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ORIGINAL ARTICLE

Patient-reported outcomes with cemiplimab monotherapy for first-line treatment of advanced non–small cell lung cancer with PD-L1 of ≥50%: The EMPOWER-Lung 1 study

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Abstract

Background: In the EMPOWER-Lung 1 trial (ClinicalTrials.gov, NCT03088540), cemiplimab conferred longer survival than platinum-doublet chemotherapy for advanced non–small cell lung cancer (NSCLC) with programmed cell death-ligand 1 (PD-L1) ≥50%. Patient-reported outcomes were evaluated among trial participants.

Methods: Adults with NSCLC and Eastern Cooperative Oncology Group performance status 0 to 1 were randomly assigned cemiplimab 350 mg every 3 weeks or platinum-doublet chemotherapy. At baseline and day 1 of each treatment cycle, patients were administered the European Organization for Research and Treatment of Cancer Quality of Life-Core 30 (QLQ-C30) and Lung Cancer Module (QLQ-LC13) questionnaires. Mixed-model repeated measures analysis estimated overall change from baseline for PD-L1 ≥50% and intention-to-treat populations. Kaplan–Meier analysis estimated time to definitive deterioration.

Results: In PD-L1 ≥50% patients (cemiplimab, $n = 283$; chemotherapy, $n = 280$), baseline QLQ-C30 and QLQ-LC13 scores showed moderate-to-high functioning and low symptom burden. Change from baseline favored cemiplimab on global health status/quality of life (GHS/QOL), functioning, and most symptom scales. Risk of definitive deterioration across functioning scales was reduced versus chemotherapy; hazard ratios were 0.48 (95% CI, 0.32-0.71) to 0.63 (95% CI, 0.41-0.96). Cemiplimab showed lower risk of definitive deterioration for disease-related (dyspnea, cough, pain in chest, pain in other body parts, fatigue) and treatment-related symptoms (peripheral neuropathy, alopecia, nausea/vomiting, appetite loss,

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constipation, diarrhea) (nominal $p < .05$). Results were similar in the intention-to-treat population.

Conclusions: Results support cemiplimab for first-line therapy of advanced NSCLC from the patient's perspective. Improved survival is accompanied by improvements versus platinum-doublet chemotherapy in GHS/QOL and functioning and reduction in symptom burden.

KEYWORDS
cemiplimab, non-small cell lung cancer, patient-reported outcomes, quality of life, symptom burden

INTRODUCTION

Lung cancer continues to be the leading cause of cancer-related deaths in the United States.[1] Non–small cell lung cancer (NSCLC) is the predominant form of lung cancer, accounting for approximately 80% of cases.[2] Although platinum-based chemotherapy has long been the standard of care for treatment of advanced NSCLC, such therapy has also been associated with a low response rate and short progression-free and overall survival.[3] Advanced NSCLC and platinum-based chemotherapy are associated with a substantial humanistic burden, as demonstrated by patient reports of lower health-related quality of life (HRQOL) and impaired functioning.[4–10] HRQOL and functioning are particularly affected by disease-related symptoms, such as shortness of breath, cough, fatigue, and pain, and chemotherapy-related symptoms, including neuropathy and sore mouth.[5–7]

In recent years, immunotherapy has been incorporated as first-line systemic therapy for advanced NSCLC,[3] with monoclonal antibodies targeting programmed cell death-1 (PD-1) playing a pivotal role, especially for the treatment of patients with advanced NSCLC who have PD-ligand 1 (PD-L1) expression in ≥50% of tumor cells and are negative for the actionable molecular markers of epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), or C-ROS oncogene 1 (*ROS1*).[11–14]

Cemiplimab is a PD-1 inhibitor that is approved as monotherapy for first-line treatment of patients with metastatic or locally advanced NSCLC who are not candidates for surgical resection or definitive chemoradiation, and whose tumors have high PD-L1 expression (tumor proportion score ≥50%) as determined by a US Food and Drug Administration–approved test, and are negative for *EGFR*, *ALK*, and *ROS1*.[15] In the EMPOWER-Lung 1 phase 3 clinical trial, cemiplimab improved survival and progression-free survival (both primary end points of the study) versus platinum-doublet chemotherapy in patients with advanced NSCLC and PD-L1 expression ≥50% (ClinicalTrials.gov identifier NCT03088540).[14] Treatment with cemiplimab was also associated with a higher objective response rate assessed by an independent review committee based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and with a longer duration of response than treatment with chemotherapy.[14]

The importance of collecting patient-reported outcomes (PROs) using validated instruments to capture the patient's perspective of the effects of therapy on HRQOL among participants in cancer clinical trials is widely recognized.[16–18] To evaluate outcomes from the patient's perspective, the European Organization for Research and Treatment of Cancer Quality of Life-Core 30 (QLQ-C30)[19] questionnaire and its Lung Cancer Module (QLQ-LC13)[20] were included in the EMPOWER-Lung 1 study as prespecified secondary end points. The objective of this analysis was to assess the effects of cemiplimab on HRQOL, including patient-reported symptom burden, functioning, and global health status/quality of life (GHS/QOL) in patients with advanced NSCLC and PD-L1 expression ≥50%.

METHODS

Study design and population

The EMPOWER-Lung 1 study was an open-label, randomized-controlled, phase 3 pivotal clinical trial that evaluated cemiplimab versus platinum-doublet chemotherapy for the treatment of adults (aged ≥18 years) with stage IIIB/IIIC or IV squamous or non-squamous NSCLC with PD-L1 expressed in ≥50% of tumor cells. Patients were required to have histologically or cytologically confirmed disease and Eastern Cooperative Oncology Group performance status ≤1. Patients with locally advanced disease (stage IIIB/IIIC) could be enrolled in the study only if deemed ineligible for definitive concomitant chemoradiotherapy. Complete methodology with full inclusion and exclusion criteria, patient attrition through study completion, and the primary efficacy and safety results have been previously described.[14] The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent before enrollment.

