3.12 [0.90; 10.78]	0.072	
Geographic Region									
Asia	136	13 (9.6)	Not reached [-; -]	79	5 (6.3)	Not reached [-; -]	1.51 [0.54; 4.23]	0.435	0.849
Europe/Israel/North America/Australia	606	39 (6.4)	Not reached [-; -]	285	9 (3.2)	Not reached [-; -]	2.14 [1.04; 4.42]	0.040	
Rest of World	41	5 (12.2)	Not reached [-; -]	25	2 (8.0)	Not reached [-; -]	1.49 [0.29; 7.68]	0.633	
Nodal Status									
Negative	376	29 (7.7)	Not reached [-; -]	193	9 (4.7)	Not reached [-; -]	1.71 [0.81; 3.61]	0.160	0.817
Positive	407	28 (6.9)	Not reached [-; -]	196	7 (3.6)	Not reached [-; -]	1.98 [0.87; 4.54]	0.105	
Tumor Size									
T1/T2	580	35 (6.0)	Not reached [-; -]	289	12 (4.2)	Not reached [-; -]	1.49 [0.78; 2.88]	0.230	0.317
T3/T4	203	22 (10.8)	Not reached [-; -]	100	4 (4.0)	Not reached [-; -]	2.79 [0.96; 8.11]	0.059	
Choice of Carboplatin									
Q3W	334	21 (6.3)	Not reached [-; -]	167	7 (4.2)	Not reached [-; -]	1.53 [0.65; 3.61]	0.327	0.597

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Weekly	444	36 (8.1)	Not reached [-; -]	220	9 (4.1)	Not reached [-; -]	2.05 [0.99; 4.25]	0.055	
SOC: Metabolism and nutrition disorders, PT[i]: Decreased appetite									
Age (Years)									
< 65	699	151 (21.6)	Not reached [-; -]	341	55 (16.1)	Not reached [-; -]	1.40 [1.03; 1.90]	0.033	0.685
≥ 65	84	27 (32.1)	Not reached [-; -]	48	10 (20.8)	Not reached [-; -]	1.63 [0.79; 3.37]	0.188	
ECOG Performance Status									
0	677	153 (22.6)	Not reached [-; -]	340	59 (17.4)	Not reached [-; -]	1.36 [1.01; 1.83]	0.046	0.375
1	106	25 (23.6)	Not reached [-; -]	49	6 (12.2)	Not reached [-; -]	2.05 [0.84; 5.00]	0.115	
Geographic Region									
Asia	136	36 (26.5)	Not reached [-; -]	79	14 (17.7)	Not reached [-; -]	1.60 [0.86; 2.96]	0.137	0.926
Europe/Israel/North America/Australia	606	133 (21.9)	Not reached [-; -]	285	47 (16.5)	Not reached [-; -]	1.39 [1.00; 1.94]	0.052	
Rest of World	41	9 (22.0)	Not reached [-; -]	25	4 (16.0)	Not reached [-; -]	1.40 [0.43; 4.54]	0.578	
Nodal Status									
Negative	376	92 (24.5)	Not reached [-; -]	193	27 (14.0)	Not reached [-; -]	1.88 [1.23; 2.89]	0.004	0.070
Positive	407	86 (21.1)	Not reached [-; -]	196	38 (19.4)	Not reached [-; -]	1.10 [0.75; 1.62]	0.610	
Tumor Size									
T1/T2	580	130 (22.4)	Not reached [-; -]	289	44 (15.2)	Not reached [-; -]	1.56 [1.11; 2.20]	0.010	0.294
T3/T4	203	48 (23.6)	Not reached [-; -]	100	21 (21.0)	Not reached [-; -]	1.12 [0.67; 1.87]	0.663	
Choice of Carboplatin									
Q3W	334	68 (20.4)	Not reached [-; -]	167	26 (15.6)	Not reached [-; -]	1.35 [0.86; 2.13]	0.189	0.797
Weekly	444	110 (24.8)	Not reached [-; -]	220	39 (17.7)	Not reached [-; -]	1.46 [1.02; 2.11]	0.041	
SOC: Metabolism and nutrition disorders, PT[i]: Dehydration									
Age (Years)									
< 65	699	33 (4.7)	Not reached [-; -]	341	9 (2.6)	Not reached [-; -]	1.82 [0.87; 3.79]	0.113	0.075
≥ 65	84	6 (7.1)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.059	
ECOG Performance Status									
0	677	34 (5.0)	Not reached [-; -]	340	7 (2.1)	Not reached [-; -]	2.48 [1.10; 5.60]	0.028	0.449
1	106	5 (4.7)	Not reached [-; -]	49	2 (4.1)	Not reached [-; -]	1.18 [0.23; 6.06]	0.847	
Geographic Region									

