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## Abstract

**Background:** In KEYNOTE-522 (NCT03036488), neoadjuvant pembrolizumab plus chemotherapy and then adjuvant pembrolizumab significantly improved pathological complete response and event-free survival vs neoadjuvant chemotherapy in early-stage triple-negative breast cancer (TNBC). We report patient-reported outcomes (PROs) from KEYNOTE-522.

**Methods:** Patients were randomized 2:1 to neoadjuvant pembrolizumab 200 mg or placebo every 3 weeks, plus 4 cycles of paclitaxel plus carboplatin and then 4 cycles of doxorubicin (or epirubicin) plus cyclophosphamide. After surgery, patients received adjuvant pembrolizumab or placebo for up to 9 cycles. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) and EORTC Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23) were prespecified secondary objectives. Between-group differences in least squares (LS) mean change from baseline (day 1 of cycle 1 in both neoadjuvant and adjuvant phases) to the prespecified latest time point with at least 60% completion and at least 80% compliance were assessed using a longitudinal model (no alpha error assigned).

**Results:** Week 21 (neoadjuvant phase) and week 24 (adjuvant phase) were the latest time points at which completion/compliance rates were  $\geq 60\%/80\%$ . In the neoadjuvant phase, between-group differences (pembrolizumab plus chemotherapy [ $n = 762$ ] vs placebo plus chemotherapy [ $n = 383$ ]) in LS mean change from baseline to week 21 in QLQ-C30 global health status/quality of life (GHS/QoL), emotional functioning, and physical functioning were  $-1.04$  (95% confidence interval =  $-3.46$  to  $1.38$ ),  $-0.69$  (95% CI =  $-3.13$  to  $1.75$ ), and  $-2.85$  (95% CI =  $-5.11$  to  $-0.60$ ), respectively. In the adjuvant phase, between-group differences (pembrolizumab [ $n = 539$ ] vs

Received: March 20, 2024. Revised: May 14, 2024. Accepted: May 30, 2024

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placebo [ $n = 308$ ]) in LS mean change from baseline to week 24 were  $-0.41$  (95% CI =  $-2.60$  to  $1.77$ ),  $-0.60$  (95% CI =  $-2.99$  to  $1.79$ ), and  $-1.57$  (95% CI =  $-3.36$  to  $0.21$ ).

**Conclusions:** No substantial differences in PRO assessments were observed between neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab vs neoadjuvant placebo plus chemotherapy in early-stage TNBC.

**Trial registration:** ClinicalTrials.gov, NCT03036488.

Patients with early-stage triple-negative breast cancer (TNBC) have poorer survival outcomes than those with other types of early-stage breast cancer (1,2). Additionally, TNBC is an aggressive tumor type with a high rate of disease recurrence. In a real-world study, nearly 50% of patients with early-stage TNBC experienced recurrence (locoregional or distant) despite treatment with chemotherapy in the neoadjuvant and adjuvant settings; median time to first recurrence (locoregional or metastatic) was approximately 4.5 years (3). Strategies to potentially improve outcomes for patients with early-stage TNBC, including the addition of immunotherapies (eg, programmed cell death protein 1 [PD-1] or programmed cell death ligand 1 [PD-L1] inhibitors) to chemotherapy and the use of targeted drugs (eg, poly [ADP-ribose] polymerase inhibitors), have been studied over the past few years, with some being approved for clinical use (4).

The addition of the anti-PD-1 antibody pembrolizumab or the anti-PD-L1 antibodies atezolizumab or durvalumab to neoadjuvant chemotherapy demonstrated manageable safety and clinical benefit in several studies of patients with high-risk, early-stage TNBC (5-10). In the phase 3 KEYNOTE-522 study, 1174 patients were randomized (2:1) across 181 sites to receive neoadjuvant pembrolizumab plus chemotherapy followed by surgery and then adjuvant pembrolizumab or neoadjuvant placebo plus chemotherapy followed by surgery and then adjuvant placebo (7,8). Treatment with pembrolizumab resulted in clinically meaningful and statistically significant improvements in the dual primary endpoints of pathological complete response (64.8% vs 51.2%;  $P < .001$ ) and event-free survival (hazard ratio = 0.63 [95% confidence interval = 0.48–0.82];  $P < .001$ ) in this patient population. Efficacy was observed regardless of tumor PD-L1 expression status as measured by PD-L1 IHC 22C3 pharmDx (7,8). The incidence and severity of adverse events were consistent with the known safety profiles of each treatment component (8). The most common treatment-related adverse events of grade 3 or greater throughout the study were neutropenia (34.5% with pembrolizumab plus chemotherapy vs 33.4% with chemotherapy alone), decreased neutrophil count (18.6% vs 23.1%), anemia (18.0% vs 14.9%), and increased alanine aminotransferase (5.5% vs 2.3%) (8). The results from the KEYNOTE-522 study led to approval of the regimen in many countries (eg, United States, 27 European Union member states, United Kingdom, some Asian countries) and its recommendation as a standard-of-care treatment for patients with high-risk, early-stage TNBC in the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO) guidelines (11-13).

Patients with cancer and their oncology clinicians report that quality of life is an important priority in making treatment decisions (14). Breast cancer treatments, including chemotherapy, may increase symptom burden and negatively affect patient health-related quality of life (HRQoL) (15-17). Here, we report the prespecified secondary and exploratory patient-reported outcome (PRO) results from the KEYNOTE-522 study.

## Methods

Methods for the global, phase 3, randomized, double-blind, placebo-controlled KEYNOTE-522 study (ClinicalTrials.gov, NCT03036488)

(18) were previously published in detail (7,8) and are briefly summarized here. The study protocol was approved by an independent institutional review board or ethics committee before being initiated at each study site.

