Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial

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Summary

Background Pembrolizumab plus pemetrexed–platinum led to superior overall survival and progression-free survival, and a higher proportion of patients with a confirmed complete or partial response over placebo plus pemetrexed–platinum in the KEYNOTE-189 study. We aimed to evaluate prespecified exploratory patient-reported outcomes (PROs) in patients in KEYNOTE-189.

Methods In the multicentre, double-blind, randomised, placebo-controlled, phase 3 KEYNOTE-189 study done at 126 cancer centres in 16 countries, eligible patients aged 18 years or older with histologically or cytologically confirmed metastatic non-squamous non-small-cell lung cancer without sensitising *EGFR* or *ALK* alterations, measurable disease as per Response Evaluation Criteria in Solid Tumors (version 1.1), and an Eastern Cooperative Oncology Group performance status of 0 or 1 were enrolled. Patients were randomly assigned (2:1) to receive intravenous pembrolizumab (200 mg) or saline placebo every 3 weeks for up to 2 years (35 cycles); all patients received four cycles of intravenous pemetrexed (500 mg/m²) with carboplatin (5 mg/mL per min) or cisplatin (75 mg/m²; investigator's choice) every 3 weeks for four cycles, followed by pemetrexed maintenance therapy every 3 weeks. Permuted block randomisation (block size six) was done with an interactive voice-response system and stratified by PD-L1 expression, choice of platinum, and smoking status. Patients, investigators, and other study personnel were unaware of treatment assignment. The European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 (QLQ-C30) and Lung Cancer 13 (QLQ-LC13) were administered at cycles 1–5, every three cycles thereafter during year 1, and every four cycles during years 2–3. The primary endpoints (overall survival and progression-free survival) have been published previously. Key PRO endpoints were change from baseline to week 12 (during chemotherapy) and week 21 (following chemotherapy) in QLQ-C30 global health status/quality of life (GHS/QOL) score, and time to deterioration in cough, chest pain, or dyspnoea. PROs were analysed in all randomly assigned patients who received at least one dose of study medication and who completed at least one PRO assessment, and the results are provided with two-sided, nominal p values. This ongoing study is registered with ClinicalTrials.gov, number NCT02578680.

Findings Between Feb 26, 2016, and March 6, 2017, 616 patients were enrolled; median follow-up was 10·5 months (range 0·2–20·4) as of data cutoff on Nov 8, 2017. 402 (99%) of 405 patients in the pembrolizumab plus pemetrexed–platinum group and 200 (99%) of 202 patients in the placebo plus pemetrexed–platinum-treated group completed at least one PRO assessment. At baseline, 359 (89%) of 402 patients in the pembrolizumab plus pemetrexed–platinum group and 180 (90%) of 200 in the placebo plus pemetrexed–platinum group were compliant with QLQ-C30; at week 12, 319 (90%) of 354 and 149 (89%) of 167 patients were compliant, respectively; and at week 21, 249 (76%) of 326 and 91 (64%) of 143 patients were compliant, respectively. From baseline to week 12, GHS/QOL scores were maintained with both pembrolizumab plus pemetrexed–platinum (least-squares mean change: 1·0 point [95% CI –1·3 to 3·2] increase) and placebo plus pemetrexed–platinum (–2·6 points [–5·8 to 0·5] decrease; between-group difference: 3·6 points [–0·1 to 7·2]; p=0·053). From baseline to week 21, GHS/QOL scores were better maintained with pembrolizumab plus pemetrexed–platinum (least-squares mean change: 1·3 points [95% CI –1·2 to 3·6] increase) than with placebo plus pemetrexed–platinum (–4·0 points [–7·7 to –0·3] decrease; between-group difference: 5·3 points [1·1 to 9·5]; p=0·014). Median time to deterioration in cough, chest pain, or dyspnoea was not reached (95% CI 10·2 months to not reached) with pembrolizumab plus pemetrexed–platinum, and was 7·0 months (4·8 months to not reached) with placebo plus pemetrexed–platinum (hazard ratio 0·81 [95% CI 0·60–1·09], p=0·16).