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Asia	136	2 (1.5)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.278	0.265
Europe/Israel/North America/Australia	606	34 (5.6)	Not reached [-; -]	285	9 (3.2)	Not reached [-; -]	1.81 [0.87; 3.78]	0.113	
Rest of World	41	3 (7.3)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.183	
Nodal Status									
Negative	376	25 (6.6)	Not reached [-; -]	193	7 (3.6)	Not reached [-; -]	1.87 [0.81; 4.33]	0.142	0.471
Positive	407	14 (3.4)	Not reached [-; -]	196	2 (1.0)	Not reached [-; -]	3.42 [0.78; 15.06]	0.104	
Tumor Size									
T1/T2	580	33 (5.7)	Not reached [-; -]	289	7 (2.4)	Not reached [-; -]	2.42 [1.07; 5.46]	0.034	0.596
T3/T4	203	6 (3.0)	Not reached [-; -]	100	2 (2.0)	Not reached [-; -]	1.48 [0.30; 7.33]	0.632	
Choice of Carboplatin									
Q3W	334	12 (3.6)	Not reached [-; -]	167	2 (1.2)	Not reached [-; -]	3.04 [0.68; 13.57]	0.146	0.594
Weekly	444	27 (6.1)	Not reached [-; -]	220	7 (3.2)	Not reached [-; -]	1.95 [0.85; 4.47]	0.117	
SOC: Metabolism and nutrition disorders, PT[i]: Hypokalaemia									
Age (Years)									
< 65	699	75 (10.7)	Not reached [-; -]	341	22 (6.5)	Not reached [-; -]	1.71 [1.06; 2.75]	0.027	0.224
≥ 65	84	13 (15.5)	Not reached [-; -]	48	2 (4.2)	Not reached [-; -]	4.34 [0.98; 19.28]	0.053	
ECOG Performance Status									
0	677	67 (9.9)	Not reached [-; -]	340	22 (6.5)	Not reached [-; -]	1.57 [0.97; 2.55]	0.065	0.073
1	106	21 (19.8)	Not reached [-; -]	49	2 (4.1)	Not reached [-; -]	5.54 [1.30; 23.66]	0.021	
Geographic Region									
Asia	136	4 (2.9)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.126	0.188
Europe/Israel/North America/Australia	606	77 (12.7)	Not reached [-; -]	285	23 (8.1)	Not reached [-; -]	1.65 [1.03; 2.62]	0.036	
Rest of World	41	7 (17.1)	Not reached [-; -]	25	1 (4.0)	Not reached [-; -]	4.43 [0.54; 36.01]	0.164	
Nodal Status									
Negative	376	37 (9.8)	Not reached [-; -]	193	8 (4.1)	Not reached [-; -]	2.46 [1.14; 5.28]	0.021	0.363
Positive	407	51 (12.5)	Not reached [-; -]	196	16 (8.2)	Not reached [-; -]	1.60 [0.91; 2.81]	0.100	
Tumor Size									
T1/T2	580	63 (10.9)	Not reached [-; -]	289	13 (4.5)	Not reached [-; -]	2.55 [1.40; 4.63]	0.002	0.082
T3/T4	203	25	Not reached	100	11	Not reached	1.12	0.762	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(12.3)	[-; -]		(11.0)	[-; -]	[0.55; 2.27]		
Choice of Carboplatin									
Q3W	334	47 (14.1)	Not reached [-; -]	167	12 (7.2)	Not reached [-; -]	2.05 [1.09; 3.86]	0.027	0.738
Weekly	444	41 (9.2)	Not reached [-; -]	220	12 (5.5)	Not reached [-; -]	1.74 [0.92; 3.32]	0.090	
SOC: Musculoskeletal and connective tissue disorders, PT[i]: Muscular weakness									
Age (Years)									
< 65	699	21 (3.0)	Not reached [-; -]	341	2 (0.6)	Not reached [-; -]	5.36 [1.26; 22.87]	0.023	0.584
≥ 65	84	4 (4.8)	Not reached [-; -]	48	1 (2.1)	Not reached [-; -]	2.36 [0.26; 21.08]	0.443	
ECOG Performance Status									
0	677	21 (3.1)	Not reached [-; -]	340	2 (0.6)	Not reached [-; -]	5.50 [1.29; 23.44]	0.021	0.471
1	106	4 (3.8)	Not reached [-; -]	49	1 (2.0)	Not reached [-; -]	1.98 [0.22; 17.71]	0.543	
Geographic Region									
Asia	136	2 (1.5)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.268	0.653
Europe/Israel/North America/Australia	606	22 (3.6)	Not reached [-; -]	285	3 (1.1)	Not reached [-; -]	3.60 [1.08; 12.04]	0.037	
Rest of World	41	1 (2.4)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.439	
Nodal Status									
Negative	376	18 (4.8)	Not reached [-; -]	193	1 (0.5)	Not reached [-; -]	9.76 [1.30; 73.10]	0.027	0.171
Positive	407	7 (1.7)	Not reached [-; -]	196	2 (1.0)	Not reached [-; -]	1.76 [0.36; 8.45]	0.483	
Tumor Size									
T1/T2	580	20 (3.4)	Not reached [-; -]	289	1 (0.3)	Not reached [-; -]	10.45 [1.40; 77.91]	0.022	0.097
T3/T4	203	5 (2.5)	Not reached [-; -]	100	2 (2.0)	Not reached [-; -]	1.27 [0.25; 6.55]	0.775	
Choice of Carboplatin									
Q3W	334	9 (2.7)	Not reached [-; -]	167	2 (1.2)	Not reached [-; -]	2.29 [0.50; 10.61]	0.289	0.304
Weekly	444	16 (3.6)	Not reached [-; -]	220	1 (0.5)	Not reached [-; -]	8.48 [1.12; 63.95]	0.038	
SOC: Musculoskeletal and connective tissue disorders, PT[i]: Neck pain									
Age (Years)									
< 65	699	16 (2.3)	Not reached [-; -]	341	18 (5.3)	Not reached [-; -]	0.45 [0.23; 0.89]	0.021	0.227
≥ 65	84	4 (4.8)	Not reached [-; -]	48	2 (4.2)	Not reached [-; -]	1.38 [0.25; 7.61]	0.712	
ECOG Performance Status									
0	677	15	Not reached	340	16	Not reached	0.50	0.054	0.769

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(2.2)	[-; -]		(4.7)	[-; -]	[0.25; 1.01]		
1	106	5 (4.7)	Not reached [-; -]	49	4 (8.2)	Not reached [-; -]	0.58 [0.16; 2.16]	0.418	
Geographic Region									
Asia	136	0 (0.0)	Not reached [-; -]	79	2 (2.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.073	0.271
Europe/Israel/North America/Australia	606	19 (3.1)	Not reached [-; -]	285	17 (6.0)	Not reached [-; -]	0.56 [0.29; 1.07]	0.080	
Rest of World	41	1 (2.4)	Not reached [-; -]	25	1 (4.0)	Not reached [-; -]	0.62 [0.04; 9.96]	0.738	
Nodal Status									
Negative	376	11 (2.9)	Not reached [-; -]	193	10 (5.2)	Not reached [-; -]	0.60 [0.25; 1.40]	0.237	0.657
Positive	407	9 (2.2)	Not reached [-; -]	196	10 (5.1)	Not reached [-; -]	0.46 [0.19; 1.14]	0.092	
Tumor Size									
T1/T2	580	15 (2.6)	Not reached [-; -]	289	19 (6.6)	Not reached [-; -]	0.42 [0.21; 0.82]	0.011	0.071
T3/T4	203	5 (2.5)	Not reached [-; -]	100	1 (1.0)	Not reached [-; -]	2.60 [0.30; 22.28]	0.383	
Choice of Carboplatin									
Q3W	334	8 (2.4)	Not reached [-; -]	167	4 (2.4)	Not reached [-; -]	1.05 [0.32; 3.50]	0.932	0.159
Weekly	444	12 (2.7)	Not reached [-; -]	220	16 (7.3)	Not reached [-; -]	0.39 [0.18; 0.82]	0.014	
SOC: Respiratory, thoracic and mediastinal disorders, PT[i]: Nasal congestion									
Age (Years)									
< 65	699	27 (3.9)	Not reached [-; -]	341	5 (1.5)	Not reached [-; -]	2.74 [1.05; 7.10]	0.039	0.997
≥ 65	84	0 (0.0)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
ECOG Performance Status									
0	677	25 (3.7)	Not reached [-; -]	340	4 (1.2)	Not reached [-; -]	3.28 [1.14; 9.42]	0.027	0.397
1	106	2 (1.9)	Not reached [-; -]	49	1 (2.0)	Not reached [-; -]	0.96 [0.09; 10.57]	0.972	
Geographic Region									
Asia	136	2 (1.5)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.299	0.531
Europe/Israel/North America/Australia	606	24 (4.0)	Not reached [-; -]	285	5 (1.8)	Not reached [-; -]	2.36 [0.90; 6.19]	0.080	
Rest of World	41	1 (2.4)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.395	
Nodal Status									
Negative	376	13 (3.5)	Not reached [-; -]	193	3 (1.6)	Not reached [-; -]	2.36 [0.67; 8.28]	0.181	0.675
Positive	407	14 (3.4)	Not reached [-; -]	196	2 (1.0)	Not reached [-; -]	3.48 [0.79; 15.31]	0.099	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Tumor Size									
T1/T2	580	19 (3.3)	Not reached [-; -]	289	4 (1.4)	Not reached [-; -]	2.46 [0.84; 7.22]	0.102	0.667
T3/T4	203	8 (3.9)	Not reached [-; -]	100	1 (1.0)	Not reached [-; -]	4.09 [0.51; 32.68]	0.184	
Choice of Carboplatin									
Q3W	334	11 (3.3)	Not reached [-; -]	167	2 (1.2)	Not reached [-; -]	2.84 [0.63; 12.80]	0.175	0.977
Weekly	444	16 (3.6)	Not reached [-; -]	220	3 (1.4)	Not reached [-; -]	2.79 [0.81; 9.56]	0.104	
SOC: Skin and subcutaneous tissue disorders, PT[i]: Dermatitis acneiform									
Age (Years)									
< 65	699	54 (7.7)	Not reached [-; -]	341	13 (3.8)	Not reached [-; -]	2.08 [1.14; 3.81]	0.018	0.228
≥ 65	84	3 (3.6)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.188	
ECOG Performance Status									
0	677	52 (7.7)	Not reached [-; -]	340	10 (2.9)	Not reached [-; -]	2.69 [1.37; 5.30]	0.004	0.137
1	106	5 (4.7)	Not reached [-; -]	49	3 (6.1)	Not reached [-; -]	0.76 [0.18; 3.17]	0.705	
Geographic Region									
Asia	136	23 (16.9)	Not reached [-; -]	79	5 (6.3)	Not reached [-; -]	2.88 [1.10; 7.59]	0.032	0.495
Europe/Israel/North America/Australia	606	32 (5.3)	Not reached [-; -]	285	8 (2.8)	Not reached [-; -]	1.91 [0.88; 4.14]	0.102	
Rest of World	41	2 (4.9)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.266	
Nodal Status									
Negative	376	32 (8.5)	Not reached [-; -]	193	9 (4.7)	Not reached [-; -]	1.86 [0.89; 3.90]	0.099	0.428
Positive	407	25 (6.1)	Not reached [-; -]	196	4 (2.0)	Not reached [-; -]	3.11 [1.08; 8.92]	0.035	
Tumor Size									
T1/T2	580	41 (7.1)	Not reached [-; -]	289	11 (3.8)	Not reached [-; -]	1.90 [0.98; 3.70]	0.058	0.322
T3/T4	203	16 (7.9)	Not reached [-; -]	100	2 (2.0)	Not reached [-; -]	4.07 [0.94; 17.69]	0.061	
Choice of Carboplatin									
Q3W	334	23 (6.9)	Not reached [-; -]	167	7 (4.2)	Not reached [-; -]	1.67 [0.72; 3.89]	0.235	0.373
Weekly	444	34 (7.7)	Not reached [-; -]	220	6 (2.7)	Not reached [-; -]	2.90 [1.22; 6.90]	0.016	
SOC: Skin and subcutaneous tissue disorders, PT[i]: Dermatitis allergic									
Age (Years)									
< 65	699	11 (1.6)	Not reached [-; -]	341	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.018	0.997