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Treatment

Patients were randomized to cemiplimab 350 mg intravenously every 3 weeks for up to 36 treatment cycles or four to six cycles of investigator's choice of platinum-doublet chemotherapy determined before randomization. Patients were treated for the specified duration or number of cycles or until RECIST 1.1–defined disease progression. Maintenance chemotherapy with pemetrexed was allowed for patients with nonsquamous NSCLC who had received a pemetrexed-containing platinum-doublet chemotherapy.

Outcomes

At baseline and day 1 of each treatment cycle, patients were administered the QLQ-C30[19] and QLQ-LC13 before treatment administration.[20] The QLQ-C30 assesses HRQOL over the past week using a GHS/QOL scale, and five functioning (physical, role, cognitive, emotional, and social) and eight symptom (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, and diarrhea) scales. Functioning and symptoms items are assessed on a 4-point Likert scale, and GHS/QOL is assessed on a 7-point Likert scale. Item scores are subsequently transformed to a 0 to 100 scale; high scores on functioning domains and GHS/QOL and low scores on symptoms reflect better outcomes. A change in score of ≥10 points in the transformed score is considered to be clinically meaningful.[21] Although other thresholds for considering a clinically meaningful change have also been explored in patients with NSCLC,[22] they have not been formally validated, nor have appropriate anchors been established for determining these thresholds.

Statistical analysis

Sample size was calculated based on estimates related to the primary end points of overall survival and progression-free survival as previously reported,[14] and the study was not specifically powered for secondary PRO end points. Because tumor samples from patients tested before August 2018 were not consistently analyzed per assay instructions for use (with omitted or incorrect controls used), a PD-L1 ≥50% population was prespecified to include only patients with assay results based on assay manufacturer's instructions (i.e., PD-L1 ≥50% on retest and those tested after August 2018 who were not affected by the testing issue). Although the PD-L1 ≥50% population was the primary population of interest, analyses were also conducted on the intention-to-treat (ITT) population that consisted of all randomized patients.

All PRO analyses and definitions were prespecified. Descriptive statistics included demographic and clinical characteristics and PRO completion rates. Completion rates were defined as the proportion of patients who answered all items on the PROs among those who were expected to complete the PRO (i.e., alive and still on study). Mixed-model repeated measures (MMRM) analysis was used to estimate least-squares (LS) mean change from baseline and 95% CIs on all scales among patients with a baseline and ≥1 postbaseline score up to cycle 15, which represents approximately 1 year of treatment. The sample size in the chemotherapy group was <10 after cycle 15. In the MMRM analysis, time was treated as a categorical variable so that no restriction was imposed on the trajectory of the means over time. The model adjusted for the stratification factors used for randomization (histology [nonsquamous or squamous] and geographic region [Europe, Asia, or rest of world]), as well as for treatment, time, baseline PRO score, and interactions of time by treatment and baseline score by time. An unstructured variance-covariance matrix was used to model the covariance structure for each patient's repeated measures. Standardized mean differences (SMDs) between treatments were estimated based on Hedges g,[23] with effect sizes of 0.2, 0.5, and 0.8 considered small, moderate, and large, respectively. MMRM analyses used all available data and assumed that missing observations are missing at random. To address the possibility that missing data were not missing at random, pattern mixture modeling (PMM) was conducted as a sensitivity analysis.[24] The PMM used sequential modeling with multiple imputation by reasons of discontinuation and delta adjustment.

Kaplan–Meier survival analysis over the study period estimated time to definitive deterioration, which has been recommended as a useful longitudinal outcome in patients with advanced or metastatic cancer.[25] Log-rank tests were used for comparison of survival function between treatment groups. Time to definitive deterioration was defined as the time from randomization to clinically meaningful worsening (i.e., ≥10-point change) from baseline that was sustained at all subsequent time points or followed by patient withdrawal after worsening, resulting in missing data. Patients who did not experience definitive deterioration before the clinical data cutoff (March 1, 2020) were censored at the date of the last available PRO assessment (i.e., date of the last nonmissing value). Patients with no baseline assessment or patients with no postbaseline assessments were censored at the date of randomization. Hazard ratios (HRs) with 95% CIs were derived by means of a stratified Cox proportional hazards model to assess the magnitude of the treatment difference, with strata being the stratification factors used for randomization. Two-sided nominal p values were calculated, with no adjustments made for multiple comparisons. Significance testing was set at $\alpha = 0.05$.

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Between June 27, 2017, and February 27, 2020, 710 patients were randomized to cemiplimab ($n = 356$) or chemotherapy ($n = 354$) and represent the ITT population. The PD-L1 ≥50% population consisted

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of 563 patients, of which 283 were randomized to cemiplimab and 280 to chemotherapy, with PD-L1 results based on the assay manufacturer's instructions for use. In the PD-L1 ≥50% population, overall median (interquartile range) duration of follow-up was 10.8 (7.6-15.8) months and 10.9 (7.8-15.6) months for cemiplimab and chemotherapy, respectively.

Demographic and clinical characteristics were similar between the two treatment groups in both the PD-L1 ≥50% and ITT populations (Table 1). Most patients (~84%) had metastatic (stage IV) disease and approximately 12% of patients had brain metastases.

The PROs were completed by >98% of patients at baseline in both treatment groups of the PD-L1 ≥50% population. High rates of completion were maintained across the study period; ≥87.5% in the cemiplimab group and ≥90.0% in the chemotherapy group answered all questions on the PROs.