## Patients

Eligible patients were at least 18 years of age; had centrally confirmed TNBC as defined by the American Society of Clinical Oncology–College of American Pathologists guidelines (19,20); had newly diagnosed, previously untreated, locally advanced disease (T1c N1–N2 or T2–T4 N0–N2); had an Eastern Cooperative Oncology Group performance status of 0 or 1; provided a biopsy from the primary tumor for PD-L1 assessment at a central laboratory using PD-L1 IHC 22C3 pharmDx (Agilent Technologies) with PD-L1 expression characterized according to the combined positive score (CPS); and provided written informed consent to participate.

## Study design and treatment

Patients were stratified before randomization according to nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4), and carboplatin regimen (every 3 weeks vs weekly). Patients were randomly assigned 2:1 to receive neoadjuvant pembrolizumab 200 mg or placebo every 3 weeks, together with chemotherapy. Randomization was performed using a block method (block size of 6) and a central interactive voice-response system with an integrated Web-response system. Neoadjuvant chemotherapy comprised carboplatin area under the curve (AUC) 5 (maximum dose, 750 mg) every 3 weeks or AUC 1.5 (maximum dose, 225 mg) every week plus paclitaxel 80 mg/m<sup>2</sup> every week for 4 cycles (12 weeks), followed by doxorubicin 60 mg/m<sup>2</sup> or epirubicin 90 mg/m<sup>2</sup> every 3 weeks plus cyclophosphamide 600 mg/m<sup>2</sup> every 3 weeks for 4 cycles (12 weeks). Patients then underwent definitive surgery and began adjuvant treatment with pembrolizumab 200 mg or placebo every 3 weeks for up to 9 cycles (27 weeks). All study medication was administered intravenously. Treatment was continued for the maximum number of cycles for each component or until disease progression, recurrence, or unacceptable toxicity.

## Endpoints

The dual primary endpoints of the study were pathological complete response (ypT0/Tis ypN0) and investigator-assessed event-free survival in the intention-to-treat population. PROs measured with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) and the EORTC Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23) were prespecified secondary objectives, and those measured with the EuroQol 5-Dimension Questionnaire visual analog scale (EQ-5D VAS) were exploratory objectives.

## Assessments

Questionnaires were available in the local language or languages (eg, Dutch, French, and German for Belgium; German, French,

and Italian for Switzerland) for all countries included in the study. PROs were administered (EQ-5D first, QLQ-C30 second, and QLQ-BR23 third) by trained study site personnel and completed electronically by the patients themselves. PROs were assessed before treatment on day 1 of cycles 1, 5, and 8 during the neoadjuvant phase; on day 1 of cycles 1, 5, and 9 during the adjuvant phase; and then every 12 months for 2 years or until disease progression or recurrence, whichever was earlier.

The QLQ-C30 is a self-reported, 30-item, cancer-specific instrument that assesses 15 domains: 5 functional scales (physical, role, emotional, cognitive, and social functioning), 9 symptom scales or single items (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and global health status/quality of life (GHS/QoL) (21, 22). The QLQ-BR23 is a breast-specific module that includes 23 items composed of 4 functional scales (body image, sexual functioning, sexual enjoyment, and future perspective) and 4 symptom scales (systemic therapy side effects, breast symptoms, arm symptoms, and upset by hair loss) (23). Scores range from 0 to 100 for the QLQ-C30 and QLQ-BR23; a higher score for GHS/QoL or functional scales represents a higher (better) QoL or level of functioning, respectively, whereas a higher score for symptom scales or items represents a worse level of symptoms (22). EQ-5D is a standardized measure of health status consisting of 2 separate elements, utility score and VAS. EQ-5D VAS scores range from 0 ("worst imaginable health state") to 100 ("best imaginable health state") (24).

## Statistical analysis

PROs were analyzed for the PRO full analysis set, defined as all randomized patients who had at least 1 PRO assessment and received  $\geq 1$  study treatment. PROs were also analyzed for the subgroup of patients with PD-L1 CPS  $\geq 1$  tumors. The prespecified primary analysis time point for PROs was the latest time at which there was a  $\geq 60\%$  completion rate and a  $\geq 80\%$  compliance rate. Completion rate was defined as the number of patients who completed at least 1 score/item at each time point over the number of patients in the PRO full analysis set population. Compliance rate was defined as the number of patients who completed at least 1 score/item at each time point over the number of patients expected to complete at each time point, excluding those missing by design (eg, due to death, discontinuation, translations unavailable, or visit not scheduled).

Between-group differences in least-squares (LS) mean change from baseline (neoadjuvant baseline in neoadjuvant phase, adjuvant baseline in adjuvant phase) in PROs at the primary analysis time point were assessed using a constrained longitudinal data analysis model (25). No alpha error was assigned. PRO score was the response variable in the model, and treatment by time point interaction and stratification stratum were covariates. The model implicitly treated missing data as missing at random. Only PRO data up to the primary analysis time point were included. Some scores were imputed as per the EORTC Scoring Manual.

## Results

### Patients

Between March 2017 and September 2018, 1174 patients were randomly assigned to the pembrolizumab plus chemotherapy arm ( $n = 784$ ) or the placebo plus chemotherapy arm ( $n = 390$ ). At the March 23, 2021, data cutoff, the median duration of follow-up was 39.1 (range = 30.0–48.0) months. As reported previously (7,8),

patient demographics and baseline disease characteristics were similar between the 2 treatment groups.