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
≥ 65	84	1 (1.2)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.444	
ECOG Performance Status									
0	677	10 (1.5)	Not reached [-; -]	340	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.023	0.997
1	106	2 (1.9)	Not reached [-; -]	49	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.313	
Geographic Region									
Asia	136	2 (1.5)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.279	> 0.999
Europe/Israel/North America/Australia	606	10 (1.7)	Not reached [-; -]	285	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.026	
Rest of World	41	0 (0.0)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
Nodal Status									
Negative	376	5 (1.3)	n.c.	193	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Positive	407	7 (1.7)	n.c.	196	0 (0.0)	n.c.	n.c.	n.c.	
Tumor Size									
T1/T2	580	11 (1.9)	Not reached [-; -]	289	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.017	0.997
T3/T4	203	1 (0.5)	Not reached [-; -]	100	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.484	
Choice of Carboplatin									
Q3W	334	0 (0.0)	Not reached [-; -]	167	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	0.996
Weekly	444	12 (2.7)	Not reached [-; -]	220	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.013	
SOC: Skin and subcutaneous tissue disorders, PT[i]: Nail toxicity									
Age (Years)									
< 65	699	6 (0.9)	Not reached [-; -]	341	6 (1.8)	Not reached [-; -]	0.49 [0.16; 1.51]	0.214	0.449
≥ 65	84	2 (2.4)	Not reached [-; -]	48	5 (10.4)	Not reached [-; -]	0.23 [0.04; 1.19]	0.080	
ECOG Performance Status									
0	677	7 (1.0)	Not reached [-; -]	340	11 (3.2)	Not reached [-; -]	0.32 [0.12; 0.82]	0.018	0.187
1	106	1 (0.9)	Not reached [-; -]	49	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.488	
Geographic Region									
Asia	136	0 (0.0)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	> 0.999
Europe/Israel/North America/Australia	606	8 (1.3)	Not reached [-; -]	285	11 (3.9)	Not reached [-; -]	0.34 [0.14; 0.85]	0.021	
Rest of World	41	0 (0.0)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Nodal Status									
Negative	376	6 (1.6)	Not reached [-; -]	193	7 (3.6)	Not reached [-; -]	0.44 [0.15; 1.31]	0.142	0.548
Positive	407	2 (0.5)	Not reached [-; -]	196	4 (2.0)	Not reached [-; -]	0.24 [0.04; 1.31]	0.099	
Tumor Size									
T1/T2	580	6 (1.0)	Not reached [-; -]	289	8 (2.8)	Not reached [-; -]	0.38 [0.13; 1.08]	0.070	0.888
T3/T4	203	2 (1.0)	Not reached [-; -]	100	3 (3.0)	Not reached [-; -]	0.32 [0.05; 1.92]	0.212	
Choice of Carboplatin									
Q3W	334	2 (0.6)	Not reached [-; -]	167	6 (3.6)	Not reached [-; -]	0.17 [0.03; 0.82]	0.027	0.191
Weekly	444	6 (1.4)	Not reached [-; -]	220	5 (2.3)	Not reached [-; -]	0.59 [0.18; 1.95]	0.390	
SOC: Skin and subcutaneous tissue disorders, PT[i]: Pruritus									
Age (Years)									
< 65	699	135 (19.3)	Not reached [-; -]	341	49 (14.4)	Not reached [-; -]	1.44 [1.04; 2.00]	0.028	0.577
≥ 65	84	12 (14.3)	Not reached [-; -]	48	7 (14.6)	Not reached [-; -]	1.17 [0.46; 2.99]	0.738	
ECOG Performance Status									
0	677	126 (18.6)	Not reached [-; -]	340	43 (12.6)	Not reached [-; -]	1.60 [1.13; 2.26]	0.008	0.087
1	106	21 (19.8)	Not reached [-; -]	49	13 (26.5)	Not reached [-; -]	0.79 [0.39; 1.58]	0.500	
Geographic Region									
Asia	136	46 (33.8)	Not reached [-; -]	79	17 (21.5)	Not reached [-; -]	1.74 [1.00; 3.04]	0.051	0.371
Europe/Israel/North America/Australia	606	97 (16.0)	Not reached [-; -]	285	35 (12.3)	Not reached [-; -]	1.42 [0.96; 2.09]	0.076	
Rest of World	41	4 (9.8)	Not reached [-; -]	25	4 (16.0)	Not reached [-; -]	0.57 [0.14; 2.29]	0.431	
Nodal Status									
Negative	376	71 (18.9)	Not reached [-; -]	193	30 (15.5)	Not reached [-; -]	1.31 [0.85; 2.00]	0.220	0.607
Positive	407	76 (18.7)	Not reached [-; -]	196	26 (13.3)	Not reached [-; -]	1.53 [0.98; 2.39]	0.060	
Tumor Size									
T1/T2	580	114 (19.7)	Not reached [-; -]	289	46 (15.9)	Not reached [-; -]	1.34 [0.95; 1.89]	0.091	0.521
T3/T4	203	33 (16.3)	Not reached [-; -]	100	10 (10.0)	Not reached [-; -]	1.74 [0.86; 3.53]	0.126	
Choice of Carboplatin									
Q3W	334	53 (15.9)	Not reached [-; -]	167	23 (13.8)	Not reached [-; -]	1.22 [0.75; 1.99]	0.426	0.462
Weekly	444	94	Not reached	220	33	Not reached	1.55	0.032	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(21.2)	[-; -]		(15.0)	[-; -]	[1.04; 2.30]		
SOC: Skin and subcutaneous tissue disorders, PT[i]: Rash									
Age (Years)									
< 65	699	206 (29.5)	Not reached [-; -]	341	83 (24.3)	Not reached [-; -]	1.31 [1.02; 1.69]	0.038	0.208
≥ 65	84	28 (33.3)	Not reached [-; -]	48	9 (18.8)	Not reached [-; -]	2.09 [0.99; 4.44]	0.055	
ECOG Performance Status									
0	677	205 (30.3)	Not reached [-; -]	340	79 (23.2)	Not reached [-; -]	1.43 [1.10; 1.85]	0.007	0.510
1	106	29 (27.4)	Not reached [-; -]	49	13 (26.5)	Not reached [-; -]	1.10 [0.57; 2.13]	0.767	
Geographic Region									
Asia	136	58 (42.6)	Not reached [45.1; -]	79	18 (22.8)	Not reached [-; -]	2.20 [1.30; 3.73]	0.004	0.109
Europe/Israel/North America/Australia	606	171 (28.2)	Not reached [-; -]	285	72 (25.3)	Not reached [-; -]	1.21 [0.92; 1.60]	0.170	
Rest of World	41	5 (12.2)	Not reached [-; -]	25	2 (8.0)	Not reached [-; -]	1.46 [0.28; 7.55]	0.649	
Nodal Status									
Negative	376	130 (34.6)	Not reached [72.3; -]	193	49 (25.4)	Not reached [-; -]	1.50 [1.08; 2.09]	0.015	0.483
Positive	407	104 (25.6)	Not reached [-; -]	196	43 (21.9)	Not reached [-; -]	1.27 [0.89; 1.81]	0.190	
Tumor Size									
T1/T2	580	185 (31.9)	Not reached [-; -]	289	75 (26.0)	Not reached [-; -]	1.37 [1.05; 1.79]	0.022	0.773
T3/T4	203	49 (24.1)	Not reached [-; -]	100	17 (17.0)	Not reached [-; -]	1.48 [0.85; 2.56]	0.167	
Choice of Carboplatin									
Q3W	334	94 (28.1)	Not reached [-; -]	167	36 (21.6)	Not reached [-; -]	1.39 [0.95; 2.04]	0.094	0.934
Weekly	444	140 (31.5)	Not reached [-; -]	220	56 (25.5)	Not reached [-; -]	1.38 [1.01; 1.88]	0.044	
SOC: Vascular disorders, PT[i]: Hypotension									
Age (Years)									
< 65	699	33 (4.7)	Not reached [-; -]	341	7 (2.1)	Not reached [-; -]	2.36 [1.04; 5.32]	0.040	0.915
≥ 65	84	7 (8.3)	Not reached [-; -]	48	2 (4.2)	Not reached [-; -]	2.13 [0.44; 10.25]	0.346	
ECOG Performance Status									
0	677	33 (4.9)	Not reached [-; -]	340	8 (2.4)	Not reached [-; -]	2.12 [0.98; 4.60]	0.056	0.672
1	106	7 (6.6)	Not reached [-; -]	49	1 (2.0)	Not reached [-; -]	3.33 [0.41; 27.07]	0.261	
Geographic Region									
Asia	136	1	Not reached	79	0	Not reached	n.a.	0.442	0.609