Lancet Oncol 2020; 21: 387–97

Published Online February 6, 2020 https://doi.org/10.1016/S1470-2045(19)30801-0

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Interpretation **The addition of pembrolizumab to standard chemotherapy maintained GHS/QOL, with improved GHS/QOL scores at week 21 in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group. These data further support use of pembrolizumab plus pemetrexed–platinum as first-line therapy for patients with metastatic non-squamous non-small-cell lung cancer.**

Funding **Merck Sharp & Dohme.**

Introduction

Patients with metastatic non-small-cell lung cancer have a substantial burden of illness from disease-associated symptoms, including fatigue, loss of appetite, pain, dyspnoea, and cough.[1,2] Effective treatments for non-small-cell lung cancer might potentially improve health-related quality of life (HRQOL) by reducing such symptoms. In addition to extending overall survival (hazard ratio [HR] 0·60, 95% CI 0·41–0·89; p=0·005) and progression-free survival (HR 0·50, 95% CI 0·37–0·68; p<0·001),[3] monotherapy with the anti-PD-1 monoclonal antibody pembrolizumab provided clinically meaningful improvements in HRQOL over platinum-based chemotherapy in patients with previously untreated metastatic non-small-cell lung cancer with a PD-L1 tumour proportion score of 50% or more and no sensitising *EGFR* mutations or *ALK* translocations in the phase 3 KEYNOTE-024 study.[4] Global health status/quality of life (GHS/QOL) scores and time to deterioration in chest symptoms were improved in patients who received pembrolizumab compared with those who received chemotherapy.[4]

Pembrolizumab has also been evaluated in combination with pemetrexed and platinum chemotherapy in the phase 3 KEYNOTE-189 study, which demonstrated superior efficacy outcomes with pembrolizumab plus pemetrexed–platinum versus placebo plus pemetrexed-platinum in patients with previously untreated metastatic non-squamous non-small-cell lung cancer without sensitising *EGFR* mutations or *ALK* translocations, regardless of tumour PD-L1 expression.[5] After median follow-up of 10·5 months, overall survival (HR 0·49, 95% CI 0·38–0·64; p<0·001) and progression-free survival (HR 0·52, 95% CI 0·43–0·64; p<0·001) were longer, and the proportion of patients with an objective response was significantly higher (47·6% *vs* 18·9%; p<0·001) in the pembrolizumab plus pemetrexed–platinum group than in the placebo plus pemetrexed–platinum group.[6] The incidence and severity of adverse events were generally similar between treatment groups.[5]

Research in context

Evidence before this study

We searched PubMed for research articles published from database inception to Oct 24, 2018, using the keywords "MK-3475 OR pembrolizumab AND quality of life", and no language restriction was applied. Abstracts from the following conferences were also searched using the same keywords, and the additional term "non-small-cell lung cancer": 2017 World Conference on Lung Cancer, 2017 European Society for Medical Oncology, 2018 European Lung Cancer Congress, and 2018 American Society of Clinical Oncology Annual Meeting. On the basis of the findings of this search, pembrolizumab monotherapy has shown favourable patient-reported outcomes compared with platinum-based chemotherapy as a first-line treatment for patients with metastatic non-small-cell lung cancer with a PD-L1 tumour proportion score of 50% or more. However, the patient health-related quality-of-life effects of pembrolizumab plus platinum-based chemotherapy have not previously been evaluated in patients with metastatic non-small-cell lung cancer.

Added value of this study

We analysed the prespecified exploratory patient-reported outcomes in KEYNOTE-189, an international, multicentre, double-blind, randomised, placebo-controlled, phase 3 study. In patients with non-squamous non-small-cell lung cancer without sensitising *EGFR* mutations or *ALK* translocations, health-related quality of life was maintained or better with pembrolizumab plus pemetrexed–platinum chemotherapy over placebo plus chemotherapy, and median time to deterioration in lung cancer symptoms was not reached in the pembrolizumab plus pemetrexed–platinum group and 7·0 months in the placebo plus pemetrexed–platinum group (hazard ratio 0·81 [95% CI 0·60–1·09], p=0·16).

Implications of all the available evidence

These health-related quality-of-life findings complement those showing superior efficacy demonstrated with pembrolizumab plus chemotherapy over placebo plus chemotherapy in the KEYNOTE-189 study, and further support use of pembrolizumab plus pemetrexed–platinum as a first-line therapy for patients with metastatic non-squamous non-small-cell lung cancer without sensitising *EGFR* mutations or *ALK* translocations.

Patient-reported outcomes (PROs) were evaluated as a prespecified exploratory objective in KEYNOTE-189 to determine whether pembrolizumab plus pemetrexed–platinum could improve HRQOL and delay time to deterioration in lung cancer symptoms compared with pemetrexed–platinum alone. We report results from these PRO analyses.