The mean (SD) transformed baseline scores on the QLQ-C30 and QLQ-LC13 were similar between treatment groups, and ranged from 74.1 (20.8) to 89.7 (16.8) on functioning scales and 2.6 (11.4) to 35.6 (25.1) on symptom scales (Figure 1); mean (SD) GHS/QOL scores were 60.1 (21.6) and 59.1 (21.1) in the cemiplimab and chemotherapy groups, respectively. The LS mean changes from baseline across the first year of treatment showed significant improvements with cemiplimab on QLQ-C30 GHS/QOL and the physical and emotional functioning scales, with no significant changes on the other functioning scales (Figure 2A). Chemotherapy was associated with significant improvement in emotional functioning and significant worsening in cognitive and social functioning (Figure 2A). Patients treated with cemiplimab reported significant reductions in all QLQ-C30 symptoms (Figure 2B) and in most symptoms on the QLQ-LC13 (Figure 2C), while worsening in nausea/vomiting, constipation, sore mouth, peripheral neuropathy,

TABLE 1 Baseline characteristics

	PD-L1 ≥ 50% population		ITT population	
Characteristic	**Cemiplimab (*n* = 283)**	**Chemotherapy (*n* = 280)**	**Cemiplimab (*n* = 356)**	**Chemotherapy (*n* = 354)**
Age, y				
Mean (SD)	63.1 (8.2)	63.9 (8.5)	63.0 (8.2)	63.3 (8.6)
Median (IQR)	63.0 (58.0-69.0)	64.0 (58.0-70.0)	63.0 (58.0-69.0)	64.0 (57.0-69.0)
Age ≥ 65 y	126 (44.5)	133 (47.5)	156 (43.8)	164 (46.3)
Male	248 (87.6)	231 (82.5)	312 (87.6)	294 (83.1)
Region of enrollment				
Europe	215 (76.0)	216 (77.1)	275 (77.2)	278 (78.5)
Asia	31 (11.0)	29 (10.4)	39 (11.0)	38 (10.7)
Rest of world	37 (13.1)	35 (12.5)	42 (11.8)	38 (10.7)
Eastern Cooperative Oncology Group performance status				
0	77 (27.2)	75 (26.8)	96 (27.0)	96 (27.1)
1	206 (72.8)	205 (73.2)	260 (73.0)	258 (72.9)
Smoking status				
Current smoker	105 (37.1)	92 (32.9)	133 (37.4)	120 (33.9)
Past smoker	178 (62.9)	188 (67.1)	223 (62.6)	234 (66.1)
Histology				
Squamous	122 (43.1)	121 (43.2)	159 (44.7)	152 (42.9)
Nonsquamous	161 (56.9)	159 (56.8)	197 (55.3)	202 (57.1)
Brain metastases	34 (12.0)	34 (12.1)	44 (12.4)	39 (11.0)
Stage at screening				
Locally advanced	45 (15.9)	42 (15.0)	63 (17.7)	52 (14.7)
Metastatic	238 (84.1)	238 (85.0)	293 (82.3)	302 (85.3)
Previous systemic neoadjuvant therapy	3 (1.0)	4 (1.4)	4 (1.1)	7 (2.0)
Previous systemic adjuvant therapy	5 (1.8)	12 (4.3)	9 (2.5)	15 (4.2)

Note: Data are *n* (%) unless otherwise specified; values may not sum to 100% because of rounding.

Abbreviations: IQR, interquartile range; ITT, intention-to-treat; PD-L1, programmed cell death-ligand 1; SD, standard deviation.

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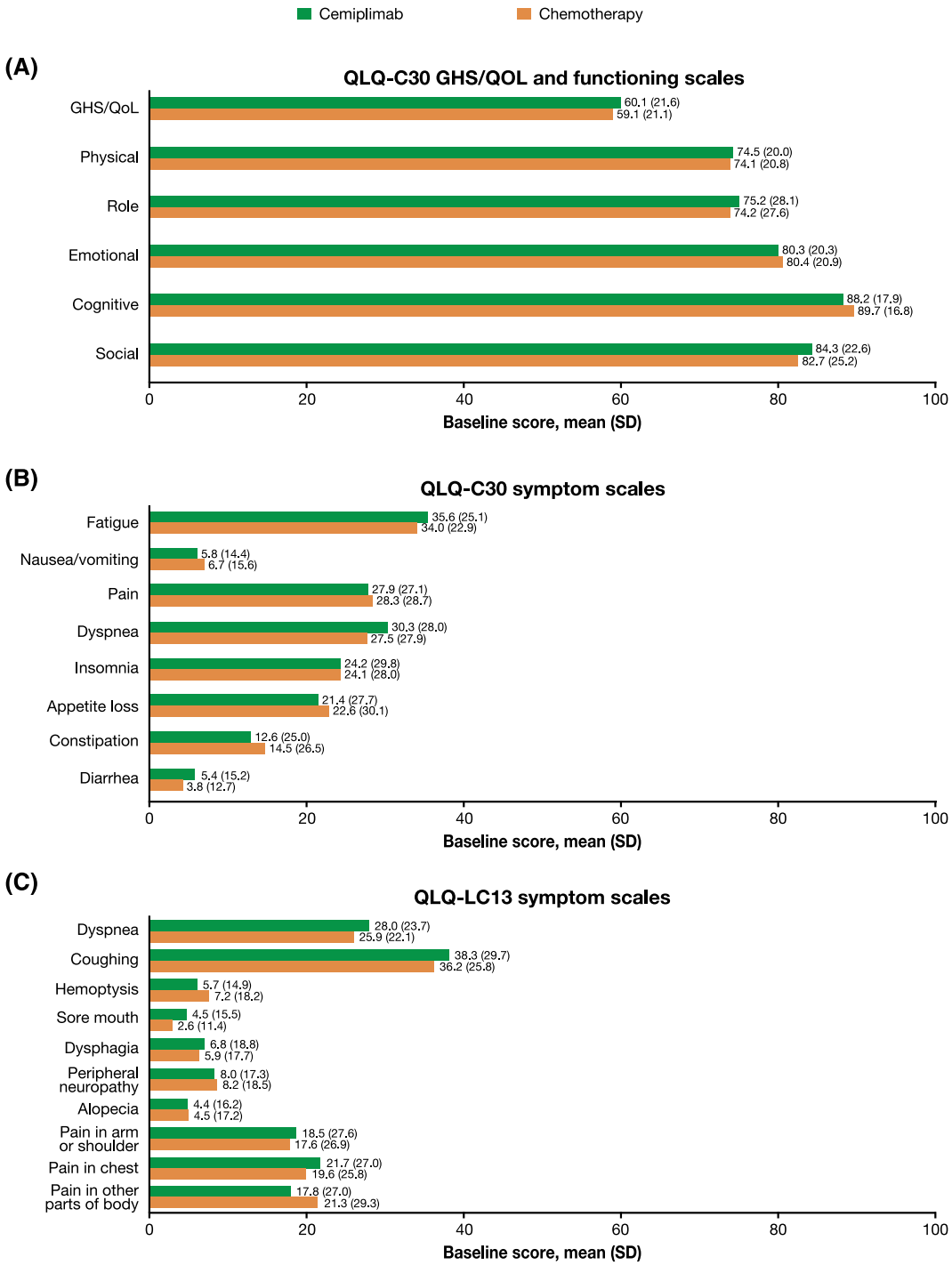

