Dokumentvorlage, Version vom 21.02.2019

Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD Sharp & Dohme GmbH

Modul 4 A

Anhang 4G: weitere Ergebnisse

Neoadjuvante und adjuvante Behandlung des lokal fortgeschrittenen oder frühen triple-negativen Mammakarzinoms mit hohem Rezidivrisiko

Medizinischer Nutzen und
medizinischer Zusatznutzen,
Patientengruppen mit therapeutisch
bedeutsamem Zusatznutzen

Stand: 30.09.2024

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Anhang 4-G1: Folgetherapien nach Therapielinie

Im Folgenden werden die Folgetherapien nach Therapielinie dargestellt.

Alle Ergebnisse beziehen sich auf den siebten Datenschnitt (22.März 2024).

Tabelle 4-G1: Folgetherapien nach Therapielinie

Study: KEYNOTE 522[a]	**Participants with Event n (%)**	
Line of Therapy[d] **Therapy Term[e]**	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab (N[f]=784)**	**Placebo + Chemotherapy[c] / Placebo (N[f]=390)**
Participants with one or more subsequent oncologic therapy	144 (18.37)	98 (25.13)
1 - NEO-ADJUVANT	9 (1.15)	5 (1.28)
paclitaxel albumin	3 (0.38)	1 (0.26)
docetaxel	3 (0.38)	0 (0.00)
capecitabine	0 (0.00)	1 (0.26)
cisplatin	0 (0.00)	1 (0.26)
cisplatin+fluorouracil+gemcitabine	0 (0.00)	1 (0.26)
cyclophosphamide+docetaxel+epirubicin	0 (0.00)	1 (0.26)
fluorouracil	1 (0.13)	0 (0.00)
fluorouracil/gemcitabine	1 (0.13)	0 (0.00)
tamoxifen	1 (0.13)	0 (0.00)
2 - ADJUVANT	49 (6.25)	28 (7.18)
capecitabine	29 (3.70)	17 (4.36)
cyclophosphamide+doxorubicin	1 (0.13)	3 (0.77)
olaparib	1 (0.13)	2 (0.51)
letrozole	2 (0.26)	1 (0.26)
anastrozole+letrozole+tamoxifen	0 (0.00)	1 (0.26)
capecitabine/cancer multi-epitope folate receptor alpha peptide vaccine (unspecified)	0 (0.00)	1 (0.26)
capecitabine/paclitaxel albumin	0 (0.00)	1 (0.26)
cyclophosphamide	0 (0.00)	1 (0.26)
cyclophosphamide+doxorubicin hydrochloride	2 (0.26)	0 (0.00)
paclitaxel+pertuzumab+trastuzumab	0 (0.00)	1 (0.26)
anastrozole/letrozole/exemestane	1 (0.13)	0 (0.00)
cancer multi-epitope folate receptor alpha peptide vaccine (unspecified)+cyclophosphamide	1 (0.13)	0 (0.00)
carboplatin+paclitaxel	1 (0.13)	0 (0.00)
carboplatin+paclitaxel+pembrolizumab	1 (0.13)	0 (0.00)
cyclophosphamide+doxorubicin+fluorouracil	1 (0.13)	0 (0.00)
cyclophosphamide+fluorouracil+methotrexate	1 (0.13)	0 (0.00)
exemestane+tamoxifen	1 (0.13)	0 (0.00)
gimeracil (+) oteracil potassium (+) tegafur+oxaliplatin	1 (0.13)	0 (0.00)
olaparib/capecitabine/agatolimod (+) monophosphoryl lipid A (+) saponin adjuvant (unspecified)	1 (0.13)	0 (0.00)
paclitaxel albumin/capecitabine	1 (0.13)	0 (0.00)
tamoxifen	1 (0.13)	0 (0.00)
tamoxifen citrate	1 (0.13)	0 (0.00)
trastuzumab	1 (0.13)	0 (0.00)
trastuzumab+vinorelbine tartrate	1 (0.13)	0 (0.00)
3 - FIRST LINE	87 (11.10)	61 (15.64)
capecitabine	20 (2.55)	12 (3.08)
eribulin mesylate	7 (0.89)	4 (1.03)
capecitabine+vinorelbine tartrate	3 (0.38)	3 (0.77)
olaparib	1 (0.13)	3 (0.77)
atezolizumab+ipatasertib+paclitaxel	0 (0.00)	3 (0.77)
atezolizumab+paclitaxel albumin	0 (0.00)	3 (0.77)
cisplatin	2 (0.26)	2 (0.51)
cyclophosphamide+docetaxel	2 (0.26)	1 (0.26)

Study: KEYNOTE 522[a]	**Participants with Event n (%)**	
Line of Therapy[d] **Therapy Term[e]**	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab (N[f]=784)**	**Placebo + Chemotherapy[c] / Placebo (N[f]=390)**
docetaxel	2 (0.26)	1 (0.26)
carboplatin+paclitaxel	0 (0.00)	2 (0.51)
atezolizumab+paclitaxel	1 (0.13)	1 (0.26)
gemcitabine	1 (0.13)	1 (0.26)
methotrexate	1 (0.13)	1 (0.26)
bevacizumab+paclitaxel	3 (0.38)	0 (0.00)
carboplatin+gemcitabine	3 (0.38)	0 (0.00)
amcenestrant+investigational drug (unspecified)+palbociclib	0 (0.00)	1 (0.26)
anetumab ravtansine	0 (0.00)	1 (0.26)
anti-HER2 antibody drug conjugate (DXd conjugate)+durvalumab	0 (0.00)	1 (0.26)
antineoplastic (unspecified)	0 (0.00)	1 (0.26)
antineoplastic (unspecified)+paclitaxel	0 (0.00)	1 (0.26)
bevacizumab+paclitaxel/atezolizumab+paclitaxel albumin	0 (0.00)	1 (0.26)
capecitabine+investigational drug (unspecified)	0 (0.00)	1 (0.26)
carboplatin+etoposide	0 (0.00)	1 (0.26)
carboplatin+gemcitabine+paclitaxel albumin	0 (0.00)	1 (0.26)
carboplatin+gemcitabine+pembrolizumab	0 (0.00)	1 (0.26)
carboplatin/cisplatin	0 (0.00)	1 (0.26)
cisplatin+docetaxel	0 (0.00)	1 (0.26)
cisplatin/carboplatin	0 (0.00)	1 (0.26)
cyclophosphamide+docetaxel/paclitaxel	0 (0.00)	1 (0.26)
cyclophosphamide+doxorubicin/cyclophosphamide	0 (0.00)	1 (0.26)
cyclophosphamide+epirubicin	2 (0.26)	0 (0.00)
cyclophosphamide+epirubicin+fluorouracil	0 (0.00)	1 (0.26)
cytarabine+gilteritinib	0 (0.00)	1 (0.26)
docetaxel+fluorouracil+leucovorin calcium+oxaliplatin	0 (0.00)	1 (0.26)
eribulin	2 (0.26)	0 (0.00)
fluorouracil+vinorelbine tartrate	0 (0.00)	1 (0.26)
gimeracil (+) oteracil potassium (+) tegafur	0 (0.00)	1 (0.26)
gimeracil (+) oteracil potassium (+) tegafur/denosumab	0 (0.00)	1 (0.26)
letrozole	2 (0.26)	0 (0.00)
methotrexate/capecitabine	0 (0.00)	1 (0.26)
paclitaxel	2 (0.26)	0 (0.00)
paclitaxel albumin	2 (0.26)	0 (0.00)
paclitaxel+pembrolizumab	2 (0.26)	0 (0.00)
pembrolizumab	0 (0.00)	1 (0.26)
sacituzumab govitecan	0 (0.00)	1 (0.26)
afatinib	1 (0.13)	0 (0.00)
anastrozole	1 (0.13)	0 (0.00)
atezolizumab+carboplatin+gemcitabine	1 (0.13)	0 (0.00)
bevacizumab+capecitabine+carboplatin+paclitaxel	1 (0.13)	0 (0.00)
bevacizumab+carboplatin+paclitaxel	1 (0.13)	0 (0.00)
bevacizumab+cyclophosphamide+paclitaxel	1 (0.13)	0 (0.00)
bevacizumab+paclitaxel/eribulin mesylate	1 (0.13)	0 (0.00)
capecitabine+carboplatin+paclitaxel	1 (0.13)	0 (0.00)
capecitabine+cyclophosphamide+doxorubicin	1 (0.13)	0 (0.00)
capecitabine+cyclophosphamide+methotrexate	1 (0.13)	0 (0.00)
capecitabine+paclitaxel	1 (0.13)	0 (0.00)
capecitabine+vinorelbine tartrate/cyclophosphamide/capecitabine+vinorelbine tartrate	1 (0.13)	0 (0.00)
carbamazepine+pemetrexed disodium	1 (0.13)	0 (0.00)
carboplatin+gemcitabine+pembrolizumab/sacituzumab	1 (0.13)	0 (0.00)
cisplatin+gemcitabine	1 (0.13)	0 (0.00)
cyclophosphamide+docetaxel+doxorubicin	1 (0.13)	0 (0.00)
cyclophosphamide+docetaxel+epirubicin/paclitaxel	1 (0.13)	0 (0.00)
cyclophosphamide+doxorubicin	1 (0.13)	0 (0.00)
cyclophosphamide+epirubicin+paclitaxel	1 (0.13)	0 (0.00)

Study: KEYNOTE 522[a]	Participants with Event n (%)	
Line of Therapy[d] **Therapy Term[e]**	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab (N[f]=784)**	**Placebo + Chemotherapy[c] / Placebo (N[f]=390)**
cyclophosphamide+epirubicin/capecitabine	1 (0.13)	0 (0.00)
cyclophosphamide+fluorouracil+methotrexate	1 (0.13)	0 (0.00)
exemestane	1 (0.13)	0 (0.00)
fluorouracil	1 (0.13)	0 (0.00)
gemcitabine+paclitaxel albumin	1 (0.13)	0 (0.00)
investigational drug (unspecified)+paclitaxel	1 (0.13)	0 (0.00)
ladiratuzumab vedotin/carboplatin+gemcitabine	1 (0.13)	0 (0.00)
letrozole+palbociclib	1 (0.13)	0 (0.00)
prexasertib	1 (0.13)	0 (0.00)
vinorelbine tartrate	1 (0.13)	0 (0.00)
4 - SECOND LINE	48 (6.12)	48 (12.31)
capecitabine	7 (0.89)	8 (2.05)
eribulin mesylate	6 (0.77)	5 (1.28)
olaparib	2 (0.26)	2 (0.51)
cyclophosphamide+docetaxel	3 (0.38)	1 (0.26)
bevacizumab+paclitaxel	2 (0.26)	1 (0.26)
atezolizumab+paclitaxel albumin	0 (0.00)	2 (0.51)
carboplatin	0 (0.00)	2 (0.51)
cisplatin+gemcitabine	0 (0.00)	2 (0.51)
gemcitabine+paclitaxel	0 (0.00)	2 (0.51)
atezolizumab+paclitaxel	1 (0.13)	1 (0.26)
cyclophosphamide+fluorouracil+methotrexate	1 (0.13)	1 (0.26)
doxorubicin	1 (0.13)	1 (0.26)
gemcitabine	1 (0.13)	1 (0.26)
atezolizumab+bevacizumab+selicrelumab	0 (0.00)	1 (0.26)
bevacizumab+cisplatin+gemcitabine	0 (0.00)	1 (0.26)
capecitabine+cyclophosphamide	0 (0.00)	1 (0.26)
capecitabine+docetaxel+granisetron+ondansetron+palonosetron hydrochloride+tropisetron	0 (0.00)	1 (0.26)
capecitabine+gemcitabine	0 (0.00)	1 (0.26)
capecitabine/vinorelbine tartrate/gemcitabine	0 (0.00)	1 (0.26)
carboplatin+cyclophosphamide+vinorelbine tartrate/carboplatin+cyclophosphamide+methotrexate	0 (0.00)	1 (0.26)
carboplatin+docetaxel+gimeracil (+) oteracil potassium (+) tegafur/carboplatin+eribulin mesylate+gimeracil (+) oteracil potassium (+) tegafur	0 (0.00)	1 (0.26)
carboplatin+gemcitabine	2 (0.26)	0 (0.00)
carboplatin+gemcitabine+trilaciclib	0 (0.00)	1 (0.26)
carboplatin+gemcitabine/capecitabine+docetaxel/bevacizumab+paclitaxel	0 (0.00)	1 (0.26)
denosumab+docetaxel	0 (0.00)	1 (0.26)
docetaxel+gemcitabine	0 (0.00)	1 (0.26)
docetaxel+oxaliplatin	0 (0.00)	1 (0.26)
eribulin mesylate+pembrolizumab	0 (0.00)	1 (0.26)
eribulin mesylate/picibanil	0 (0.00)	1 (0.26)
fluorouracil	0 (0.00)	1 (0.26)
letrozole+palbociclib	0 (0.00)	1 (0.26)
paclitaxel albumin	0 (0.00)	1 (0.26)
paclitaxel+pertuzumab+trastuzumab	0 (0.00)	1 (0.26)
tamoxifen	2 (0.26)	0 (0.00)
alpelisib+fulvestrant	1 (0.13)	0 (0.00)
anetumab ravtansine	1 (0.13)	0 (0.00)
avelumab+eribulin mesylate	1 (0.13)	0 (0.00)
bevacizumab+carboplatin+gemcitabine	1 (0.13)	0 (0.00)
bevacizumab+paclitaxel albumin	1 (0.13)	0 (0.00)
capecitabine+docetaxel	1 (0.13)	0 (0.00)
capecitabine+vinorelbine tartrate/sacituzumab govitecan	1 (0.13)	0 (0.00)
cisplatin/cyclophosphamide+fluorouracil+methotrexate	1 (0.13)	0 (0.00)
cyclophosphamide	1 (0.13)	0 (0.00)

Study: KEYNOTE 522[a]	Participants with Event n (%)	
Line of Therapy[d] **Therapy Term[e]**	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab (N[f]=784)**	**Placebo + Chemotherapy[c] / Placebo (N[f]=390)**
cyclophosphamide+epirubicin	1 (0.13)	0 (0.00)
enfortumab vedotin+pembrolizumab	1 (0.13)	0 (0.00)
eribulin	1 (0.13)	0 (0.00)
everolimus	1 (0.13)	0 (0.00)
gimeracil (+) oteracil potassium (+) tegafur	1 (0.13)	0 (0.00)
ixabepilone	1 (0.13)	0 (0.00)
sacituzumab govitecan	1 (0.13)	0 (0.00)
sacituzumab govitecan-hziy	1 (0.13)	0 (0.00)
tegafur (+) uracil/capecitabine	1 (0.13)	0 (0.00)
trastuzumab deruxtecan	1 (0.13)	0 (0.00)
vinorelbine tartrate	1 (0.13)	0 (0.00)
5 - THIRD LINE	22 (2.81)	25 (6.41)
eribulin mesylate	6 (0.77)	0 (0.00)
vinorelbine tartrate	2 (0.26)	2 (0.51)
sacituzumab govitecan	2 (0.26)	1 (0.26)
paclitaxel	0 (0.00)	2 (0.51)
bevacizumab+vinorelbine tartrate	1 (0.13)	1 (0.26)
carboplatin	1 (0.13)	1 (0.26)
anthracyclines (unspecified)	0 (0.00)	1 (0.26)
atezolizumab+gemcitabine	0 (0.00)	1 (0.26)
atezolizumab+paclitaxel	0 (0.00)	1 (0.26)
bevacizumab+capecitabine	0 (0.00)	1 (0.26)
bevacizumab+paclitaxel	0 (0.00)	1 (0.26)
bevacizumab+paclitaxel albumin	0 (0.00)	1 (0.26)
capecitabine+cyclophosphamide	0 (0.00)	1 (0.26)
capecitabine+lapatinib	0 (0.00)	1 (0.26)
capecitabine+vinorelbine tartrate	0 (0.00)	1 (0.26)
carboplatin (+) gemcitabine	0 (0.00)	1 (0.26)
carboplatin+gemcitabine	0 (0.00)	1 (0.26)
cisplatin+fosaprepitant dimeglumine+gemcitabine hydrochloride+granisetron+ondansetron+palonosetron hydrochloride+tropisetron	0 (0.00)	1 (0.26)
cisplatin+gemcitabine	0 (0.00)	1 (0.26)
cisplatin/carboplatin	0 (0.00)	1 (0.26)
cyclophosphamide+epirubicin	0 (0.00)	1 (0.26)
olaparib	0 (0.00)	1 (0.26)
paclitaxel+pembrolizumab	0 (0.00)	1 (0.26)
pembrolizumab	0 (0.00)	1 (0.26)
anti-4-1BB/anti-PD-L1 bispecific monoclonal antibody	1 (0.13)	0 (0.00)
bevacizumab+docetaxel	1 (0.13)	0 (0.00)
capecitabine	1 (0.13)	0 (0.00)
cyclophosphamide+fluorouracil+methotrexate	1 (0.13)	0 (0.00)
doxorubicin	1 (0.13)	0 (0.00)
eribulin	1 (0.13)	0 (0.00)
eribulin mesylate+methotrexate+prednisolone acetate	1 (0.13)	0 (0.00)
gemcitabine	1 (0.13)	0 (0.00)
trastuzumab deruxtecan	1 (0.13)	0 (0.00)
vinorelbine tartrate/cyclophosphamide+doxorubicin hydrochloride	1 (0.13)	0 (0.00)
6 - FOURTH LINE	11 (1.40)	13 (3.33)
capecitabine	3 (0.38)	1 (0.26)
eribulin mesylate	0 (0.00)	2 (0.51)
gemcitabine	0 (0.00)	2 (0.51)
paclitaxel	0 (0.00)	2 (0.51)
bevacizumab+paclitaxel	0 (0.00)	1 (0.26)
capecitabine+docetaxel	0 (0.00)	1 (0.26)
cisplatin	0 (0.00)	1 (0.26)
cisplatin+gemcitabine	2 (0.26)	0 (0.00)
doxorubicin	2 (0.26)	0 (0.00)

Study: KEYNOTE 522[a]	Participants with Event n (%)	
Line of Therapy[d] **Therapy Term[e]**	**Pembrolizumab + Chemotherapy[b] / Pembrolizumab (N[f]=784)**	**Placebo + Chemotherapy[c] / Placebo (N[f]=390)**
doxorubicin hydrochloride	2 (0.26)	0 (0.00)
olaparib+trastuzumab	0 (0.00)	1 (0.26)
sacituzumab	0 (0.00)	1 (0.26)
sacituzumab govitecan	0 (0.00)	1 (0.26)
cyclophosphamide	1 (0.13)	0 (0.00)
cyclophosphamide+doxorubicin	1 (0.13)	0 (0.00)
7 - FIFTH LINE OR GREATER	7 (0.89)	9 (2.31)
atezolizumab+paclitaxel albumin	0 (0.00)	1 (0.26)
bevacizumab+gemcitabine/bevacizumab+paclitaxel	0 (0.00)	1 (0.26)
cisplatin+etoposide	0 (0.00)	1 (0.26)
cyclophosphamide+fluorouracil+methotrexate	0 (0.00)	1 (0.26)
docetaxel	0 (0.00)	1 (0.26)
eribulin mesylate	0 (0.00)	1 (0.26)
eribulin mesylate/capecitabine	0 (0.00)	1 (0.26)
etoposide	2 (0.26)	0 (0.00)
sacituzumab/capecitabine+vinorelbine tartrate/eribulin mesylate	0 (0.00)	1 (0.26)
trastuzumab deruxtecan	0 (0.00)	1 (0.26)
NLRP3 agonist (unspecified)+ipilimumab+nivolumab/trastuzumab deruxtecan	1 (0.13)	0 (0.00)
bevacizumab+carboplatin+paclitaxel/capecitabine	1 (0.13)	0 (0.00)
cisplatin	1 (0.13)	0 (0.00)
doxorubicin	1 (0.13)	0 (0.00)
vinorelbine tartrate	1 (0.13)	0 (0.00)
8 - NOT APPLICABLE	6 (0.77)	3 (0.77)
anastrozole	0 (0.00)	1 (0.26)
cisplatin+paclitaxel/olaparib	0 (0.00)	1 (0.26)
doxorubicin	0 (0.00)	1 (0.26)
busulfan+cyclophosphamide+cytarabine+fludarabine phosphate+idarubicin hydrochloride+thiotepa	1 (0.13)	0 (0.00)
cytarabine+etoposide+idarubicin hydrochloride	1 (0.13)	0 (0.00)
cytarabine+idarubicin hydrochloride/cytarabine+idarubicin hydrochloride/cytarabine/busulfan+fludarabine phosphate+methotrexate/methotrexate/cladribine+cytarabine+mitoxantrone hydrochloride/cladribine+cytarabine/busulfan+fludarabine phosphate+methotrexate/methotrexate	1 (0.13)	0 (0.00)
docetaxel/capecitabine/cisplatin+gemcitabine	1 (0.13)	0 (0.00)
fludarabine phosphate+treosulfan/azacitidine/cytarabine+fludarabine phosphate+idarubicin hydrochloride+venetoclax/bisantrene hydrochloride+clofarabine+fludarabine phosphate	1 (0.13)	0 (0.00)
olaparib	1 (0.13)	0 (0.00)

a: Database Cutoff Date: 22MAR2024

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: Every participant is counted a single time for each applicable specific therapy. A participant with multiple medications within a specific line of therapy is counted a single time for that combination (therapies combined with '+' sign when started on the same day and with '/' sign when started on different day)

e: In neoadjuvant (reason in the form of Oncology drugs and Biologics - Follow-up (ODBF) is neoadjuvant), for both treatment groups the following are considered study treatments although collected in ODBF: 'carboplatin', 'cyclophosphamide', 'doxorubicin', 'doxorubicin hydrochloride', 'epirubicin' or 'paclitaxel'; so they won't be included in the table. A line of therapy or specific therapy appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding

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

Anhang 4-G2: 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 siebten Datenschnitt (22.März 2024).

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

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

Study: KEYNOTE 522[a]		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**	**Placebo + Chemotherapy[c] / Placebo**
Visit	**EORTC QLQ-C30**	**N[d] = 772 n (%)**	**N[d] = 386 n (%)**
Neoadjuvant Baseline	Expected to Complete Questionnaires[e]	772 (100.0)	384 (99.5)
	Completed	701 (90.8)	367 (95.1)
	Compliance (% in those expected to complete questionnaires)[f]	701 (90.8)	367 (95.6)
	Not completed	71 (9.2)	17 (4.4)
	Subject was physically unable to complete	1 (0.1)	0 (0.0)
	Subject refused for other reasons	3 (0.4)	0 (0.0)
	Not completed due to site staff error	20 (2.6)	7 (1.8)
	Other	21 (2.7)	7 (1.8)
	With visit, no record	26 (3.4)	3 (0.8)
	Missing by Design	0 (0.0)	2 (0.5)
	Translation not available in subjects language	0 (0.0)	2 (0.5)
Neoadjuvant Week 12	Expected to Complete Questionnaires[e]	721 (93.4)	365 (94.6)
	Completed	649 (84.1)	330 (85.5)
	Compliance (% in those expected to complete questionnaires)[f]	649 (90.0)	330 (90.4)
	Not completed	72 (9.3)	35 (9.1)
	Subject did not complete due to side effect of treatment	3 (0.4)	0 (0.0)
	Subject did not complete due to disease under study	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	2 (0.3)	1 (0.3)
	Subject lost to follow-up/unable to contact	1 (0.1)	0 (0.0)
	Subject refused for other reasons	3 (0.4)	5 (1.3)
	Not completed due to site staff error	23 (3.0)	12 (3.1)
	Other	24 (3.1)	8 (2.1)
	With visit, no record	15 (1.9)	9 (2.3)
	Missing by Design	51 (6.6)	21 (5.4)
	Subject died	1 (0.1)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	2 (0.5)
	No visit scheduled	50 (6.5)	19 (4.9)
Neoadjuvant Week 21	Expected to Complete Questionnaires[e]	697 (90.3)	351 (90.9)
	Completed	614 (79.5)	309 (80.1)
	Compliance (% in those expected to complete questionnaires)[f]	614 (88.1)	309 (88.0)
	Not completed	83 (10.8)	42 (10.9)
	Subject did not complete due to side effect of treatment	2 (0.3)	1 (0.3)
	Subject did not complete due to disease under study	1 (0.1)	0 (0.0)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.3)
	Subject refused for other reasons	10 (1.3)	3 (0.8)
	Not completed due to site staff error	28 (3.6)	19 (4.9)
	Other	31 (4.0)	11 (2.8)
	With visit, no record	10 (1.3)	6 (1.6)

Study: KEYNOTE 522[a]		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**	**Placebo + Chemotherapy[c] / Placebo**
Visit	**EORTC QLQ-C30**	**N[d] = 772 n (%)**	**N[d] = 386 n (%)**
	Missing by Design	75 (9.7)	35 (9.1)
	Subject died	3 (0.4)	0 (0.0)
	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)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	No visit scheduled	61 (7.9)	29 (7.5)
Adjuvant Baseline	Expected to Complete Questionnaires[e]	546 (70.7)	311 (80.6)
	Completed	490 (63.5)	283 (73.3)
	Compliance (% in those expected to complete questionnaires)[f]	490 (89.7)	283 (91.0)
	Not completed	56 (7.3)	28 (7.3)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	Subject refused for other reasons	3 (0.4)	2 (0.5)
	Not completed due to site staff error	25 (3.2)	10 (2.6)
	Other	12 (1.6)	7 (1.8)
	With visit, no record	16 (2.1)	8 (2.1)
	Missing by Design	226 (29.3)	75 (19.4)
	Subject died	3 (0.4)	0 (0.0)
	Discontinued due to adverse event	47 (6.1)	14 (3.6)
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)
	Discontinued due to physician decision	21 (2.7)	7 (1.8)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	7 (0.9)	5 (1.3)
	Discontinued due to withdrawal by subject	20 (2.6)	7 (1.8)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	No visit scheduled	120 (15.5)	32 (8.3)
Adjuvant Week 12	Expected to Complete Questionnaires[e]	534 (69.2)	305 (79.0)
	Completed	475 (61.5)	263 (68.1)
	Compliance (% in those expected to complete questionnaires)[f]	475 (89.0)	263 (86.2)
	Not completed	59 (7.6)	42 (10.9)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.3)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	Subject refused for other reasons	5 (0.6)	1 (0.3)
	Not completed due to site staff error	26 (3.4)	16 (4.1)
	Other	8 (1.0)	9 (2.3)
	With visit, no record	19 (2.5)	14 (3.6)
	Missing by Design	238 (30.8)	81 (21.0)
	Subject died	3 (0.4)	0 (0.0)
	Discontinued due to adverse event	47 (6.1)	14 (3.6)
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)
	Discontinued due to physician decision	21 (2.7)	7 (1.8)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	7 (0.9)	5 (1.3)
	Discontinued due to withdrawal by subject	20 (2.6)	7 (1.8)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	No visit scheduled	132 (17.1)	38 (9.8)
Adjuvant Week 24	Expected to Complete Questionnaires[e]	490 (63.5)	285 (73.8)
	Completed	435 (56.3)	245 (63.5)