The PRO full analysis set included 1145 patients for QLQ-C30, 1141 patients for QLQ-BR23, and 1146 patients for EQ-5D in the neoadjuvant phase and 847, 844, and 850 patients, respectively, in the adjuvant phase (Figure 1). In both treatment groups, completion and compliance rates for QLQ-C30, QLQ-BR23, and EQ-5D were greater than 90% at baseline in the neoadjuvant and adjuvant phases (Table 1). Week 21 in the neoadjuvant phase (calculated from day 1 of cycle 1 of the neoadjuvant phase and corresponding to day 1 of cycle 5 of the neoadjuvant phase) and week 24 in the adjuvant phase (calculated from day 1 of cycle 1 of the adjuvant phase and corresponding to day 1 of cycle 6 of the adjuvant phase) were selected for analysis because these were the latest time points at which completion and compliance rates were at least 60% and at least 80%, respectively. Completion and compliance rates among patients with PD-L1 CPS  $\geq 1$  are shown in Supplementary Table 1 (available online).

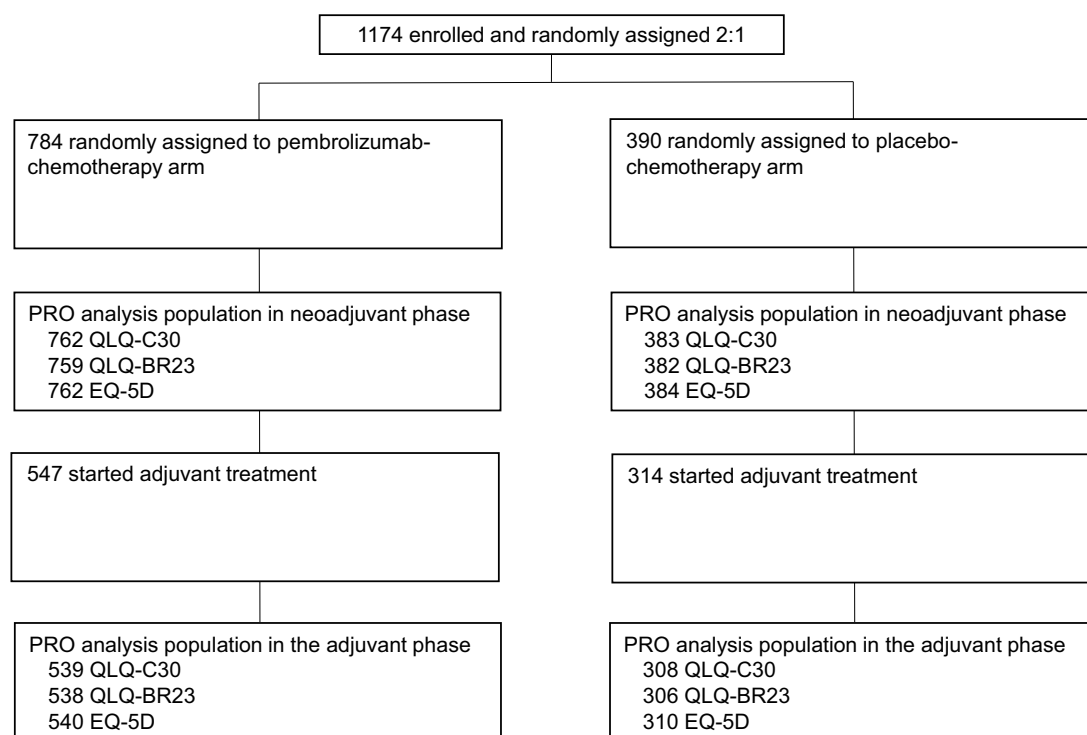
## Patient-reported outcomes

Results for the PRO full analysis set are described in the text. Results for the PD-L1 CPS  $\geq 1$  population were similar (see Supplementary Table 2, Supplementary Figures 1 and 2, available online for details).

### EORTC QLQ-C30

In the neoadjuvant phase, LS mean scores for QLQ-C30 GHS/QoL and physical functioning decreased from baseline to week 21 in both treatment groups, whereas scores for QLQ-C30 emotional functioning were unchanged in both treatment groups (Table 2, Figure 2, A). Between-group differences were  $-1.04$  (95% CI =  $-3.46$  to  $1.38$ ),  $-2.85$  (95% CI =  $-5.11$  to  $-0.60$ ), and  $-0.69$  (95% CI =  $-3.13$  to  $1.75$ ), respectively. LS mean scores for QLQ-C30 role functioning, cognitive functioning, and social functioning similarly decreased from baseline to week 21 in both treatment groups (Figure 2, A). LS mean scores for QLQ-C30 symptom scales or items including fatigue, nausea and vomiting, pain, dyspnea, appetite loss, constipation, and financial difficulties similarly increased from baseline to week 21 (indicative of worse symptoms) in both treatment groups (Figure 2, B). Scores for insomnia and diarrhea increased in the pembrolizumab plus chemotherapy group (95% CIs did not include 0) but remained unchanged in the placebo plus chemotherapy group (95% CIs included 0).

In the adjuvant phase, LS mean scores for QLQ-C30 GHS/QoL and physical functioning increased from baseline to week 24 in both treatment groups, whereas scores for QLQ-C30 emotional functioning decreased in the pembrolizumab group and were unchanged in the placebo group (Table 2, Figure 3, A). Between-group differences were  $-0.41$  (95% CI =  $-2.60$  to  $1.77$ ),  $-1.57$  (95% CI =  $-3.36$  to  $0.21$ ), and  $-0.60$  (95% CI =  $-2.99$  to  $1.79$ ), respectively. LS mean scores for QLQ-C30 role functioning and social functioning similarly increased from baseline to week 24 in both treatment groups, whereas scores for cognitive functioning were unchanged (Figure 3, A). LS mean scores for QLQ-C30 symptom scales or items including pain, insomnia, and appetite loss similarly decreased from baseline to week 24 (indicative of symptom improvement) in both treatment groups (Figure 3, B). Scores for nausea and vomiting, dyspnea, constipation, and diarrhea remained unchanged in both treatment groups (95% CIs included 0), whereas scores for fatigue decreased in the pembrolizumab group (95% CI did not include 0) but were unchanged in the placebo group, and scores of financial difficulties were unchanged in the pembrolizumab group but decreased in the placebo group.