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
		(0.7)	[-; -]		(0.0)	[-; -]	[n.a.; n.a.]		
Europe/Israel/North America/Australia	606	38 (6.3)	Not reached [-; -]	285	9 (3.2)	Not reached [-; -]	2.05 [0.99; 4.24]	0.053	
Rest of World	41	1 (2.4)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.429	
Nodal Status									
Negative	376	25 (6.6)	Not reached [-; -]	193	5 (2.6)	Not reached [-; -]	2.65 [1.01; 6.92]	0.047	0.628
Positive	407	15 (3.7)	Not reached [-; -]	196	4 (2.0)	Not reached [-; -]	1.85 [0.61; 5.57]	0.275	
Tumor Size									
T1/T2	580	34 (5.9)	Not reached [-; -]	289	8 (2.8)	Not reached [-; -]	2.18 [1.01; 4.72]	0.047	0.774
T3/T4	203	6 (3.0)	Not reached [-; -]	100	1 (1.0)	Not reached [-; -]	2.99 [0.36; 24.81]	0.311	
Choice of Carboplatin									
Q3W	334	18 (5.4)	Not reached [-; -]	167	3 (1.8)	Not reached [-; -]	3.08 [0.91; 10.45]	0.071	0.499
Weekly	444	22 (5.0)	Not reached [-; -]	220	6 (2.7)	Not reached [-; -]	1.86 [0.75; 4.59]	0.178	

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

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

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

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

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

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

j: Unrounded p-value < 0.050

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 participants per subgroup and at least 10 events in one of the subgroups necessary; PT: Preferred Term; Q3W: Every 3 Weeks; SOC: System Organ Class

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-85: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**			**Placebo + Chemotherapy[c] / Placebo**			**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**		
Serious Adverse Events	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
SOC[i]: Endocrine disorders									
Age (Years)									
< 65	699	20 (2.9)	Not reached [-; -]	341	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	0.997
≥ 65	84	4 (4.8)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.125	
ECOG Performance Status									
0	677	21 (3.1)	Not reached [-; -]	340	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	0.997
1	106	3 (2.8)	Not reached [-; -]	49	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.227	
Geographic Region									
Asia	136	3 (2.2)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.184	> 0.999
Europe/Israel/North America/Australia	606	21 (3.5)	Not reached [-; -]	285	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	
Rest of World	41	0 (0.0)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
Nodal Status									
Negative	376	14 (3.7)	Not reached [-; -]	193	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.006	0.997
Positive	407	10 (2.5)	Not reached [-; -]	196	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.027	
Tumor Size									
T1/T2	580	20 (3.4)	Not reached [-; -]	289	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	0.997
T3/T4	203	4 (2.0)	Not reached [-; -]	100	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.158	
Choice of Carboplatin									
Q3W	334	15 (4.5)	Not reached [-; -]	167	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.005	0.997
Weekly	444	9 (2.0)	Not reached [-; -]	220	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.033	
SOC[i]: Gastrointestinal disorders									
Age (Years)									
< 65	699	32 (4.6)	Not reached [-; -]	341	8 (2.3)	Not reached [-; -]	1.99 [0.92; 4.32]	0.082	0.715
≥ 65	84	5 (6.0)	Not reached [-; -]	48	1 (2.1)	Not reached [-; -]	3.44 [0.39; 30.07]	0.264	
ECOG Performance Status									
0	677	28 (4.1)	Not reached [-; -]	340	8 (2.4)	Not reached [-; -]	1.79 [0.82; 3.93]	0.146	0.379