Study: KEYNOTE 522[a]		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**	**Placebo + Chemotherapy[c] / Placebo**
Visit	**EORTC QLQ-C30**	**N[d] = 772 n (%)**	**N[d] = 386 n (%)**
	Compliance (% in those expected to complete questionnaires)[f]	435 (88.8)	245 (86.0)
	Not completed	55 (7.1)	40 (10.4)
	Subject refused for other reasons	2 (0.3)	5 (1.3)
	Not completed due to site staff error	17 (2.2)	12 (3.1)
	Other	14 (1.8)	8 (2.1)
	With visit, no record	22 (2.8)	15 (3.9)
	Missing by Design	282 (36.5)	101 (26.2)
	Subject died	3 (0.4)	0 (0.0)
	Discontinued due to adverse event	66 (8.5)	16 (4.1)
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)
	Discontinued due to physician decision	28 (3.6)	8 (2.1)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	16 (2.1)	12 (3.1)
	Discontinued due to withdrawal by subject	29 (3.8)	15 (3.9)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	No visit scheduled	132 (17.1)	40 (10.4)
LTFU Year 1	Expected to Complete Questionnaires[e]	629 (81.5)	323 (83.7)
	Completed	522 (67.6)	264 (68.4)
	Compliance (% in those expected to complete questionnaires)[f]	522 (83.0)	264 (81.7)
	Not completed	107 (13.9)	59 (15.3)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.5)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	1 (0.1)	0 (0.0)
	Subject lost to follow-up/unable to contact	2 (0.3)	3 (0.8)
	Subject refused for other reasons	10 (1.3)	10 (2.6)
	Not completed due to site staff error	24 (3.1)	12 (3.1)
	Other	68 (8.8)	31 (8.0)
	With visit, no record	1 (0.1)	1 (0.3)
	Missing by Design	143 (18.5)	63 (16.3)
	Subject died	5 (0.6)	2 (0.5)
	Discontinued due to adverse event	50 (6.5)	14 (3.6)
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)
	Discontinued due to physician decision	23 (3.0)	7 (1.8)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	13 (1.7)	9 (2.3)
	Discontinued due to withdrawal by subject	23 (3.0)	8 (2.1)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	No visit scheduled	21 (2.7)	13 (3.4)
LTFU Year 2	Expected to Complete Questionnaires[e]	641 (83.0)	327 (84.7)
	Completed	273 (35.4)	128 (33.2)
	Compliance (% in those expected to complete questionnaires)[f]	273 (42.6)	128 (39.1)
	Not completed	368 (47.7)	199 (51.6)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.5)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	1 (0.1)	0 (0.0)
	Subject lost to follow-up/unable to contact	2 (0.3)	4 (1.0)
	Subject refused for other reasons	12 (1.6)	8 (2.1)
	Not completed due to site staff error	32 (4.1)	16 (4.1)
	Other	320 (41.5)	169 (43.8)
	Missing by Design	131 (17.0)	59 (15.3)
	Subject died	6 (0.8)	2 (0.5)
	Discontinued due to adverse event	48 (6.2)	14 (3.6)

Study: KEYNOTE 522[a]		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**	**Placebo + Chemotherapy[c] / Placebo**
Visit	**EORTC QLQ-C30**	**N[d] = 772 n (%)**	**N[d] = 386 n (%)**
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)
	Discontinued due to physician decision	23 (3.0)	7 (1.8)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	13 (1.7)	9 (2.3)
	Discontinued due to withdrawal by subject	22 (2.8)	8 (2.1)
	No visit scheduled	11 (1.4)	10 (2.6)

a: Database Cutoff Date: 22MAR2024

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: 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; LTFU: Long-Term Follow-up

Anhang 4-G2.2: Rücklaufquoten des EORTC QLQ-BR23

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

Study: KEYNOTE 522[a]		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**	**Placebo + Chemotherapy[c] / Placebo**
Visit	**EORTC QLQ-BR23**	**N[d] = 770 n (%)**	**N[d] = 386 n (%)**
Neoadjuvant Baseline	Expected to Complete Questionnaires[e]	770 (100.0)	384 (99.5)
	Completed	697 (90.5)	363 (94.0)
	Compliance (% in those expected to complete questionnaires)[f]	697 (90.5)	363 (94.5)
	Not completed	73 (9.5)	21 (5.4)
	Subject was physically unable to complete	1 (0.1)	0 (0.0)
	Subject refused for other reasons	3 (0.4)	0 (0.0)
	Not completed due to site staff error	22 (2.9)	10 (2.6)
	Other	21 (2.7)	8 (2.1)
	With visit, no record	26 (3.4)	3 (0.8)
	Missing by Design	0 (0.0)	2 (0.5)
	Translation not available in subjects language	0 (0.0)	2 (0.5)
Neoadjuvant Week 12	Expected to Complete Questionnaires[e]	720 (93.5)	365 (94.6)
	Completed	647 (84.0)	330 (85.5)
	Compliance (% in those expected to complete questionnaires)[f]	647 (89.9)	330 (90.4)
	Not completed	73 (9.5)	35 (9.1)
	Subject did not complete due to side effect of treatment	3 (0.4)	0 (0.0)
	Subject did not complete due to disease under study	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	2 (0.3)	1 (0.3)
	Subject lost to follow-up/unable to contact	1 (0.1)	0 (0.0)
	Subject refused for other reasons	3 (0.4)	5 (1.3)
	Not completed due to site staff error	25 (3.2)	12 (3.1)
	Other	23 (3.0)	8 (2.1)
	With visit, no record	15 (1.9)	9 (2.3)
	Missing by Design	50 (6.5)	21 (5.4)
	Subject died	1 (0.1)	0 (0.0)

Study: KEYNOTE 522[a]		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**	**Placebo + Chemotherapy[c] / Placebo**
Visit	**EORTC QLQ-BR23**	**N[d] = 770 n (%)**	**N[d] = 386 n (%)**
	Translation not available in subjects language	0 (0.0)	2 (0.5)
	No visit scheduled	49 (6.4)	19 (4.9)
Neoadjuvant Week 21	Expected to Complete Questionnaires[e]	696 (90.4)	351 (90.9)
	Completed	612 (79.5)	308 (79.8)
	Compliance (% in those expected to complete questionnaires)[f]	612 (87.9)	308 (87.7)
	Not completed	84 (10.9)	43 (11.1)
	Subject did not complete due to side effect of treatment	2 (0.3)	1 (0.3)
	Subject did not complete due to disease under study	1 (0.1)	0 (0.0)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.3)
	Subject refused for other reasons	10 (1.3)	3 (0.8)
	Not completed due to site staff error	30 (3.9)	20 (5.2)
	Other	30 (3.9)	11 (2.8)
	With visit, no record	10 (1.3)	6 (1.6)
	Missing by Design	74 (9.6)	35 (9.1)
	Subject died	3 (0.4)	0 (0.0)
	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)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	No visit scheduled	60 (7.8)	29 (7.5)
Adjuvant Baseline	Expected to Complete Questionnaires[e]	545 (70.8)	310 (80.3)
	Completed	488 (63.4)	282 (73.1)
	Compliance (% in those expected to complete questionnaires)[f]	488 (89.5)	282 (91.0)
	Not completed	57 (7.4)	28 (7.3)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	Subject refused for other reasons	3 (0.4)	2 (0.5)
	Not completed due to site staff error	24 (3.1)	9 (2.3)
	Other	13 (1.7)	8 (2.1)
	With visit, no record	17 (2.2)	8 (2.1)
	Missing by Design	225 (29.2)	76 (19.7)
	Subject died	3 (0.4)	0 (0.0)
	Discontinued due to adverse event	47 (6.1)	14 (3.6)
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)
	Discontinued due to physician decision	21 (2.7)	7 (1.8)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	7 (0.9)	5 (1.3)
	Discontinued due to withdrawal by subject	20 (2.6)	7 (1.8)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	No visit scheduled	119 (15.5)	33 (8.5)
Adjuvant Week 12	Expected to Complete Questionnaires[e]	533 (69.2)	304 (78.8)
	Completed	473 (61.4)	261 (67.6)
	Compliance (% in those expected to complete questionnaires)[f]	473 (88.7)	261 (85.9)
	Not completed	60 (7.8)	43 (11.1)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.3)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	Subject refused for other reasons	5 (0.6)	1 (0.3)

Study: KEYNOTE 522[a]		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**	**Placebo + Chemotherapy[c] / Placebo**
Visit	**EORTC QLQ-BR23**	**N[d] = 770 n (%)**	**N[d] = 386 n (%)**
	Not completed due to site staff error	26 (3.4)	15 (3.9)
	Other	9 (1.2)	11 (2.8)
	With visit, no record	19 (2.5)	14 (3.6)
	Missing by Design	237 (30.8)	82 (21.2)
	Subject died	3 (0.4)	0 (0.0)
	Discontinued due to adverse event	47 (6.1)	14 (3.6)
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)
	Discontinued due to physician decision	21 (2.7)	7 (1.8)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	7 (0.9)	5 (1.3)
	Discontinued due to withdrawal by subject	20 (2.6)	7 (1.8)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	No visit scheduled	131 (17.0)	39 (10.1)
Adjuvant Week 24	Expected to Complete Questionnaires[e]	489 (63.5)	284 (73.6)
	Completed	433 (56.2)	243 (63.0)
	Compliance (% in those expected to complete questionnaires)[f]	433 (88.5)	243 (85.6)
	Not completed	56 (7.3)	41 (10.6)
	Subject refused for other reasons	2 (0.3)	5 (1.3)
	Not completed due to site staff error	18 (2.3)	12 (3.1)
	Other	14 (1.8)	9 (2.3)
	With visit, no record	22 (2.9)	15 (3.9)
	Missing by Design	281 (36.5)	102 (26.4)
	Subject died	3 (0.4)	0 (0.0)
	Discontinued due to adverse event	66 (8.6)	16 (4.1)
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)
	Discontinued due to physician decision	28 (3.6)	8 (2.1)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	16 (2.1)	12 (3.1)
	Discontinued due to withdrawal by subject	29 (3.8)	15 (3.9)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	No visit scheduled	131 (17.0)	41 (10.6)
LTFU Year 1	Expected to Complete Questionnaires[e]	627 (81.4)	322 (83.4)
	Completed	520 (67.5)	263 (68.1)
	Compliance (% in those expected to complete questionnaires)[f]	520 (82.9)	263 (81.7)
	Not completed	107 (13.9)	59 (15.3)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.5)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	1 (0.1)	0 (0.0)
	Subject lost to follow-up/unable to contact	2 (0.3)	3 (0.8)
	Subject refused for other reasons	10 (1.3)	10 (2.6)
	Not completed due to site staff error	24 (3.1)	13 (3.4)
	Other	68 (8.8)	30 (7.8)
	With visit, no record	1 (0.1)	1 (0.3)
	Missing by Design	143 (18.6)	64 (16.6)
	Subject died	5 (0.6)	2 (0.5)
	Discontinued due to adverse event	50 (6.5)	14 (3.6)
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)
	Discontinued due to physician decision	23 (3.0)	7 (1.8)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	13 (1.7)	9 (2.3)
	Discontinued due to withdrawal by subject	23 (3.0)	8 (2.1)
	Translation not available in subjects language	0 (0.0)	1 (0.3)

Study: KEYNOTE 522[a]		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**	**Placebo + Chemotherapy[c] / Placebo**
Visit	**EORTC QLQ-BR23**	**N[d] = 770 n (%)**	**N[d] = 386 n (%)**
	No visit scheduled	21 (2.7)	14 (3.6)
LTFU Year 2	Expected to Complete Questionnaires[e]	639 (83.0)	326 (84.5)
	Completed	272 (35.3)	128 (33.2)
	Compliance (% in those expected to complete questionnaires)[f]	272 (42.6)	128 (39.3)
	Not completed	367 (47.7)	198 (51.3)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.5)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	1 (0.1)	0 (0.0)
	Subject lost to follow-up/unable to contact	2 (0.3)	4 (1.0)
	Subject refused for other reasons	12 (1.6)	8 (2.1)
	Not completed due to site staff error	31 (4.0)	15 (3.9)
	Other	320 (41.6)	169 (43.8)
	Missing by Design	131 (17.0)	60 (15.5)
	Subject died	6 (0.8)	2 (0.5)
	Discontinued due to adverse event	48 (6.2)	14 (3.6)
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)
	Discontinued due to physician decision	23 (3.0)	7 (1.8)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	13 (1.7)	9 (2.3)
	Discontinued due to withdrawal by subject	22 (2.9)	8 (2.1)
	No visit scheduled	11 (1.4)	11 (2.8)

a: Database Cutoff Date: 22MAR2024

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: 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; LTFU: Long-Term Follow-up

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

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

Study: KEYNOTE 522[a]		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**	**Placebo + Chemotherapy[c] / Placebo**
Visit	**EQ-5D**	**N[d] = 772 n (%)**	**N[d] = 386 n (%)**
Neoadjuvant Baseline	Expected to Complete Questionnaires[e]	772 (100.0)	384 (99.5)
	Completed	707 (91.6)	370 (95.9)
	Compliance (% in those expected to complete questionnaires)[f]	707 (91.6)	370 (96.4)
	Not completed	65 (8.4)	14 (3.6)
	Subject refused for other reasons	2 (0.3)	0 (0.0)
	Not completed due to site staff error	18 (2.3)	6 (1.6)
	Other	17 (2.2)	5 (1.3)
	With visit, no record	28 (3.6)	3 (0.8)
	Missing by Design	0 (0.0)	2 (0.5)
	Translation not available in subjects language	0 (0.0)	2 (0.5)
Neoadjuvant Week 12	Expected to Complete Questionnaires[e]	721 (93.4)	366 (94.8)
	Completed	658 (85.2)	337 (87.3)
	Compliance (% in those expected to complete questionnaires)[f]	658 (91.3)	337 (92.1)
	Not completed	63 (8.2)	29 (7.5)
	Subject did not complete due to side effect of treatment	2 (0.3)	0 (0.0)
	Subject did not complete due to disease under study	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	2 (0.3)	1 (0.3)
	Subject lost to follow-up/unable to contact	1 (0.1)	0 (0.0)
	Subject refused for other reasons	2 (0.3)	4 (1.0)
	Not completed due to site staff error	20 (2.6)	9 (2.3)
	Other	20 (2.6)	6 (1.6)
	With visit, no record	15 (1.9)	9 (2.3)
	Missing by Design	51 (6.6)	20 (5.2)
	Subject died	1 (0.1)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	2 (0.5)
	No visit scheduled	50 (6.5)	18 (4.7)
Neoadjuvant Week 21	Expected to Complete Questionnaires[e]	697 (90.3)	351 (90.9)
	Completed	615 (79.7)	311 (80.6)
	Compliance (% in those expected to complete questionnaires)[f]	615 (88.2)	311 (88.6)
	Not completed	82 (10.6)	40 (10.4)
	Subject did not complete due to side effect of treatment	2 (0.3)	1 (0.3)
	Subject did not complete due to disease under study	1 (0.1)	0 (0.0)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	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)
	Not completed due to site staff error	29 (3.8)	18 (4.7)
	Other	31 (4.0)	10 (2.6)
	With visit, no record	9 (1.2)	6 (1.6)
	Missing by Design	75 (9.7)	35 (9.1)
	Subject died	3 (0.4)	0 (0.0)
	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)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	No visit scheduled	61 (7.9)	29 (7.5)

Study: KEYNOTE 522[a]		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**	**Placebo + Chemotherapy[c] / Placebo**
Visit	**EQ-5D**	**N[d] = 772 n (%)**	**N[d] = 386 n (%)**
Adjuvant Baseline	Expected to Complete Questionnaires[e]	546 (70.7)	313 (81.1)
	Completed	496 (64.2)	285 (73.8)
	Compliance (% in those expected to complete questionnaires)[f]	496 (90.8)	285 (91.1)
	Not completed	50 (6.5)	28 (7.3)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	Subject refused for other reasons	2 (0.3)	2 (0.5)
	Not completed due to site staff error	22 (2.8)	10 (2.6)
	Other	10 (1.3)	7 (1.8)
	With visit, no record	16 (2.1)	8 (2.1)
	Missing by Design	226 (29.3)	73 (18.9)
	Subject died	3 (0.4)	0 (0.0)
	Discontinued due to adverse event	46 (6.0)	13 (3.4)
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)
	Discontinued due to physician decision	21 (2.7)	7 (1.8)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	7 (0.9)	5 (1.3)
	Discontinued due to withdrawal by subject	20 (2.6)	7 (1.8)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	No visit scheduled	121 (15.7)	31 (8.0)
Adjuvant Week 12	Expected to Complete Questionnaires[e]	534 (69.2)	307 (79.5)
	Completed	475 (61.5)	268 (69.4)
	Compliance (% in those expected to complete questionnaires)[f]	475 (89.0)	268 (87.3)
	Not completed	59 (7.6)	39 (10.1)
	Subject did not complete due to disease under study	0 (0.0)	1 (0.3)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	Subject refused for other reasons	5 (0.6)	1 (0.3)
	Not completed due to site staff error	26 (3.4)	13 (3.4)
	Other	8 (1.0)	9 (2.3)
	With visit, no record	19 (2.5)	14 (3.6)
	Missing by Design	238 (30.8)	79 (20.5)
	Subject died	3 (0.4)	0 (0.0)
	Discontinued due to adverse event	46 (6.0)	13 (3.4)
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)
	Discontinued due to physician decision	21 (2.7)	7 (1.8)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	7 (0.9)	5 (1.3)
	Discontinued due to withdrawal by subject	20 (2.6)	7 (1.8)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	No visit scheduled	133 (17.2)	37 (9.6)
Adjuvant Week 24	Expected to Complete Questionnaires[e]	490 (63.5)	287 (74.4)
	Completed	435 (56.3)	245 (63.5)
	Compliance (% in those expected to complete questionnaires)[f]	435 (88.8)	245 (85.4)
	Not completed	55 (7.1)	42 (10.9)
	Subject refused for other reasons	2 (0.3)	5 (1.3)
	Not completed due to site staff error	17 (2.2)	13 (3.4)
	Other	14 (1.8)	9 (2.3)
	With visit, no record	22 (2.8)	15 (3.9)
	Missing by Design	282 (36.5)	99 (25.6)
	Subject died	3 (0.4)	0 (0.0)
	Discontinued due to adverse event	65 (8.4)	15 (3.9)
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)

Study: KEYNOTE 522[a]		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab**	**Placebo + Chemotherapy[c] / Placebo**
Visit	**EQ-5D**	**N[d] = 772 n (%)**	**N[d] = 386 n (%)**
	Discontinued due to physician decision	28 (3.6)	8 (2.1)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	16 (2.1)	12 (3.1)
	Discontinued due to withdrawal by subject	29 (3.8)	15 (3.9)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	No visit scheduled	133 (17.2)	39 (10.1)
LTFU Year 1	Expected to Complete Questionnaires[e]	629 (81.5)	326 (84.5)
	Completed	522 (67.6)	265 (68.7)
	Compliance (% in those expected to complete questionnaires)[f]	522 (83.0)	265 (81.3)
	Not completed	107 (13.9)	61 (15.8)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.5)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	1 (0.1)	0 (0.0)
	Subject lost to follow-up/unable to contact	2 (0.3)	3 (0.8)
	Subject refused for other reasons	10 (1.3)	10 (2.6)
	Not completed due to site staff error	25 (3.2)	12 (3.1)
	Other	67 (8.7)	33 (8.5)
	With visit, no record	1 (0.1)	1 (0.3)
	Missing by Design	143 (18.5)	60 (15.5)
	Subject died	5 (0.6)	2 (0.5)
	Discontinued due to adverse event	49 (6.3)	13 (3.4)
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)
	Discontinued due to physician decision	23 (3.0)	7 (1.8)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	13 (1.7)	9 (2.3)
	Discontinued due to withdrawal by subject	23 (3.0)	8 (2.1)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	No visit scheduled	22 (2.8)	11 (2.8)
LTFU Year 2	Expected to Complete Questionnaires[e]	642 (83.2)	329 (85.2)
	Completed	276 (35.8)	130 (33.7)
	Compliance (% in those expected to complete questionnaires)[f]	276 (43.0)	130 (39.5)
	Not completed	366 (47.4)	199 (51.6)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.5)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	1 (0.1)	0 (0.0)
	Subject lost to follow-up/unable to contact	2 (0.3)	4 (1.0)
	Subject refused for other reasons	12 (1.6)	8 (2.1)
	Not completed due to site staff error	31 (4.0)	15 (3.9)
	Other	319 (41.3)	170 (44.0)
	Missing by Design	130 (16.8)	57 (14.8)
	Subject died	6 (0.8)	2 (0.5)
	Discontinued due to adverse event	47 (6.1)	13 (3.4)
	Discontinued due to clinical progression	2 (0.3)	2 (0.5)
	Discontinued due to physician decision	23 (3.0)	7 (1.8)
	Discontinued due to progressive disease	6 (0.8)	7 (1.8)
	Discontinued due to relapse/recurrence	13 (1.7)	9 (2.3)
	Discontinued due to withdrawal by subject	22 (2.8)	8 (2.1)
	No visit scheduled	11 (1.4)	9 (2.3)

a: Database Cutoff Date: 22MAR2024
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**
Visit	**EQ-5D**	**N[d] = 772** **n (%)**	**N[d] = 386** **n (%)**
d: Number of participants: full-analysis-set population			
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; LTFU: Long-Term Follow-up			

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

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

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

Anhang 4-G3: Nebenwirkungen

Schwerwiegende unerwünschte Ereignisse

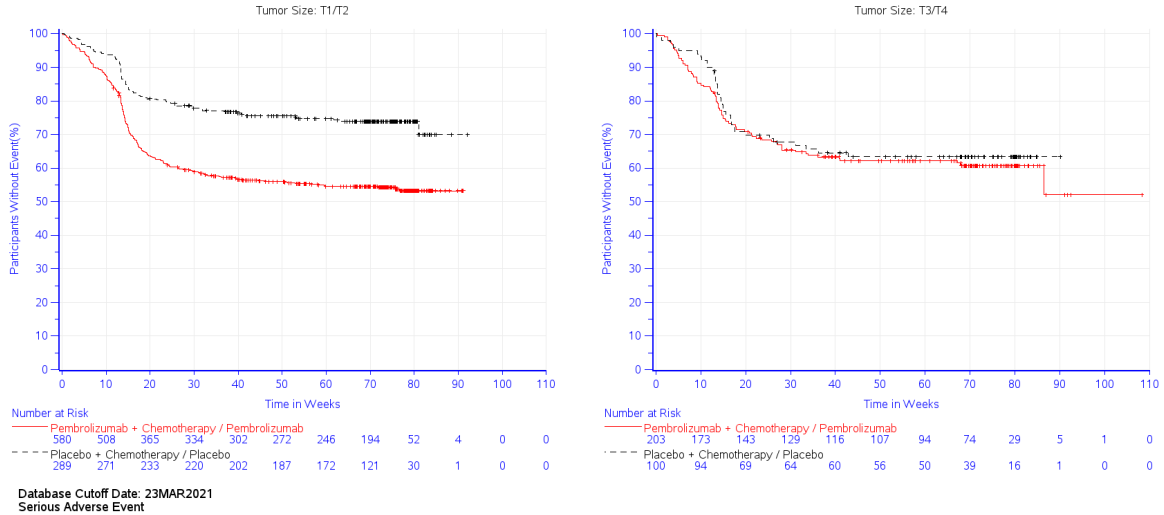

Abbildung 4G-1: Kaplan-Meier-Kurven für den Endpunkt schwerwiegende unerwünschte Ereignisse in der Subgruppenanalyse Tumorgröße

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

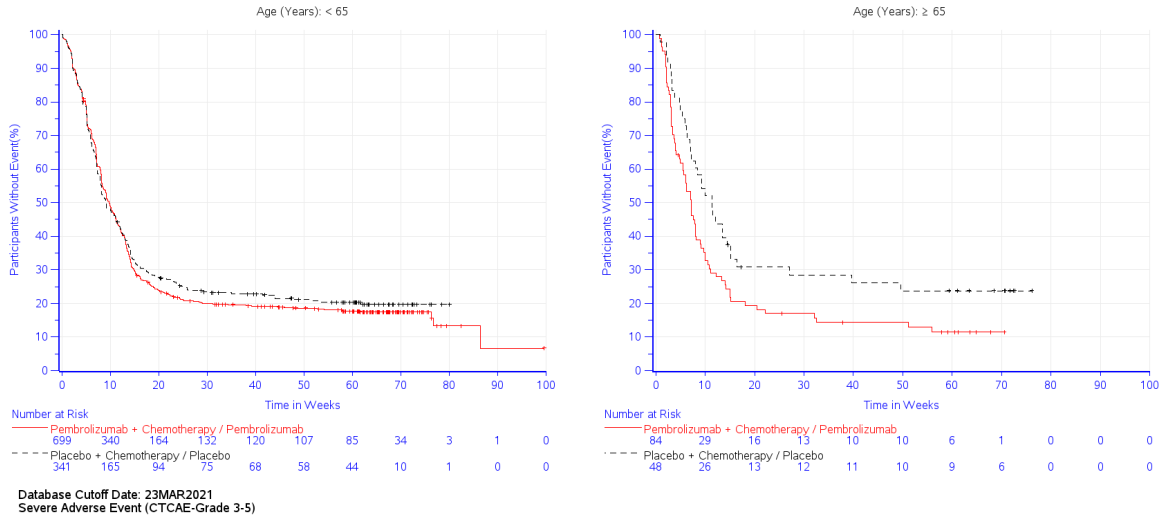

Abbildung 4G-2: Kaplan-Meier-Kurven für den Endpunkt schwere unerwünschte Ereignisse in der Subgruppenanalyse Alter (Jahre)

Unerwünschte Ereignisse nach SOC und PT

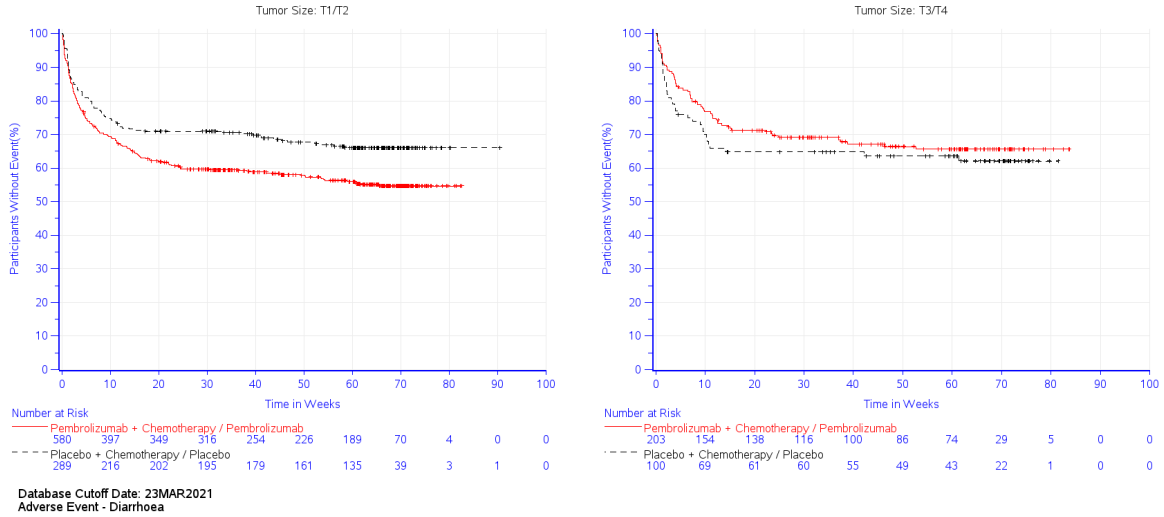

Abbildung 4G-3: Kaplan-Meier-Kurven für den Endpunkt unerwünschte Ereignisse nach SOC und PT im Endpunkt Diarrhoe in der Subgruppe Tumorgröße