**Figure 1.** Patient disposition. EQ-5D = EuroQol 5-Dimension Questionnaire; PRO = patient-reported outcome; QLQ-BR23 = European Organisation for Research and Treatment of Cancer Breast Cancer–Specific Quality of Life Questionnaire; QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30.

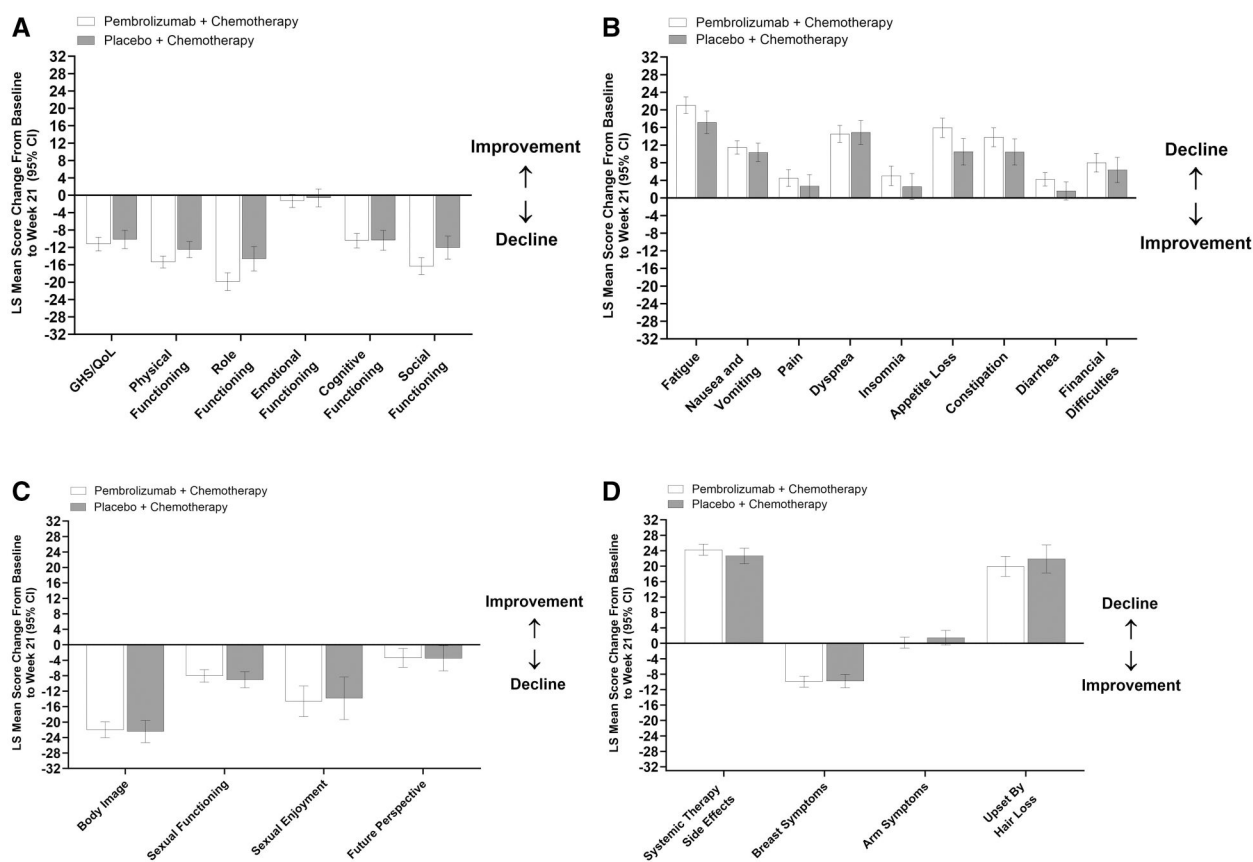
**Table 1.** Completion and compliance rates for patient-reported outcome questionnaires

	QLQ-C30		QLQ-BR23		EQ-5D	
	Pembrolizumab + Chemotherapy n = 762	Placebo + Chemotherapy n = 383	Pembrolizumab + Chemotherapy n = 759	Placebo + Chemotherapy n = 382	Pembrolizumab + Chemotherapy n = 762	Placebo + Chemotherapy n = 384
<b>Neoadjuvant phase</b>						
Baseline						
Completion, n (%) <sup>a</sup>	701 (92.0)	366 (95.6)	695 (91.6)	361 (94.5)	707 (92.8)	369 (96.1)
Compliance, n/N (%) <sup>b</sup>	701/762 (92.0)	366/382 (95.8)	695/759 (91.6)	361/381 (94.8)	707/762 (92.8)	369/383 (96.3)
Week 12						
Completion, n (%) <sup>a</sup>	648 (85.0)	329 (85.9)	644 (84.8)	328 (85.9)	657 (86.2)	336 (87.5)
Compliance, n/N (%) <sup>b</sup>	648/711 (91.1)	329/363 (90.6)	644/709 (90.8)	328/362 (90.6)	657/711 (92.4)	336/365 (92.1)
Week 21						
Completion, n (%) <sup>a</sup>	615 (80.7)	309 (80.7)	611 (80.5)	307 (80.4)	616 (80.8)	311 (81.0)
Compliance, n/N (%) <sup>b</sup>	615/688 (89.4)	309/349 (88.5)	611/686 (89.1)	307/348 (88.2)	616/688 (89.5)	311/350 (88.9)
<b>Adjuvant phase</b>						
Baseline						
Completion, n (%) <sup>a</sup>	489 (90.7)	283 (91.9)	487 (90.5)	282 (92.2)	495 (91.7)	285 (91.9)
Compliance, n/N (%) <sup>b</sup>	489/539 (90.7)	283/308 (91.9)	487/538 (90.5)	282/306 (92.2)	495/540 (91.7)	285/310 (91.9)
Week 12						
Completion, n (%) <sup>a</sup>	485 (90.0)	269 (87.3)	483 (89.8)	267 (87.3)	485 (89.8)	274 (88.4)
Compliance, n/N (%) <sup>b</sup>	485/527 (92.0)	269/302 (89.1)	483/526 (91.8)	267/300 (89.0)	485/528 (91.9)	274/304 (90.1)
Week 24						
Completion, n (%) <sup>a</sup>	444 (82.4)	249 (80.8)	442 (82.2)	247 (80.7)	444 (82.2)	249 (80.3)
Compliance, n/N (%) <sup>b</sup>	444/484 (91.7)	249/282 (88.3)	442/483 (91.5)	247/280 (88.2)	444/485 (91.5)	249/284 (87.7)