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Serious Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
1	106	9 (8.5)	Not reached [-; -]	49	1 (2.0)	Not reached [-; -]	4.31 [0.55; 34.00]	0.166	
Geographic Region									
Asia	136	5 (3.7)	Not reached [-; -]	79	1 (1.3)	Not reached [-; -]	2.87 [0.33; 24.55]	0.336	0.704
Europe/Israel/North America/Australia	606	31 (5.1)	Not reached [-; -]	285	8 (2.8)	Not reached [-; -]	1.86 [0.86; 4.06]	0.116	
Rest of World	41	1 (2.4)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.435	
Nodal Status									
Negative	376	15 (4.0)	Not reached [-; -]	193	4 (2.1)	Not reached [-; -]	1.95 [0.65; 5.88]	0.235	0.890
Positive	407	22 (5.4)	Not reached [-; -]	196	5 (2.6)	Not reached [-; -]	2.18 [0.83; 5.75]	0.116	
Tumor Size									
T1/T2	580	34 (5.9)	Not reached [-; -]	289	6 (2.1)	Not reached [-; -]	2.90 [1.22; 6.92]	0.016	0.062
T3/T4	203	3 (1.5)	Not reached [-; -]	100	3 (3.0)	Not reached [-; -]	0.49 [0.10; 2.44]	0.387	
Choice of Carboplatin									
Q3W	334	14 (4.2)	Not reached [-; -]	167	4 (2.4)	Not reached [-; -]	1.78 [0.59; 5.41]	0.309	0.717
Weekly	444	23 (5.2)	Not reached [-; -]	220	5 (2.3)	Not reached [-; -]	2.34 [0.89; 6.16]	0.085	
SOC[i]: General disorders and administration site conditions									
ECOG Performance Status									
0	677	36 (5.3)	Not reached [-; -]	340	9 (2.6)	Not reached [-; -]	2.06 [0.99; 4.27]	0.053	0.119
1	106	6 (5.7)	Not reached [-; -]	49	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.091	
Geographic Region									
Asia	136	6 (4.4)	Not reached [-; -]	79	1 (1.3)	Not reached [-; -]	3.51 [0.42; 29.17]	0.245	0.553
Europe/Israel/North America/Australia	606	34 (5.6)	Not reached [-; -]	285	8 (2.8)	Not reached [-; -]	2.06 [0.95; 4.45]	0.066	
Rest of World	41	2 (4.9)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.276	
Nodal Status									
Negative	376	18 (4.8)	Not reached [86.4; -]	193	6 (3.1)	Not reached [-; -]	1.59 [0.63; 4.00]	0.327	0.219
Positive	407	24 (5.9)	Not reached [-; -]	196	3 (1.5)	Not reached [-; -]	3.98 [1.20; 13.22]	0.024	
Tumor Size									
T1/T2	580	35 (6.0)	Not reached [-; -]	289	6 (2.1)	Not reached [-; -]	3.01 [1.27; 7.16]	0.013	0.246
T3/T4	203	7 (3.4)	Not reached [-; -]	100	3 (3.0)	Not reached [-; -]	1.10 [0.28; 4.27]	0.889	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Serious Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
Choice of Carboplatin									
Q3W	334	13 (3.9)	Not reached [-; -]	167	5 (3.0)	Not reached [-; -]	1.32 [0.47; 3.71]	0.595	0.157
Weekly	444	29 (6.5)	Not reached [-; -]	220	4 (1.8)	Not reached [-; -]	3.80 [1.33; 10.81]	0.012	
SOC[i]: Hepatobiliary disorders									
Age (Years)									
< 65	699	14 (2.0)	Not reached [-; -]	341	1 (0.3)	Not reached [-; -]	7.01 [0.92; 53.30]	0.060	0.496
≥ 65	84	3 (3.6)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.115	
ECOG Performance Status									
0	677	13 (1.9)	Not reached [-; -]	340	1 (0.3)	Not reached [-; -]	6.69 [0.87; 51.13]	0.067	0.476
1	106	4 (3.8)	Not reached [-; -]	49	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.155	
Geographic Region									
Asia	136	2 (1.5)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.295	0.799
Europe/Israel/North America/Australia	606	14 (2.3)	Not reached [-; -]	285	1 (0.4)	Not reached [-; -]	6.79 [0.89; 51.62]	0.064	
Rest of World	41	1 (2.4)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.439	
Nodal Status									
Negative	376	9 (2.4)	n.c.	193	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Positive	407	8 (2.0)	n.c.	196	1 (0.5)	n.c.	n.c.	n.c.	
Tumor Size									
T1/T2	580	15 (2.6)	Not reached [-; -]	289	1 (0.3)	Not reached [-; -]	7.78 [1.03; 58.92]	0.047	0.626
T3/T4	203	2 (1.0)	Not reached [-; -]	100	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.322	
Choice of Carboplatin									
Q3W	334	4 (1.2)	Not reached [-; -]	167	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.151	0.472
Weekly	444	13 (2.9)	Not reached [-; -]	220	1 (0.5)	Not reached [-; -]	6.68 [0.87; 51.09]	0.067	
SOC[i]: Injury, poisoning and procedural complications									
Age (Years)									
< 65	699	16 (2.3)	Not reached [-; -]	341	4 (1.2)	Not reached [-; -]	2.02 [0.68; 6.05]	0.208	0.078
≥ 65	84	7 (8.3)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.039	
ECOG Performance Status									
0	677	16 (2.4)	Not reached [-; -]	340	3 (0.9)	Not reached [-; -]	2.72 [0.79; 9.34]	0.111	0.845

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Serious Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
1	106	7 (6.6)	Not reached [-; -]	49	1 (2.0)	Not reached [-; -]	3.72 [0.46; 30.26]	0.220	
Geographic Region									
Asia	136	3 (2.2)	Not reached [-; -]	79	1 (1.3)	Not reached [-; -]	1.79 [0.19; 17.26]	0.613	0.633
Europe/Israel/North America/Australia	606	18 (3.0)	Not reached [-; -]	285	3 (1.1)	Not reached [-; -]	2.94 [0.87; 9.99]	0.084	
Rest of World	41	2 (4.9)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.290	
Nodal Status									
Negative	376	12 (3.2)	Not reached [-; -]	193	3 (1.6)	Not reached [-; -]	2.16 [0.61; 7.67]	0.232	0.428
Positive	407	11 (2.7)	Not reached [-; -]	196	1 (0.5)	Not reached [-; -]	5.38 [0.69; 41.69]	0.107	
Tumor Size									
T1/T2	580	16 (2.8)	Not reached [-; -]	289	3 (1.0)	Not reached [-; -]	2.78 [0.81; 9.56]	0.104	0.842
T3/T4	203	7 (3.4)	Not reached [-; -]	100	1 (1.0)	Not reached [-; -]	3.52 [0.43; 28.65]	0.239	

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

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

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

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

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

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

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 participants per subgroup and at least 10 events in one of the subgroups necessary; Q3W: Every 3 Weeks; SOC: System Organ Class