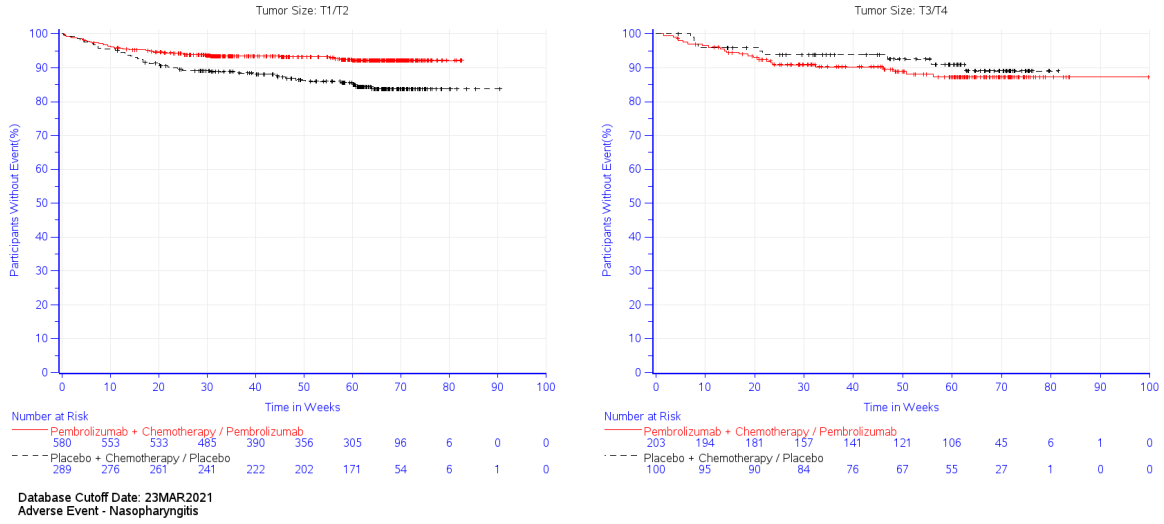

Abbildung 4G-4: Kaplan-Meier-Kurven für den Endpunkt unerwünschte Ereignisse nach SOC und PT im Endpunkt Nasopharyngitis in der Subgruppe Tumorgröße

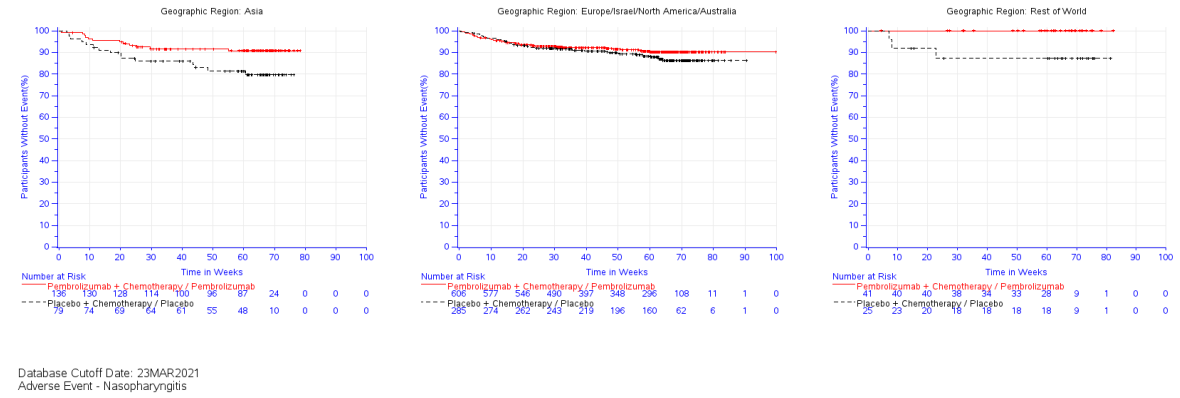

Abbildung 4G-5: Kaplan-Meier-Kurven für den Endpunkt unerwünschte Ereignisse nach SOC und PT im Endpunkt Nasopharyngitis in der Subgruppe Region

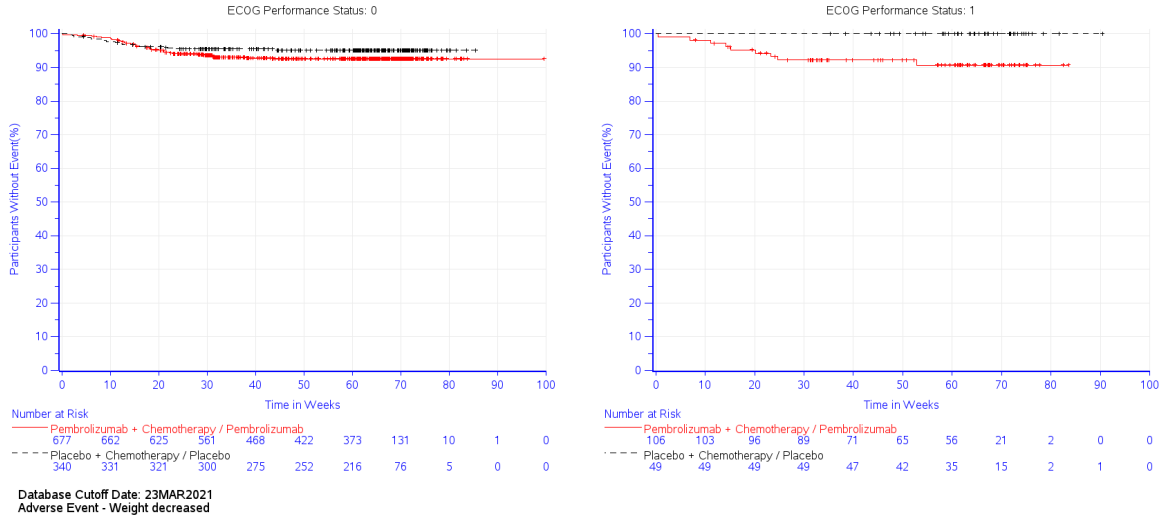

Abbildung 4G-6: Kaplan-Meier-Kurven für den Endpunkt unerwünschte Ereignisse nach SOC und PT im Endpunkt Gewicht erniedrigt in der Subgruppe ECOG Leistungsstatus

Schwerwiegende unerwünschte Ereignisse nach SOC und PT

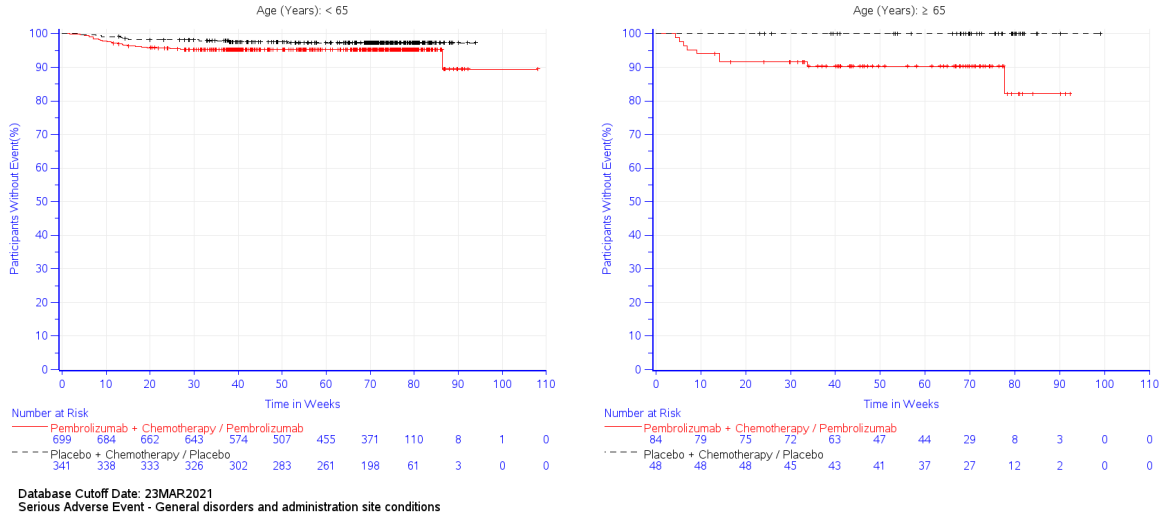

Abbildung 4G-7: Kaplan-Meier-Kurven für den Endpunkt schwerwiegende unerwünschte Ereignisse nach SOC und PT im Endpunkt Allgemeine Erkrankungen und Beschwerden am Verabreichungsort in der Subgruppe Alter (Jahre)

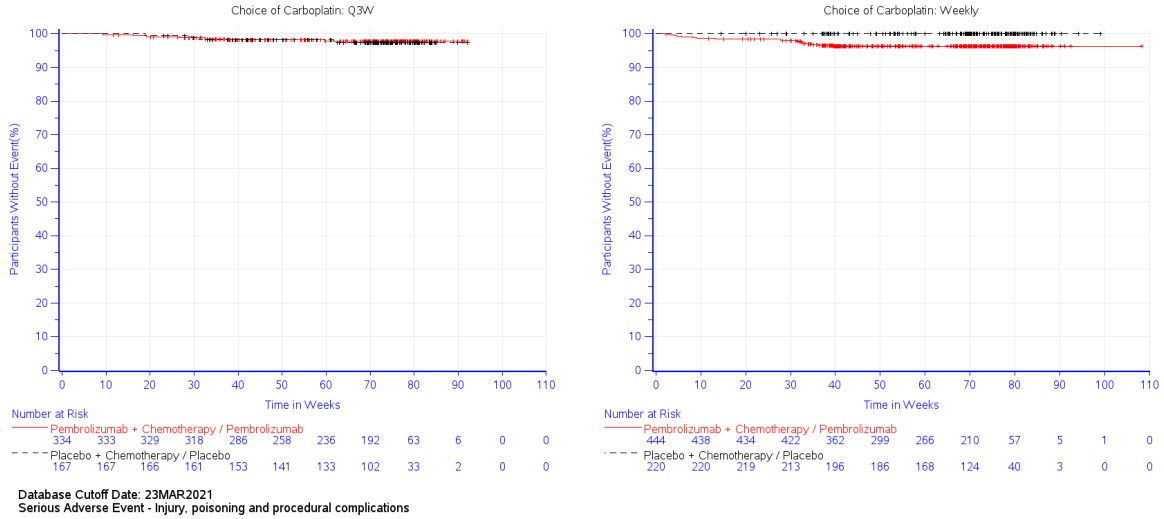

Abbildung 4G-8: Kaplan-Meier-Kurven für den Endpunkt schwerwiegende unerwünschte Ereignisse nach SOC und PT im Endpunkt Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen in der Subgruppe Wahl von Carboplatin

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

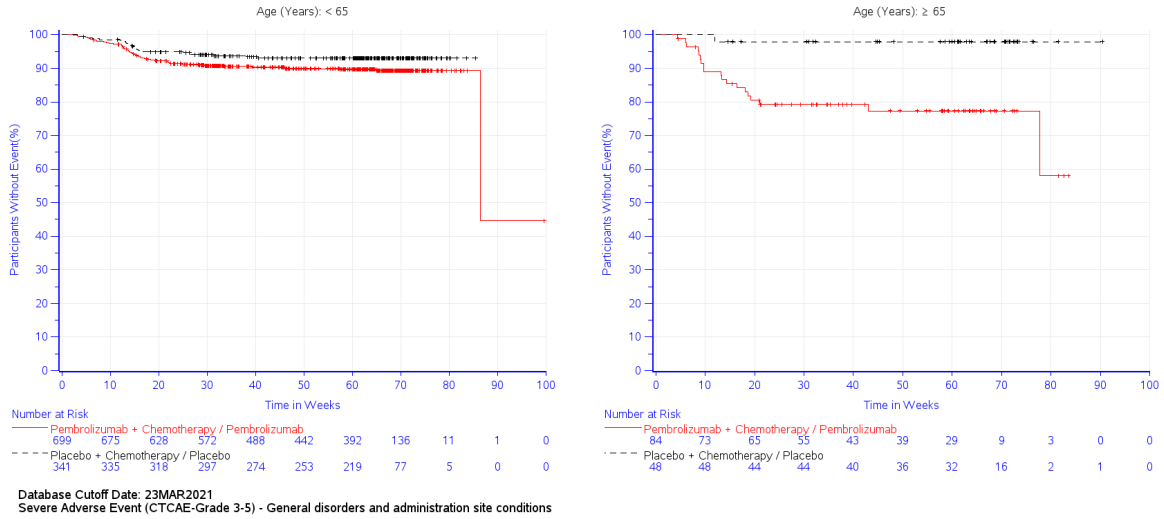

Abbildung 4G-9: Kaplan-Meier-Kurven für den Endpunkt schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) nach SOC und PT im Endpunkt Allgemeine Erkrankungen und Beschwerden am Verabreichungsort in der Subgruppe Alter (Jahre)

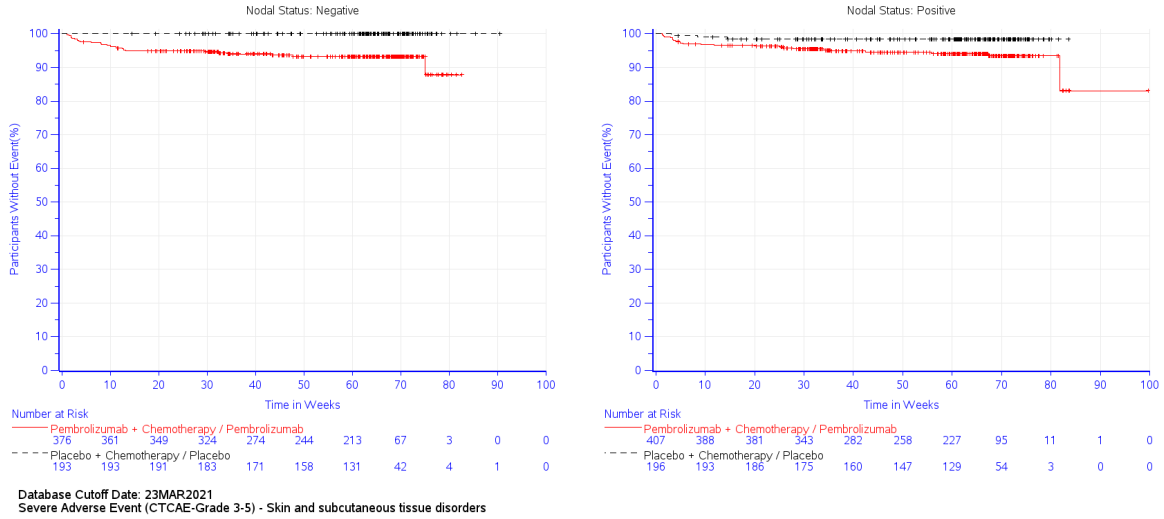

Abbildung 4G-10: Kaplan-Meier-Kurven für den Endpunkt schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) nach SOC und PT im Endpunkt Erkrankungen der Haut und des Unterhautzellgewebes in der Subgruppe Nodalstatus

Anhang 4-G4: Auswertungen über den Studienverlauf (tabellarische Darstellung)

Anhang 4-G4.1: Morbidität

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30

EORTC QLQ-C30: Symptomskala Erschöpfung

Tabelle 4G-5: Auswertung über den Studienverlauf der Symptomskala Erschöpfung des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Erschöpfung	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	701	367
Mittelwert (SD)	19,0 (20,0)	19,4 (19,7)
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
Neoadjuvante Woche 12		
N[e]	649	330
Mittelwert (SD)	42,4 (24,7)	38,0 (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
Neoadjuvante Woche 21		
N[e]	614	309
Mittelwert (SD)	39,8 (23,5)	36,6 (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
Baseline in der adjuvanten Phase		
N[e]	490	283
Mittelwert (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
Adjuvante Woche 12		
N[e]	475	263
Mittelwert (SD)	26,0 (20,3)	27,0 (20,9)
Median (Q1; Q3)	22,2 (11,1; 33,3)	33,3 (11,1; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	25,8 (21,8)	26,9 (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
LTFU Jahr 1		
N[e]	522	264
Mittelwert (SD)	26,6 (23,0)	25,5 (22,6)
Median (Q1; Q3)	22,2 (11,1; 33,3)	22,2 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0

EORTC QLQ-C30 Erschöpfung	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
LTFU Jahr 2		
N[e]	273	128
Mittelwert (SD)	21,9 (21,5)	25,3 (24,3)
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: Datenschnitt: 22. März 2024 b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen d: Anzahl der Patient:innen: Full-Analysis-Set Population e: Anzahl der Beobachtungen zu jedem Zeitpunkt EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung		

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-6: Auswertung über den Studienverlauf der Symptomskala Übelkeit und Erbrechen des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Übelkeit und Erbrechen	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	701	367
Mittelwert (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
Neoadjuvante Woche 12		
N[e]	649	330
Mittelwert (SD)	13,3 (18,9)	11,4 (18,6)
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
Neoadjuvante Woche 21		
N[e]	614	309
Mittelwert (SD)	14,4 (19,3)	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
Baseline in der adjuvanten Phase		
N[e]	490	283
Mittelwert (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
Adjuvante Woche 12		
N[e]	475	263
Mittelwert (SD)	4,1 (12,2)	3,9 (11,1)
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

EORTC QLQ-C30 Übelkeit und Erbrechen	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	4,2 (10,7)	2,9 (8,8)
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
LTFU Jahr 1		
N[e]	522	264
Mittelwert (SD)	4,6 (11,9)	3,9 (12,3)
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
LTFU Jahr 2		
N[e]	273	128
Mittelwert (SD)	2,6 (8,3)	5,5 (12,6)
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

a: Datenschnitt: 22. März 2024
b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
d: Anzahl der Patient:innen: Full-Analysis-Set Population
e: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EORTC QLQ-C30: Symptomskala Schmerzen

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

EORTC QLQ-C30 Schmerzen	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	701	367
Mittelwert (SD)	16,1 (20,1)	16,3 (18,7)
Median (Q1; Q3)	16,7 (0,0; 16,7)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Neoadjuvante Woche 12		
N[e]	649	330
Mittelwert (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
Neoadjuvante Woche 21		
N[e]	614	309
Mittelwert (SD)	20,3 (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

EORTC QLQ-C30 Schmerzen	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der adjuvanten Phase		
N[e]	490	283
Mittelwert (SD)	20,8 (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
Adjuvante Woche 12		
N[e]	475	263
Mittelwert (SD)	19,9 (20,4)	20,8 (21,7)
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
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	18,9 (20,4)	20,3 (22,2)
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
LTFU Jahr 1		
N[e]	522	264
Mittelwert (SD)	20,1 (22,8)	20,3 (22,2)
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
LTFU Jahr 2		
N[e]	273	128
Mittelwert (SD)	16,8 (21,5)	18,6 (23,8)
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: Datenschnitt: 22. März 2024

b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

d: Anzahl der Patient:innen: Full-Analysis-Set Population

e: Anzahl der Beobachtungen zu jedem Zeitpunkt

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EORTC QLQ-C30: Symptomskala Atemnot

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

EORTC QLQ-C30 Dyspnoe	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	701	367
Mittelwert (SD)	5,8 (14,8)	6,1 (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

EORTC QLQ-C30 Dyspnoe	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Neoadjuvante Woche 12		
N[e]	649	330
Mittelwert (SD)	22,3 (27,3)	22,5 (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
Neoadjuvante Woche 21		
N[e]	614	309
Mittelwert (SD)	20,0 (25,5)	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
Baseline in der adjuvanten Phase		
N[e]	490	283
Mittelwert (SD)	11,4 (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
Adjuvante Woche 12		
N[e]	475	263
Mittelwert (SD)	11,5 (19,8)	12,9 (21,4)
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
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	11,3 (18,8)	12,7 (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
LTFU Jahr 1		
N[e]	522	264
Mittelwert (SD)	12,8 (21,9)	11,6 (19,9)
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
LTFU Jahr 2		
N[e]	273	128
Mittelwert (SD)	10,1 (19,4)	12,2 (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

a: Datenschnitt: 22. März 2024

b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

d: Anzahl der Patient:innen: Full-Analysis-Set Population

e: Anzahl der Beobachtungen zu jedem Zeitpunkt

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

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

EORTC QLQ-C30 Schlaflosigkeit	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	701	367
Mittelwert (SD)	24,3 (27,0)	25,4 (27,5)
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
Neoadjuvante Woche 12		
N[e]	649	330
Mittelwert (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
Neoadjuvante Woche 21		
N[e]	614	309
Mittelwert (SD)	29,3 (27,6)	27,0 (27,4)
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
Baseline in der adjuvanten Phase		
N[e]	490	283
Mittelwert (SD)	28,2 (26,5)	29,6 (29,2)
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
Adjuvante Woche 12		
N[e]	475	263
Mittelwert (SD)	26,8 (26,0)	27,5 (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
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	25,3 (26,1)	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
LTFU Jahr 1		
N[e]	522	264
Mittelwert (SD)	25,7 (28,0)	27,1 (30,9)
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
LTFU Jahr 2		
N[e]	273	128
Mittelwert (SD)	22,3 (27,0)	21,6 (27,3)
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

a: Datenschnitt: 22. März 2024

b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

EORTC QLQ-C30 Schlaflosigkeit	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen d: Anzahl der Patient:innen: Full-Analysis-Set Population e: Anzahl der Beobachtungen zu jedem Zeitpunkt EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung		

EORTC QLQ-C30: Symptomskala Appetitverlust

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

EORTC QLQ-C30 Appetitverlust	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	701	367
Mittelwert (SD)	8,3 (17,2)	8,9 (18,3)
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
Neoadjuvante Woche 12		
N[e]	649	330
Mittelwert (SD)	23,4 (27,1)	16,9 (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
Neoadjuvante Woche 21		
N[e]	614	309
Mittelwert (SD)	23,9 (27,2)	18,9 (24,2)
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
Baseline in der adjuvanten Phase		
N[e]	490	283
Mittelwert (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
Adjuvante Woche 12		
N[e]	475	263
Mittelwert (SD)	9,0 (17,7)	7,1 (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
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	7,4 (16,4)	5,3 (13,6)
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
LTFU Jahr 1		
N[e]	522	264

EORTC QLQ-C30 Appetitverlust	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Mittelwert (SD)	8,6 (19,6)	7,8 (17,9)
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
LTFU Jahr 2		
N[e]	273	128
Mittelwert (SD)	5,9 (17,3)	8,1 (19,5)
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

a: Datenschnitt: 22. März 2024
b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
d: Anzahl der Patient:innen: Full-Analysis-Set Population
e: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EORTC QLQ-C30: Symptomskala Verstopfung

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

EORTC QLQ-C30 Verstopfung	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	701	367
Mittelwert (SD)	7,0 (17,1)	9,6 (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
Neoadjuvante Woche 12		
N[e]	649	330
Mittelwert (SD)	19,6 (27,3)	18,3 (25,7)
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
Neoadjuvante Woche 21		
N[e]	614	309
Mittelwert (SD)	21,4 (27,1)	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
Baseline in der adjuvanten Phase		
N[e]	490	283
Mittelwert (SD)	11,5 (21,1)	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
Adjuvante Woche 12		
N[e]	475	263

EORTC QLQ-C30 Verstopfung	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Mittelwert (SD)	12,1 (21,6)	11,4 (21,7)
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
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	12,7 (21,7)	11,4 (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
LTFU Jahr 1		
N[e]	522	264
Mittelwert (SD)	12,6 (23,1)	10,7 (21,3)
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
LTFU Jahr 2		
N[e]	273	128
Mittelwert (SD)	10,4 (20,5)	12,8 (23,3)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0

a: Datenschnitt: 22. März 2024
b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
d: Anzahl der Patient:innen: Full-Analysis-Set Population
e: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EORTC QLQ-C30: Symptomskala Diarrhö

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

EORTC QLQ-C30 Diarrhö	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	701	367
Mittelwert (SD)	5,3 (13,5)	4,9 (13,0)
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
Neoadjuvante Woche 12		
N[e]	649	330
Mittelwert (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
Neoadjuvante Woche 21		
N[e]	614	309

EORTC QLQ-C30 Diarrhö	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Mittelwert (SD)	9,0 (18,2)	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
Baseline in der adjuvanten Phase		
N[e]	490	283
Mittelwert (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
Adjuvante Woche 12		
N[e]	475	263
Mittelwert (SD)	5,4 (13,7)	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
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	6,1 (14,9)	4,6 (13,0)
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
LTFU Jahr 1		
N[e]	522	264
Mittelwert (SD)	5,7 (15,5)	4,0 (12,7)
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
LTFU Jahr 2		
N[e]	273	128
Mittelwert (SD)	5,0 (13,5)	4,4 (14,1)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 66,7	0,0; 100,0

a: Datenschnitt: 22. März 2024
b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
d: Anzahl der Patient:innen: Full-Analysis-Set Population
e: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EORTC QLQ-BR23

EORTC QLQ-BR23: Symptomskala Nebenwirkungen der systemischen Therapie

Tabelle 4G-13: Auswertung über den Studienverlauf der Symptomskala Nebenwirkungen der systemischen Therapie des EORTC QLQ-BR23 mit dem zu bewertenden Arzneimittel

EORTC QLQ-BR23 Nebenwirkungen der Systemischen Therapie	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 770	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		

EORTC QLQ-BR23 Nebenwirkungen der Systemischen Therapie	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 770	Placebo + Chemotherapie[c] / Placebo N[d]= 386
N[e]	695	362
Mittelwert (SD)	8,1 (10,7)	7,9 (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
Neoadjuvante Woche 12		
N[e]	645	329
Mittelwert (SD)	35,1 (18,3)	32,3 (18,6)
Median (Q1; Q3)	33,3 (23,8; 47,6)	33,3 (19,0; 42,9)
Min, Max	0,0; 100,0	0,0; 100,0
Neoadjuvante Woche 21		
N[e]	610	307
Mittelwert (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
Baseline in der adjuvanten Phase		
N[e]	488	282
Mittelwert (SD)	16,3 (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
Adjuvante Woche 12		
N[e]	473	261
Mittelwert (SD)	16,2 (13,6)	16,3 (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
Adjuvante Woche 24		
N[e]	433	243
Mittelwert (SD)	15,6 (13,6)	14,5 (14,6)
Median (Q1; Q3)	14,3 (4,8; 23,8)	9,5 (4,8; 23,8)
Min, Max	0,0; 76,2	0,0; 81,0
LTFU Jahr 1		
N[e]	520	263
Mittelwert (SD)	14,5 (14,0)	13,9 (15,5)
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
LTFU Jahr 2		
N[e]	272	128
Mittelwert (SD)	12,0 (12,8)	14,2 (15,1)
Median (Q1; Q3)	9,5 (0,0; 19,0)	9,5 (2,4; 19,0)
Min, Max	0,0; 71,4	0,0; 66,7

a: Datenschnitt: 22. März 2024

b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

d: Anzahl der Patient:innen: Full-Analysis-Set Population

e: Anzahl der Beobachtungen zu jedem Zeitpunkt

EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EORTC QLQ-BR23: Symptomskala Symptome im Brustbereich

Tabelle 4G-14: Auswertung über den Studienverlauf der Symptomskala Symptome im Brustbereich des EORTC QLQ-BR23 mit dem zu bewertenden Arzneimittel

EORTC QLQ-BR23 Symptome im Brustbereich	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 770	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	695	362
Mittelwert (SD)	18,7 (20,4)	18,4 (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
Neoadjuvante Woche 12		
N[e]	645	329
Mittelwert (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
Neoadjuvante Woche 21		
N[e]	610	307
Mittelwert (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
Baseline in der adjuvanten Phase		
N[e]	488	282
Mittelwert (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
Adjuvante Woche 12		
N[e]	473	261
Mittelwert (SD)	18,6 (17,9)	18,1 (18,5)
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
Adjuvante Woche 24		
N[e]	433	243
Mittelwert (SD)	16,8 (17,2)	17,0 (18,2)
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
LTFU Jahr 1		
N[e]	520	263
Mittelwert (SD)	15,6 (17,9)	14,7 (19,2)
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
LTFU Jahr 2		
N[e]	272	128
Mittelwert (SD)	12,7 (15,3)	11,1 (16,2)
Median (Q1; Q3)	8,3 (0,0; 16,7)	8,3 (0,0; 16,7)
Min, Max	0,0; 83,3	0,0; 100,0

a: Datenschnitt: 22. März 2024

b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

	Studie: KEYNOTE 522[a]	
EORTC QLQ-BR23 Symptome im Brustbereich	**Pembrolizumab + Chemotherapie[b] / Pembrolizumab** N[d]= 770	**Placebo + Chemotherapie[c] / Placebo** N[d]= 386
c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen d: Anzahl der Patient:innen: Full-Analysis-Set Population e: Anzahl der Beobachtungen zu jedem Zeitpunkt EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung		