Methods

Study design and participants

KEYNOTE-189, a multicentre, double-blind, randomised, placebo-controlled, phase 3 study, was done at 126 cancer centres in 16 countries. Detailed methods and primary results for KEYNOTE-189 have been reported elsewhere.[5] Briefly, eligible patients had histologically or cytologically confirmed stage IV non-squamous non-small-cell lung cancer without activating *EGFR* mutations or *ALK* translocations, were aged 18 years or older, had received no previous systemic therapy for metastatic disease, had measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) by investigator review, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and provided a tumour sample for PD-L1 status determination. Patients who had received adjuvant or neoadjuvant therapy were eligible if the adjuvant or neoadjuvant therapy was completed at least 12 months before development of metastatic disease. Patients were required to have adequate organ function. Patients were excluded if they had current pneumonitis or a history of non-infectious pneumonitis that required systemic steroid therapy. Patients with asymptomatic untreated brain metastases measuring up to 1·5 cm that did not require steroid treatment were eligible, as were patients with previously treated brain metastases if they were clinically stable for at least 2 weeks and had not received steroids within 3 days before the first dose of study treatment.

The study protocol (and all its amendments) was approved by an independent institutional review board or ethics committee at each study site, and the trial was done in compliance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written, informed consent before enrolment.

Randomisation and masking

Permuted block randomisation with a block size of six was implemented centrally using an interactive voice response system. The allocation sequence was generated and managed by Clinical Schedule Generation System (Merck Sharp & Dohme, a subsidiary of Merck & Co, Kenilworth, NJ, USA). Patients were randomly assigned (2:1) to either the pembrolizumab plus pemetrexed–platinum group or the placebo plus pemetrexed–platinum group. Patients, investigators, and other study personnel who were involved in treating or clinically evaluating patients were unaware of the treatment assigned. All patients received open-label pemetrexed plus investigator's choice of cisplatin or carboplatin (determined before randomisation). Randomisation was stratified by PD-L1 expression (tumour proportion score ≥1% *vs* <1%), choice of platinum chemotherapy (cisplatin *vs* carboplatin), and smoking status (never *vs* former or current).

Procedures

Patients received intravenous pembrolizumab 200 mg every 3 weeks or saline placebo every 3 weeks for up to 2 years (35 cycles). All patients received four cycles of pemetrexed 500 mg/m² plus investigator's choice of cisplatin 75 mg/m² or carboplatin area under the concentration–time curve 5 mg/mL per min followed by pemetrexed 500 mg/m² maintenance therapy every 3 weeks. Study treatment was continued until disease progression, unacceptable toxicity, illness precluding further treatment, investigator decision, or withdrawal of consent. Pembrolizumab dose reductions were not permitted. Crossover to pembrolizumab monotherapy was permitted for patients in the placebo plus pemetrexed–platinum group who had disease progression verified by blinded, independent central radiological review and met safety criteria.

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30),[7] Lung Cancer 13 (QLQ-LC13),[8] and EuroQoL 5D (EQ-5D) were administered by trained site personnel and electronically completed by patients at cycles 1–5; every three cycles through the remainder of year 1; every four cycles during years 2 and 3, until disease progression while on study treatment; and at treatment discontinuation and the 30-day safety follow-up visit. Patients completed the PRO instruments before administration of study treatment, adverse event assessment, and disease status notification. The QLQ-C30 was administered before the QLQ-LC13.

Outcomes

The primary endpoints of the KEYNOTE-189 study, which have been published previously,[5] were overall survival and progression-free survival as per RECIST (version 1.1) assessed by blinded, independent central radiological review, and secondary endpoints included the proportion of patients with an objective response per RECIST (version 1.1) by blinded, independent central radiological review and safety. PROs were evaluated as prespecified exploratory endpoints. Key PRO endpoints were mean change from baseline to weeks 12 and 21 in the QLQ-C30 GHS/QOL scale, and time to deterioration (defined as the time to first onset of a ≥10-point increase from baseline score, confirmed by a second consecutive increase of ≥10 points from baseline) in the composite endpoint of cough (QLQ-LC13, question 1), chest pain (QLQ-LC13, question 10), or dyspnoea (QLQ-C30, question 8). Supportive PRO endpoints included mean score change from baseline, and proportions of patients with scores that improved (≥10-point improvement),