FIGURE 1 Baseline levels of GHS/QOL, functioning, and symptoms on the QLQ-C30 and QLQ-LC13. (A) QLQ-C30 GHS/QOL and functioning scales. (B) QLQ-C30 symptom scales. (C) QLQ-LC13 symptom scales. GHS/QOL indicates global health status/quality of life; QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life-Core 30; QLQ-LC13, European Organization for Research and Treatment of Cancer Quality of Life-Lung Cancer Module; SD, standard deviation.

and alopecia was observed with chemotherapy. Chemotherapy was also associated with significant improvements in pain, dyspnea, insomnia, and diarrhea on the QLQ-C30, and cough, hemoptysis, and pain in chest on the QLQ-LC13.

Overall treatment effects across all time points significantly favored cemiplimab on GHS/QOL and all functioning scales (all two-sided nominal $p < .05$) (Figure 3). The greatest effects were on social functioning (SMD, 0.32; 95% CI, 0.15-0.50) and GHS/QOL (SMD, 0.30; 95% CI, 0.12-0.48) with differences in LS means (95% CIs) of 5.27 (2.41-8.13; two-sided nominal $p = .0003$) and 5.03 (2.11-7.96; two-sided nominal $p = .0008$), respectively. Between-group differences in LS means showed significant benefits of cemiplimab over

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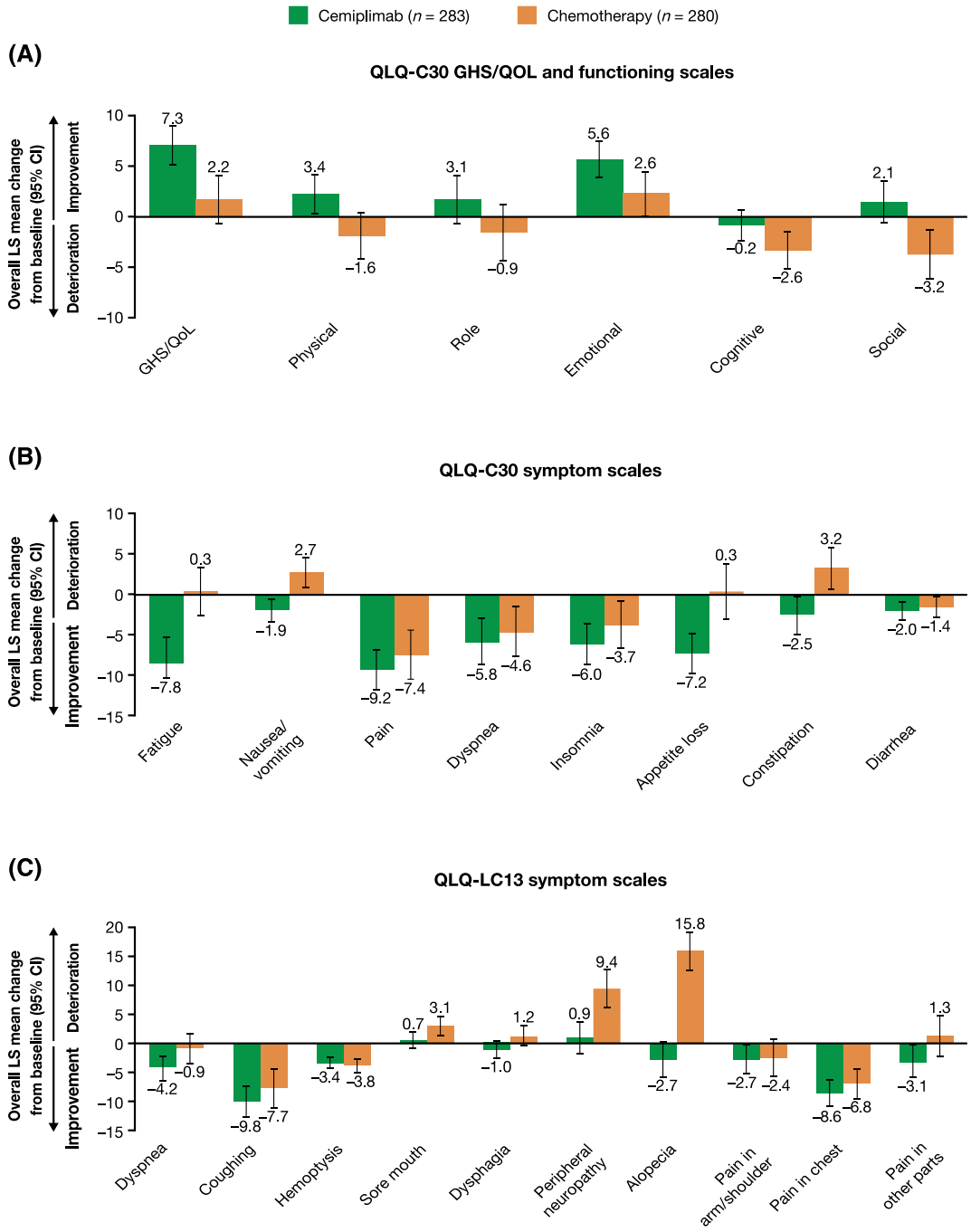