EORTC QLQ-BR23: Symptomskala Symptome im Armbereich

Tabelle 4G-15: Auswertung über den Studienverlauf der Symptomskala Symptome im Armbereich des EORTC QLQ-BR23 mit dem zu bewertenden Arzneimittel

	Studie: KEYNOTE 522[a]	
EORTC QLQ-BR23 Symptome im Armbereich	**Pembrolizumab + Chemotherapie[b] / Pembrolizumab** N[d]= 770	**Placebo + Chemotherapie[c] / Placebo** N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	695	362
Mittelwert (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
Neoadjuvante Woche 12		
N[e]	645	329
Mittelwert (SD)	11,6 (17,2)	10,8 (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
Neoadjuvante Woche 21		
N[e]	610	307
Mittelwert (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
Baseline in der adjuvanten Phase		
N[e]	488	282
Mittelwert (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
Adjuvante Woche 12		
N[e]	473	261
Mittelwert (SD)	19,6 (20,6)	20,2 (19,6)
Median (Q1; Q3)	11,1 (0,0; 33,3)	11,1 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 77,8
Adjuvante Woche 24		
N[e]	433	243
Mittelwert (SD)	20,2 (20,9)	18,8 (19,3)
Median (Q1; Q3)	11,1 (0,0; 33,3)	11,1 (0,0; 22,2)
Min, Max	0,0; 100,0	0,0; 100,0
LTFU Jahr 1		
N[e]	520	263

EORTC QLQ-BR23 Symptome im Armbereich	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 770	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Mittelwert (SD)	17,7 (21,2)	15,9 (20,9)
Median (Q1; Q3)	11,1 (0,0; 33,3)	11,1 (0,0; 22,2)
Min, Max	0,0; 100,0	0,0; 100,0
LTFU Jahr 2		
N[e]	272	128
Mittelwert (SD)	15,3 (19,1)	15,2 (17,8)
Median (Q1; Q3)	11,1 (0,0; 22,2)	11,1 (0,0; 22,2)
Min, Max	0,0; 100,0	0,0; 88,9

a: Datenschnitt: 22. März 2024
b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
d: Anzahl der Patient:innen: Full-Analysis-Set Population
e: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EORTC QLQ-BR23: Symptomskala Belastung durch Haarausfall

Tabelle 4G-16: Auswertung über den Studienverlauf der Symptomskala Belastung durch Haarausfall des EORTC QLQ-BR23 mit dem zu bewertenden Arzneimittel

EORTC QLQ-BR23 Belastung durch Haarausfall[f]	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 770	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	695	362
Mittelwert (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
Neoadjuvante Woche 12		
N[e]	645	329
Mittelwert (SD)	32,5 (36,7)	29,9 (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
Neoadjuvante Woche 21		
N[e]	610	307
Mittelwert (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
Baseline in der adjuvanten Phase		
N[e]	488	282
Mittelwert (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
Adjuvante Woche 12		
N[e]	473	261

EORTC QLQ-BR23 Belastung durch Haarausfall[f]	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 770	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Mittelwert (SD)	2,5 (14,4)	4,7 (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; 100,0
Adjuvante Woche 24		
N[e]	433	243
Mittelwert (SD)	2,9 (13,9)	3,4 (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
LTFU Jahr 1		
N[e]	520	263
Mittelwert (SD)	3,8 (16,3)	4,9 (17,1)
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
LTFU Jahr 2		
N[e]	272	128
Mittelwert (SD)	4,8 (15,6)	5,5 (15,5)
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

a: Datenschnitt: 22. März 2024
b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
d: Anzahl der Patient:innen: Full-Analysis-Set Population
e: Anzahl der Beobachtungen zu jedem Zeitpunkt
f: Bei Patient:innen ohne Haarausfall wurde die Frage "Nur bei Haarausfall ausfüllen: Hat Sie der Haarausfall belastet?" imputiert
EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EQ-5D VAS

Tabelle 4G-17: Auswertung über den Studienverlauf der EQ-5D VAS mit dem zu bewertenden Arzneimittel

EQ-5D VAS	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	707	370
Mittelwert (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
Neoadjuvante Woche 12		
N[e]	658	337
Mittelwert (SD)	73,0 (17,5)	74,2 (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
Neoadjuvante Woche 21		

EQ-5D VAS	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
N[e]	615	311
Mittelwert (SD)	72,8 (18,0)	75,0 (16,3)
Median (Q1; Q3)	78,0 (60,0; 88,0)	79,0 (65,0; 89,0)
Min, Max	10,0; 100,0	9,0; 100,0
Baseline in der adjuvanten Phase		
N[e]	496	285
Mittelwert (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
Adjuvante Woche 12		
N[e]	475	268
Mittelwert (SD)	80,1 (14,3)	79,9 (15,3)
Median (Q1; Q3)	81,0 (71,0; 90,0)	81,5 (70,5; 90,0)
Min, Max	8,0; 100,0	0,0; 100,0
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	80,9 (14,7)	81,2 (13,4)
Median (Q1; Q3)	82,0 (74,0; 91,0)	82,0 (71,0; 91,0)
Min, Max	11,0; 100,0	35,0; 100,0
LTFU Jahr 1		
N[e]	522	265
Mittelwert (SD)	78,3 (16,8)	80,0 (16,4)
Median (Q1; Q3)	81,0 (70,0; 90,0)	82,0 (72,0; 90,0)
Min, Max	7,0; 100,0	5,0; 100,0
LTFU Jahr 2		
N[e]	276	130
Mittelwert (SD)	81,7 (13,4)	81,7 (15,3)
Median (Q1; Q3)	82,0 (73,5; 91,0)	85,0 (77,0; 91,0)
Min, Max	29,0; 100,0	12,0; 100,0

a: Datenschnitt: 22. März 2024

b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

d: Anzahl der Patient:innen: Full-Analysis-Set Population

e: Anzahl der Beobachtungen zu jedem Zeitpunkt

EQ-5D VAS: European Quality of Life 5 Dimensions Visuelle Analogskala; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

Anhang 4-G4.2: Gesundheitsbezogene Lebensqualität

Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-18: Auswertung über den Studienverlauf des Globalen Gesundheitsstatus des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Globaler Gesundheitsstatus	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	701	367
Mittelwert (SD)	77,1 (18,5)	78,9 (17,1)
Median (Q1; Q3)	83,3 (66,7; 91,7)	83,3 (66,7; 91,7)
Min, Max	0,0; 100,0	25,0; 100,0
Neoadjuvante Woche 12		
N[e]	649	330
Mittelwert (SD)	64,7 (19,3)	67,9 (18,9)
Median (Q1; Q3)	66,7 (50,0; 83,3)	66,7 (58,3; 83,3)
Min, Max	0,0; 100,0	0,0; 100,0
Neoadjuvante Woche 21		
N[e]	614	309
Mittelwert (SD)	66,9 (19,2)	68,3 (17,8)
Median (Q1; Q3)	66,7 (50,0; 83,3)	66,7 (50,0; 83,3)
Min, Max	0,0; 100,0	25,0; 100,0
Baseline in der adjuvanten Phase		
N[e]	490	283
Mittelwert (SD)	73,8 (15,7)	73,1 (18,1)
Median (Q1; Q3)	75,0 (66,7; 83,3)	75,0 (66,7; 83,3)
Min, Max	16,7; 100,0	0,0; 100,0
Adjuvante Woche 12		
N[e]	475	263
Mittelwert (SD)	75,0 (16,2)	74,6 (16,8)
Median (Q1; Q3)	75,0 (66,7; 83,3)	75,0 (66,7; 83,3)
Min, Max	16,7; 100,0	0,0; 100,0
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	76,6 (16,3)	76,2 (16,6)
Median (Q1; Q3)	83,3 (66,7; 83,3)	83,3 (66,7; 83,3)
Min, Max	16,7; 100,0	16,7; 100,0
LTFU Jahr 1		
N[e]	522	264
Mittelwert (SD)	74,3 (18,8)	76,2 (17,5)
Median (Q1; Q3)	79,2 (66,7; 83,3)	83,3 (66,7; 83,3)
Min, Max	0,0; 100,0	0,0; 100,0
LTFU Jahr 2		
N[e]	273	128
Mittelwert (SD)	78,1 (15,9)	77,0 (18,5)
Median (Q1; Q3)	83,3 (66,7; 83,3)	83,3 (66,7; 83,3)
Min, Max	16,7; 100,0	8,3; 100,0
a: Datenschnitt: 22. März 2024		

EORTC QLQ-C30 Globaler Gesundheitsstatus	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	**Placebo + Chemotherapie[c] / Placebo** N[d]= 386
b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen d: Anzahl der Patient:innen: Full-Analysis-Set Population e: Anzahl der Beobachtungen zu jedem Zeitpunkt EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; QoL: Quality of Life; SD: Standardabweichung		

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-19: Auswertung über den Studienverlauf der Funktionsskala Körperliche Funktion des EORTC QLQ-C30 mit dem zu bewertenden Arzneimittel

EORTC QLQ-C30 Körperliche Funktion	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	**Placebo + Chemotherapie[c] / Placebo** N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	701	367
Mittelwert (SD)	91,9 (12,8)	91,4 (13,5)
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
Neoadjuvante Woche 12		
N[e]	649	330
Mittelwert (SD)	76,5 (19,4)	78,9 (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
Neoadjuvante Woche 21		
N[e]	614	309
Mittelwert (SD)	77,0 (18,9)	79,2 (17,2)
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
Baseline in der adjuvanten Phase		
N[e]	490	283
Mittelwert (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
Adjuvante Woche 12		
N[e]	475	263
Mittelwert (SD)	85,0 (14,9)	84,2 (15,5)
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
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	84,9 (15,7)	85,4 (15,1)
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
LTFU Jahr 1		

EORTC QLQ-C30 Körperliche Funktion	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
N[e]	522	264
Mittelwert (SD)	84,3 (17,9)	85,3 (18,5)
Median (Q1; Q3)	86,7 (80,0; 100,0)	93,3 (80,0; 100,0)
Min, Max	0,0; 100,0	0,0; 100,0
LTFU Jahr 2		
N[e]	273	128
Mittelwert (SD)	87,1 (16,2)	87,6 (16,7)
Median (Q1; Q3)	93,3 (80,0; 100,0)	93,3 (80,0; 100,0)
Min, Max	0,0; 100,0	26,7; 100,0
a: Datenschnitt: 22. März 2024 b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen d: Anzahl der Patient:innen: Full-Analysis-Set Population e: Anzahl der Beobachtungen zu jedem Zeitpunkt EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung		

EORTC QLQ-C30: Funktionsskala Rollenfunktion

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

EORTC QLQ-C30 Rollenfunktion	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	701	367
Mittelwert (SD)	90,9 (18,4)	89,0 (20,0)
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
Neoadjuvante Woche 12		
N[e]	649	330
Mittelwert (SD)	70,1 (27,0)	75,3 (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
Neoadjuvante Woche 21		
N[e]	614	309
Mittelwert (SD)	71,4 (26,8)	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
Baseline in der adjuvanten Phase		
N[e]	490	283
Mittelwert (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
Adjuvante Woche 12		

EORTC QLQ-C30 Rollenfunktion	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
N[e]	475	263
Mittelwert (SD)	83,1 (20,9)	82,2 (21,7)
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
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	84,1 (20,2)	82,2 (22,0)
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
LTFU Jahr 1		
N[e]	522	264
Mittelwert (SD)	81,9 (24,6)	84,0 (25,0)
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
LTFU Jahr 2		
N[e]	273	128
Mittelwert (SD)	86,9 (20,9)	87,0 (23,3)
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: Datenschnitt: 22. März 2024

b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

d: Anzahl der Patient:innen: Full-Analysis-Set Population

e: Anzahl der Beobachtungen zu jedem Zeitpunkt

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

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

EORTC QLQ-C30 Emotionale Funktion	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	701	367
Mittelwert (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
Neoadjuvante Woche 12		
N[e]	649	330
Mittelwert (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
Neoadjuvante Woche 21		

EORTC QLQ-C30 Emotionale Funktion	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
N[e]	614	309
Mittelwert (SD)	74,7 (20,6)	75,0 (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
Baseline in der adjuvanten Phase		
N[e]	490	283
Mittelwert (SD)	81,7 (17,8)	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
Adjuvante Woche 12		
N[e]	475	263
Mittelwert (SD)	80,8 (18,6)	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
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	79,7 (19,7)	78,6 (20,5)
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
LTFU Jahr 1		
N[e]	522	264
Mittelwert (SD)	78,6 (21,3)	77,9 (22,9)
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
LTFU Jahr 2		
N[e]	273	128
Mittelwert (SD)	82,2 (18,6)	80,7 (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

a: Datenschnitt: 22. März 2024
b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
d: Anzahl der Patient:innen: Full-Analysis-Set Population
e: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

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

EORTC QLQ-C30 Kognitive Funktion	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		

EORTC QLQ-C30 Kognitive Funktion	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
N[e]	701	367
Mittelwert (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
Neoadjuvante Woche 12		
N[e]	649	330
Mittelwert (SD)	79,4 (20,5)	80,9 (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
Neoadjuvante Woche 21		
N[e]	614	309
Mittelwert (SD)	78,5 (21,5)	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
Baseline in der adjuvanten Phase		
N[e]	490	283
Mittelwert (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
Adjuvante Woche 12		
N[e]	475	263
Mittelwert (SD)	82,0 (19,3)	80,9 (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
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	80,9 (20,3)	80,2 (21,7)
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
LTFU Jahr 1		
N[e]	522	264
Mittelwert (SD)	81,2 (21,1)	81,7 (21,7)
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
LTFU Jahr 2		
N[e]	273	128
Mittelwert (SD)	83,1 (20,0)	81,8 (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

a: Datenschnitt: 22. März 2024

b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

d: Anzahl der Patient:innen: Full-Analysis-Set Population

e: Anzahl der Beobachtungen zu jedem Zeitpunkt

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EORTC QLQ-C30: Funktionsskala Soziale Funktion

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

EORTC QLQ-C30 Soziale Funktion	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	701	367
Mittelwert (SD)	87,4 (20,0)	86,8 (21,0)
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
Neoadjuvante Woche 12		
N[e]	649	330
Mittelwert (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
Neoadjuvante Woche 21		
N[e]	614	309
Mittelwert (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
Baseline in der adjuvanten Phase		
N[e]	490	283
Mittelwert (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
Adjuvante Woche 12		
N[e]	475	263
Mittelwert (SD)	84,9 (18,6)	83,3 (22,1)
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
Adjuvante Woche 24		
N[e]	435	245
Mittelwert (SD)	84,0 (22,2)	83,1 (22,5)
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
LTFU Jahr 1		
N[e]	522	264
Mittelwert (SD)	84,5 (23,7)	84,0 (24,5)
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
LTFU Jahr 2		
N[e]	273	128
Mittelwert (SD)	88,4 (21,5)	88,4 (21,5)
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

EORTC QLQ-C30 Soziale Funktion	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 772	Placebo + Chemotherapie[c] / Placebo N[d]= 386
a: Datenschnitt: 22. März 2024 b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen d: Anzahl der Patient:innen: Full-Analysis-Set Population e: Anzahl der Beobachtungen zu jedem Zeitpunkt EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung		

EORTC QLQ-BR23

EORTC QLQ-BR23: Funktionsskala Körperbild

Tabelle 4G-24: Auswertung über den Studienverlauf der Funktionsskala Körperbild des EORTC QLQ-BR23 mit dem zu bewertenden Arzneimittel

EORTC QLQ-BR23 Körperbild	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 770	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	695	362
Mittelwert (SD)	90,8 (16,1)	90,8 (16,3)
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
Neoadjuvante Woche 12		
N[e]	645	329
Mittelwert (SD)	68,3 (27,5)	69,8 (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
Neoadjuvante Woche 21		
N[e]	610	307
Mittelwert (SD)	68,5 (27,3)	68,9 (28,7)
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
Baseline in der adjuvanten Phase		
N[e]	488	282
Mittelwert (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
Adjuvante Woche 12		
N[e]	473	261
Mittelwert (SD)	79,0 (22,0)	78,4 (24,2)
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
Adjuvante Woche 24		
N[e]	433	243
Mittelwert (SD)	81,2 (22,0)	77,9 (24,1)
Median (Q1; Q3)	91,7 (66,7; 100,0)	83,3 (66,7; 100,0)

EORTC QLQ-BR23 Körperbild	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 770	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Min, Max	0,0; 100,0	0,0; 100,0
LTFU Jahr 1		
N[e]	520	263
Mittelwert (SD)	80,3 (24,9)	80,8 (23,4)
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
LTFU Jahr 2		
N[e]	272	128
Mittelwert (SD)	84,2 (22,0)	83,7 (23,0)
Median (Q1; Q3)	91,7 (75,0; 100,0)	100,0 (70,8; 100,0)
Min, Max	0,0; 100,0	0,0; 100,0

a: Datenschnitt: 22. März 2024
b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
d: Anzahl der Patient:innen: Full-Analysis-Set Population
e: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EORTC QLQ-BR23: Funktionsskala Sexuelle Aktivität

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

EORTC QLQ-BR23 Sexuelle Aktivität	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 770	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	678	353
Mittelwert (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
Neoadjuvante Woche 12		
N[e]	632	320
Mittelwert (SD)	15,1 (20,9)	14,6 (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
Neoadjuvante Woche 21		
N[e]	598	302
Mittelwert (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
Baseline in der adjuvanten Phase		
N[e]	480	279
Mittelwert (SD)	16,9 (20,8)	16,6 (21,3)
Median (Q1; Q3)	16,7 (0,0; 33,3)	0,0 (0,0; 33,3)

EORTC QLQ-BR23 Sexuelle Aktivität	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 770	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Min, Max	0,0; 100,0	0,0; 100,0
Adjuvante Woche 12		
N[e]	469	256
Mittelwert (SD)	19,9 (22,2)	19,6 (23,0)
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
Adjuvante Woche 24		
N[e]	424	237
Mittelwert (SD)	20,5 (23,6)	21,0 (21,6)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 83,3
LTFU Jahr 1		
N[e]	515	262
Mittelwert (SD)	20,5 (24,5)	20,7 (24,3)
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
LTFU Jahr 2		
N[e]	268	128
Mittelwert (SD)	23,0 (25,6)	21,6 (26,4)
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

a: Datenschnitt: 22. März 2024
b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen
d: Anzahl der Patient:innen: Full-Analysis-Set Population
e: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EORTC QLQ-BR23: Funktionsskala Sexueller Genuss

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

EORTC QLQ-BR23 Sexueller Genuss[f]	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 770	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	321	160
Mittelwert (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
Neoadjuvante Woche 12		
N[e]	228	112
Mittelwert (SD)	47,4 (28,8)	48,5 (26,8)
Median (Q1; Q3)	33,3 (33,3; 66,7)	33,3 (33,3; 66,7)

EORTC QLQ-BR23 Sexueller Genuss[f]	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 770	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Min, Max	0,0; 100,0	0,0; 100,0
Neoadjuvante Woche 21		
N[e]	202	89
Mittelwert (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
Baseline in der adjuvanten Phase		
N[e]	178	104
Mittelwert (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
Adjuvante Woche 12		
N[e]	214	113
Mittelwert (SD)	45,6 (25,8)	47,5 (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
Adjuvante Woche 24		
N[e]	195	115
Mittelwert (SD)	48,9 (26,5)	44,3 (24,5)
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
LTFU Jahr 1		
N[e]	239	127
Mittelwert (SD)	50,2 (25,7)	47,8 (27,7)
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
LTFU Jahr 2		
N[e]	128	57
Mittelwert (SD)	51,6 (25,0)	48,5 (25,3)
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: Datenschnitt: 22. März 2024

b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

d: Anzahl der Patient:innen: Full-Analysis-Set Population

e: Anzahl der Beobachtungen zu jedem Zeitpunkt

f: Bei Patienten, die nicht sexuell aktiv waren, wurde auf das Item "Sexueller Genuss" keine Antwort gegeben.

EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

EORTC QLQ-BR23: Funktionsskala Zukunftsperspektive

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

EORTC QLQ-BR23 Zukunftsperspektive	Studie: KEYNOTE 522[a]	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 770	Placebo + Chemotherapie[c] / Placebo N[d]= 386
Baseline in der neoadjuvanten Phase		
N[e]	695	362
Mittelwert (SD)	53,7 (31,3)	54,3 (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
Neoadjuvante Woche 12		
N[e]	645	329
Mittelwert (SD)	52,2 (31,1)	50,3 (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
Neoadjuvante Woche 21		
N[e]	610	307
Mittelwert (SD)	49,9 (31,7)	50,9 (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
Baseline in der adjuvanten Phase		
N[e]	488	282
Mittelwert (SD)	59,4 (29,2)	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
Adjuvante Woche 12		
N[e]	473	261
Mittelwert (SD)	60,3 (29,8)	59,0 (31,1)
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
Adjuvante Woche 24		
N[e]	433	243
Mittelwert (SD)	59,3 (30,4)	57,2 (32,2)
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
LTFU Jahr 1		
N[e]	520	263
Mittelwert (SD)	59,6 (31,5)	61,1 (31,1)
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
LTFU Jahr 2		
N[e]	272	128
Mittelwert (SD)	65,2 (29,3)	65,9 (27,9)
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

a: Datenschnitt: 22. März 2024

b: Pembrolizumab + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Pembrolizumab + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen

EORTC QLQ-BR23 Zukunftsperspektive	**Studie: KEYNOTE 522[a]**	
	Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[d]= 770	**Placebo + Chemotherapie[c] / Placebo** N[d]= 386
c: Placebo + Paclitaxel + Carboplatin x 4 Zyklen, gefolgt von Placebo + [Doxorubicin oder Epirubicin] + Cyclophosphamid x 4 Zyklen d: Anzahl der Patient:innen: Full-Analysis-Set Population e: Anzahl der Beobachtungen zu jedem Zeitpunkt EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23; LTFU: Long-Term Follow-up; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung		

Anhang 4-G5: 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 siebten Datenschnitt (22.März.2024).

Anhang 4-G5.1: Mortalität

Gesamtüberleben

Tabelle 4G-28: 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	93 (13.3)	Not reached [-; -]	342	72 (21.1)	Not reached [-; -]	0.62 [0.45; 0.84]	0.002	0.267
≥ 65	84	22 (26.2)	Not reached [79.0; -]	48	13 (27.1)	Not reached [-; -]	0.96 [0.48; 1.91]	0.912	
ECOG Performance Status									
0	678	92 (13.6)	Not reached [-; -]	341	74 (21.7)	Not reached [-; -]	0.60 [0.44; 0.82]	0.001	0.165
1	106	23 (21.7)	Not reached [-; -]	49	11 (22.4)	Not reached [-; -]	1.03 [0.50; 2.12]	0.929	
Geographic Region									
Asia	136	12 (8.8)	Not reached [-; -]	80	16 (20.0)	Not reached [-; -]	0.41 [0.19; 0.86]	0.018	0.351
Europe/Israel/North America/Australia	607	90 (14.8)	Not reached [-; -]	285	60 (21.1)	Not reached [-; -]	0.70 [0.50; 0.97]	0.032	
Rest of World	41	13 (31.7)	Not reached [-; -]	25	9 (36.0)	Not reached [50.8; -]	0.86 [0.37; 2.00]	0.721	
Nodal Status									
Negative	376	37 (9.8)	Not reached [-; -]	194	29 (14.9)	Not reached [-; -]	0.65 [0.40; 1.05]	0.077	0.988
Positive	408	78 (19.1)	Not reached [-; -]	196	56 (28.6)	Not reached [-; -]	0.65 [0.46; 0.91]	0.013	
Tumor Size									
T1/T2	580	54 (9.3)	Not reached [-; -]	290	51 (17.6)	Not reached [-; -]	0.51 [0.35; 0.75]	< 0.001	0.062
T3/T4	204	61 (29.9)	Not reached [-; -]	100	34 (34.0)	Not reached [-; -]	0.88 [0.58; 1.34]	0.548	
Choice of Carboplatin									
Q3W	334	46 (13.8)	Not reached [-; -]	167	36 (21.6)	Not reached [-; -]	0.63 [0.41; 0.97]	0.037	0.841
Weekly	444	68 (15.3)	Not reached [-; -]	220	49 (22.3)	Not reached [-; -]	0.67 [0.46; 0.96]	0.031	

a: Database Cutoff Date: 22MAR2024
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
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-G5.2: Morbidität

Ereignisfreies Überleben

Tabelle 4G-29: 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	130 (18.6)	Not reached [-; -]	342	98 (28.7)	Not reached [-; -]	0.61 [0.47; 0.80]	< 0.001	0.147
≥ 65	84	29 (34.5)	Not reached [79.0; -]	48	16 (33.3)	Not reached [-; -]	0.99 [0.54; 1.82]	0.976	
ECOG Performance Status									
0	678	132 (19.5)	Not reached [-; -]	341	98 (28.7)	Not reached [-; -]	0.63 [0.49; 0.82]	< 0.001	0.475
1	106	27 (25.5)	Not reached [-; -]	49	16 (32.7)	Not reached [-; -]	0.80 [0.43; 1.49]	0.487	
Geographic Region									
Asia	136	18 (13.2)	Not reached [-; -]	80	22 (27.5)	Not reached [-; -]	0.43 [0.23; 0.81]	0.008	0.268
Europe/Israel/North America/Australia	607	126 (20.8)	Not reached [-; -]	285	83 (29.1)	Not reached [-; -]	0.68 [0.52; 0.90]	0.007	
Rest of World	41	15 (36.6)	Not reached [42.2; -]	25	9 (36.0)	Not reached [23.6; -]	0.95 [0.42; 2.18]	0.910	
Nodal Status									
Negative	376	57 (15.2)	Not reached [-; -]	194	49 (25.3)	Not reached [-; -]	0.56 [0.38; 0.82]	0.003	0.343
Positive	408	102 (25.0)	Not reached [-; -]	196	65 (33.2)	Not reached [-; -]	0.72 [0.53; 0.98]	0.036	
Tumor Size									
T1/T2	580	91 (15.7)	Not reached [-; -]	290	76 (26.2)	Not reached [-; -]	0.55 [0.41; 0.75]	< 0.001	0.090
T3/T4	204	68 (33.3)	Not reached [-; -]	100	38 (38.0)	Not reached [-; -]	0.86 [0.58; 1.28]	0.464	
Choice of Carboplatin									
Q3W	334	65	Not reached	167	45	Not reached	0.68	0.049	0.723