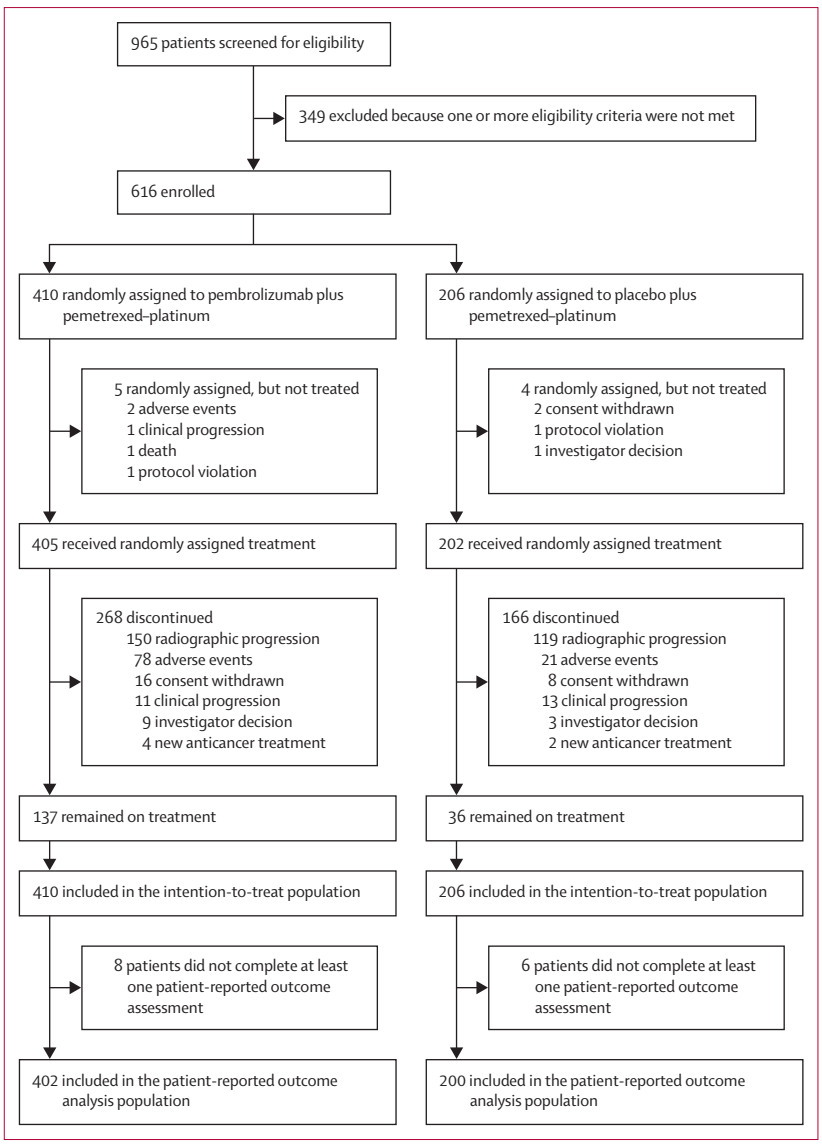

Figure 1: **Trial profile**

See Online for appendix

remained stable, or deteriorated (≥10-point worsening) from baseline to weeks 12 and 21 on the QLQ-C30 GHS/QOL scale, functional subscales, and symptom subscales. Additional supportive analyses evaluated the effect of disease progression and treatment on mean changes from baseline to weeks 12 and 21 in QLQ-C30 GHS/QOL score. The two prespecified timepoints for analysis of the key and supportive PRO endpoints (ie, weeks 12 and 21) were selected from the planned PRO assessments to separately represent changes in outcome during and after platinum therapy. The EQ-5D was primarily included to generate population-based utility weights for use in a cost-effectiveness analysis, the results of which have been reported elsewhere.[9] None of the protocol amendments in the study affected the assessment of PROs.

Statistical analysis

For the primary analyses, the study had 90% power to detect a HR of 0·7 for disease progression or death, with a one-sided α value of 0·0095 (based on 468 progression-free survival events), and for death, with a one-sided α value of 0·0155 (based on 416 deaths). Statistical methods for the primary analyses have been described previously.[5] We did no power calculation for PROs; p values for these analyses are nominal, and all are two-sided. There was no adjustment for multiplicity.