FIGURE 2 MMRM analysis of overall change from baseline across 15 cycles (1 year) of treatment. (A) QLQ-C30 GHS/QOL and functioning scales. (B) QLQ-C30 symptom scales. (C) QLQ-LC13 symptom scales. CI indicates confidence interval; GHS/QOL, global health status/quality of life; LS, least squares; MMRM, mixed-model repeated measures; QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life-Core 30; QLQ-LC13, European Organization for Research and Treatment of Cancer Quality of Life-Lung Cancer Module.

chemotherapy on key disease-related symptoms of fatigue, dyspnea (QLQ-LC13 only), and pain in other parts, and treatment-related symptoms of nausea/vomiting, appetite loss, sore mouth, constipation, peripheral neuropathy, dysphagia, and alopecia (all two-sided nominal $p < .05$), although these differences did not exceed the clinically meaningful threshold. The largest effect sizes were for fatigue (SMD, −0.44; 95% CI, −0.61 to −0.26) and appetite loss (SMD, −0.37; 95% CI, −0.55 to −0.20) on the QLQ-C30 symptoms, and alopecia (SMD, −0.91; 95% CI, −1.09 to −0.73) and peripheral neuropathy (SMD, −0.44; 95% CI, −0.62 to −0.27) on the QLQ-LC13 symptoms.

Significant improvements in GHS/QOL with cemiplimab versus chemotherapy were reported as early as cycle 2 and were maintained to cycle 9 (all two-sided nominal $p < .05$) (Figure 4). At cycles 12 and 15, the LS mean changes from baseline in the cemiplimab group were numerically higher than in the chemotherapy group but failed to

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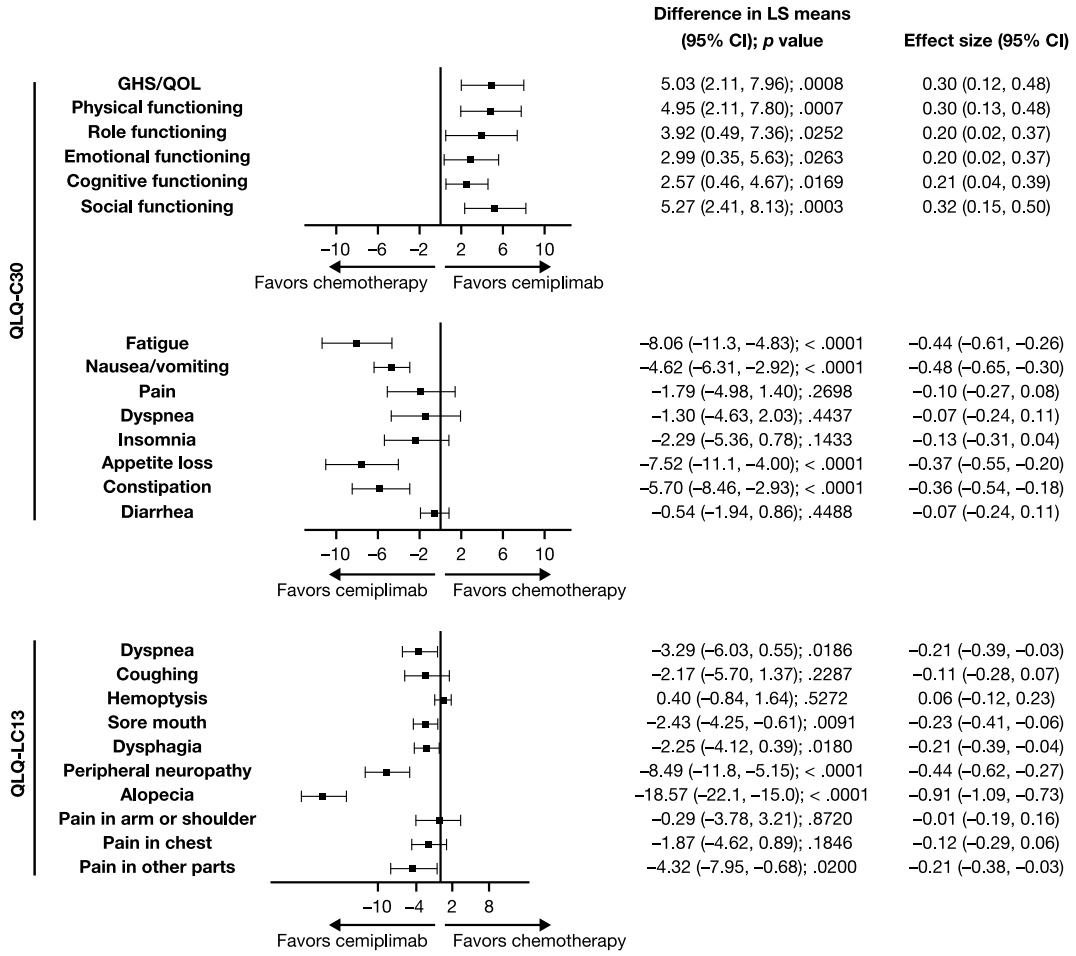

FIGURE 3 MMRM analysis of overall difference in treatment effects across 15 cycles (1 year) of treatment. Statistical significance indicated using two-sided nominal *p* values. CI indicates confidence interval; GHS/QOL, global health status/quality of life; LS, least squares; MMRM, mixed-model repeated measures; QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life-Core 30; QLQ-LC13, European Organization for Research and Treatment of Cancer Quality of Life-Lung Cancer Module.

reach statistical significance, likely because of the large variability and small sample size in the chemotherapy group.