Study: KEYNOTE 522[a]	Pembrolizumab + Chemotherapy[b] / Pembrolizumab			Placebo + Chemotherapy[c] / Placebo			Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo		p-Value for Interaction Test[h]
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]	
		(19.5)	[-; -]		(26.9)	[-; -]	[0.47; 1.00]		
Weekly	444	92 (20.7)	Not reached [-; -]	220	69 (31.4)	Not reached [-; -]	0.62 [0.46; 0.85]	0.003	
PD-L1 CPS 1 Cutoff									
PD-L1 CPS ≥ 1	656	128 (19.5)	Not reached [-; -]	317	86 (27.1)	Not reached [-; -]	0.68 [0.52; 0.90]	0.006	0.351
PD-L1 CPS < 1	128	31 (24.2)	Not reached [-; -]	69	28 (40.6)	Not reached [61.7; -]	0.53 [0.31; 0.88]	0.015	
PD-L1 CPS 10 Cutoff									
PD-L1 CPS ≥ 10	393	55 (14.0)	Not reached [-; -]	177	39 (22.0)	Not reached [-; -]	0.59 [0.39; 0.89]	0.012	0.512
PD-L1 CPS < 10	391	104 (26.6)	Not reached [-; -]	209	75 (35.9)	Not reached [-; -]	0.71 [0.53; 0.96]	0.024	
PD-L1 CPS 20 Cutoff									
PD-L1 CPS ≥ 20	247	28 (11.3)	Not reached [-; -]	121	27 (22.3)	Not reached [-; -]	0.46 [0.27; 0.78]	0.004	0.168
PD-L1 CPS < 20	537	131 (24.4)	Not reached [-; -]	265	87 (32.8)	Not reached [-; -]	0.71 [0.54; 0.93]	0.013	
Menopausal Status									
Pre-menopausal	438	75 (17.1)	Not reached [-; -]	221	56 (25.3)	Not reached [-; -]	0.64 [0.46; 0.91]	0.013	0.852
Post-menopausal	345	84 (24.3)	Not reached [-; -]	169	58 (34.3)	Not reached [-; -]	0.66 [0.48; 0.93]	0.017	
Ethnic Origin									
Hispanic or Latino	85	29 (34.1)	Not reached [-; -]	39	15 (38.5)	Not reached [28.9; -]	0.80 [0.43; 1.49]	0.476	0.495
Not Hispanic or Latino	616	110 (17.9)	Not reached [-; -]	307	83 (27.0)	Not reached [-; -]	0.63 [0.47; 0.83]	0.001	
HER2 Status									
0-1+ by IHC	595	121 (20.3)	Not reached [-; -]	286	85 (29.7)	Not reached [-; -]	0.64 [0.49; 0.85]	0.002	0.755
2+ by IHC (but FISH-)	188	38 (20.2)	Not reached [-; -]	104	29 (27.9)	Not reached [-; -]	0.70 [0.43; 1.14]	0.155	
Baseline Lactate Dehydrogenase (LDH)									
≤ ULN	631	125 (19.8)	Not reached [-; -]	309	82 (26.5)	Not reached [-; -]	0.71 [0.53; 0.93]	0.014	0.336
> ULN	149	33 (22.1)	Not reached [-; -]	80	31 (38.8)	Not reached [70.1; -]	0.54 [0.33; 0.88]	0.013	

a: Database Cutoff Date: 22MAR2024

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 subgroups, 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

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

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

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]
subgroups, unstratified Cox regression model is used (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-30: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 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
PD-L1 CPS < 10	391	196 (50.1)	209	95 (45.5)	1.10 [0.92; 1.32]	0.282	

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
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-31: 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]		p-Value for Interaction[g]
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]	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
1	106	36 (34.0)	49	21 (42.9)	0.79 [0.52; 1.20]	0.276	

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**
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

EORTC QLQ-C30: Symptomskala Erschöpfung

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

Study: KEYNOTE 522[a] EORTC QLQ-C30 Fatigue	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	628	19.04 (19.96)	466	26.56 (23.26)	690	7.53 [5.45; 9.62]	1.19	0.483	-	0.339
Placebo + Chemotherapy[c] / Placebo	324	19.27 (19.79)	230	25.07 (21.95)	338	6.35 [3.51; 9.18]	[-2.13; 4.50]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	73	19.03 (20.16)	56	26.79 (20.74)	82	7.67 [1.30; 14.04]	-0.89	0.853	-	
Placebo + Chemotherapy[c] / Placebo	43	20.16 (19.44)	34	28.76 (26.68)	47	8.56 [0.71; 16.42]	[-10.45; 8.66]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	602	18.66 (19.69)	449	26.16 (22.66)	667	7.53 [5.42; 9.65]	0.43	0.801	-	0.522
Placebo + Chemotherapy[c] / Placebo	318	18.52 (19.04)	225	25.09 (22.43)	336	7.10 [4.26; 9.95]	[-2.91; 3.77]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	21.32 (21.51)	73	29.22 (24.88)	105	7.36 [1.59; 13.13]	2.88	0.526	-	
Placebo + Chemotherapy[c] / Placebo	49	24.94 (23.19)	39	28.21 (23.62)	49	4.48 [-3.10; 12.06]	[-6.09; 11.86]			

Study: KEYNOTE 522[a] EORTC QLQ-C30 Fatigue	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	22.81 (17.38)	99	26.82 (19.38)	135	5.37 [1.12; 9.62]	5.66	0.072	-	0.236
Placebo + Chemotherapy[c] / Placebo	79	19.27 (17.94)	60	20.00 (20.02)	79	-0.29 [-5.53; 4.94]	[-0.51; 11.84]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	533	18.43 (20.52)	393	26.97 (23.81)	598	7.86 [5.55; 10.16]	-0.20	0.914	-	
Placebo + Chemotherapy[c] / Placebo	263	20.15 (20.59)	186	27.18 (22.16)	281	8.06 [4.88; 11.24]	[-3.92; 3.51]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	14.20 (18.90)	30	20.74 (22.74)	39	10.16 [0.35; 19.97]	-6.86	0.373	-	
Placebo + Chemotherapy[c] / Placebo	25	11.56 (13.79)	18	27.16 (31.94)	25	17.02 [4.68; 29.36]	[-22.19; 8.47]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	336	17.69 (19.89)	253	27.01 (22.94)	372	8.84 [6.01; 11.67]	0.42	0.850	-	0.671
Placebo + Chemotherapy[c] / Placebo	181	18.78 (19.57)	133	25.90 (22.92)	191	8.41 [4.68; 12.15]	[-4.00; 4.84]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	365	20.27 (19.98)	269	26.19 (23.05)	400	6.29 [3.50; 9.08]	1.10	0.627	-	
Placebo + Chemotherapy[c] / Placebo	186	19.95 (19.91)	131	25.19 (22.34)	194	5.19 [1.39; 9.00]	[-3.34; 5.54]			
Tumor Size										
T1/T2										

Study: KEYNOTE 522[a] EORTC QLQ-C30 Fatigue	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	520	17.93 (18.57)	397	25.61 (22.21)	572	7.34 [5.15; 9.54]	1.10	0.530	-	0.947
Placebo + Chemotherapy[c] / Placebo	275	20.04 (19.79)	204	24.89 (22.02)	287	6.24 [3.32; 9.16]	[-2.34; 4.55]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	22.22 (23.28)	125	29.69 (25.12)	200	8.51 [4.00; 13.02]	-0.04	0.992	-	
Placebo + Chemotherapy[c] / Placebo	92	17.39 (19.51)	60	27.78 (24.51)	98	8.54 [2.32; 14.77]	[-7.26; 7.19]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	293	20.82 (20.46)	222	27.58 (24.42)	331	7.63 [4.41; 10.85]	1.16	0.659	-	0.541
Placebo + Chemotherapy[c] / Placebo	158	18.14 (19.96)	109	23.75 (23.98)	164	6.47 [2.08; 10.86]	[-4.00; 6.32]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	408	17.76 (19.52)	300	25.85 (21.87)	441	7.43 [4.92; 9.94]	0.07	0.973	-	
Placebo + Chemotherapy[c] / Placebo	207	20.18 (19.57)	154	26.98 (21.52)	219	7.36 [4.02; 10.70]	[-3.85; 3.98]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-33: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Übelkeit und Erbrechen aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Nausea And Vomiting	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	602	2.85 (9.74)	449	4.64 (12.15)	667	2.06 [0.79; 3.33]	0.74	0.459	-	0.883
Placebo + Chemotherapy[c] / Placebo	318	2.78 (9.46)	225	3.93 (12.62)	336	1.32 [-0.38; 3.02]	[-1.22; 2.70]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	2.36 (10.38)	73	4.11 (10.68)	105	1.22 [-1.34; 3.79]	1.42	0.470	-	
Placebo + Chemotherapy[c] / Placebo	49	5.10 (13.69)	39	3.85 (10.44)	49	-0.20 [-3.52; 3.13]	[-2.46; 5.29]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	3.91 (12.67)	99	3.87 (12.33)	135	1.30 [-1.41; 4.01]	2.24	0.266	-	0.882
Placebo + Chemotherapy[c] / Placebo	79	2.32 (6.39)	60	2.22 (9.44)	79	-0.94 [-4.30; 2.42]	[-1.72; 6.20]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	533	2.38 (8.15)	393	4.28 (11.45)	598	1.61 [0.38; 2.84]	0.40	0.689	-	
Placebo + Chemotherapy[c] / Placebo	263	3.55 (11.38)	186	3.94 (11.34)	281	1.21 [-0.48; 2.90]	[-1.54; 2.33]			
Rest of World										
Pembrolizumab + Chemotherapy[b] /	36	4.63 (17.64)	30	10.56 (15.46)	39	9.38 [1.23; 17.53]	2.54	0.669	-	

Study: KEYNOTE 522[a] EORTC QLQ-C30 Nausea And Vomiting	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	25	0.67 (3.33)	18	9.26 (24.40)	25	6.84 [-3.27; 16.95]	[-9.34; 14.42]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	336	2.23 (6.75)	253	5.20 (12.87)	372	3.00 [1.41; 4.59]	1.30	0.327	-	0.637
Placebo + Chemotherapy[c] / Placebo	181	2.30 (7.20)	133	3.76 (11.89)	191	1.70 [-0.44; 3.85]	[-1.30; 3.89]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	365	3.29 (11.97)	269	3.97 (11.00)	400	0.85 [-0.82; 2.51]	0.26	0.832	-	
Placebo + Chemotherapy[c] / Placebo	186	3.85 (12.32)	131	4.07 (12.76)	194	0.59 [-1.59; 2.77]	[-2.15; 2.67]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	520	2.60 (8.73)	397	4.11 (11.23)	572	1.42 [0.23; 2.61]	0.99	0.276	-	0.642
Placebo + Chemotherapy[c] / Placebo	275	3.39 (10.87)	204	3.27 (9.22)	287	0.43 [-1.12; 1.99]	[-0.79; 2.76]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	3.31 (12.47)	125	6.00 (13.94)	200	3.54 [0.54; 6.55]	-0.25	0.919	-	
Placebo + Chemotherapy[c] / Placebo	92	2.17 (7.50)	60	6.11 (19.40)	98	3.80 [-0.38; 7.97]	[-5.13; 4.63]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	293	2.84 (10.11)	222	4.80 (11.73)	331	2.28 [0.41; 4.15]	0.59	0.695	-	0.856

Study: KEYNOTE 522[a] EORTC QLQ-C30 Nausea And Vomiting	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo + Chemotherapy[c] / Placebo	158	2.64 (7.87)	109	4.28 (14.94)	164	1.69 [-0.84; 4.23]	[-2.36; 3.53]			
Weekly Pembrolizumab + Chemotherapy[b] / Pembrolizumab	408	2.74 (9.63)	300	4.39 (12.12)	441	1.59 [0.12; 3.06]	0.58	0.607	-	
Placebo + Chemotherapy[c] / Placebo	207	3.30 (11.43)	154	3.68 (10.13)	219	1.01 [-0.92; 2.94]	[-1.64; 2.81]			

a: Database Cutoff Date: 22MAR2024
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 timepoint
e: Number of participants in full-analysis-set population with data available for analysis in combined phases
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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Schmerzen

Tabelle 4G-34: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Schmerzen aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Pain	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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										

Study: KEYNOTE 522[a] EORTC QLQ-C30 Pain	Neoadjuvant Baseline		LTFU Year 1		Change from Neoadjuvant Baseline to LTFU Year 1		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo			p-Value for Interaction Test[h]
							Mean Difference at LTFU Year 1		Standardized Mean Difference at LTFU Year 1	
	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] / Pembrolizumab	628	16.00 (19.99)	466	20.28 (23.18)	690	4.58 [2.48; 6.68]	-0.01	0.994	-	0.919
Placebo + Chemotherapy[c] / Placebo	324	16.46 (18.22)	230	20.65 (21.97)	338	4.59 [1.74; 7.44]	[-3.35; 3.32]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	73	16.89 (21.06)	56	19.05 (19.44)	82	3.07 [-3.42; 9.56]	2.50	0.579	-	
Placebo + Chemotherapy[c] / Placebo	43	15.50 (22.24)	34	17.65 (24.25)	47	0.58 [-7.20; 8.35]	[-6.40; 11.39]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	602	16.00 (20.09)	449	20.12 (22.85)	667	4.58 [2.43; 6.73]	-0.49	0.775	-	0.343
Placebo + Chemotherapy[c] / Placebo	318	15.72 (18.37)	225	20.67 (22.19)	336	5.07 [2.18; 7.96]	[-3.87; 2.88]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	16.67 (20.20)	73	20.32 (22.61)	105	3.23 [-2.27; 8.73]	3.39	0.426	-	
Placebo + Chemotherapy[c] / Placebo	49	20.41 (20.49)	39	17.95 (22.74)	49	-0.15 [-7.36; 7.06]	[-5.00; 11.78]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	17.30 (17.03)	99	18.18 (17.51)	135	2.20 [-1.67; 6.08]	2.74	0.306	-	0.940
Placebo + Chemotherapy[c] / Placebo	79	13.71 (14.80)	60	14.44 (15.49)	79	-0.54 [-5.21; 4.13]	[-2.53; 8.01]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	533	15.23 (20.31)	393	20.14 (23.52)	598	5.01 [2.69; 7.33]	-0.10	0.957	-	

Study: KEYNOTE 522[a] EORTC QLQ-C30 Pain	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo + Chemotherapy[c] / Placebo	263	16.98 (19.78)	186	21.42 (22.39)	281	5.11 [1.92; 8.31]	[-3.81; 3.61]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	24.54 (25.04)	30	26.67 (27.54)	39	6.29 [-5.29; 17.87]	-3.02	0.732	-	
Placebo + Chemotherapy[c] / Placebo	25	18.00 (17.95)	18	27.78 (34.30)	25	9.31 [-5.10; 23.71]	[-20.57; 14.54]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	336	14.78 (19.22)	253	19.89 (22.85)	372	5.49 [2.73; 8.26]	-0.68	0.757	-	0.461
Placebo + Chemotherapy[c] / Placebo	181	13.90 (16.90)	133	20.43 (21.58)	191	6.18 [2.52; 9.84]	[-5.02; 3.65]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	365	17.31 (20.81)	269	20.38 (22.78)	400	3.37 [0.49; 6.24]	1.10	0.632	-	
Placebo + Chemotherapy[c] / Placebo	186	18.73 (20.07)	131	20.10 (22.99)	194	2.27 [-1.64; 6.17]	[-3.41; 5.61]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	520	13.91 (17.71)	397	19.35 (22.00)	572	5.69 [3.54; 7.85]	-0.09	0.957	-	0.474
Placebo + Chemotherapy[c] / Placebo	275	15.58 (19.07)	204	20.59 (21.34)	287	5.79 [2.91; 8.67]	[-3.50; 3.31]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	22.38 (24.74)	125	22.67 (25.08)	200	0.82 [-3.90; 5.55]	1.20	0.750	-	
Placebo + Chemotherapy[c] / Placebo	92	18.66 (17.44)	60	19.17 (25.27)	98	-0.37 [-6.82; 6.08]	[-6.20; 8.59]			
a: Database Cutoff Date: 22MAR2024										

Study: KEYNOTE 522[a] EORTC QLQ-C30 Pain	Neoadjuvant Baseline		LTFU Year 1		Change from Neoadjuvant Baseline to LTFU Year 1		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo			p-Value for Interaction Test[h]
							Mean Difference at LTFU Year 1		Standardized Mean Difference at LTFU Year 1	
	N[d]	Mean (SD)	N[d]	Mean (SD)	N[e]	Mean [95 %-CI][f]	[95 %-CI][f]	p-Value	[95 %-CI][g]	
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 timepoint										
e: Number of participants in full-analysis-set population with data available for analysis in combined phases										
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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; SD: Standard Deviation										

EORTC QLQ-C30: Symptomskala Dyspnoe

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

Study: KEYNOTE 522[a] EORTC QLQ-C30 Dyspnoea	Neoadjuvant Baseline		LTFU Year 1		Change from Neoadjuvant Baseline to LTFU Year 1		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo			p-Value for Interaction Test[h]
							Mean Difference at LTFU Year 1		Standardized Mean Difference at LTFU Year 1	
	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] / Pembrolizumab	628	5.47 (14.47)	466	13.09 (22.14)	690	7.48 [5.60; 9.37]	1.81	0.254	-	0.361
Placebo + Chemotherapy[c] / Placebo	324	5.76 (15.77)	230	11.45 (20.17)	338	5.67 [3.06; 8.28]	[-1.30; 4.93]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	73	9.13 (16.91)	56	10.71 (20.21)	82	0.93 [-4.27; 6.13]	-1.34	0.736	-	
Placebo + Chemotherapy[c] /	43	8.53 (17.96)	34	12.75 (18.38)	47	2.27 [-4.19; 8.73]	[-9.21; 6.53]			

Study: KEYNOTE 522[a] EORTC QLQ-C30 Dyspnoea	Neoadjuvant Baseline		LTFU Year 1		Change from Neoadjuvant Baseline to LTFU Year 1		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo			p-Value for Interaction Test[h]
							Mean Difference at LTFU Year 1		Standardized Mean Difference at LTFU Year 1	
	N[d]	Mean (SD)	N[d]	Mean (SD)	N[e]	Mean [95 %-CI][f]	[95 %-CI][f]	p-Value	[95 %-CI][g]	
Placebo										
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	602	5.87 (14.60)	449	12.69 (21.59)	667	6.81 [4.92; 8.71]	1.33	0.398	-	0.683
Placebo + Chemotherapy[c] / Placebo	318	5.14 (14.68)	225	11.11 (19.42)	336	5.48 [2.89; 8.07]	[-1.76; 4.42]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	5.72 (15.82)	73	13.70 (24.11)	105	7.99 [3.01; 12.97]	4.57	0.273	-	
Placebo + Chemotherapy[c] / Placebo	49	12.24 (22.25)	39	14.53 (22.68)	49	3.41 [-3.29; 10.12]	[-3.65; 12.80]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	6.31 (13.11)	99	13.47 (20.71)	135	6.88 [2.87; 10.89]	4.16	0.175	-	0.087
Placebo + Chemotherapy[c] / Placebo	79	6.75 (16.35)	60	9.44 (16.34)	79	2.72 [-2.28; 7.72]	[-1.88; 10.20]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	533	5.75 (15.17)	393	12.98 (22.30)	598	6.97 [4.94; 9.00]	1.55	0.368	-	
Placebo + Chemotherapy[c] / Placebo	263	5.96 (16.29)	186	11.65 (19.03)	281	5.42 [2.57; 8.27]	[-1.83; 4.93]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	5.56 (14.91)	30	8.89 (21.32)	39	1.18 [-6.26; 8.61]	-8.84	0.147	-	
Placebo + Chemotherapy[c] / Placebo	25	5.33 (12.47)	18	18.52 (34.72)	25	10.02 [0.63; 19.41]	[-20.88; 3.19]			
Nodal Status										

Study: KEYNOTE 522[a] EORTC QLQ-C30 Dyspnoea	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	336	4.46 (13.50)	253	12.91 (22.03)	372	7.85 [5.33; 10.37]	2.47	0.238	-	0.843
Placebo + Chemotherapy[c] / Placebo	181	5.89 (14.56)	133	11.28 (20.05)	191	5.37 [1.98; 8.77]	[-1.64; 6.59]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	365	7.12 (15.76)	269	12.76 (21.89)	400	5.86 [3.36; 8.37]	0.91	0.664	-	
Placebo + Chemotherapy[c] / Placebo	186	6.27 (17.40)	131	11.96 (19.86)	194	4.95 [1.48; 8.42]	[-3.20; 5.02]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	520	5.26 (13.17)	397	12.17 (21.19)	572	6.57 [4.59; 8.55]	1.70	0.300	-	0.834
Placebo + Chemotherapy[c] / Placebo	275	6.55 (16.28)	204	10.95 (18.86)	287	4.87 [2.19; 7.55]	[-1.52; 4.92]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	7.55 (18.54)	125	14.93 (24.12)	200	7.31 [3.42; 11.20]	0.31	0.925	-	
Placebo + Chemotherapy[c] / Placebo	92	4.71 (15.30)	60	13.89 (23.20)	98	7.00 [1.51; 12.49]	[-6.22; 6.84]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	293	6.60 (15.91)	222	13.36 (23.01)	331	6.67 [3.77; 9.58]	1.33	0.583	-	0.914
Placebo + Chemotherapy[c] / Placebo	158	5.27 (15.29)	109	11.01 (19.80)	164	5.35 [1.34; 9.35]	[-3.43; 6.08]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	408	5.31 (13.89)	300	12.44 (21.13)	441	7.01 [4.80; 9.21]	1.84	0.319	-	

Study: KEYNOTE 522[a] EORTC QLQ-C30 Dyspnoea	Neoadjuvant Baseline		LTFU Year 1		Change from Neoadjuvant Baseline to LTFU Year 1		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo			p-Value for Interaction Test[h]
							Mean Difference at LTFU Year 1		Standardized Mean Difference at LTFU Year 1	
	N[d]	Mean (SD)	N[d]	Mean (SD)	N[e]	Mean [95 %-CI][f]	[95 %-CI][f]	p-Value	[95 %-CI][g]	
Placebo + Chemotherapy[c] / Placebo	207	6.44 (16.14)	154	12.12 (20.10)	219	5.16 [2.15; 8.18]	[-1.79; 5.48]			

a: Database Cutoff Date: 22MAR2024
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 timepoint
e: Number of participants in full-analysis-set population with data available for analysis in combined phases
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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

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

Study: KEYNOTE 522[a] EORTC QLQ-C30 Insomnia	Neoadjuvant Baseline		LTFU Year 1		Change from Neoadjuvant Baseline to LTFU Year 1		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo			p-Value for Interaction Test[h]
							Mean Difference at LTFU Year 1		Standardized Mean Difference at LTFU Year 1	
	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] / Pembrolizumab	628	23.73 (26.72)	466	25.75 (27.99)	690	1.93 [-0.81; 4.67]	-0.89	0.681	-	0.214
Placebo + Chemotherapy[c] / Placebo	324	24.59 (27.18)	230	26.52 (30.95)	338	2.82 [-0.86; 6.51]	[-5.16; 3.37]			
≥ 65										

Study: KEYNOTE 522[a] EORTC QLQ-C30 Insomnia	Neoadjuvant Baseline		LTFU Year 1		Change from Neoadjuvant Baseline to LTFU Year 1		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo			p-Value for Interaction Test[h]
							Mean Difference at LTFU Year 1		Standardized Mean Difference at LTFU Year 1	
	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] / Pembrolizumab	73	28.77 (29.04)	56	25.00 (27.89)	82	-4.56 [-12.62; 3.51]	-5.64	0.341	-	
Placebo + Chemotherapy[c] / Placebo	43	31.78 (29.05)	34	31.37 (30.64)	47	1.08 [-8.80; 10.96]	[-17.35; 6.07]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	602	24.47 (27.24)	449	25.39 (27.71)	667	0.72 [-2.08; 3.51]	-2.43	0.269	-	0.274
Placebo + Chemotherapy[c] / Placebo	318	25.58 (27.57)	225	27.41 (31.41)	336	3.15 [-0.58; 6.88]	[-6.75; 1.88]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	22.90 (25.49)	73	27.40 (29.58)	105	4.30 [-2.48; 11.07]	3.39	0.527	-	
Placebo + Chemotherapy[c] / Placebo	49	24.49 (27.02)	39	25.64 (28.06)	49	0.90 [-8.03; 9.84]	[-7.18; 13.96]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	22.47 (23.84)	99	25.59 (26.87)	135	4.57 [-0.63; 9.77]	7.99	0.043	0.33	0.068
Placebo + Chemotherapy[c] / Placebo	79	20.25 (26.38)	60	16.67 (22.55)	79	-3.42 [-9.87; 3.02]	[0.27; 15.71]		[0.01; 0.65]	
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	533	24.58 (27.69)	393	25.70 (27.94)	598	0.29 [-2.74; 3.33]	-3.96	0.101	-	
Placebo + Chemotherapy[c] / Placebo	263	28.01 (28.03)	186	30.47 (31.63)	281	4.25 [0.12; 8.38]	[-8.69; 0.77]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	25.93 (27.73)	30	25.56 (32.38)	39	0.46 [-12.05; 12.97]	-9.58	0.329	-	

Study: KEYNOTE 522[a] EORTC QLQ-C30 Insomnia	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo + Chemotherapy[c] / Placebo	25	14.67 (19.44)	18	27.78 (40.02)	25	10.05 [-5.60; 25.69]	[-29.07; 9.90]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	336	24.90 (27.95)	253	27.14 (27.72)	372	1.82 [-1.91; 5.56]	-1.05	0.715	-	0.993
Placebo + Chemotherapy[c] / Placebo	181	27.44 (27.48)	133	28.07 (30.66)	191	2.87 [-1.99; 7.74]	[-6.69; 4.59]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	365	23.65 (26.10)	269	24.29 (28.15)	400	0.70 [-2.91; 4.30]	-2.05	0.479	-	
Placebo + Chemotherapy[c] / Placebo	186	23.48 (27.37)	131	26.21 (31.22)	194	2.75 [-2.15; 7.64]	[-7.73; 3.63]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	520	23.91 (26.80)	397	26.03 (28.42)	572	1.81 [-1.18; 4.79]	-0.38	0.870	-	0.417
Placebo + Chemotherapy[c] / Placebo	275	25.45 (28.88)	204	26.96 (30.64)	287	2.19 [-1.74; 6.11]	[-4.93; 4.17]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	25.23 (27.59)	125	24.53 (26.49)	200	-0.33 [-5.59; 4.93]	-4.54	0.291	-	
Placebo + Chemotherapy[c] / Placebo	92	25.36 (22.84)	60	27.78 (31.99)	98	4.21 [-3.05; 11.46]	[-12.99; 3.91]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	293	26.73 (27.76)	222	26.28 (29.84)	331	-0.02 [-4.06; 4.02]	-1.58	0.624	-	0.800
Placebo + Chemotherapy[c] / Placebo	158	25.11 (28.57)	109	25.99 (29.87)	164	1.56 [-3.88; 7.00]	[-7.90; 4.75]			

Study: KEYNOTE 522[a] EORTC QLQ-C30 Insomnia	Neoadjuvant Baseline		LTFU Year 1		Change from Neoadjuvant Baseline to LTFU Year 1		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo			p-Value for Interaction Test[h]
							Mean Difference at LTFU Year 1		Standardized Mean Difference at LTFU Year 1	
	N[d]	Mean (SD)	N[d]	Mean (SD)	N[e]	Mean [95 %-CI][f]	[95 %-CI][f]	p-Value	[95 %-CI][g]	
Weekly Pembrolizumab + Chemotherapy[b] / Pembrolizumab	408	22.47 (26.31)	300	25.22 (26.52)	441	1.96 [-1.42; 5.33]	-1.78	0.498	-	
Placebo + Chemotherapy[c] / Placebo	207	25.76 (26.72)	154	28.14 (31.69)	219	3.74 [-0.72; 8.20]	[-6.95; 3.38]			

a: Database Cutoff Date: 22MAR2024
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 timepoint
e: Number of participants in full-analysis-set population with data available for analysis in combined phases
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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Appetitverlust