EQ-5D = EuroQol 5-Dimension Questionnaire; PRO = patient-reported outcome; QLQ-BR23 = European Organisation for Research and Treatment of Cancer Breast Cancer–Specific Quality of Life Questionnaire; QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30.

<sup>a</sup> Completion rate: number of patients who completed at least 1 score/item over the number of patients in the PRO full analysis set population at each time point.

<sup>b</sup> Compliance rate: number of patients who completed at least 1 score/item over the number of patients expected to complete at each time point excluding those missing by design (eg, due to death, discontinuation, translation unavailable).



**Figure 2.** Change from baseline to week 21 in the neoadjuvant phase: **A)** QLQ-C30 GHS/QoL and functional scales, **B)** QLQ-C30 symptom scales or items, **C)** QLQ-BR23 functional scales or items, and **D)** QLQ-BR23 symptom scales or items. For GHS/QoL score and all functional scales, a higher score denotes better HRQoL or function. For symptoms scales or items, a higher score denotes worse symptoms. CI = confidence interval; GHS/QoL = global health status/quality of life; HRQoL = health-related quality of life; LS = least squares; QLQ-BR23 = European Organisation for Research and Treatment of Cancer Breast Cancer–Specific Quality of Life Questionnaire; QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30.

### QLQ-BR23

LS mean score changes from baseline for QLQ-BR23 functional scales and symptom scales or items were similar in both treatment groups in the neoadjuvant (Figure 2, C and D) and adjuvant (Figure 3, C and D) phases.

### EQ-5D VAS

As shown in Table 2, LS mean scores for 5Q-5D VAS decreased from baseline to week 21 in both treatment groups in the neoadjuvant phase (between-group difference,  $-1.61$  [95% CI =  $-3.87$  to  $0.64$ ]), whereas scores increased from baseline to week 24 in both treatment groups in the adjuvant phase (between-group difference,  $-0.59$  [95% CI =  $-2.40$  to  $1.23$ ]).