The MMRM results for the ITT population were generally consistent with the PD-L1 ≥50% population: moderate to high levels of functioning and low symptom burden at baseline (Figure S1) with changes from baseline and generally small effect sizes that favored cemiplimab for GHS/QOL, all functioning scales, and most symptoms (Figures S2 and S3). Significant divergence from chemotherapy for the LS mean change in GHS/QOL score was also observed at cycle 2 in the ITT population and was maintained to cycle 9, with numerically higher scores at cycles 12 and 15 (Figure S4).

Results of the PMM sensitivity analysis in both the PD-L1 ≥50% and ITT populations were consistent with the main analysis and confirmed the MMRM results; differences in scores were directionally similar and favored cemiplimab (Table S1).

Although the median time to definitive deterioration was not reached for most scales, first quartiles of the time-to-event analysis indicated that time to definitive deterioration may be longer or not reached with cemiplimab relative to chemotherapy for GHS/QOL and on all functioning scales (Figure 5). Furthermore, HRs <1 showed that cemiplimab-treated patients had a significantly lower risk of definitive deterioration versus chemotherapy on all QLQ-C30 functioning scales, with HRs that ranged from 0.62 (95% CI, 0.42-0.93) for role functioning to 0.48 (95% CI, 0.32-0.71) for social functioning (all two-sided nominal $p < .05$). For GHS/QOL, the HR of 0.70 (95% CI, 0.48-1.04; two-sided nominal $p = .0725$) also indicated a lower risk of definitive deterioration with cemiplimab relative to chemotherapy that trended toward significance.

The first quartiles generally supported longer time to definitive deterioration with cemiplimab on most symptoms (Figure 5). The HRs also indicated that cemiplimab-treated patients had a significantly lower risk for definitive deterioration versus chemotherapy for key disease-related symptoms of dyspnea, cough, pain in chest, pain in other body parts, and fatigue, as well as treatment-related symptoms of peripheral neuropathy, alopecia, nausea/vomiting, appetite loss, constipation, and diarrhea (all two-sided nominal $p < .05$) (Figure 5). Alopecia showed the greatest reduction in risk (HR, 0.13; 95% CI, 0.08-0.23), followed by nausea/vomiting (HR, 0.26; 95% CI, 0.15-0.43) and peripheral neuropathy (HR, 0.34; 95% CI, 0.22-0.52) (all two-sided nominal $p < .0001$).

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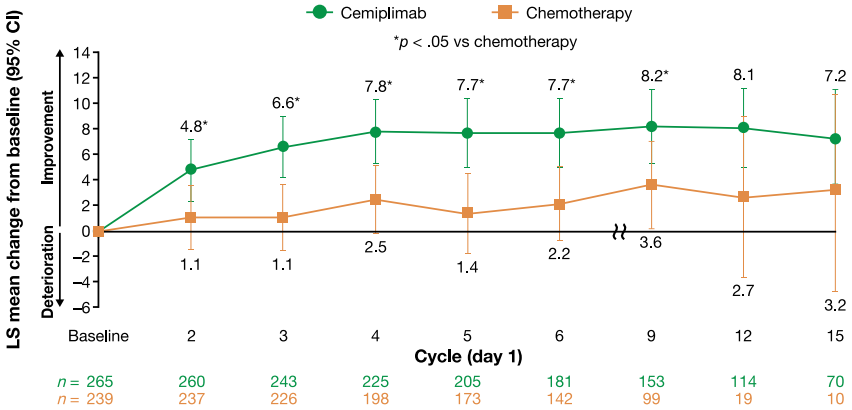

FIGURE 4 MMRM estimated change from baseline in QLQ-C30 GHS/QOL at each cycle. Statistical significance indicated using two-sided nominal *p* values. CI indicates confidence interval; GHS/QOL, global health status/quality of life; LS, least squares; MMRM, mixed-model repeated measures; QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life-Core 30.

Similar trends were observed in the ITT population with regard to first quartiles, indicative of longer time to definitive deterioration with cemiplimab than chemotherapy (Figure S5). The risk for definitive deterioration in the ITT population was also reduced with cemiplimab compared with chemotherapy (Figure S5) with magnitude of effects that were generally consistent with those observed in the PD-L1 ≥50% population.

DISCUSSION

Lung cancer has had a generally poor prognosis, but changes in the treatment landscape of NSCLC with the recent introduction of immunotherapy have improved survival outcomes in these patients. Consequently, preserving if not improving function and HRQOL has become of increasing importance to patients. Consistent with regulatory agency guidance on incorporating PROs in clinical trials to understand treatment effects and the benefit/risk profile of cancer therapies from the patient's perspective, symptom burden, functioning, and HRQOL were assessed in the EMPOWER-Lung 1 phase 3 trial.[17,18]

Patients with advanced NSCLC and PD-L1 ≥50% reported baseline scores on the QLQ-C30 and QLQ-LC13 that were similar to European Organization for Research and Treatment of Cancer reference values for NSCLC and overall cancer patients,[26] and generally reflect moderate to high levels of functioning and low symptom burden. While chemotherapy appeared to maintain GHS/QOL despite significant worsening from baseline in cognitive and social functioning, cemiplimab significantly improved GHS/QOL, functioning, and many key symptoms of importance to patients[5–7] versus chemotherapy over the first year of treatment, and also delayed time to definitive deterioration of these outcomes and reduced the risk of such deterioration. These trends are generally consistent with what has been reported with pembrolizumab,[27] and somewhat better than the results for atezolizumab versus chemotherapy as first-line treatment for advanced NSCLC,[28] although differences in methodology preclude direct comparison.

The similar results in both the target PD-L1 ≥50% and the ITT populations suggest that inclusion of patients whose tumors did not have PD-L1 ≥50% did not appear to diminish the benefits that were obtained with cemiplimab. These benefits were consistent with the primary analysis of significant improvements in survival obtained with cemiplimab in both the PD-L1 ≥50% and ITT populations,[14] and complement those results by demonstrating maintenance of outcomes of importance to patients. Limited data from previous studies indicated that changes in QLQ-C30 GHS/QOL or functioning scales may be associated with or predictive of survival in patients with advanced NSCLC,[27,29,30] suggesting further exploration of the relationship between survival and the treatment effects of cemiplimab on PROs is warranted.