Tabelle 4G-37: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Appetitverlust aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Appetite Loss	Neoadjuvant Baseline		LTFU Year 1		Change from Neoadjuvant Baseline to LTFU Year 1		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo			p-Value for Interaction Test[h]
							Mean Difference at LTFU Year 1		Standardized Mean Difference at LTFU Year 1	
	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)	466	8.37 (19.28)	690	-0.12 [-2.01; 1.78]	1.76	0.221	-	0.109

Study: KEYNOTE 522[a] EORTC QLQ-C30 Appetite Loss	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	324	8.85 (18.09)	230	6.52 (15.91)	338	-1.87 [-4.37; 0.63]	[-1.06; 4.58]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	73	8.22 (15.50)	56	10.71 (22.12)	82	2.02 [-4.61; 8.66]	-5.32	0.303	-	
Placebo + Chemotherapy[c] / Placebo	43	9.30 (19.69)	34	16.67 (26.27)	47	7.34 [-0.99; 15.67]	[-15.51; 4.88]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	602	8.03 (16.55)	449	8.17 (18.97)	667	-0.05 [-1.98; 1.88]	0.73	0.622	-	0.718
Placebo + Chemotherapy[c] / Placebo	318	8.39 (17.55)	225	7.41 (17.38)	336	-0.78 [-3.34; 1.77]	[-2.18; 3.65]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	9.76 (20.89)	73	11.42 (23.05)	105	2.09 [-3.42; 7.60]	2.43	0.565	-	
Placebo + Chemotherapy[c] / Placebo	49	12.24 (22.25)	39	10.26 (20.45)	49	-0.34 [-7.49; 6.82]	[-5.91; 10.77]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	9.85 (18.76)	99	8.42 (17.39)	135	-0.95 [-4.68; 2.77]	1.61	0.534	-	0.766
Placebo + Chemotherapy[c] / Placebo	79	7.59 (16.84)	60	5.56 (12.53)	79	-2.56 [-7.05; 1.93]	[-3.48; 6.70]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	533	8.01 (16.93)	393	8.57 (19.99)	598	0.06 [-2.10; 2.22]	0.17	0.920	-	
Placebo + Chemotherapy[c] /	263	9.51 (18.83)	186	8.78 (18.68)	281	-0.11 [-3.04; 2.82]	[-3.16; 3.50]			

Study: KEYNOTE 522[a] EORTC QLQ-C30 Appetite Loss	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo										
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	6.48 (15.57)	30	10.00 (21.71)	39	1.71 [-6.82; 10.25]	4.44	0.501	-	
Placebo + Chemotherapy[c] / Placebo	25	6.67 (16.67)	18	5.56 (23.57)	25	-2.72 [-13.44; 7.99]	[-8.71; 17.58]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	336	7.54 (15.96)	253	10.01 (20.70)	372	2.06 [-0.61; 4.72]	2.84	0.170	-	0.246
Placebo + Chemotherapy[c] / Placebo	181	8.47 (17.97)	133	7.02 (17.43)	191	-0.78 [-4.27; 2.70]	[-1.23; 6.90]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	365	8.95 (18.30)	269	7.31 (18.44)	400	-1.65 [-4.16; 0.87]	-1.03	0.587	-	
Placebo + Chemotherapy[c] / Placebo	186	9.32 (18.58)	131	8.65 (18.30)	194	-0.62 [-3.94; 2.70]	[-4.74; 2.69]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	520	8.27 (17.25)	397	8.40 (18.86)	572	-0.25 [-2.24; 1.75]	2.43	0.104	-	0.063
Placebo + Chemotherapy[c] / Placebo	275	9.45 (18.88)	204	6.21 (15.33)	287	-2.68 [-5.26; -0.09]	[-0.50; 5.36]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	8.29 (17.18)	125	9.33 (21.83)	200	1.54 [-2.71; 5.79]	-3.94	0.256	-	
Placebo + Chemotherapy[c] / Placebo	92	7.25 (16.26)	60	13.33 (23.93)	98	5.47 [-0.39; 11.34]	[-10.74; 2.87]			
Choice of Carboplatin										

Study: KEYNOTE 522[a] EORTC QLQ-C30 Appetite Loss	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	293	7.62 (16.97)	222	8.86 (20.95)	331	1.06 [-1.82; 3.94]	1.96	0.390	-	0.458
Placebo + Chemotherapy[c] / Placebo	158	8.02 (17.42)	109	6.73 (18.02)	164	-0.90 [-4.78; 2.98]	[-2.52; 6.44]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	408	8.74 (17.40)	300	8.44 (18.56)	441	-0.59 [-2.98; 1.80]	-0.17	0.923	-	
Placebo + Chemotherapy[c] / Placebo	207	9.50 (18.89)	154	8.66 (17.80)	219	-0.42 [-3.52; 2.68]	[-3.68; 3.33]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Verstopfung

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

Study: KEYNOTE 522[a] EORTC QLQ-C30 Constipation	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	628	6.63 (16.31)	466	12.37 (22.76)	690	5.01 [2.99; 7.02]	2.46	0.137	-	0.405
Placebo + Chemotherapy[c] / Placebo	324	9.77 (19.20)	230	10.58 (21.34)	338	2.54 [-0.21; 5.30]	[-0.79; 5.71]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	73	10.50 (22.82)	56	14.88 (26.15)	82	4.52 [-1.97; 11.00]	-0.34	0.944	-	
Placebo + Chemotherapy[c] / Placebo	43	8.53 (16.42)	34	11.76 (21.53)	47	4.86 [-3.07; 12.79]	[-9.98; 9.29]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	602	7.14 (17.27)	449	12.92 (23.28)	667	5.21 [3.12; 7.30]	2.38	0.163	-	0.741
Placebo + Chemotherapy[c] / Placebo	318	9.54 (18.81)	225	10.67 (21.47)	336	2.83 [-0.01; 5.66]	[-0.97; 5.73]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	6.40 (16.27)	73	10.96 (22.26)	105	3.99 [-0.83; 8.81]	1.77	0.648	-	
Placebo + Chemotherapy[c] / Placebo	49	10.20 (19.49)	39	11.11 (20.71)	49	2.21 [-4.23; 8.65]	[-5.89; 9.44]			
Geographic Region										
Asia										
Pembrolizumab +	132	9.85 (18.30)	99	14.81 (23.44)	135	2.67 [-1.67; 7.01]	4.84	0.142	-	0.369

Study: KEYNOTE 522[a] EORTC QLQ-C30 Constipation	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Chemotherapy[b] / Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	79	15.61 (23.17)	60	10.00 (17.68)	79	-2.17 [-7.55; 3.22]	[-1.63; 11.30]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	533	6.44 (16.92)	393	11.70 (22.81)	598	5.02 [2.87; 7.16]	2.25	0.207	-	
Placebo + Chemotherapy[c] / Placebo	263	8.11 (17.28)	186	9.68 (20.26)	281	2.77 [-0.21; 5.75]	[-1.25; 5.75]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	5.56 (14.91)	30	17.78 (25.87)	39	11.76 [0.98; 22.54]	-6.11	0.478	-	
Placebo + Chemotherapy[c] / Placebo	25	6.67 (16.67)	18	24.07 (35.80)	25	17.87 [4.05; 31.70]	[-23.27; 11.05]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	336	6.45 (15.28)	253	15.42 (25.28)	372	7.36 [4.54; 10.18]	4.92	0.036	0.22	0.216
Placebo + Chemotherapy[c] / Placebo	181	10.68 (18.16)	133	11.03 (22.74)	191	2.44 [-1.35; 6.22]	[0.33; 9.51]		[0.01; 0.42]	
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	365	7.58 (18.66)	269	10.04 (20.63)	400	2.75 [0.12; 5.37]	0.22	0.917	-	
Placebo + Chemotherapy[c] / Placebo	186	8.60 (19.55)	131	10.43 (19.86)	194	2.53 [-1.00; 6.06]	[-3.84; 4.27]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	520	6.86 (16.87)	397	12.51 (22.66)	572	5.04 [2.90; 7.17]	2.15	0.217	-	0.766

Study: KEYNOTE 522[a] EORTC QLQ-C30 Constipation	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo + Chemotherapy[c] / Placebo	275	9.82 (18.58)	204	11.11 (21.36)	287	2.89 [0.03; 5.75]	[-1.26; 5.57]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	7.55 (17.87)	125	13.07 (24.65)	200	5.17 [0.88; 9.47]	2.58	0.464	-	
Placebo + Chemotherapy[c] / Placebo	92	9.06 (19.83)	60	9.44 (21.34)	98	2.60 [-3.36; 8.55]	[-4.35; 9.50]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	293	6.94 (17.70)	222	13.51 (24.51)	331	6.31 [3.26; 9.35]	3.21	0.196	-	0.299
Placebo + Chemotherapy[c] / Placebo	158	8.44 (18.41)	109	8.87 (19.59)	164	3.09 [-1.05; 7.24]	[-1.66; 8.09]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	408	7.11 (16.72)	300	12.00 (22.07)	441	4.04 [1.57; 6.52]	1.23	0.542	-	
Placebo + Chemotherapy[c] / Placebo	207	10.31 (19.18)	154	12.12 (22.49)	219	2.81 [-0.52; 6.15]	[-2.73; 5.19]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-C30: Symptomskala Diarrhö

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

Study: KEYNOTE 522[a] EORTC QLQ-C30 Diarrhea	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	628	5.41 (13.54)	466	5.87 (14.95)	690	0.70 [-0.78; 2.18]	1.80	0.114	-	0.959
Placebo + Chemotherapy[c] / Placebo	324	5.14 (13.41)	230	4.20 (13.10)	338	-1.10 [-3.07; 0.87]	[-0.43; 4.03]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	73	4.57 (12.81)	56	4.76 (19.52)	82	0.33 [-4.48; 5.14]	0.30	0.935	-	
Placebo + Chemotherapy[c] / Placebo	43	3.10 (9.80)	34	2.94 (9.60)	47	0.04 [-5.88; 5.95]	[-6.84; 7.43]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	602	5.43 (13.19)	449	5.94 (15.89)	667	0.86 [-0.69; 2.40]	2.21	0.065	-	0.473
Placebo + Chemotherapy[c] / Placebo	318	4.82 (12.88)	225	3.85 (12.40)	336	-1.35 [-3.40; 0.70]	[-0.14; 4.55]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	4.71 (15.07)	73	4.57 (12.81)	105	0.80 [-2.69; 4.29]	0.16	0.953	-	
Placebo + Chemotherapy[c] / Placebo	49	5.44 (14.19)	39	5.13 (14.38)	49	0.64 [-3.88; 5.15]	[-5.12; 5.43]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b] /	132	8.08 (14.92)	99	6.06 (16.05)	135	-2.01 [-5.36; 1.33]	2.17	0.351	-	0.563

Study: KEYNOTE 522[a] EORTC QLQ-C30 Diarrhea	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	79	8.02 (15.30)	60	3.89 (10.79)	79	-4.18 [-8.23; -0.14]	[-2.41; 6.76]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	533	4.88 (13.29)	393	5.68 (15.02)	598	1.17 [-0.38; 2.71]	2.10	0.085	-	
Placebo + Chemotherapy[c] / Placebo	263	4.18 (12.50)	186	3.58 (11.46)	281	-0.93 [-3.03; 1.17]	[-0.29; 4.48]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	1.85 (7.74)	30	5.56 (19.74)	39	5.81 [-3.10; 14.72]	1.57	0.822	-	
Placebo + Chemotherapy[c] / Placebo	25	2.67 (9.23)	18	9.26 (25.06)	25	4.24 [-7.05; 15.54]	[-12.44; 15.57]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	336	6.05 (15.01)	253	6.06 (16.22)	372	0.34 [-1.77; 2.46]	1.80	0.258	-	0.599
Placebo + Chemotherapy[c] / Placebo	181	5.52 (13.84)	133	4.51 (12.83)	191	-1.46 [-4.19; 1.28]	[-1.33; 4.93]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	365	4.66 (11.83)	269	5.45 (14.80)	400	1.19 [-0.72; 3.09]	2.09	0.162	-	
Placebo + Chemotherapy[c] / Placebo	186	4.30 (12.23)	131	3.56 (12.58)	194	-0.91 [-3.47; 1.66]	[-0.84; 5.03]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	520	5.13 (13.06)	397	5.63 (15.14)	572	0.51 [-1.09; 2.12]	1.90	0.115	-	0.745
Placebo + Chemotherapy[c] / Placebo	275	5.58 (14.00)	204	3.92 (11.74)	287	-1.38 [-3.47; 0.71]	[-0.46; 4.26]			

Study: KEYNOTE 522[a] EORTC QLQ-C30 Diarrhea	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	5.89 (14.56)	125	6.13 (16.60)	200	1.84 [-1.17; 4.86]	1.96	0.433	-	
Placebo + Chemotherapy[c] / Placebo	92	2.90 (9.44)	60	4.44 (15.61)	98	-0.11 [-4.30; 4.08]	[-2.95; 6.87]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	293	5.23 (12.76)	222	5.71 (14.79)	331	1.15 [-1.01; 3.31]	1.93	0.257	-	0.907
Placebo + Chemotherapy[c] / Placebo	158	4.43 (12.54)	109	4.28 (14.42)	164	-0.78 [-3.69; 2.12]	[-1.41; 5.28]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	408	5.39 (13.95)	300	5.78 (16.01)	441	0.61 [-1.28; 2.50]	1.95	0.174	-	
Placebo + Chemotherapy[c] / Placebo	207	5.15 (13.35)	154	3.90 (11.40)	219	-1.34 [-3.81; 1.13]	[-0.86; 4.77]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-BR23

EORTC QLQ-BR23: Symptomskala Nebenwirkungen der systemischen Therapie

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

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Systemic Therapy Side Effects	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	624	8.02 (10.65)	465	14.48 (13.66)	689	6.70 [5.45; 7.95]	0.63	0.552	-	0.529
Placebo + Chemotherapy[c] / Placebo	320	8.07 (11.00)	229	13.89 (15.87)	338	6.07 [4.33; 7.80]	[-1.45; 2.71]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	71	8.92 (11.49)	55	14.81 (16.72)	81	6.24 [2.07; 10.41]	0.54	0.869	-	
Placebo + Chemotherapy[c] / Placebo	42	7.03 (8.36)	34	13.87 (12.86)	47	5.70 [0.51; 10.90]	[-5.89; 6.96]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	597	7.98 (10.70)	448	14.56 (14.07)	666	6.86 [5.55; 8.17]	0.37	0.737	-	0.788
Placebo + Chemotherapy[c] / Placebo	314	7.54 (10.75)	224	14.01 (15.80)	336	6.49 [4.69; 8.29]	[-1.79; 2.53]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	98	8.94 (10.97)	72	14.22 (13.67)	104	5.18 [2.14; 8.22]	1.24	0.619	-	
Placebo + Chemotherapy[c] / Placebo	48	10.62 (10.27)	39	13.19 (13.80)	49	3.94 [-0.14; 8.02]	[-3.68; 6.15]			
Geographic Region										

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Systemic Therapy Side Effects	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Asia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	131	10.47 (10.65)	99	12.17 (12.38)	135	2.12 [-0.35; 4.58]	1.02	0.584	-	0.263
Placebo + Chemotherapy[c] / Placebo	79	9.64 (11.74)	60	10.48 (10.40)	79	1.10 [-1.95; 4.16]	[-2.64; 4.67]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	528	7.37 (10.47)	391	14.81 (14.05)	596	7.61 [6.27; 8.95]	0.87	0.450	-	
Placebo + Chemotherapy[c] / Placebo	258	7.18 (10.05)	185	13.98 (14.81)	281	6.73 [4.83; 8.64]	[-1.39; 3.14]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	10.45 (13.36)	30	18.41 (17.27)	39	8.81 [1.13; 16.49]	-6.52	0.290	-	
Placebo + Chemotherapy[c] / Placebo	25	10.48 (13.33)	18	24.34 (28.19)	25	15.33 [5.56; 25.10]	[-18.76; 5.72]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	333	7.35 (10.01)	252	15.17 (14.47)	371	7.84 [6.13; 9.55]	0.46	0.748	-	0.785
Placebo + Chemotherapy[c] / Placebo	178	6.55 (8.74)	132	14.03 (14.23)	191	7.38 [5.08; 9.69]	[-2.33; 3.25]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	362	8.81 (11.33)	268	13.89 (13.54)	399	5.49 [3.80; 7.19]	0.56	0.695	-	
Placebo + Chemotherapy[c] / Placebo	184	9.29 (12.22)	131	13.74 (16.72)	194	4.93 [2.57; 7.29]	[-2.25; 3.38]			
Tumor Size										
T1/T2										
Pembrolizumab +	516	7.50 (9.89)	396	14.17 (13.75)	571	6.82 [5.49; 8.16]	1.41	0.199	-	0.138

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Systemic Therapy Side Effects	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Chemotherapy[b] / Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	271	8.40 (11.35)	204	13.31 (13.80)	287	5.41 [3.61; 7.21]	[-0.74; 3.57]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	179	9.87 (12.73)	124	15.63 (14.76)	199	5.75 [3.04; 8.46]	-3.27	0.168	-	
Placebo + Chemotherapy[c] / Placebo	91	6.59 (8.48)	59	15.90 (20.31)	98	9.02 [5.16; 12.88]	[-7.93; 1.39]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	292	8.50 (11.60)	221	14.91 (14.81)	330	7.03 [5.15; 8.92]	0.23	0.884	-	0.772
Placebo + Chemotherapy[c] / Placebo	155	7.04 (8.48)	109	13.32 (15.70)	164	6.80 [4.18; 9.42]	[-2.92; 3.39]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	403	7.83 (10.07)	299	14.22 (13.39)	440	6.36 [4.81; 7.91]	0.38	0.769	-	
Placebo + Chemotherapy[c] / Placebo	205	8.39 (11.88)	153	14.38 (15.40)	219	5.98 [3.87; 8.09]	[-2.16; 2.91]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-BR23: Symptomskala Symptome im Brustbereich

Tabelle 4G-41: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Symptome im Brustbereich aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Breast Symptoms	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	597	18.27 (19.98)	448	15.79 (18.15)	666	-2.13 [-4.04; -0.23]	-0.18	0.903	-	0.858
Placebo + Chemotherapy[c] / Placebo	314	17.60 (19.12)	224	15.07 (19.53)	336	-1.96 [-4.45; 0.53]	[-2.99; 2.64]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	98	21.09 (22.46)	72	14.24 (16.46)	104	-7.66 [-12.25; -3.08]	1.06	0.738	-	
Placebo + Chemotherapy[c] / Placebo	48	23.96 (19.80)	39	12.82 (17.51)	49	-8.72 [-14.42; -3.02]	[-5.18; 7.29]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	131	19.34 (18.93)	99	16.75 (17.11)	135	-1.75 [-5.48; 1.98]	1.43	0.579	-	0.478
Placebo + Chemotherapy[c] / Placebo	79	16.56 (14.03)	60	13.06 (13.58)	79	-3.18 [-7.69; 1.32]	[-3.66; 6.53]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	528	17.80 (19.69)	391	15.32 (18.36)	596	-2.31 [-4.28; -0.33]	0.19	0.904	-	
Placebo + Chemotherapy[c] / Placebo	258	17.73 (18.03)	185	15.00 (19.31)	281	-2.49 [-5.16; 0.17]	[-2.84; 3.21]			
Rest of World										
Pembrolizumab + Chemotherapy[b] /	36	28.94 (30.44)	30	15.00 (14.75)	39	-15.52 [-26.64; -4.41]	-7.31	0.299	-	

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Breast Symptoms	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	25	31.67 (35.84)	18	17.59 (31.69)	25	-8.22 [-21.31; 4.88]	[-21.32; 6.71]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	333	15.39 (17.19)	252	15.64 (19.15)	371	-0.00 [-2.42; 2.41]	1.73	0.352	-	0.443
Placebo + Chemotherapy[c] / Placebo	178	15.54 (16.32)	132	13.57 (16.23)	191	-1.73 [-4.88; 1.42]	[-1.92; 5.37]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	362	21.69 (22.49)	268	15.52 (16.71)	399	-5.51 [-8.07; -2.95]	-1.23	0.513	-	
Placebo + Chemotherapy[c] / Placebo	184	21.24 (21.48)	131	15.90 (21.84)	194	-4.28 [-7.62; -0.95]	[-4.91; 2.46]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	516	14.28 (15.46)	396	15.26 (18.01)	571	0.95 [-0.86; 2.76]	1.17	0.414	-	0.345
Placebo + Chemotherapy[c] / Placebo	271	15.47 (15.90)	204	14.09 (16.74)	287	-0.21 [-2.60; 2.18]	[-1.63; 3.96]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	179	31.33 (26.59)	124	16.60 (17.64)	199	-13.92 [-18.20; -9.65]	-2.53	0.421	-	
Placebo + Chemotherapy[c] / Placebo	91	27.29 (25.09)	59	16.95 (26.12)	98	-11.39 [-17.03; -5.76]	[-8.71; 3.65]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	292	19.01 (20.29)	221	15.20 (18.34)	330	-3.02 [-5.68; -0.35]	-1.39	0.499	-	0.622

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Breast Symptoms	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo + Chemotherapy[c] / Placebo Weekly	155	16.67 (18.46)	109	14.14 (19.63)	164	-1.63 [-5.16; 1.90]	[-5.41; 2.64]			
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	403	18.42 (20.43)	299	15.86 (17.62)	440	-2.77 [-5.13; -0.42]	0.69	0.689	-	
Placebo + Chemotherapy[c] / Placebo	205	19.63 (19.88)	153	15.25 (19.02)	219	-3.46 [-6.49; -0.43]	[-2.68; 4.06]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-BR23: Symptomskala Symptome im Armbereich

Tabelle 4G-42: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Symptome im Armbereich aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Arm Symptoms	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	624	10.65 (16.52)	465	18.04 (21.16)	689	7.51 [5.69; 9.34]	1.84	0.231	-	0.287
Placebo + Chemotherapy[c] / Placebo	320	10.69 (15.56)	229	16.21 (21.24)	338	5.68 [3.16; 8.19]	[-1.17; 4.85]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	71	9.39 (15.33)	55	14.55 (21.69)	81	6.09 [0.39; 11.80]	-1.41	0.743	-	
Placebo + Chemotherapy[c] / Placebo	42	4.76 (9.23)	34	14.05 (18.41)	47	7.50 [0.54; 14.47]	[-9.92; 7.10]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	597	10.55 (16.54)	448	17.46 (21.03)	666	7.28 [5.39; 9.17]	1.54	0.326	-	0.763
Placebo + Chemotherapy[c] / Placebo	314	9.87 (14.85)	224	15.67 (21.02)	336	5.74 [3.16; 8.32]	[-1.54; 4.63]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	98	10.32 (15.57)	72	18.98 (22.49)	104	7.50 [2.92; 12.07]	0.05	0.990	-	
Placebo + Chemotherapy[c] / Placebo	48	10.88 (16.61)	39	17.38 (20.20)	49	7.45 [1.33; 13.56]	[-7.41; 7.50]			
Geographic Region										
Asia										
Pembrolizumab +	131	12.38 (13.76)	99	20.76 (21.51)	135	9.68 [5.62; 13.74]	4.35	0.169	-	0.759

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Arm Symptoms	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Chemotherapy[b] / Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	79	8.58 (11.25)	60	14.44 (16.66)	79	5.33 [0.23; 10.42]	[-1.87; 10.58]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	528	9.81 (16.59)	391	16.48 (20.52)	596	6.69 [4.73; 8.64]	0.99	0.547	-	
Placebo + Chemotherapy[c] / Placebo	258	10.21 (15.82)	185	15.98 (20.81)	281	5.69 [2.96; 8.43]	[-2.24; 4.23]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	14.20 (21.18)	30	22.96 (27.52)	39	9.24 [-0.40; 18.88]	2.64	0.735	-	
Placebo + Chemotherapy[c] / Placebo	25	12.44 (17.66)	18	20.37 (32.17)	25	6.60 [-5.76; 18.96]	[-12.94; 18.22]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	333	7.97 (12.73)	252	15.78 (19.98)	371	7.38 [5.03; 9.74]	2.74	0.155	-	0.608
Placebo + Chemotherapy[c] / Placebo	178	8.30 (13.71)	132	12.71 (17.54)	191	4.64 [1.49; 7.79]	[-1.04; 6.53]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	362	12.86 (18.88)	268	19.44 (22.22)	399	7.31 [4.74; 9.87]	-0.00	0.999	-	
Placebo + Chemotherapy[c] / Placebo	184	11.65 (16.15)	131	19.17 (23.39)	194	7.31 [3.76; 10.86]	[-4.23; 4.23]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	516	9.26 (14.51)	396	16.22 (20.05)	571	6.83 [4.91; 8.76]	1.52	0.335	-	0.799

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Arm Symptoms	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo + Chemotherapy[c] / Placebo	271	9.88 (15.55)	204	14.71 (18.89)	287	5.32 [2.73; 7.90]	[-1.57; 4.60]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	179	14.15 (20.53)	124	22.31 (24.11)	199	8.56 [4.60; 12.51]	-0.41	0.904	-	
Placebo + Chemotherapy[c] / Placebo	91	10.38 (13.64)	59	20.15 (26.38)	98	8.97 [3.35; 14.59]	[-7.14; 6.31]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	292	10.24 (16.05)	221	17.70 (21.23)	330	7.78 [5.15; 10.42]	4.41	0.048	0.22	0.097
Placebo + Chemotherapy[c] / Placebo	155	10.25 (13.84)	109	12.84 (20.46)	164	3.38 [-0.27; 7.02]	[0.04; 8.78]		[0.00; 0.44]	
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	403	10.73 (16.66)	299	17.65 (21.25)	440	7.01 [4.69; 9.32]	-0.99	0.604	-	
Placebo + Chemotherapy[c] / Placebo	205	9.70 (15.96)	153	18.23 (20.97)	219	8.00 [4.87; 11.12]	[-4.73; 2.75]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-BR23: Symptomskala Belastung durch Haarausfall

Tabelle 4G-43: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Belastung durch Haarausfall aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Upset by Hair Loss (Imputed)[i]	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	624	2.35 (11.40)	465	3.73 (16.39)	689	1.54 [-0.03; 3.10]	-0.57	0.661	-	0.413
Placebo + Chemotherapy[c] / Placebo	320	2.40 (12.57)	229	4.37 (15.93)	338	2.10 [-0.04; 4.25]	[-3.09; 1.96]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	71	0.94 (5.55)	55	4.24 (15.78)	81	2.49 [-2.45; 7.43]	-3.60	0.362	-	
Placebo + Chemotherapy[c] / Placebo	42	3.17 (12.34)	34	8.82 (23.65)	47	6.09 [-0.08; 12.26]	[-11.39; 4.19]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	597	2.12 (11.06)	448	3.42 (15.55)	666	1.18 [-0.41; 2.78]	-1.75	0.177	-	0.147
Placebo + Chemotherapy[c] / Placebo	314	2.76 (13.30)	224	5.36 (17.89)	336	2.93 [0.77; 5.09]	[-4.29; 0.79]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	98	2.72 (10.35)	72	6.02 (20.42)	104	3.56 [-0.59; 7.71]	2.43	0.485	-	
Placebo + Chemotherapy[c] / Placebo	48	0.69 (4.81)	39	2.56 (11.81)	49	1.13 [-4.46; 6.71]	[-4.45; 9.32]			
Geographic Region										
Asia										
Pembrolizumab +	131	3.82 (14.11)	99	5.72 (18.47)	135	2.27 [-1.26; 5.80]	-0.11	0.967	-	0.768