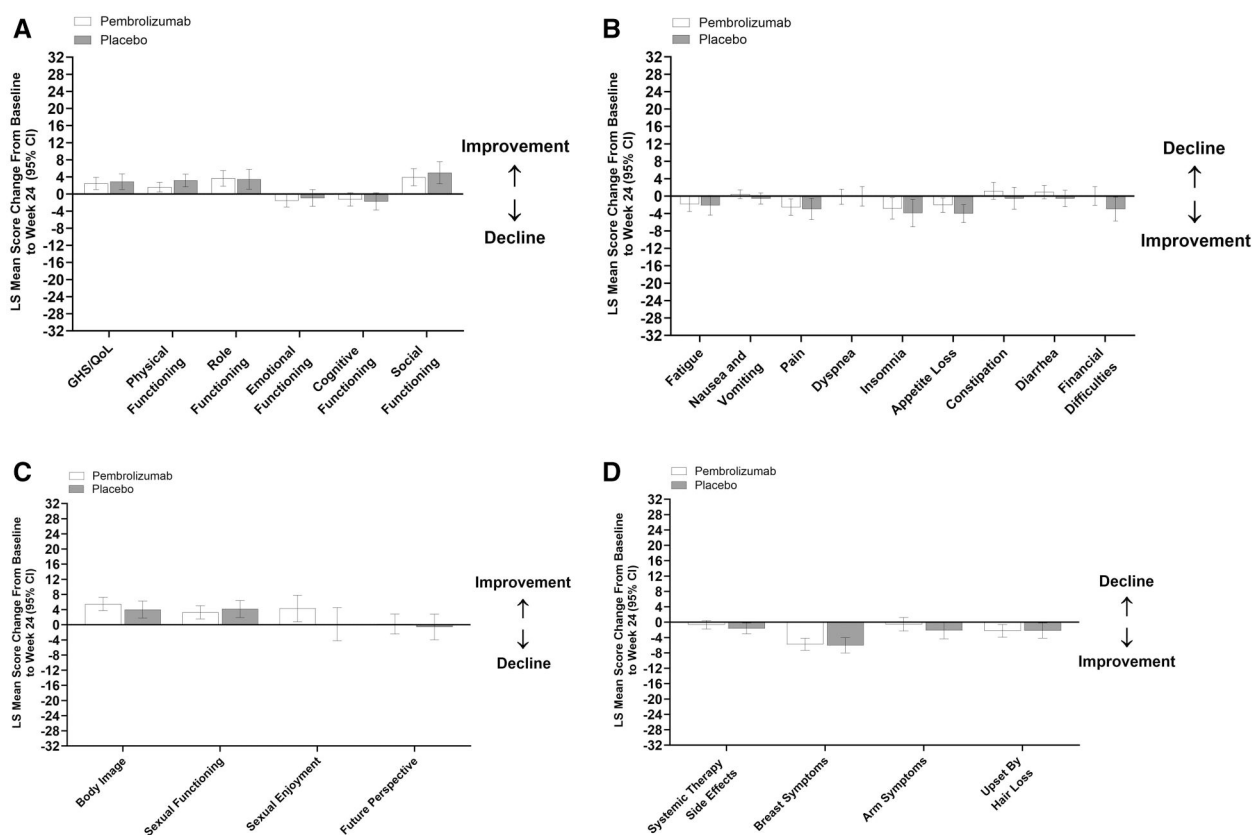
## Discussion

In the KEYNOTE-522 study, completion and compliance rates for all PRO instruments (QLQ-C30, QLQ-BR23, and EQ-5D) were high at baseline (above 90%) and remained above 80% through week 21 of the neoadjuvant phase and week 24 of the adjuvant phase. Treatment with neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab alone did not adversely impact HRQoL compared with neoadjuvant placebo plus chemotherapy followed by adjuvant placebo alone. In both treatment groups, the prespecified QLQ-C30 GHS/QoL and physical functioning scales similarly decreased during the neoadjuvant phase

and similarly increased during the adjuvant phase. QLQ-C30 emotional functioning was largely unchanged during both treatment phases. No substantial between-group differences were observed for any of the PRO assessments. Results for patients with PD-L1 CPS  $\geq 1$  tumors were similar to those for the overall study population.

In both treatment groups, increases from baseline in QLQ-C30 symptom scales (ie, fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea) were observed during the neoadjuvant phase, whereas no changes or slight decreases were noted during the adjuvant phase. This is consistent with the pattern of treatment-related adverse events that were reported during the study. Treatment-related adverse events for overlapping terms captured by the QLQ-C30 symptom scales occurred more frequently in the neoadjuvant phase than in the adjuvant phase and at rates that were generally similar in both treatment groups during both treatment phases (8,26).

Our findings are consistent with those from the phase 3 Impassion031 study in which patients with high-risk, early-stage TNBC were treated with neoadjuvant atezolizumab plus chemotherapy followed by adjuvant atezolizumab compared with neoadjuvant placebo plus chemotherapy (27). In that study, a total of 328 patients were included in the analysis of the prespecified secondary objectives of QLQ-C30 GHS/QoL, physical functioning, and role functioning. Baseline values for each of these PRO endpoints were comparable to those in KEYNOTE-522, and a similar



**Figure 3.** Change from baseline to week 24 in the adjuvant phase: **A)** QLQ-C30 GHS/QoL and functional scales, **B)** QLQ-C30 symptom scales or items, **C)** QLQ-BR23 functional scales or items, and **D)** QLQ-BR23 symptom scales or items. For GHS/QoL score and all functional scales, a higher score denotes better HRQoL or function. For symptoms scales or items, a higher score denotes worse symptoms. CI = confidence interval; GHS/QoL = global health status/quality of life; HRQoL = health-related quality of life; LS = least squares; QLQ-BR23 = European Organisation for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire; QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.

pattern of changes occurred during the neoadjuvant and adjuvant phases with no apparent differences between the 2 treatment groups (27). Other studies in which PD-1 or PD-L1 inhibitors were added to neoadjuvant chemotherapy in patients with early-stage TNBC did not report PRO results (5,6,9,28).

The KEYNOTE-522 study has some limitations. It was not powered for PRO endpoints, and the related analyses were not controlled for multiplicity. As expected, completion rates decreased over the course of the study as the number of evaluable patients decreased; however, completion/compliance rates for QLQ-C30, QLQ-BR23, and EQ-5D remained above 60%/80% throughout the study in the neoadjuvant and adjuvant phases. The PRO instruments used in the study were not specifically designed to assess outcomes in patients treated with immunotherapies and therefore may not capture the impact of some toxicities on PROs. Immune checkpoint inhibitors are known to be associated with certain immune-related adverse events, some of which may be severe in nature, highlighting the importance of patient monitoring and management during treatment (29). In the KEYNOTE-522 study (combined neoadjuvant and adjuvant phases), immune-mediated adverse events of grade 3 or greater occurred in 12.9% of patients in the pembrolizumab arm and 1.0% of patients in the placebo arm; the most common grade 3 or greater events were severe skin reaction (4.7% vs 0.3%), hypophysitis (1.3% vs 0%), and adrenal insufficiency (1.0% vs 0%) (8). The proportion of patients who started adjuvant treatment was higher in the placebo arm (80.5%) than in the pembrolizumab

arm (69.8%) (8). The results of the adjuvant phase should be interpreted with caution because this was a nonrandomized analysis.

In conclusion, patients with high-risk, early-stage TNBC did not experience substantial differences in any PRO assessments during treatment with neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant placebo plus chemotherapy followed by adjuvant placebo. Taken together with the previously reported efficacy and safety findings from the KEYNOTE-522 study, these PRO results support neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab as an effective standard of care treatment regimen in this setting.

## Data availability

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data-sharing website (available at: [http://engagezone.msd.com/ds\\_documentation.php](http://engagezone.msd.com/ds_documentation.php)) outlines the process and requirements for submitting a data request.