Tabelle 4G-86: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Serious Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
SOC: General disorders and administration site conditions, PT[i]: Pyrexia									
Age (Years)									
< 65	699	25 (3.6)	Not reached [-; -]	341	2 (0.6)	Not reached [-; -]	6.19 [1.47; 26.13]	0.013	0.411
≥ 65	84	4 (4.8)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.127	
ECOG Performance Status									
0	677	25 (3.7)	Not reached [-; -]	340	2 (0.6)	Not reached [-; -]	6.37 [1.51; 26.91]	0.012	0.466
1	106	4 (3.8)	Not reached [-; -]	49	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.169	
Geographic Region									
Asia	136	4 (2.9)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.126	0.645
Europe/Israel/North America/Australia	606	24 (4.0)	Not reached [-; -]	285	2 (0.7)	Not reached [-; -]	5.74 [1.36; 24.29]	0.018	
Rest of World	41	1 (2.4)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.435	
Nodal Status									
Negative	376	15 (4.0)	Not reached [-; -]	193	2 (1.0)	Not reached [-; -]	3.90 [0.89; 17.05]	0.071	0.121
Positive	407	14 (3.4)	Not reached [-; -]	196	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.009	
Tumor Size									
T1/T2	580	26 (4.5)	Not reached [-; -]	289	1 (0.3)	Not reached [-; -]	13.27 [1.80; 97.79]	0.011	0.176
T3/T4	203	3 (1.5)	Not reached [-; -]	100	1 (1.0)	Not reached [-; -]	1.47 [0.15; 14.15]	0.738	
Choice of Carboplatin									
Q3W	334	10 (3.0)	Not reached [-; -]	167	1 (0.6)	Not reached [-; -]	5.06 [0.65; 39.53]	0.122	0.666
Weekly	444	19 (4.3)	Not reached [-; -]	220	1 (0.5)	Not reached [-; -]	9.57 [1.28; 71.49]	0.028	

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

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

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

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

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

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

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Serious Adverse Events	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); PT: Preferred Term; Q3W: Every 3 Weeks; SOC: System Organ Class									

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

Tabelle 4G-87: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
SOC[i]: Endocrine disorders									
Age (Years)									
< 65	699	21 (3.0)	Not reached [-; -]	341	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	0.997
≥ 65	84	4 (4.8)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.109	
ECOG Performance Status									
0	677	22 (3.2)	Not reached [-; -]	340	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
1	106	3 (2.8)	Not reached [-; -]	49	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.218	
Geographic Region									
Asia	136	2 (1.5)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.281	> 0.999
Europe/Israel/North America/Australia	606	23 (3.8)	Not reached [-; -]	285	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Rest of World	41	0 (0.0)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
Nodal Status									
Negative	376	15 (4.0)	Not reached [-; -]	193	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.004	0.997
Positive	407	10 (2.5)	Not reached [-; -]	196	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.026	
Tumor Size									
T1/T2	580	21 (3.6)	Not reached [-; -]	289	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
T3/T4	203	4 (2.0)	Not reached [-; -]	100	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.158	
Choice of Carboplatin									
Q3W	334	16	Not reached	167	0	Not reached	n.a.	0.004	0.997

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
		(4.8)	[-; -]		(0.0)	[-; -]	[n.a.; n.a.]		
Weekly	444	9 (2.0)	Not reached [-; -]	220	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.031	
SOC[i]: Gastrointestinal disorders									
Age (Years)									
< 65	699	78 (11.2)	Not reached [-; -]	341	23 (6.7)	Not reached [-; -]	1.72 [1.08; 2.74]	0.023	0.982
≥ 65	84	14 (16.7)	Not reached [78.4; -]	48	5 (10.4)	Not reached [-; -]	1.63 [0.59; 4.52]	0.351	
ECOG Performance Status									
0	677	74 (10.9)	Not reached [-; -]	340	26 (7.6)	Not reached [-; -]	1.47 [0.94; 2.30]	0.092	0.098
1	106	18 (17.0)	Not reached [-; -]	49	2 (4.1)	Not reached [-; -]	4.49 [1.04; 19.37]	0.044	
Geographic Region									
Asia	136	7 (5.1)	78.4 [78.4; -]	79	1 (1.3)	Not reached [-; -]	3.49 [0.42; 28.96]	0.248	0.601
Europe/Israel/North America/Australia	606	79 (13.0)	Not reached [-; -]	285	25 (8.8)	Not reached [-; -]	1.55 [0.99; 2.43]	0.056	
Rest of World	41	6 (14.6)	Not reached [-; -]	25	2 (8.0)	Not reached [-; -]	1.88 [0.38; 9.31]	0.440	
Nodal Status									
Negative	376	40 (10.6)	Not reached [78.4; -]	193	15 (7.8)	Not reached [-; -]	1.41 [0.78; 2.55]	0.261	0.428
Positive	407	52 (12.8)	Not reached [-; -]	196	13 (6.6)	Not reached [-; -]	2.00 [1.09; 3.67]	0.025	
Tumor Size									
T1/T2	580	69 (11.9)	Not reached [-; -]	289	18 (6.2)	Not reached [-; -]	2.00 [1.19; 3.36]	0.009	0.232
T3/T4	203	23 (11.3)	Not reached [-; -]	100	10 (10.0)	Not reached [-; -]	1.15 [0.55; 2.41]	0.714	
Choice of Carboplatin									
Q3W	334	35 (10.5)	Not reached [-; -]	167	14 (8.4)	Not reached [-; -]	1.28 [0.69; 2.38]	0.438	0.252
Weekly	444	57 (12.8)	Not reached [-; -]	220	14 (6.4)	Not reached [-; -]	2.11 [1.17; 3.78]	0.013	
SOC[i]: General disorders and administration site conditions									
ECOG Performance Status									
0	677	74 (10.9)	86.4 [86.4; -]	340	20 (5.9)	Not reached [-; -]	1.91 [1.17; 3.14]	0.010	0.856
1	106	16 (15.1)	Not reached [-; -]	49	4 (8.2)	Not reached [-; -]	1.99 [0.67; 5.97]	0.217	
Geographic Region									
Asia	136	5 (3.7)	77.7 [77.7; -]	79	1 (1.3)	Not reached [-; -]	2.38 [0.27; 21.28]	0.438	0.697
Europe/Israel/North America/Australia	606	79 (13.0)	86.4 [86.4; -]	285	22 (7.7)	Not reached [-; -]	1.78 [1.11; 2.86]	0.017	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
Rest of World	41	6 (14.6)	Not reached [-; -]	25	1 (4.0)	Not reached [-; -]	3.81 [0.46; 31.67]	0.216	
Nodal Status									
Negative	376	41 (10.9)	86.4 [-; -]	193	12 (6.2)	Not reached [-; -]	1.89 [0.99; 3.60]	0.053	0.875
Positive	407	49 (12.0)	Not reached [-; -]	196	12 (6.1)	Not reached [-; -]	2.03 [1.08; 3.81]	0.028	
Tumor Size									
T1/T2	580	68 (11.7)	Not reached [-; -]	289	15 (5.2)	Not reached [-; -]	2.40 [1.37; 4.20]	0.002	0.147
T3/T4	203	22 (10.8)	86.4 [86.4; -]	100	9 (9.0)	Not reached [-; -]	1.19 [0.54; 2.59]	0.669	
Choice of Carboplatin									
Q3W	334	35 (10.5)	Not reached [-; -]	167	12 (7.2)	Not reached [-; -]	1.51 [0.78; 2.91]	0.218	0.312
Weekly	444	55 (12.4)	86.4 [86.4; -]	220	12 (5.5)	Not reached [-; -]	2.40 [1.28; 4.48]	0.006	
SOC[i]: Hepatobiliary disorders									
Age (Years)									
< 65	699	20 (2.9)	Not reached [-; -]	341	2 (0.6)	Not reached [-; -]	5.10 [1.19; 21.83]	0.028	0.362
≥ 65	84	4 (4.8)	Not reached [78.3; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.133	
ECOG Performance Status									
0	677	18 (2.7)	Not reached [-; -]	340	1 (0.3)	Not reached [-; -]	9.39 [1.25; 70.37]	0.029	0.475
1	106	6 (5.7)	Not reached [-; -]	49	1 (2.0)	Not reached [-; -]	3.04 [0.36; 25.27]	0.304	
Geographic Region									
Asia	136	4 (2.9)	78.3 [78.3; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.178	0.600
Europe/Israel/North America/Australia	606	19 (3.1)	Not reached [-; -]	285	2 (0.7)	Not reached [-; -]	4.70 [1.09; 20.19]	0.037	
Rest of World	41	1 (2.4)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.458	
Nodal Status									
Negative	376	12 (3.2)	Not reached [78.3; -]	193	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.010	0.097
Positive	407	12 (2.9)	Not reached [-; -]	196	2 (1.0)	Not reached [-; -]	2.96 [0.66; 13.25]	0.155	
Tumor Size									
T1/T2	580	18 (3.1)	Not reached [-; -]	289	2 (0.7)	Not reached [-; -]	4.92 [1.14; 21.22]	0.033	0.313
T3/T4	203	6 (3.0)	Not reached [-; -]	100	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.082	
Choice of Carboplatin									
Q3W	334	7	Not reached	167	1	Not reached	3.65	0.226	0.536