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Upset by Hair Loss (Imputed)[i]	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Chemotherapy[b] / Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	79	3.38 (16.53)	60	5.00 (14.81)	79	2.38 [-2.04; 6.80]	[-5.54; 5.31]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	528	1.58 (9.61)	391	3.24 (15.50)	596	1.62 [-0.08; 3.31]	-1.03	0.468	-	
Placebo + Chemotherapy[c] / Placebo	258	2.20 (11.37)	185	4.86 (17.90)	281	2.64 [0.28; 5.01]	[-3.80; 1.75]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	5.56 (14.91)	30	4.44 (19.04)	39	0.43 [-7.33; 8.18]	-3.35	0.551	-	
Placebo + Chemotherapy[c] / Placebo	25	2.67 (9.23)	18	5.56 (17.15)	25	3.78 [-5.78; 13.34]	[-14.58; 7.87]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	333	1.90 (9.31)	252	4.63 (18.36)	371	2.88 [0.74; 5.03]	0.36	0.841	-	0.352
Placebo + Chemotherapy[c] / Placebo	178	1.31 (8.21)	132	4.55 (15.83)	191	2.52 [-0.38; 5.42]	[-3.16; 3.88]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	362	2.49 (12.28)	268	2.99 (14.11)	399	0.32 [-1.78; 2.42]	-2.44	0.147	-	
Placebo + Chemotherapy[c] / Placebo	184	3.62 (15.55)	131	5.34 (18.41)	194	2.76 [-0.09; 5.61]	[-5.73; 0.86]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	516	2.00 (10.50)	396	4.12 (17.18)	571	2.26 [0.49; 4.04]	-0.21	0.886	-	0.290

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Upset by Hair Loss (Imputed)[i]	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo + Chemotherapy[c] / Placebo	271	2.71 (13.79)	204	4.74 (17.33)	287	2.47 [0.07; 4.87]	[-3.08; 2.66]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	179	2.79 (12.17)	124	2.69 (13.17)	199	-0.09 [-2.84; 2.66]	-3.17	0.152	-	
Placebo + Chemotherapy[c] / Placebo	91	1.83 (7.64)	59	5.65 (16.55)	98	3.08 [-0.69; 6.86]	[-7.51; 1.17]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	292	1.94 (9.17)	221	4.07 (16.77)	330	2.67 [0.43; 4.92]	-1.51	0.436	-	0.501
Placebo + Chemotherapy[c] / Placebo	155	0.65 (4.61)	109	4.89 (15.60)	164	4.19 [1.03; 7.35]	[-5.34; 2.31]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	403	2.40 (12.09)	299	3.57 (15.99)	440	0.62 [-1.38; 2.62]	-1.04	0.507	-	
Placebo + Chemotherapy[c] / Placebo	205	3.74 (15.90)	153	5.01 (18.25)	219	1.66 [-0.99; 4.30]	[-4.11; 2.03]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EQ-5D VAS

Tabelle 4G-44: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EQ-5D VAS	Neoadjuvant Baseline		LTFU Year 1		Change from Neoadjuvant Baseline to LTFU Year 1		Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo			p-Value for Interaction Test[h]
							Mean Difference at LTFU Year 1		Standardized Mean Difference at LTFU Year 1	
	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] / Pembrolizumab	633	81.30 (18.14)	466	78.95 (16.51)	690	-2.75 [-4.41; -1.09]	-0.69	0.575	-	0.813
Placebo + Chemotherapy[c] / Placebo	326	83.00 (16.87)	231	80.68 (15.58)	338	-2.07 [-4.23; 0.09]	[-3.09; 1.72]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	74	79.38 (17.47)	56	72.98 (18.15)	82	-6.25 [-11.59; -0.90]	-1.86	0.642	-	
Placebo + Chemotherapy[c] / Placebo	44	79.59 (17.51)	34	75.62 (20.58)	47	-4.38 [-10.99; 2.22]	[-9.79; 6.06]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	608	81.08 (18.17)	449	78.71 (16.82)	667	-2.77 [-4.50; -1.03]	-0.66	0.607	-	0.647
Placebo + Chemotherapy[c] / Placebo	321	82.95 (17.47)	226	80.55 (16.56)	336	-2.10 [-4.36; 0.15]	[-3.19; 1.86]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	81.19 (17.49)	73	75.86 (16.39)	105	-4.85 [-8.83; -0.88]	-1.93	0.516	-	
Placebo + Chemotherapy[c] / Placebo	49	80.24 (13.03)	39	77.00 (14.96)	49	-2.93 [-8.05; 2.19]	[-7.78; 3.92]			
Geographic Region										
Asia										
Pembrolizumab + Chemotherapy[b] /	132	80.69 (15.13)	99	77.75 (17.35)	135	-3.29 [-6.45; -0.13]	-5.18	0.029	-0.35	0.091

Study: KEYNOTE 522[a] EQ-5D VAS	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	79	81.95 (13.46)	60	83.98 (11.71)	79	1.89 [-2.02; 5.81]	[-9.84; -0.53]		[-0.67; -0.04]	
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	539	81.05 (18.61)	393	78.21 (16.56)	598	-2.95 [-4.79; -1.11]	0.09	0.949	-	
Placebo + Chemotherapy[c] / Placebo	266	82.44 (17.90)	187	78.80 (16.38)	281	-3.04 [-5.46; -0.61]	[-2.59; 2.77]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	83.33 (19.94)	30	81.43 (17.89)	39	-5.39 [-14.36; 3.58]	1.71	0.799	-	
Placebo + Chemotherapy[c] / Placebo	25	86.24 (16.70)	18	79.61 (25.84)	25	-7.10 [-18.28; 4.09]	[-11.73; 15.14]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	341	80.95 (18.18)	253	77.80 (17.54)	372	-3.59 [-5.96; -1.21]	-2.01	0.239	-	0.494
Placebo + Chemotherapy[c] / Placebo	182	83.42 (17.15)	134	81.34 (14.90)	191	-1.57 [-4.59; 1.44]	[-5.36; 1.34]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	366	81.23 (17.99)	269	78.79 (16.05)	400	-2.81 [-4.94; -0.68]	-0.09	0.955	-	
Placebo + Chemotherapy[c] / Placebo	188	81.80 (16.78)	131	78.69 (17.67)	194	-2.72 [-5.55; 0.11]	[-3.30; 3.12]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	526	81.78 (17.87)	397	78.86 (16.49)	572	-3.27 [-5.06; -1.49]	-1.29	0.321	-	0.771
Placebo + Chemotherapy[c] / Placebo	277	83.34 (15.77)	205	80.74 (14.85)	287	-1.98 [-4.27; 0.31]	[-3.84; 1.26]			

Study: KEYNOTE 522[a] EQ-5D VAS	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	79.10 (18.54)	125	76.57 (17.61)	200	-2.58 [-6.09; 0.93]	0.60	0.828	-	
Placebo + Chemotherapy[c] / Placebo	93	80.39 (20.02)	60	77.62 (20.64)	98	-3.18 [-7.93; 1.58]	[-4.82; 6.01]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	296	81.50 (16.72)	222	78.05 (17.84)	331	-4.05 [-6.55; -1.56]	-1.86	0.336	-	0.429
Placebo + Chemotherapy[c] / Placebo	159	82.97 (17.17)	109	80.99 (16.64)	164	-2.19 [-5.51; 1.12]	[-5.64; 1.93]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	411	80.80 (18.99)	300	78.50 (15.97)	441	-2.39 [-4.46; -0.31]	-0.08	0.956	-	
Placebo + Chemotherapy[c] / Placebo	209	82.45 (16.76)	155	79.28 (16.19)	219	-2.31 [-4.96; 0.35]	[-3.02; 2.86]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation; VAS: Visual Analog Scale

Anhang 4-G5.3: Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30

Tabelle 4G-45: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den globalen Gesundheitsstatus aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Global Health Status/QoL	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	628	77.34 (18.44)	466	74.62 (18.49)	690	-3.29 [-5.04; -1.53]	-0.39	0.772	-	0.693
Placebo + Chemotherapy[c] / Placebo	324	79.32 (16.80)	230	76.59 (16.95)	338	-2.90 [-5.23; -0.56]	[-3.05; 2.27]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	73	74.89 (18.97)	56	71.28 (21.43)	82	-3.73 [-9.89; 2.44]	-1.62	0.722	-	
Placebo + Chemotherapy[c] / Placebo	43	75.97 (19.26)	34	73.77 (20.73)	47	-2.11 [-9.72; 5.49]	[-10.63; 7.39]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	602	77.24 (18.51)	449	74.37 (19.16)	667	-3.72 [-5.57; -1.86]	-0.33	0.818	-	0.538
Placebo + Chemotherapy[c] / Placebo	318	80.08 (16.81)	225	76.67 (17.82)	336	-3.38 [-5.84; -0.93]	[-3.16; 2.50]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	76.09 (18.43)	73	73.63 (16.73)	105	-0.88 [-5.08; 3.31]	-0.99	0.743	-	
Placebo + Chemotherapy[c] / Placebo	49	71.43 (17.35)	39	73.72 (15.24)	49	0.11 [-5.22; 5.44]	[-6.97; 4.99]			
Geographic Region										

Study: KEYNOTE 522[a] EORTC QLQ-C30 Global Health Status/QoL	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Asia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	132	73.17 (18.37)	99	72.22 (17.54)	135	-1.52 [-5.25; 2.21]	-4.45	0.087	-	0.173
Placebo + Chemotherapy[c] / Placebo	79	76.16 (17.44)	60	79.03 (13.94)	79	2.93 [-1.57; 7.43]	[-9.56; 0.66]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	533	77.74 (18.03)	393	74.62 (19.14)	598	-3.32 [-5.26; -1.37]	0.84	0.588	-	
Placebo + Chemotherapy[c] / Placebo	263	78.99 (16.92)	186	74.51 (17.97)	281	-4.16 [-6.81; -1.51]	[-2.21; 3.89]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	81.71 (23.39)	30	76.39 (18.96)	39	-8.57 [-17.70; 0.56]	-1.25	0.841	-	
Placebo + Chemotherapy[c] / Placebo	25	87.00 (16.15)	18	84.72 (19.85)	25	-7.32 [-18.31; 3.66]	[-13.72; 11.22]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	336	77.53 (17.85)	253	73.91 (19.52)	372	-4.23 [-6.73; -1.73]	-0.55	0.775	-	0.591
Placebo + Chemotherapy[c] / Placebo	181	80.76 (15.77)	133	76.25 (16.99)	191	-3.68 [-6.93; -0.43]	[-4.30; 3.21]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	365	76.67 (19.08)	269	74.60 (18.19)	400	-2.54 [-4.86; -0.23]	-0.70	0.695	-	
Placebo + Chemotherapy[c] / Placebo	186	77.15 (18.19)	131	76.21 (18.00)	194	-1.84 [-4.93; 1.24]	[-4.21; 2.81]			
Tumor Size										
T1/T2										
Pembrolizumab +	520	78.14 (17.75)	397	74.90 (18.41)	572	-3.34 [-5.24; -1.44]	-0.83	0.563	-	0.835

Study: KEYNOTE 522[a] EORTC QLQ-C30 Global Health Status/QoL	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Chemotherapy[b] / Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	275	78.82 (17.46)	204	76.88 (15.86)	287	-2.52 [-4.98; -0.05]	[-3.63; 1.98]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	74.03 (20.23)	125	72.27 (20.05)	200	-3.73 [-7.50; 0.04]	0.24	0.938	-	
Placebo + Chemotherapy[c] / Placebo	92	79.26 (16.13)	60	74.03 (22.08)	98	-3.97 [-9.16; 1.22]	[-5.78; 6.25]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	293	76.59 (17.66)	222	73.16 (19.52)	331	-4.62 [-7.17; -2.07]	-2.01	0.328	-	0.381
Placebo + Chemotherapy[c] / Placebo	158	79.54 (16.12)	109	76.99 (17.89)	164	-2.61 [-6.06; 0.84]	[-6.04; 2.02]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	408	77.43 (19.08)	300	75.08 (18.29)	441	-2.27 [-4.55; 0.00]	0.75	0.656	-	
Placebo + Chemotherapy[c] / Placebo	207	78.58 (17.90)	154	75.65 (17.24)	219	-3.03 [-5.97; -0.08]	[-2.56; 4.07]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-46: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Körperliche Funktion aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Physical Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	628	92.41 (12.23)	466	84.79 (17.62)	690	-7.56 [-9.04; -6.07]	-1.55	0.221	-	0.586
Placebo + Chemotherapy[c] / Placebo	324	92.12 (12.54)	230	86.38 (17.27)	338	-6.01 [-8.07; -3.94]	[-4.04; 0.93]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	73	87.40 (16.35)	56	79.76 (19.45)	82	-7.95 [-13.44; -2.46]	-0.37	0.932	-	
Placebo + Chemotherapy[c] / Placebo	43	85.58 (18.22)	34	78.24 (24.47)	47	-7.58 [-14.46; -0.71]	[-8.86; 8.13]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	602	92.49 (12.15)	449	84.91 (17.50)	667	-7.60 [-9.14; -6.07]	-0.89	0.497	-	0.328
Placebo + Chemotherapy[c] / Placebo	318	92.87 (11.65)	225	86.25 (18.29)	336	-6.72 [-8.84; -4.59]	[-3.46; 1.68]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	88.22 (15.76)	73	80.18 (19.66)	105	-7.13 [-11.46; -2.79]	-3.15	0.366	-	
Placebo + Chemotherapy[c] / Placebo	49	81.50 (19.26)	39	80.00 (19.10)	49	-3.98 [-9.74; 1.78]	[-10.01; 3.71]			
Geographic Region										
Asia										
Pembrolizumab +	132	91.46 (11.42)	99	84.51 (17.71)	135	-6.56 [-9.48; -3.65]	-5.35	0.022	-0.36	0.176

Study: KEYNOTE 522[a] EORTC QLQ-C30 Physical Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Chemotherapy[b] / Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	79	91.98 (10.85)	60	90.89 (10.98)	79	-1.21 [-4.91; 2.49]	[-9.93; -0.77]		[-0.68; -0.05]	
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	533	91.94 (13.18)	393	84.22 (17.45)	598	-7.60 [-9.21; -5.98]	-0.51	0.713	-	
Placebo + Chemotherapy[c] / Placebo	263	91.31 (14.06)	186	84.19 (18.16)	281	-7.09 [-9.36; -4.82]	[-3.21; 2.20]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	92.59 (12.01)	30	83.78 (23.66)	39	-7.87 [-18.09; 2.34]	7.80	0.349	-	
Placebo + Chemotherapy[c] / Placebo	25	89.87 (14.80)	18	78.52 (33.42)	25	-15.68 [-28.75; -2.61]	[-8.78; 24.39]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	336	92.84 (11.63)	253	85.16 (16.72)	372	-7.67 [-9.59; -5.74]	-1.37	0.392	-	0.899
Placebo + Chemotherapy[c] / Placebo	181	92.89 (12.22)	133	87.02 (17.02)	191	-6.29 [-8.89; -3.70]	[-4.53; 1.78]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	365	91.01 (13.74)	269	83.40 (18.89)	400	-7.48 [-9.65; -5.32]	-1.17	0.527	-	
Placebo + Chemotherapy[c] / Placebo	186	89.86 (14.44)	131	83.61 (19.82)	194	-6.31 [-9.34; -3.28]	[-4.80; 2.46]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	520	92.92 (11.30)	397	86.01 (15.76)	572	-6.94 [-8.40; -5.48]	-1.94	0.114	-	0.616

Study: KEYNOTE 522[a] EORTC QLQ-C30 Physical Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo + Chemotherapy[c] / Placebo	275	91.35 (13.74)	204	86.70 (17.29)	287	-5.00 [-6.99; -3.01]	[-4.35; 0.47]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	88.91 (16.01)	125	78.67 (22.53)	200	-9.89 [-13.74; -6.04]	0.05	0.987	-	
Placebo + Chemotherapy[c] / Placebo	92	91.38 (12.68)	60	80.67 (21.67)	98	-9.94 [-15.37; -4.51]	[-6.40; 6.50]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	293	90.99 (13.18)	222	83.93 (18.07)	331	-7.61 [-9.90; -5.33]	-2.47	0.204	-	0.356
Placebo + Chemotherapy[c] / Placebo	158	92.45 (12.09)	109	87.58 (17.86)	164	-5.14 [-8.32; -1.97]	[-6.28; 1.35]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	408	92.53 (12.49)	300	84.49 (17.75)	441	-7.48 [-9.36; -5.60]	-0.53	0.739	-	
Placebo + Chemotherapy[c] / Placebo	207	90.50 (14.44)	154	83.68 (18.89)	219	-6.96 [-9.53; -4.39]	[-3.63; 2.58]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-47: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Rollenfunktion aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Role Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	628	90.95 (18.35)	466	82.44 (24.44)	690	-8.03 [-10.31; -5.76]	-2.28	0.223	-	0.980
Placebo + Chemotherapy[c] / Placebo	324	88.73 (20.21)	230	84.42 (24.87)	338	-5.75 [-8.87; -2.64]	[-5.95; 1.39]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	73	90.64 (18.63)	56	77.08 (25.34)	82	-13.02 [-20.46; -5.57]	-3.56	0.524	-	
Placebo + Chemotherapy[c] / Placebo	43	90.70 (18.65)	34	80.88 (26.31)	47	-9.46 [-18.67; -0.24]	[-14.60; 7.48]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	602	91.14 (18.16)	449	82.52 (24.66)	667	-8.33 [-10.71; -5.95]	-1.85	0.339	-	0.409
Placebo + Chemotherapy[c] / Placebo	318	89.99 (19.60)	225	84.52 (25.17)	336	-6.48 [-9.71; -3.25]	[-5.65; 1.95]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	89.56 (19.57)	73	77.85 (23.74)	105	-10.62 [-16.15; -5.10]	-6.33	0.157	-	
Placebo + Chemotherapy[c] / Placebo	49	82.31 (21.63)	39	80.77 (24.34)	49	-4.29 [-11.64; 3.06]	[-15.14; 2.48]			
Geographic Region										
Asia										
Pembrolizumab +	132	91.41 (17.41)	99	82.32 (24.26)	135	-9.90 [-14.31; -5.49]	-5.18	0.127	-	0.647

Study: KEYNOTE 522[a] EORTC QLQ-C30 Role Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Chemotherapy[b] / Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	79	93.67 (13.42)	60	89.17 (15.29)	79	-4.72 [-10.24; 0.80]	[-11.85; 1.49]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	533	90.87 (18.51)	393	82.23 (23.87)	598	-7.64 [-10.13; -5.15]	-1.32	0.520	-	
Placebo + Chemotherapy[c] / Placebo	263	87.33 (21.50)	186	82.89 (25.96)	281	-6.32 [-9.77; -2.86]	[-5.36; 2.71]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	89.81 (20.03)	30	75.56 (33.26)	39	-13.29 [-27.01; 0.43]	-0.69	0.948	-	
Placebo + Chemotherapy[c] / Placebo	25	91.33 (19.32)	18	77.78 (37.49)	25	-12.60 [-29.84; 4.65]	[-21.80; 20.41]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	336	91.82 (17.47)	253	82.87 (24.28)	372	-8.18 [-11.30; -5.06]	-1.00	0.689	-	0.330
Placebo + Chemotherapy[c] / Placebo	181	89.41 (20.33)	133	84.46 (24.38)	191	-7.19 [-11.32; -3.05]	[-5.90; 3.91]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	365	90.09 (19.14)	269	80.92 (24.84)	400	-8.87 [-11.97; -5.78]	-3.46	0.173	-	
Placebo + Chemotherapy[c] / Placebo	186	88.53 (19.76)	131	83.46 (25.78)	194	-5.41 [-9.66; -1.17]	[-8.44; 1.52]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	520	92.08 (17.09)	397	83.04 (23.49)	572	-8.36 [-10.74; -5.97]	-3.21	0.095	-	0.471

Study: KEYNOTE 522[a] EORTC QLQ-C30 Role Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo + Chemotherapy[c] / Placebo	275	88.79 (20.15)	204	85.70 (23.30)	287	-5.15 [-8.34; -1.96]	[-6.98; 0.56]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	87.57 (21.31)	125	78.13 (27.47)	200	-9.41 [-14.54; -4.28]	1.74	0.684	-	
Placebo + Chemotherapy[c] / Placebo	92	89.49 (19.72)	60	78.06 (29.67)	98	-11.15 [-18.30; -3.99]	[-6.66; 10.13]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	293	90.73 (18.72)	222	81.76 (23.60)	331	-8.83 [-12.04; -5.62]	-4.32	0.098	-	0.279
Placebo + Chemotherapy[c] / Placebo	158	89.56 (20.73)	109	86.24 (23.44)	164	-4.51 [-8.88; -0.14]	[-9.44; 0.80]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	408	91.05 (18.13)	300	81.94 (25.30)	441	-8.42 [-11.40; -5.44]	-0.66	0.784	-	
Placebo + Chemotherapy[c] / Placebo	207	88.81 (19.21)	154	82.25 (26.10)	219	-7.76 [-11.77; -3.74]	[-5.42; 4.10]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-48: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Emotionale Funktion aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Emotional Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	628	76.02 (19.50)	466	78.56 (21.53)	690	3.31 [1.33; 5.28]	2.10	0.190	-	0.535
Placebo + Chemotherapy[c] / Placebo	324	75.13 (20.83)	230	77.21 (23.16)	338	1.20 [-1.48; 3.89]	[-1.04; 5.25]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	73	77.17 (19.59)	56	79.32 (19.40)	82	3.78 [-1.34; 8.90]	-1.20	0.754	-	
Placebo + Chemotherapy[c] / Placebo	43	75.78 (19.57)	34	82.60 (20.35)	47	4.98 [-1.30; 11.25]	[-8.74; 6.34]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	602	76.16 (19.16)	449	78.84 (20.88)	667	3.40 [1.42; 5.38]	2.04	0.202	-	0.439
Placebo + Chemotherapy[c] / Placebo	318	75.63 (20.35)	225	78.04 (23.35)	336	1.36 [-1.31; 4.03]	[-1.09; 5.18]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	76.01 (21.54)	73	77.40 (23.83)	105	2.81 [-2.33; 7.95]	-1.39	0.730	-	
Placebo + Chemotherapy[c] / Placebo	49	72.45 (22.64)	39	77.14 (20.03)	49	4.20 [-2.55; 10.94]	[-9.32; 6.55]			
Geographic Region										
Asia										
Pembrolizumab +	132	78.03 (15.66)	99	81.06 (16.66)	135	3.73 [0.43; 7.03]	-5.10	0.036	-0.34	0.071

Study: KEYNOTE 522[a] EORTC QLQ-C30 Emotional Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Chemotherapy[b] / Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	79	76.27 (19.39)	60	86.94 (14.50)	79	8.84 [4.78; 12.89]	[-9.88; -0.33]		[-0.65; -0.02]	
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	533	75.48 (20.06)	393	78.39 (22.10)	598	4.01 [1.85; 6.16]	3.38	0.057	-	
Placebo + Chemotherapy[c] / Placebo	263	74.27 (21.27)	186	75.49 (23.07)	281	0.63 [-2.35; 3.61]	[-0.11; 6.86]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	78.94 (23.19)	30	73.89 (23.75)	39	-6.53 [-17.27; 4.21]	3.81	0.636	-	
Placebo + Chemotherapy[c] / Placebo	25	81.67 (17.18)	18	72.69 (34.28)	25	-10.35 [-23.63; 2.93]	[-12.25; 19.88]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	336	76.17 (19.37)	253	78.03 (20.80)	372	3.14 [0.63; 5.66]	2.31	0.252	-	0.463
Placebo + Chemotherapy[c] / Placebo	181	75.28 (19.42)	133	77.13 (22.63)	191	0.83 [-2.50; 4.16]	[-1.65; 6.27]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	365	76.12 (19.63)	269	79.21 (21.77)	400	3.51 [0.82; 6.21]	1.13	0.603	-	
Placebo + Chemotherapy[c] / Placebo	186	75.13 (21.86)	131	78.69 (23.14)	194	2.38 [-1.29; 6.05]	[-3.14; 5.41]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	520	76.44 (18.93)	397	79.37 (20.43)	572	3.90 [1.85; 5.95]	1.55	0.342	-	0.869

Study: KEYNOTE 522[a] EORTC QLQ-C30 Emotional Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo + Chemotherapy[c] / Placebo	275	74.15 (21.65)	204	77.86 (22.79)	287	2.35 [-0.36; 5.07]	[-1.65; 4.74]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	75.28 (21.06)	125	76.33 (23.77)	200	1.49 [-2.67; 5.66]	2.20	0.526	-	
Placebo + Chemotherapy[c] / Placebo	92	78.35 (17.12)	60	78.06 (23.27)	98	-0.71 [-6.52; 5.10]	[-4.63; 9.03]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	293	75.51 (20.18)	222	77.63 (23.27)	331	3.04 [0.09; 5.99]	1.68	0.485	-	0.639
Placebo + Chemotherapy[c] / Placebo	158	74.37 (20.36)	109	77.68 (22.82)	164	1.36 [-2.66; 5.37]	[-3.05; 6.42]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	408	76.59 (19.00)	300	79.39 (19.71)	441	3.38 [1.03; 5.74]	1.77	0.346	-	
Placebo + Chemotherapy[c] / Placebo	207	75.97 (20.88)	154	77.92 (22.96)	219	1.61 [-1.53; 4.75]	[-1.91; 5.45]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-49: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Kognitive Funktion aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Cognitive Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	628	88.38 (17.52)	466	81.01 (21.50)	690	-7.37 [-9.28; -5.46]	-0.51	0.744	-	0.105
Placebo + Chemotherapy[c] / Placebo	324	88.27 (18.35)	230	81.74 (22.02)	338	-6.86 [-9.46; -4.25]	[-3.58; 2.56]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	73	87.44 (19.60)	56	83.04 (17.26)	82	-5.41 [-10.12; -0.70]	4.57	0.196	-	
Placebo + Chemotherapy[c] / Placebo	43	91.09 (15.15)	34	81.37 (19.58)	47	-9.98 [-15.76; -4.20]	[-2.40; 11.54]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	602	88.46 (17.49)	449	81.63 (20.73)	667	-6.98 [-8.88; -5.08]	0.87	0.575	-	0.199
Placebo + Chemotherapy[c] / Placebo	318	88.63 (17.83)	225	81.26 (22.29)	336	-7.85 [-10.42; -5.28]	[-2.17; 3.91]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	87.21 (19.17)	73	78.77 (23.12)	105	-8.61 [-13.66; -3.56]	-4.91	0.218	-	
Placebo + Chemotherapy[c] / Placebo	49	88.44 (19.31)	39	84.19 (17.91)	49	-3.70 [-10.37; 2.96]	[-12.75; 2.94]			
Geographic Region										
Asia										
Pembrolizumab +	132	90.91 (14.32)	99	82.32 (16.81)	135	-8.79 [-12.19; -5.39]	-6.16	0.017	-0.38	0.064

Study: KEYNOTE 522[a] EORTC QLQ-C30 Cognitive Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Chemotherapy[b] / Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	79	89.66 (15.17)	60	87.78 (16.20)	79	-2.63 [-6.86; 1.60]	[-11.22; -1.11]		[-0.69; -0.07]	
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	533	87.62 (18.36)	393	80.87 (21.78)	598	-6.59 [-8.64; -4.54]	1.63	0.338	-	
Placebo + Chemotherapy[c] / Placebo	263	88.40 (18.64)	186	80.29 (21.64)	281	-8.22 [-11.07; -5.37]	[-1.71; 4.97]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	88.43 (19.03)	30	82.22 (24.73)	39	-6.25 [-16.79; 4.30]	6.67	0.406	-	
Placebo + Chemotherapy[c] / Placebo	25	87.33 (20.00)	18	75.93 (32.95)	25	-12.92 [-26.04; 0.21]	[-9.28; 22.62]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	336	89.43 (17.61)	253	79.84 (21.72)	372	-9.23 [-11.70; -6.76]	-1.53	0.451	-	0.351
Placebo + Chemotherapy[c] / Placebo	181	88.49 (16.79)	133	81.45 (22.06)	191	-7.70 [-11.01; -4.39]	[-5.52; 2.46]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	365	87.21 (17.80)	269	82.53 (20.42)	400	-5.39 [-7.95; -2.83]	1.28	0.531	-	
Placebo + Chemotherapy[c] / Placebo	186	88.71 (19.17)	131	81.93 (21.39)	194	-6.67 [-10.13; -3.20]	[-2.73; 5.29]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	520	88.69 (17.30)	397	81.57 (20.44)	572	-7.43 [-9.43; -5.44]	-1.15	0.473	-	0.211