Cemiplimab resulted in significantly greater benefits than chemotherapy on most symptoms measured across the QLQ-C30 and QLQ-LC13 scales, although effect sizes were generally small. The disease-related symptom of fatigue, which patients with NSCLC report as being one of the most impactful on function and HRQOL,[4,5,8,31] was significantly improved with cemiplimab. Additionally, peripheral neuropathy and alopecia, which are key treatment-related symptoms associated with chemotherapy, were the symptoms that displayed the largest effect sizes. Cemiplimab was also associated with a significant reduction in risk for definitive deterioration in dyspnea (on both the QLQ-C30 and QLQ-LC13), cough, and chest pain. These symptoms were evaluated in other trials, sometimes as a composite end point.[27]

Treatment with cemiplimab also resulted in significant improvements compared with chemotherapy for GHS/QOL and all functioning scales. Improvement in GHS/QOL with cemiplimab versus chemotherapy was observed at the earliest evaluated time point (cycle 2) and was generally maintained at each subsequent assessment. These improvements in functioning and GHS/QOL likely resulted, at least in part, from the benefits conveyed by cemiplimab

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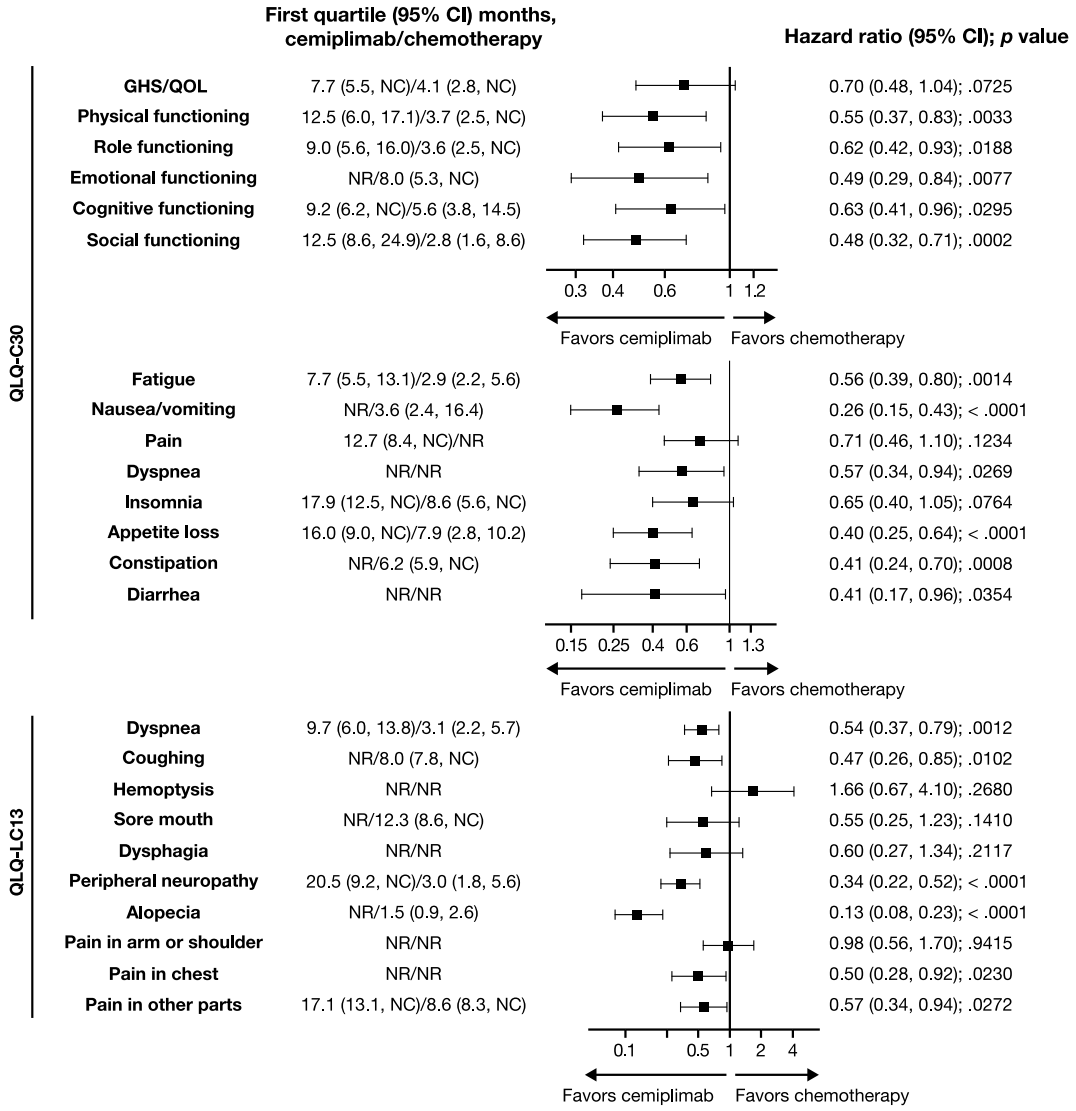

FIGURE 5 Definitive deterioration over the study duration as indicated by time to event (first quartiles) and likelihood of event (hazard ratios). Definitive deterioration was defined as clinically meaningful worsening (i.e., ≥10-point change) from baseline that was sustained at all subsequent time points or followed by patient withdrawal after worsening. Statistical significance indicated using two-sided nominal *p* values. CI indicates confidence interval; GHS/QOL, global health status/quality of life; LS, least squares; NC, not calculated; NR, not reached; QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life-Core 30; QLQ-LC13, European Organization for Research and Treatment of Cancer Quality of Life-Lung Cancer Module.

on symptom burden. Global issues reflecting the impact of symptoms, such as effects on HRQOL and maintaining activities, are ranked as having higher importance by patients than the symptoms themselves.[8] Other studies also noted the substantial impairment of HRQOL and daily function resulting from the symptom burden.[5–7] The greatest functional effects observed with cemiplimab were on social and physical functioning, both of which are especially relevant to daily activities. The benefits of cemiplimab were also supported by the delay in definitive deterioration on all QLQ-C30 functioning scales relative to chemotherapy as well as a lower risk of such deterioration.