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
		(2.1)	[-; -]		(0.6)	[-; -]	[0.45; 29.64]		
Weekly	444	17 (3.8)	Not reached [-; -]	220	1 (0.5)	Not reached [-; -]	9.07 [1.21; 68.23]	0.032	
SOC[i]: Skin and subcutaneous tissue disorders									
Age (Years)									
< 65	699	42 (6.0)	Not reached [81.7; -]	341	3 (0.9)	Not reached [-; -]	7.10 [2.20; 22.93]	0.001	0.297
≥ 65	84	7 (8.3)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.033	
ECOG Performance Status									
0	677	44 (6.5)	Not reached [81.7; -]	340	3 (0.9)	Not reached [-; -]	7.66 [2.38; 24.69]	< 0.001	0.437
1	106	5 (4.7)	Not reached [-; -]	49	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.105	
Geographic Region									
Asia	136	6 (4.4)	81.7 [-; -]	79	1 (1.3)	Not reached [-; -]	2.94 [0.34; 25.13]	0.326	0.681
Europe/Israel/North America/Australia	606	42 (6.9)	Not reached [-; -]	285	2 (0.7)	Not reached [-; -]	10.59 [2.56; 43.75]	0.001	
Rest of World	41	1 (2.4)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.445	
Tumor Size									
T1/T2	580	33 (5.7)	Not reached [81.7; -]	289	3 (1.0)	Not reached [-; -]	5.94 [1.82; 19.38]	0.003	0.141
T3/T4	203	16 (7.9)	Not reached [-; -]	100	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.004	
Choice of Carboplatin									
Q3W	334	19 (5.7)	Not reached [-; -]	167	1 (0.6)	Not reached [-; -]	10.03 [1.34; 74.99]	0.025	0.862
Weekly	444	30 (6.8)	Not reached [81.7; -]	220	2 (0.9)	Not reached [-; -]	7.80 [1.86; 32.63]	0.005	

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

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

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

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

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

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

CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); Q3W: Every 3 Weeks; SOC: System Organ Class

Tabelle 4G-88: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a]	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**			**Placebo + Chemotherapy[c] / Placebo**			**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
SOC: General disorders and administration site conditions, PT[i]: Fatigue									
Age (Years)									
< 65	699	25 (3.6)	Not reached [-; -]	341	6 (1.8)	Not reached [-; -]	2.08 [0.85; 5.07]	0.108	0.126
≥ 65	84	5 (6.0)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.086	
ECOG Performance Status									
0	677	27 (4.0)	Not reached [-; -]	340	6 (1.8)	Not reached [-; -]	2.31 [0.95; 5.60]	0.063	0.294
1	106	3 (2.8)	Not reached [-; -]	49	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.230	
Geographic Region									
Asia	136	0 (0.0)	Not reached [-; -]	79	1 (1.3)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.188	0.093
Europe/Israel/North America/Australia	606	29 (4.8)	Not reached [-; -]	285	4 (1.4)	Not reached [-; -]	3.53 [1.24; 10.05]	0.018	
Rest of World	41	1 (2.4)	Not reached [-; -]	25	1 (4.0)	Not reached [-; -]	0.56 [0.03; 8.91]	0.679	
Nodal Status									
Negative	376	16 (4.3)	Not reached [-; -]	193	2 (1.0)	Not reached [-; -]	4.27 [0.98; 18.57]	0.053	0.315
Positive	407	14 (3.4)	Not reached [-; -]	196	4 (2.0)	Not reached [-; -]	1.70 [0.56; 5.18]	0.347	
Tumor Size									
T1/T2	580	23 (4.0)	Not reached [-; -]	289	5 (1.7)	Not reached [-; -]	2.36 [0.90; 6.20]	0.082	0.726
T3/T4	203	7 (3.4)	Not reached [-; -]	100	1 (1.0)	Not reached [-; -]	3.55 [0.44; 28.87]	0.236	
Choice of Carboplatin									
Q3W	334	9 (2.7)	Not reached [-; -]	167	2 (1.2)	Not reached [-; -]	2.30 [0.50; 10.66]	0.286	0.868
Weekly	444	21 (4.7)	Not reached [-; -]	220	4 (1.8)	Not reached [-; -]	2.65 [0.91; 7.73]	0.074	
SOC: Investigations, PT[i]: Alanine aminotransferase increased									
Age (Years)									
< 65	699	45 (6.4)	Not reached [-; -]	341	10 (2.9)	Not reached [-; -]	2.27 [1.14; 4.50]	0.019	0.780
≥ 65	84	5 (6.0)	Not reached [-; -]	48	1 (2.1)	Not reached [-; -]	3.20 [0.37; 27.53]	0.290	
ECOG Performance Status									
0	677	44 (6.5)	Not reached [-; -]	340	9 (2.6)	Not reached [-; -]	2.55 [1.24; 5.22]	0.011	0.549
1	106	6	Not reached	49	2	Not reached	1.42	0.668	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
		(5.7)	[-; -]		(4.1)	[-; -]	[0.29; 7.03]		
Geographic Region									
Asia	136	10 (7.4)	Not reached [-; -]	79	3 (3.8)	Not reached [-; -]	1.97 [0.54; 7.14]	0.305	0.816
Europe/Israel/North America/Australia	606	38 (6.3)	Not reached [-; -]	285	7 (2.5)	Not reached [-; -]	2.66 [1.19; 5.95]	0.018	
Rest of World	41	2 (4.9)	Not reached [-; -]	25	1 (4.0)	Not reached [-; -]	1.25 [0.11; 13.83]	0.853	
Nodal Status									
Negative	376	22 (5.9)	Not reached [-; -]	193	3 (1.6)	Not reached [-; -]	3.93 [1.18; 13.14]	0.026	0.250
Positive	407	28 (6.9)	Not reached [-; -]	196	8 (4.1)	Not reached [-; -]	1.74 [0.79; 3.82]	0.168	
Tumor Size									
T1/T2	580	42 (7.2)	Not reached [-; -]	289	10 (3.5)	Not reached [-; -]	2.19 [1.10; 4.36]	0.026	0.566
T3/T4	203	8 (3.9)	Not reached [-; -]	100	1 (1.0)	Not reached [-; -]	4.01 [0.50; 32.02]	0.191	
Choice of Carboplatin									
Q3W	334	18 (5.4)	Not reached [-; -]	167	5 (3.0)	Not reached [-; -]	1.83 [0.68; 4.94]	0.231	0.544
Weekly	444	32 (7.2)	Not reached [-; -]	220	6 (2.7)	Not reached [-; -]	2.77 [1.16; 6.62]	0.022	
SOC: Investigations, PT[i]: Aspartate aminotransferase increased									
Age (Years)									
< 65	699	22 (3.1)	Not reached [-; -]	341	2 (0.6)	Not reached [-; -]	5.58 [1.31; 23.75]	0.020	0.438
≥ 65	84	3 (3.6)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.186	
ECOG Performance Status									
0	677	21 (3.1)	Not reached [-; -]	340	2 (0.6)	Not reached [-; -]	5.50 [1.29; 23.45]	0.021	0.421
1	106	4 (3.8)	Not reached [-; -]	49	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.167	
Geographic Region									
Asia	136	5 (3.7)	Not reached [-; -]	79	2 (2.5)	Not reached [-; -]	1.44 [0.28; 7.45]	0.661	0.067
Europe/Israel/North America/Australia	606	20 (3.3)	Not reached [-; -]	285	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	
Rest of World	41	0 (0.0)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
Nodal Status									
Negative	376	11 (2.9)	Not reached [-; -]	193	2 (1.0)	Not reached [-; -]	2.99 [0.66; 13.50]	0.154	0.085
Positive	407	14 (3.4)	Not reached [-; -]	196	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.009	
Tumor Size									
T1/T2	580	20	Not reached	289	2	Not reached	5.25	0.025	0.362