Study: KEYNOTE 522[a] EORTC QLQ-C30 Cognitive Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo + Chemotherapy[c] / Placebo	275	88.24 (18.21)	204	82.60 (20.68)	287	-6.29 [-8.94; -3.63]	[-4.28; 1.99]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	87.11 (18.91)	125	80.13 (23.06)	200	-6.11 [-9.98; -2.25]	4.58	0.158	-	
Placebo + Chemotherapy[c] / Placebo	92	89.67 (17.44)	60	78.61 (24.76)	98	-10.69 [-16.09; -5.30]	[-1.80; 10.96]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	293	88.62 (17.81)	222	81.83 (22.15)	331	-6.89 [-9.69; -4.10]	-0.89	0.696	-	0.386
Placebo + Chemotherapy[c] / Placebo	158	88.82 (18.47)	109	83.64 (21.51)	164	-6.00 [-9.81; -2.20]	[-5.37; 3.59]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	408	88.03 (17.69)	300	80.78 (20.29)	441	-7.36 [-9.66; -5.05]	0.95	0.611	-	
Placebo + Chemotherapy[c] / Placebo	207	88.41 (17.76)	154	80.19 (21.79)	219	-8.31 [-11.42; -5.20]	[-2.72; 4.63]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-50: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Soziale Funktion aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-C30 Social Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	628	87.23 (20.11)	466	84.33 (23.80)	690	-2.73 [-4.96; -0.51]	0.41	0.821	-	0.803
Placebo + Chemotherapy[c] / Placebo	324	86.21 (21.07)	230	83.70 (24.65)	338	-3.14 [-6.17; -0.11]	[-3.14; 3.96]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	73	89.04 (19.09)	56	86.01 (22.87)	82	-2.95 [-9.69; 3.78]	0.47	0.925	-	
Placebo + Chemotherapy[c] / Placebo	43	91.47 (19.71)	34	86.27 (23.74)	47	-3.42 [-11.73; 4.88]	[-9.44; 10.38]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	602	87.21 (19.88)	449	84.48 (23.84)	667	-2.51 [-4.83; -0.20]	0.70	0.706	-	0.731
Placebo + Chemotherapy[c] / Placebo	318	86.95 (21.10)	225	84.00 (25.07)	336	-3.22 [-6.33; -0.10]	[-2.96; 4.36]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	99	88.72 (20.73)	73	84.70 (22.86)	105	-3.63 [-8.82; 1.56]	-0.26	0.950	-	
Placebo + Chemotherapy[c] / Placebo	49	86.05 (20.23)	39	84.19 (21.27)	49	-3.38 [-10.23; 3.47]	[-8.35; 7.84]			
Geographic Region										
Asia										
Pembrolizumab +	132	81.94 (21.70)	99	87.04 (20.28)	135	2.66 [-1.36; 6.69]	-1.36	0.628	-	0.779

Study: KEYNOTE 522[a] EORTC QLQ-C30 Social Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Chemotherapy[b] / Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	79	88.82 (20.10)	60	89.44 (14.71)	79	4.02 [-0.84; 8.88]	[-6.88; 4.16]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	533	88.62 (19.25)	393	84.22 (24.57)	598	-3.40 [-5.89; -0.91]	1.48	0.474	-	
Placebo + Chemotherapy[c] / Placebo	263	85.93 (21.37)	186	82.44 (26.04)	281	-4.88 [-8.35; -1.42]	[-2.58; 5.55]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	89.81 (21.56)	30	80.00 (22.06)	39	-9.57 [-20.42; 1.28]	-1.67	0.837	-	
Placebo + Chemotherapy[c] / Placebo	25	90.00 (19.25)	18	82.41 (32.07)	25	-7.90 [-21.39; 5.59]	[-17.91; 14.57]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	336	88.19 (18.91)	253	82.94 (25.15)	372	-4.86 [-7.92; -1.79]	-2.15	0.378	-	0.356
Placebo + Chemotherapy[c] / Placebo	181	87.85 (20.10)	133	85.84 (21.95)	191	-2.71 [-6.76; 1.34]	[-6.94; 2.64]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	365	86.71 (20.95)	269	86.00 (22.17)	400	-0.69 [-3.61; 2.24]	2.99	0.208	-	
Placebo + Chemotherapy[c] / Placebo	186	85.84 (21.78)	131	82.19 (26.81)	194	-3.68 [-7.67; 0.32]	[-1.67; 7.65]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	520	88.11 (18.86)	397	85.18 (23.23)	572	-2.73 [-5.05; -0.40]	-1.29	0.481	-	0.153

Study: KEYNOTE 522[a] EORTC QLQ-C30 Social Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo + Chemotherapy[c] / Placebo	275	86.85 (21.45)	204	85.87 (22.08)	287	-1.43 [-4.51; 1.64]	[-4.90; 2.31]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	181	85.45 (22.91)	125	82.40 (25.07)	200	-2.60 [-7.42; 2.23]	7.21	0.075	-	
Placebo + Chemotherapy[c] / Placebo	92	86.78 (19.54)	60	77.78 (30.79)	98	-9.80 [-16.53; -3.07]	[-0.74; 15.15]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	293	88.96 (19.05)	222	83.71 (25.09)	331	-5.08 [-8.29; -1.88]	-2.48	0.350	-	0.162
Placebo + Chemotherapy[c] / Placebo	158	87.55 (20.69)	109	86.09 (22.85)	164	-2.60 [-7.00; 1.80]	[-7.69; 2.73]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	408	86.32 (20.60)	300	85.11 (22.62)	441	-0.93 [-3.73; 1.88]	2.86	0.196	-	
Placebo + Chemotherapy[c] / Placebo	207	86.47 (21.21)	154	82.47 (25.62)	219	-3.79 [-7.51; -0.06]	[-1.48; 7.21]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC QLQ-BR23

EORTC-QLQ-BR23: Funktionsskala Körperbild

Tabelle 4G-51: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Körperbild aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Body Image	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	624	90.41 (16.69)	465	80.13 (24.97)	689	-10.18 [-12.27; -8.09]	0.58	0.744	-	0.832
Placebo + Chemotherapy[c] / Placebo	320	90.42 (16.81)	229	80.17 (23.54)	338	-10.76 [-13.67; -7.85]	[-2.92; 4.09]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	71	94.60 (9.03)	55	81.52 (24.15)	81	-12.37 [-18.41; -6.33]	-2.21	0.653	-	
Placebo + Chemotherapy[c] / Placebo	42	93.85 (10.74)	34	85.29 (22.01)	47	-10.16 [-17.79; -2.53]	[-11.94; 7.52]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	597	90.70 (16.71)	448	80.86 (24.17)	666	-9.88 [-12.00; -7.76]	1.18	0.513	-	0.081
Placebo + Chemotherapy[c] / Placebo	314	91.35 (15.94)	224	80.73 (23.86)	336	-11.06 [-13.99; -8.13]	[-2.35; 4.71]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	98	91.67 (11.91)	72	76.62 (28.72)	104	-13.83 [-19.04; -8.62]	-6.49	0.147	-	
Placebo + Chemotherapy[c] / Placebo	48	87.33 (17.95)	39	81.41 (20.63)	49	-7.34 [-14.44; -0.24]	[-15.30; 2.32]			
Geographic Region										

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Body Image	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Asia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	131	88.93 (14.30)	99	80.64 (22.23)	135	-7.87 [-11.87; -3.87]	-2.90	0.360	-	0.421
Placebo + Chemotherapy[c] / Placebo	79	88.40 (19.86)	60	85.42 (18.52)	79	-4.97 [-10.02; 0.09]	[-9.14; 3.34]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	528	91.22 (16.15)	391	80.41 (25.19)	596	-10.91 [-13.19; -8.63]	1.48	0.459	-	
Placebo + Chemotherapy[c] / Placebo	258	91.51 (15.18)	185	79.23 (24.22)	281	-12.39 [-15.64; -9.13]	[-2.44; 5.39]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	36	92.13 (21.08)	30	77.22 (29.19)	39	-12.77 [-23.27; -2.28]	-3.71	0.653	-	
Placebo + Chemotherapy[c] / Placebo	25	91.33 (14.13)	18	81.94 (27.90)	25	-9.06 [-22.38; 4.26]	[-20.20; 12.77]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	333	91.17 (15.26)	252	80.03 (24.45)	371	-10.81 [-13.49; -8.13]	-0.73	0.746	-	0.908
Placebo + Chemotherapy[c] / Placebo	178	91.90 (14.59)	132	82.01 (21.20)	191	-10.07 [-13.72; -6.43]	[-5.19; 3.73]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	362	90.54 (16.89)	268	80.50 (25.30)	399	-9.93 [-12.79; -7.06]	1.48	0.547	-	
Placebo + Chemotherapy[c] / Placebo	184	89.76 (17.69)	131	79.64 (25.41)	194	-11.40 [-15.42; -7.39]	[-3.35; 6.31]			
Tumor Size										
T1/T2										
Pembrolizumab +	516	92.12 (14.25)	396	81.02 (24.59)	571	-10.83 [-13.03; -8.64]	-0.44	0.813	-	0.553

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Body Image	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Chemotherapy[b] / Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	271	90.99 (16.42)	204	81.78 (21.00)	287	-10.39 [-13.39; -7.39]	[-4.08; 3.20]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	179	87.15 (20.17)	124	77.89 (25.68)	199	-8.68 [-13.08; -4.29]	3.89	0.310	-	
Placebo + Chemotherapy[c] / Placebo	91	90.29 (15.82)	59	77.54 (30.18)	98	-12.58 [-18.85; -6.30]	[-3.65; 11.43]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	292	90.61 (16.44)	221	79.00 (26.47)	330	-11.91 [-14.94; -8.88]	-1.65	0.532	-	0.597
Placebo + Chemotherapy[c] / Placebo	155	92.26 (13.13)	109	83.03 (23.60)	164	-10.26 [-14.52; -5.99]	[-6.85; 3.55]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	403	91.00 (15.90)	299	81.22 (23.61)	440	-9.14 [-11.73; -6.55]	2.11	0.329	-	
Placebo + Chemotherapy[c] / Placebo	205	89.72 (18.29)	153	79.14 (23.18)	219	-11.25 [-14.78; -7.72]	[-2.13; 6.35]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-BR23: Funktionsskala Sexuelle Aktivität

Tabelle 4G-52: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Sexuelle Aktivität aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Sexual Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	611	22.64 (24.28)	460	21.59 (24.72)	687	-0.95 [-3.05; 1.15]	-0.46	0.786	-	0.500
Placebo + Chemotherapy[c] / Placebo	311	23.69 (25.68)	228	23.03 (24.73)	338	-0.49 [-3.34; 2.35]	[-3.79; 2.87]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	67	14.18 (21.37)	55	10.91 (20.34)	79	-1.09 [-5.01; 2.84]	1.65	0.580	-	
Placebo + Chemotherapy[c] / Placebo	42	7.54 (15.70)	34	4.90 (12.67)	47	-2.74 [-7.56; 2.08]	[-4.24; 7.54]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	584	22.52 (24.08)	444	21.02 (24.84)	662	-1.28 [-3.38; 0.83]	-0.27	0.873	-	0.650
Placebo + Chemotherapy[c] / Placebo	305	22.90 (25.89)	223	21.82 (25.00)	336	-1.00 [-3.84; 1.84]	[-3.60; 3.06]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	94	17.38 (24.06)	71	16.90 (22.09)	104	1.48 [-3.30; 6.25]	2.65	0.479	-	
Placebo + Chemotherapy[c] / Placebo	48	14.58 (19.33)	39	14.10 (18.55)	49	-1.17 [-7.34; 5.00]	[-4.74; 10.04]			
Geographic Region										
Asia										
Pembrolizumab +	128	12.50 (19.17)	99	11.78 (18.63)	135	0.59 [-2.22; 3.40]	1.59	0.465	-	0.184

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Sexual Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Chemotherapy[b] / Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	78	6.84 (14.32)	60	6.94 (12.76)	79	-1.00 [-4.49; 2.50]	[-2.69; 5.86]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	515	23.62 (24.51)	386	22.63 (25.35)	592	-0.83 [-3.21; 1.55]	0.13	0.947	-	
Placebo + Chemotherapy[c] / Placebo	251	25.30 (25.83)	184	23.46 (24.78)	281	-0.96 [-4.24; 2.32]	[-3.67; 3.93]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	35	29.05 (26.61)	30	21.11 (24.73)	39	-10.36 [-19.18; -1.54]	-11.81	0.075	-	
Placebo + Chemotherapy[c] / Placebo	24	33.33 (27.80)	18	37.96 (28.47)	25	1.45 [-9.42; 12.32]	[-24.87; 1.25]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	323	22.39 (23.66)	250	21.40 (24.47)	369	-1.28 [-3.97; 1.41]	-0.86	0.684	-	0.549
Placebo + Chemotherapy[c] / Placebo	174	24.81 (27.69)	132	22.98 (24.15)	191	-0.42 [-3.94; 3.10]	[-5.02; 3.30]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	355	21.27 (24.56)	265	19.56 (24.53)	397	-0.43 [-3.19; 2.34]	0.98	0.665	-	
Placebo + Chemotherapy[c] / Placebo	179	18.81 (22.28)	130	18.33 (24.28)	194	-1.41 [-5.19; 2.38]	[-3.46; 5.41]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	505	22.31 (24.36)	393	21.54 (24.93)	570	-0.04 [-2.27; 2.20]	1.46	0.412	-	0.258

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Sexual Functioning	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo + Chemotherapy[c] / Placebo	264	21.46 (25.13)	203	20.44 (23.96)	287	-1.49 [-4.46; 1.48]	[-2.03; 4.95]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	173	20.33 (23.42)	122	16.94 (22.78)	196	-3.67 [-7.46; 0.12]	-3.63	0.244	-	
Placebo + Chemotherapy[c] / Placebo	89	22.66 (25.65)	59	21.47 (25.53)	98	-0.04 [-5.24; 5.17]	[-9.77; 2.50]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	285	21.52 (24.20)	220	18.86 (22.78)	328	-1.67 [-4.59; 1.26]	-0.65	0.778	-	0.769
Placebo + Chemotherapy[c] / Placebo	152	20.18 (24.16)	109	19.42 (22.85)	164	-1.02 [-4.93; 2.89]	[-5.17; 3.87]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	393	22.01 (24.10)	295	21.64 (25.68)	438	-0.47 [-3.05; 2.10]	0.46	0.826	-	
Placebo + Chemotherapy[c] / Placebo	199	22.86 (26.07)	152	21.49 (25.35)	219	-0.93 [-4.39; 2.52]	[-3.64; 4.56]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-BR23: Funktionsskala Sexueller Genuss

Tabelle 4G-53: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Sexueller Genuss aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Sexual Enjoyment[i]	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	300	57.22 (28.39)	227	50.66 (25.54)	460	-7.19 [-10.87; -3.50]	3.32	0.220	-	0.981
Placebo + Chemotherapy[c] / Placebo	153	58.39 (32.05)	122	48.09 (28.12)	233	-10.50 [-15.21; -5.80]	[-1.99; 8.62]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	21	53.97 (26.82)	12	41.67 (28.87)	n.e.	n.e.	n.e.	n.e.	-	
Placebo + Chemotherapy[c] / Placebo	7	47.62 (32.53)	5	40.00 (14.91)	n.e.	n.e.				
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	287	57.26 (28.16)	213	51.33 (25.99)	433	-6.93 [-10.71; -3.15]	2.97	0.293	-	0.387
Placebo + Chemotherapy[c] / Placebo	145	58.16 (32.82)	111	48.95 (28.00)	217	-9.89 [-14.79; -5.00]	[-2.57; 8.50]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	34	54.90 (29.45)	26	41.03 (21.72)	n.e.	n.e.	n.e.	n.e.	-	
Placebo + Chemotherapy[c] / Placebo	15	55.56 (24.12)	16	39.58 (25.00)	n.e.	n.e.				
Geographic Region										
Asia										
Pembrolizumab +	37	43.24 (24.68)	30	36.67 (22.06)	58	-2.69 [-11.60; 6.21]	8.93	0.216	-	0.592

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Sexual Enjoyment[i]	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Chemotherapy[b] / Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	16	31.25 (22.67)	11	27.27 (13.48)	32	-11.62 [-24.82; 1.58]	[-5.41; 23.27]			
Europe/Israel/North America/Australia										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	263	59.70 (28.35)	193	52.85 (24.87)	403	-7.87 [-11.85; -3.88]	4.32	0.138	-	
Placebo + Chemotherapy[c] / Placebo	130	62.31 (30.04)	103	49.51 (28.34)	191	-12.19 [-17.28; -7.10]	[-1.40; 10.05]			
Rest of World										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	21	47.62 (24.88)	16	43.75 (33.82)	28	-3.23 [-15.99; 9.53]	-6.13	0.496	-	
Placebo + Chemotherapy[c] / Placebo	14	47.62 (42.80)	13	51.28 (25.88)	23	2.90 [-12.15; 17.95]	[-24.33; 12.08]			
Nodal Status										
Negative										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	160	57.08 (27.06)	117	49.29 (25.74)	231	-11.05 [-16.00; -6.10]	2.46	0.493	-	0.721
Placebo + Chemotherapy[c] / Placebo	83	66.27 (30.13)	72	50.00 (26.83)	126	-13.51 [-19.59; -7.42]	[-4.60; 9.51]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	161	56.94 (29.50)	122	51.09 (25.78)	258	-3.57 [-8.73; 1.59]	4.51	0.252	-	
Placebo + Chemotherapy[c] / Placebo	77	48.92 (31.80)	55	44.85 (28.84)	120	-8.08 [-15.10; -1.06]	[-3.23; 12.26]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	243	57.61 (28.59)	188	50.35 (26.81)	372	-8.34 [-12.30; -4.37]	2.88	0.332	-	0.585

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Sexual Enjoyment[i]	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo + Chemotherapy[c] / Placebo	120	58.61 (31.75)	102	48.69 (27.62)	184	-11.22 [-16.31; -6.12]	[-2.95; 8.70]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	78	55.13 (27.30)	51	49.67 (21.47)	117	-4.68 [-12.67; 3.31]	7.60	0.179	-	
Placebo + Chemotherapy[c] / Placebo	40	55.83 (33.24)	25	44.00 (28.41)	62	-12.28 [-22.46; -2.10]	[-3.56; 18.76]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	129	61.24 (27.89)	97	48.45 (24.54)	205	-11.70 [-17.57; -5.84]	0.45	0.916	-	0.306
Placebo + Chemotherapy[c] / Placebo	60	57.78 (34.10)	50	49.33 (28.76)	101	-12.15 [-19.73; -4.57]	[-7.90; 8.79]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	192	54.17 (28.23)	142	51.41 (26.52)	284	-4.88 [-9.31; -0.45]	5.78	0.084	-	
Placebo + Chemotherapy[c] / Placebo	98	58.84 (30.57)	76	46.93 (27.31)	143	-10.66 [-16.36; -4.96]	[-0.78; 12.33]			

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; n.e.: not estimated (model did not converge); PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

EORTC-QLQ-BR23: Funktionsskala Zukunftsperspektive

Tabelle 4G-54: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Zukunftsperspektive aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Future Perspective	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	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] / Pembrolizumab	624	53.21 (31.15)	465	59.28 (31.42)	689	5.84 [2.87; 8.81]	-0.54	0.818	-	0.968
Placebo + Chemotherapy[c] / Placebo	320	54.06 (30.96)	229	60.12 (31.08)	338	6.38 [2.40; 10.36]	[-5.11; 4.03]			
≥ 65										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	71	57.75 (32.83)	55	62.42 (32.11)	81	7.72 [-1.72; 17.17]	-2.05	0.760	-	
Placebo + Chemotherapy[c] / Placebo	42	56.35 (36.43)	34	67.65 (31.23)	47	9.78 [-1.64; 21.19]	[-15.36; 11.26]			
ECOG Performance Status										
0										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	597	53.88 (31.17)	448	60.64 (30.75)	666	6.73 [3.66; 9.80]	-0.07	0.978	-	0.519
Placebo + Chemotherapy[c] / Placebo	314	54.14 (31.62)	224	61.46 (32.00)	336	6.80 [2.72; 10.87]	[-4.74; 4.60]			
1										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	98	52.38 (32.46)	72	53.24 (35.23)	104	2.86 [-4.39; 10.11]	-3.29	0.561	-	
Placebo + Chemotherapy[c] / Placebo	48	55.56 (31.76)	39	58.97 (25.89)	49	6.15 [-3.32; 15.62]	[-14.44; 7.87]			
Nodal Status										
Negative										
Pembrolizumab +	333	55.16 (31.12)	252	57.54 (30.93)	371	3.87 [-0.06; 7.81]	-3.51	0.246	-	0.197

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Future Perspective	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Chemotherapy[b] / Pembrolizumab										
Placebo + Chemotherapy[c] / Placebo	178	53.00 (31.00)	132	62.12 (29.92)	191	7.38 [2.26; 12.51]	[-9.44; 2.43]			
Positive										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	362	52.30 (31.52)	268	61.57 (31.91)	399	8.04 [3.97; 12.11]	2.02	0.528	-	
Placebo + Chemotherapy[c] / Placebo	184	55.62 (32.20)	131	60.05 (32.40)	194	6.02 [0.55; 11.50]	[-4.25; 8.28]			
Tumor Size										
T1/T2										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	516	55.23 (29.82)	396	60.61 (30.51)	571	5.44 [2.26; 8.61]	-0.22	0.926	-	0.622
Placebo + Chemotherapy[c] / Placebo	271	55.60 (31.04)	204	61.44 (29.87)	287	5.66 [1.51; 9.81]	[-5.01; 4.56]			
T3/T4										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	179	49.16 (35.03)	124	56.45 (34.32)	199	7.72 [1.52; 13.91]	-2.12	0.668	-	
Placebo + Chemotherapy[c] / Placebo	91	50.55 (33.10)	59	59.89 (35.44)	98	9.84 [1.35; 18.33]	[-11.87; 7.62]			
Choice of Carboplatin										
Q3W										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	292	53.31 (30.78)	221	57.77 (34.17)	330	5.17 [0.69; 9.66]	-2.81	0.430	-	0.671
Placebo + Chemotherapy[c] / Placebo	155	54.84 (30.33)	109	63.00 (31.21)	164	7.98 [1.95; 14.01]	[-9.80; 4.18]			
Weekly										
Pembrolizumab + Chemotherapy[b] / Pembrolizumab	403	53.93 (31.77)	299	60.98 (29.30)	440	6.69 [3.03; 10.35]	0.79	0.778	-	
Placebo + Chemotherapy[c] /	205	53.82 (32.72)	153	59.69 (31.22)	219	5.90 [1.11; 10.70]	[-4.69; 6.26]			

Study: KEYNOTE 522[a] EORTC QLQ-BR23 Future Perspective	**Neoadjuvant Baseline**		**LTFU Year 1**		**Change from Neoadjuvant Baseline to LTFU Year 1**		**Pembrolizumab + Chemotherapy[b] / Pembrolizumab vs. Placebo + Chemotherapy[c] / Placebo**			**p-Value for Interaction Test[h]**
							Mean Difference at LTFU Year 1		**Standardized Mean Difference at LTFU Year 1**	
	N[d]	**Mean (SD)**	**N[d]**	**Mean (SD)**	**N[e]**	**Mean [95 %-CI][f]**	**[95 %-CI][f]**	**p-Value**	**[95 %-CI][g]**	
Placebo										

a: Database Cutoff Date: 22MAR2024

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 timepoint

e: Number of participants in full-analysis-set population with data available for analysis in combined phases

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; LTFU: Long-Term Follow-up; PRO: Patient Reported Outcome; Q3W: Every 3 Weeks; SD: Standard Deviation

Anhang 4-G5.4: Nebenwirkungen

Unerwünschte Ereignisse

Unerwünschte Ereignisse gesamt

Tabelle 4G-55: 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

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]
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									

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-56: 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									

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]
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									

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

Tabelle 4G-57: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 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

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]
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	

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-58: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 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

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]**
Positive	407	110 (27.0)	Not reached [-; -]	196	32 (16.3)	Not reached [-; -]	1.77 [1.19; 2.62]	0.005	
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-59: 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	Not reached	340	30	Not reached	3.15	< 0.001	0.701

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]
		(24.1)	[-; -]		(8.8)	[-; -]	[2.14; 4.66]		
1	106	21 (19.8)	Not reached [-; -]	49	3 (6.1)	Not reached [-; -]	3.97 [1.18; 13.34]	0.026	
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	

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	496 (85.5)	3.1 [3.1; 3.3]	289	253 (87.5)	4.0 [3.3; 4.3]	1.13 [0.98; 1.32]	0.102	0.360
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-60: 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	

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	2 (1.5)	Not reached [-; -]	79	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.283	> 0.999
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

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]**
T3/T4	203	6 (3.0)	Not reached [-; -]	100	1 (1.0)	Not reached [-; -]	3.07 [0.37; 25.48]	0.299	
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									

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	677	103 (15.2)	Not reached [-; -]	340	19 (5.6)	Not reached [-; -]	3.07 [1.88; 5.01]	< 0.001	0.902
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	Not reached	196	64	Not reached	1.12	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]
		(35.6)	[-; -]		(32.7)	[-; -]	[0.83; 1.50]		
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	Not reached	340	6	Not reached	3.18	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]
		(5.5)	[-; -]		(1.8)	[-; -]	[1.34; 7.54]		
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-61: 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	**Participants with Event**		**Median Time[e] in Weeks**	**Participants with Event**		**Median Time[e] in Weeks**	**Hazard Ratio**		**p-Value for Interaction Test[h]**
	N[d]	**n (%)**	**[95 %-CI]**	**N[d]**	**n (%)**	**[95 %-CI]**	**[95 %-CI][f]**	**p-Value[f,g]**	
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-62: 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)									

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]
< 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

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-63: 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 (4.8)	Not reached [-; -]	167	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.004	0.997
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

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]**
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	
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	

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]**
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 (2.1)	Not reached [-; -]	167	1 (0.6)	Not reached [-; -]	3.65 [0.45; 29.64]	0.226	0.536
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

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]**
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-64: 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	Not reached	341	6	Not reached	2.08	0.108	0.126

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]**
		(3.6)	[-; -]		(1.8)	[-; -]	[0.85; 5.07]		
≥ 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 (5.7)	Not reached [-; -]	49	2 (4.1)	Not reached [-; -]	1.42 [0.29; 7.03]	0.668	
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	

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]**
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 (3.4)	Not reached [-; -]	289	2 (0.7)	Not reached [-; -]	5.25 [1.23; 22.46]	0.025	0.362
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	Not reached	220	1	Not reached	9.83	0.026	

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]**
		(4.3)	[-; -]		(0.5)	[-; -]	[1.32; 73.43]		
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	
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	Not reached	79	0	Not reached	n.a.	0.446	> 0.999

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]**
		(0.7)	[-; -]		(0.0)	[-; -]	[n.a.; n.a.]		
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-G6: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT

Tabelle 4G-65: 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