**Table 2.** LS mean score changes from baseline for each PRO in the neoadjuvant and adjuvant treatment phases

PRO instrument	Neoadjuvant phase		Adjuvant phase	
	Pembrolizumab + Chemotherapy	Placebo + Chemotherapy	Pembrolizumab	Placebo
<b>QLQ-C30 GHS/QoL</b> Mean (SD) at baseline <sup>a</sup>	77.08 (18.49) n = 701	78.96 (17.12) n = 366	73.82 (15.68) n = 489	73.14 (18.15) n = 283
Mean (SD) at week 21 or 24 <sup>b</sup>	66.79 (19.39) n = 615	68.26 (17.82) n = 309	76.26 (16.67) n = 444	76.24 (16.56) n = 249
LS mean (95% CI) change from baseline to week 21 or 24 <sup>a, b</sup>	-11.24 (-12.82 to -9.66) n = 762	-10.20 (-12.30 to -8.10) n = 383	2.47 (1.05 to 3.88) n = 539	2.88 (1.05 to 4.71) n = 308
Difference in LS means (95% CI)	-1.04 (-3.46 to 1.38)		-0.41 (-2.60 to 1.77)	
<b>QLQ-C30 Physical Functioning</b> Mean (SD) at baseline <sup>a</sup>	91.89 (12.80) n = 701	91.51 (13.13) n = 366	83.30 (15.32) n = 489	81.63 (16.61) n = 283
Mean (SD) at week 21 or 24 <sup>b</sup>	77.01 (18.99) n = 615	79.18 (17.13) n = 309	84.82 (15.68) n = 444	85.38 (15.03) n = 249
LS mean (95% CI) change from baseline to week 21 or 24 <sup>a, b</sup>	-15.37 (-16.71 to -14.03) n = 762	-12.52 (-14.38 to -10.65) n = 383	1.60 (0.46 to 2.75) n = 539	3.18 (1.70 to 4.66) n = 308
Difference in LS means (95% CI)	-2.85 (-5.11 to -0.60)		-1.57 (-3.36 to 0.21)	
<b>QLQ-C30 Emotional Functioning</b> Mean (SD) at baseline <sup>a</sup>	76.14 (19.50) n = 701	75.20 (20.69) n = 366	81.75 (17.72) n = 489	78.98 (20.81) n = 283
Mean (SD) at week 21 or 24 <sup>b</sup>	74.61 (20.79) n = 615	74.95 (21.64) n = 309	79.62 (19.64) n = 444	78.41 (20.44) n = 249
LS mean (95% CI) change from baseline to week 21 or 24 <sup>a, b</sup>	-1.31 (-2.82 to 0.21) n = 762	-0.62 (-2.67 to 1.44) n = 383	-1.53 (-3.03 to -0.03) n = 539	-0.92 (-2.88 to 1.04) n = 308
Difference in LS means (95% CI)	-0.69 (-3.13 to 1.75)		-0.60 (-2.99 to 1.79)	
<b>QLQ-BR23 Breast Symptoms</b> Mean (SD) at baseline <sup>a</sup>	18.67 (20.36) n = 695	18.47 (19.32) n = 361	22.23 (18.71) n = 487	23.02 (20.24) n = 282
Mean (SD) at week 21 or 24 <sup>b</sup>	8.82 (12.92) n = 611	8.50 (14.03) n = 307	16.84 (17.19) n = 442	16.70 (18.14) n = 247
LS mean (95% CI) change from baseline to week 21 or 24 <sup>a, b</sup>	-9.92 (-11.34 to -8.49) n = 759	-9.78 (-11.53 to -8.03) n = 382	-5.73 (-7.32 to -4.15) n = 538	-6.02 (-8.04 to -4.01) n = 306
Difference in LS means (95% CI)	-0.13 (-1.92 to 1.65)		0.29 (-2.05 to 2.63)	
<b>EQ-5D VAS</b> Mean (SD) at baseline <sup>a</sup>	81.10 (18.07) n = 707	82.60 (16.98) n = 369	78.43 (14.58) n = 495	78.79 (14.54) n = 285
Mean (SD) at week 21 or 24 <sup>b</sup>	72.76 (18.14) n = 616	74.99 (16.37) n = 311	80.58 (14.86) n = 444	81.20 (13.35) n = 249
LS mean (95% CI) change from baseline to week 21 or 24 <sup>a, b</sup>	-8.98 (-10.48 to -7.47) n = 762	-7.36 (-9.34 to -5.38) n = 384	1.83 (0.66 to 3.00) n = 540	2.42 (0.91 to 3.93) n = 310
Difference in LS means (95% CI)	-1.61 (-3.87 to 0.64)		-0.59 (-2.40 to 1.23)	

CI = confidence interval; EQ-5D VAS = EuroQol 5-Dimension Questionnaire visual analog scale; GHS/QoL = global health status/quality of life; LS = least squares; PRO = patient-reported outcome; QLQ-BR23 = European Organisation for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire; QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; SD = standard deviation.

<sup>a</sup> Baseline refers to the baseline time point for the respective phase (neoadjuvant or adjuvant).  
<sup>b</sup> The analysis time point was week 21 in the neoadjuvant phase and week 24 in the adjuvant phase.

Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD either will perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

## Funding

Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

## Conflicts of interest

**R. Dent:** Advisory/Consultancy: AstraZeneca, Novartis; Advisory/Consultancy, Travel/Accommodation/Expenses: Eisai, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Pfizer, Roche.

**J. Cortés:** Honoraria (self), Advisory/Consultancy, Research Grant/Funding (institution), Travel/Accommodation/Expenses: Roche; Honoraria (self), Travel/Accommodation/Expenses: Novartis; Honoraria (self), Advisory/Consultancy: Celgene, Lilly; Honoraria (self), Research Grant/Funding (institution), Travel/Accommodation/Expenses: Eisai, Pfizer; Honoraria (self): Samsung Bioepis; Honoraria (self), Advisory/Consultancy, Research grant/Funding (institution): Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; Advisory/Consultancy: Atenex, Biothera Pharmaceuticals, Cellestia, Erytech, Merus, Polyphor, Seattle Genetics, Servier; Advisory/Consultancy, Research grant/Funding (institution): AstraZeneca; Advisory/Consultancy, Travel/Accommodation/Expenses: Daiichi Sankyo; Research Grant/Funding (institution): Ariad Pharmaceuticals, Baxalta GMBH/Servier Affaires, Bayer Healthcare, Guardian Health, Piquor Therapeutics, Puma C, Queen Mary University of London, Seagen; Shareholder/Stockholder/Stock Options: MedSIR.