Although the overall within-arm changes from baseline did not reach the threshold of ≥10 points[21] frequently used to indicate a clinically meaningful change, other thresholds as low as 4 points have been explored.[22] However, these thresholds may differ across individual scales and are relative to the anchors used for defining the threshold.[22] This lack of standardization suggests additional research is needed to define and validate the changes in QLQ-C30 and QLQ-LC13 scores that can be considered clinically meaningful from the patient's perspective.

A clinically relevant strength of this study is that it included patients with adequately treated, clinically stable brain metastases. Inclusion of these patients, who have been underrepresented in NSCLC clinical trials,[11,12] is more reflective of a real-world setting and was on the basis of resolution of neurological symptoms following brain metastasis therapy that did not require

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demonstration of radiologic stability.[14] However, a limitation of this study is that, because of more specific inclusion and exclusion criteria, clinical trial participants tend not to be representative of "real-world" clinical settings. Other study limitations include the open-label study design, although reports suggest the magnitude of bias resulting from such a study design is low.[32–34] Low bias is further supported in the current study by the similar baseline scores in the randomized treatment groups and by the similarly high completion rates of the measures in the two treatment arms, in contrast to studies that suggested lower completion rates in experimental treatment arms.[35,36] An additional limitation is that because the PROs were secondary end points, the study was not powered to support these analyses, which were not controlled for multiplicity. Finally, the high crossover of patients from chemotherapy to cemiplimab (74%), which was allowed in the presence of disease progression,[14] may represent a confounding factor.

In conclusion, patients with advanced NSCLC and PD-L1 expression ≥50% receiving cemiplimab reported significant benefits versus chemotherapy on GHS/QOL, functioning, and most symptoms over the first year of treatment. Cemiplimab was also associated with a longer time to (based on first quartiles) and significantly lower risk for definitive deterioration across all functioning scales and most symptoms relative to chemotherapy over the study period. These results support the benefits of cemiplimab for first-line therapy of advanced NSCLC from the patient's perspective and show that improved survival is accompanied by improvements in GHS/QOL and functioning, and a reduction in symptom burden, especially for key disease-related symptoms and symptoms generally associated with chemotherapy (e.g., alopecia, peripheral neuropathy).

AUTHOR CONTRIBUTIONS

Mahmut Gümüş: Patient recruitment and data collection. **Cristina Ivanescu:** Data analysis. **Saadettin Kilickap**: Patient recruitment and data collection. **Igor Bondarenko:** Study conception and design, patient recruitment and data collection. **Mustafa Özgüroğlu:** Patient recruitment and data collection. **Miranda Gogishvili:** Patient recruitment and data collection. **Haci M. Turk:** Patient recruitment and data collection. **Irfan Cicin:** Patient recruitment and data collection. **Siyu Li:** Data analysis. **Giuseppe Gullo:** Study conception and design. **Petra Rietschel:** Study conception and design. **Ahmet Sezer:** Patient recruitment and data collection. All authors had full access to and verified the data, contributed to the data interpretation, and provided critical review, revision, and approval of the manuscript.

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CONFLICT OF INTEREST

Mahmut Gümüş reports consulting or advisory role at Amgen, Gen Ilac, Lilly, Novartis, and Roche; speakers bureau at MSD Oncology, Novartis, and Roche; travel, accommodations, and expenses from Pfizer; honoraria to institution from MSD Oncology; and institutional research funding from Amgen. Chieh-I Chen, Vera Mastey, Siyu Li, and Giuseppe Gullo report employment and stock interests at Regeneron Pharmaceuticals. Cristina Ivanescu reports employment at IQVIA and institutional research funding from Regeneron Pharmaceuticals. Saadettin Kilickap reports consulting or advisory roles at MSD Oncology, Pfizer, Roche, and Takeda; and speakers bureau at MSD Oncology, Pfizer, and Roche. Mustafa Özgüroğlu reports consulting or advisory roles for AstraZeneca and MSD Oncology; speakers bureau at AstraZeneca; travel, accommodations, and expenses from AstraZeneca; and honoraria from Astellas Pharma, Janssen Oncology, and Novartis. Irfan Cicin reports consulting or advisory roles from AbbVie, Abdi Ibrahim, Bristol-Myers Squibb, Janssen Oncology, Lilly, MSD Oncology, Nobelpharma, Novartis/Ispen, Pfizer, Roche, Servier, and Teva; and speakers bureau at Abdi Ibrahim, Bristol-Myers Squibb, Novartis, Pfizer, and Roche. James Harnett reports employment and stock interests at Regeneron Pharmaceuticals, and stock interests at Pfizer. Ulrike Naumann reports employment and consulting or advisory role at IQVIA. Matthew Reaney reports employment at IQVIA. Gerasimos Konidaris reports employment at Sanofi. Medha Sasane reports employment, leadership, and stock interests at Sanofi. Keri J. S. Brady reports employment at Sanofi, and an immediate family member with employment and stock interests at CVS Health. Petra Rietschel reports employment, stock interests, and patents, royalties, other intellectual property at Regeneron Pharmaceuticals. Ahmet Sezer reports speakers bureau at Roche, Pfizer, Amgen, and Bristol-Myers Squibb; travel, accommodations, and expenses at Amgen, Bristol-Myers Squibb, and Roche; institutional honoraria from Pfizer and Roche; and institutional research funding from Regeneron Pharmaceuticals, MSD Oncology, Pfizer, Novartis, and Merck Serono. The other authors report no conflicts of interest.

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