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**N[d]**	**Participants with Event n (%)**	**Median Time[e] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][f]**	**p-Value[f,g]**	**p-Value for Interaction Test[h]**
		(3.4)	[-; -]		(0.7)	[-; -]	[1.23; 22.46]		
T3/T4	203	5 (2.5)	Not reached [-; -]	100	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.113	
Choice of Carboplatin									
Q3W	334	6 (1.8)	Not reached [-; -]	167	1 (0.6)	Not reached [-; -]	3.11 [0.37; 25.84]	0.294	0.441
Weekly	444	19 (4.3)	Not reached [-; -]	220	1 (0.5)	Not reached [-; -]	9.83 [1.32; 73.43]	0.026	
SOC: Investigations, PT[i]: Neutrophil count decreased									
Age (Years)									
< 65	699	134 (19.2)	Not reached [-; -]	341	80 (23.5)	Not reached [-; -]	0.78 [0.59; 1.03]	0.074	0.745
≥ 65	84	15 (17.9)	Not reached [-; -]	48	12 (25.0)	Not reached [-; -]	0.68 [0.32; 1.46]	0.326	
ECOG Performance Status									
0	677	138 (20.4)	Not reached [-; -]	340	81 (23.8)	Not reached [-; -]	0.81 [0.62; 1.07]	0.143	0.168
1	106	11 (10.4)	Not reached [-; -]	49	11 (22.4)	Not reached [-; -]	0.44 [0.19; 1.02]	0.054	
Geographic Region									
Asia	136	62 (45.6)	Not reached [19.9; -]	79	34 (43.0)	Not reached [15.1; -]	0.98 [0.64; 1.48]	0.911	0.429
Europe/Israel/North America/Australia	606	81 (13.4)	Not reached [-; -]	285	52 (18.2)	Not reached [-; -]	0.71 [0.50; 1.00]	0.052	
Rest of World	41	6 (14.6)	Not reached [-; -]	25	6 (24.0)	Not reached [-; -]	0.56 [0.18; 1.75]	0.319	
Nodal Status									
Negative	376	72 (19.1)	Not reached [-; -]	193	44 (22.8)	Not reached [-; -]	0.80 [0.55; 1.17]	0.246	0.726
Positive	407	77 (18.9)	Not reached [-; -]	196	48 (24.5)	Not reached [-; -]	0.73 [0.51; 1.05]	0.090	
Tumor Size									
T1/T2	580	114 (19.7)	Not reached [-; -]	289	69 (23.9)	Not reached [-; -]	0.80 [0.59; 1.07]	0.137	0.591
T3/T4	203	35 (17.2)	Not reached [-; -]	100	23 (23.0)	Not reached [-; -]	0.68 [0.40; 1.15]	0.146	
Choice of Carboplatin									
Q3W	334	51 (15.3)	Not reached [-; -]	167	31 (18.6)	Not reached [-; -]	0.79 [0.50; 1.23]	0.294	0.864
Weekly	444	98 (22.1)	Not reached [-; -]	220	61 (27.7)	Not reached [-; -]	0.74 [0.54; 1.02]	0.070	
SOC: Skin and subcutaneous tissue disorders, PT[i]: Rash maculo-papular									
Age (Years)									
< 65	699	14 (2.0)	Not reached [-; -]	341	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.008	0.997
≥ 65	84	1 (1.2)	Not reached [-; -]	48	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.450	

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		
Severe Adverse Events (CTCAE-Grade 3-5)	Participants with Event N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Participants with Event N[d]	Participants with Event n (%)	Median Time[e] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][f]	p-Value[f,g]	p-Value for Interaction Test[h]
ECOG Performance Status									
0	677	15 (2.2)	Not reached [-; -]	340	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.006	0.996
1	106	0 (0.0)	Not reached [-; -]	49	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
Geographic Region									
Asia	136	1 (0.7)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.446	> 0.999
Europe/Israel/North America/Australia	606	14 (2.3)	Not reached [-; -]	285	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.009	
Rest of World	41	0 (0.0)	Not reached [-; -]	25	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
Nodal Status									
Negative	376	6 (1.6)	n.c.	193	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Positive	407	9 (2.2)	n.c.	196	0 (0.0)	n.c.	n.c.	n.c.	
Tumor Size									
T1/T2	580	11 (1.9)	Not reached [-; -]	289	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.018	0.997
T3/T4	203	4 (2.0)	Not reached [-; -]	100	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.159	
Choice of Carboplatin									
Q3W	334	7 (2.1)	n.c.	167	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Weekly	444	8 (1.8)	n.c.	220	0 (0.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 23MAR2021

b: Pembrolizumab + paclitaxel + carboplatin x 4 cycles, followed by pembrolizumab + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

c: Placebo + paclitaxel + carboplatin x 4 cycles, followed by placebo + [doxorubicin or epirubicin] + cyclophosphamide x 4 cycles

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

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

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

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

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

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

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; PT: Preferred Term; Q3W: Every 3 Weeks; SOC: System Organ Class

Anhang 4-G4: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT

Tabelle 4G-89: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) Version 19.0 basierend auf MedDRA Version 23.1 anhand der zugeordneten PT in der Studie KEYNOTE 522

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Pneumonitis	Acute interstitial pneumonitis, Autoimmune lung disease, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organising pneumonia, Immune-mediated pneumonitis	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	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic 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

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Type 1 Diabetes Mellitus	Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus, Euglycaemic diabetic ketoacidosis, Diabetic ketosis, Ketosis-prone diabetes mellitus	Yes
Severe Skin Reactions Including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): or	Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Pemphigoid, Pemphigus, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, SJS-TEN overlap	Yes
Severe Skin (continued): If Grade 3 or higher:	Rash, Rash erythematous, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus genital, Lichen planus, Oral lichen planus, Cutaneous vasculitis, Vasculitic rash	Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis, Vogt-Koyanagi-Harada disease, Chorioretinitis, Choroiditis, Immune-mediated uveitis	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,	No

AEOSI	Preferred Terms	Immune-mediated (yes/no)
	Infusion related reaction, Infusion related hypersensitivity reaction	
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