**L. Pusztai:** Honoraria (self), Advisory/Consultancy, Research Grant/Funding (institution), Travel/Accommodation/Expenses: AstraZeneca, Merck & Co., Inc., Rahway, NJ, USA, Seattle Genetics; Honoraria (self), Advisory/Consultancy, Travel/Accommodation/Expenses: Almac, Eisai, Genentech, Immunomedics, Novartis, Pieris, Syndax.

**H. McArthur:** Consultancy: AstraZeneca, Bristol Myers Squibb, Crown Bioscience, Daiichi-Sankyo, Eli Lilly, Gilead, Pfizer, Puma, Seattle Genetics, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; Research Support: Bristol Myers Squibb, BTG, LLC/AstraZeneca, MedImmune, Merck Sharp

& Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

**S. Kummel:** Advisory/Consultancy: Agendia, Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Genomic Health, Gilead Sciences, Hologic, Lilly, Novartis, Pfizer, PFM Medical, Roche/Genentech, Seagen, Somatex, Sonoscape, Stryker, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; Travel/Accommodation/Expenses: Daiichi Sankyo, Gilead Sciences, Roche; Uncompensated relationships: WSG Study Group.

**J. Bergh:** Research Grant/Funding (institution): Amgen, AstraZeneca, Bayer, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Pfizer, Roche, Sanofi Aventis; Chapter Honoraria: from UpToDate to Asklepios Medicin Hb. Stocks: Stratipath AB, Coronis, Asklepios Cancer Research AB.

**C. Denkert:** Honoraria (self): Novartis, Pfizer, Roche, Teva; Honoraria (self), Advisory/Consultancy: Amgen; Advisory/Consultancy: Daiichi Sankyo, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; Licensing/Royalties: VmScope.

**Y.H. Park:** Consultancy or Advisory Board Member: AstraZeneca, Eisai, Novartis, Pfizer, Roche; Research Funding: Alteogen, AstraZeneca, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Novartis, Pfizer, Roche.

**R. Hui:** Personal Fees for Advisory Boards: Amgen, AstraZeneca, BMS, Eisai, Eli Lilly, Merck KGaA, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Novartis, Oncosec, Pfizer, Roche, Seagen, Takeda, Zai Lab; Speaker Honoraria: AstraZeneca, Eli Lilly, Janssen, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Novartis, Roche; Study Funding (institution): AstraZeneca, BMS, Corvus, Eisai, Eli Lilly, Janssen, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Novartis, Oncosec, Roche, Seagen.

**N. Harbeck:** Stock and Other Ownership Interests: West German Study Group; Honoraria: Amgen, AstraZeneca, Daiichi Sankyo, Gilead, Lilly, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, Seagen, Viatrix, Zuelligpharma; Consulting or Advisory Role: Gilead, Roche, Sandoz, Seagen; Research Funding (institution): Lilly, Novartis, Pfizer, Roche/Genentech, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

**M. Takahashi:** Honoraria (self): AstraZeneca, Lilly, Pfizer; Honoraria (self), Research Grant/Funding (self): Eisai; Research Grant/Funding (self): Kyowa-Hakko Kirin, Nippon Kayaku, Taiho.

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**P.A. Fasching:** Consulting Fees: Agendia, AstraZeneca, Daiichi Sankyo, Eisai, Hexal, Lilly, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Novartis, Pfizer, Pierre Fabre, Roche, Seagen; Fees for Non-CME Services Received Directly from Commercial Interest or their Agents: Daiichi Sankyo, Lilly, Novartis, Seagen; Research Grant: Biontech, Cepheid.



**F. Cardoso:** Consultancy/Advisory Role: Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, Genentech, GE Oncology, Gilead, GlaxoSmithKline, Iqvia, Macrogenics, Medscape, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Merck & Co., Inc., Rahway, NJ, USA, Merus BV, Mundipharma, Mylan, Novartis, Pfizer, Pierre-Fabre, prime Oncology, Roche, Samsung Bioepis, Sanofi, Seagen, Teva, Touchime.

**A. Haiderali, L. Jia, A.M. Nguyen, and W. Pan:** Employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and stockholders in Merck & Co., Inc., Rahway, NJ, USA.

**J. O'Shaughnessy:** Consulting Fees: AbbVie, Agendia, Amgen, Aptitude Health, AstraZeneca, Bayer, BMS, Celgene, Clovis Oncology, Daiichi Sankyo, Eisai, G1 Therapeutics, Genentech, Gilead Sciences, GRAIL, Halozyme, Heron Therapeutics, Immunomedics, Ipsen Biopharmaceuticals, Lilly, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Myriad, Nektar Therapeutics, Novartis, Pfizer, Pharmacyclics, Pierre Fabre, Prime Oncology, Puma Biotechnology, Roche, Samsung Bioepis, Sanofi, Seagen, Syndax Pharmaceuticals, Synthron, Taiho Oncology, Takeda.

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## Acknowledgments

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, was involved in the conception, design, or planning of the study; analysis of the data; interpretation of the results; drafting and reviewing of the manuscript; and the decision to submit the manuscript for publication. We thank the patients and their families and caregivers for participating in this study, along with all investigators and site personnel. Medical writing assistance was provided by Autumn Kelly, MA, and Michael S. McNamara, MS, of ICON plc (Blue Bell, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

A portion of these results have been presented at the European Society for Medical Oncology (ESMO) Congress; September 9-13, 2022; Paris, France; Abstract 135MO.

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