PRO analyses included all randomly assigned patients who received at least one dose of study treatment and completed at least one PRO assessment, analysed according to allocated treatment. Patients were considered to have completed at least one PRO assessment if they completed at least one item on a PRO instrument. Compliance with the PRO assessments was defined as the proportion of patients who completed at least one item among those expected to complete the questionnaires (ie, those who remained on treatment, and had a scheduled study visit).

We evaluated mean changes from baseline to weeks 12 and 21 in the QLQ-C30 GHS/QOL score using a constrained longitudinal data analysis model (for full details, see appendix p 5), with the PRO score as the response variable and treatment by study visit interaction and randomisation stratification factors as covariates (supportive analyses of the effect of disease progression on PROs also included progression status as a time-varied covariate). This model implicitly treats missing data as missing at random.

We assessed between-group differences in time to deterioration in the composite of cough, chest pain, or dyspnoea using a stratified log-rank test, with the HR determined using a Cox model stratified by the randomisation factors with treatment as a covariate. To inform clinical relevance of changes from baseline to weeks 12 and 21, we used a responder analysis, in which a change of 10 points or more was used to classify score changes as improved or deteriorated because patients perceive this magnitude of change to be clinically meaningful.[10] We summarised proportions of patients with improved, stable, and deteriorated QLQ-C30 GHS/QOL scores, functional subscales, and symptom subscales at weeks 12 and 21, with missing data accounted for using the Markov chain Monte Carlo (MCMC) method with multiple imputation with a missing at random assumption. The MCMC method created 50 imputations and imputed for a subset of missing values so that each imputed dataset had a monotone missing pattern. We then imputed one value for each missing value in the monotone missingness dataset. To obtain the count of patients for each category, we added up the counts of the patients qualifying for that category from each of the 50 imputed datasets, and then divided the total by 50. QLQ-C30 and QLQ-LC13 scores were standardised to a scale ranging from 0 to 100 by linear transformation; higher scores for GHS/QOL and

	Pembrolizumab plus pemetrexed–platinum group (n=402)	Placebo plus pemetrexed–platinum group (n=200)
QLQ-C30		
Baseline	359 (89%)	180 (90%)
Week 3		
Completion	362 (90%)	171 (86%)
Compliance	362/389 (93%)	171/186 (92%)
Week 6		
Completion	342 (85%)	154 (77%)
Compliance	342/360 (95%)	154/175 (88%)
Week 9		
Completion	308 (77%)	140 (70%)
Compliance	308/342 (90%)	140/158 (89%)
Week 12		
Completion	319 (79%)	149 (75%)
Compliance	319/354 (90%)	149/167 (89%)
Week 21		
Completion	249 (62%)	91 (46%)
Compliance	249/326 (76%)	91/143 (64%)
Week 30		
Completion	210 (52%)	63 (32%)
Compliance	210/278 (76%)	63/88 (72%)
QLQ-LC13		
Baseline	357 (89%)	179 (90%)
Week 3		
Completion	361 (90%)	170 (85%)
Compliance	361/389 (93%)	170/186 (91%)
Week 6		
Completion	341 (85%)	153 (77%)
Compliance	341/360 (95%)	153/175 (87%)
Week 9		
Completion	306 (76%)	140 (70%)
Compliance	306/341 (90%)	140/158 (89%)
Week 12		
Completion	317 (79%)	148 (74%)
Compliance	317/354 (90%)	148/167 (89%)
Week 21		
Completion	245 (61%)	90 (45%)
Compliance	245/326 (75%)	90/143 (63%)
Week 30		
Completion	211 (53%)	63 (32%)
Compliance	211/278 (76%)	63/88 (72%)

Data are n (%) or n/N (%). Completion was defined as completing at least one item among the total patient-reported outcome analysis population. Compliance was defined as completing at least one item at each timepoint, as listed in the numerator for each group, among patients who were expected to complete at each timepoint (eg, among those who had not discontinued study treatment), as listed in the denominator for each group. QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. QLQ-LC13=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 items.

Table 1: **Proportion of patients who completed and were compliant with quality-of-life instruments**

	Pembrolizumab plus pemetrexed–platinum group (n=402)	Placebo plus pemetrexed–platinum group (n=200)	Between-group difference (95% CI)
Baseline			
Completed questionnaire	359	180	..
Mean score (SD)	62·0 (21·3)	60·6 (21·4)	..
Week 12			
Completed questionnaire	319	150	..
Mean score (SD)	63·8 (21·5)	61·1 (20·8)	..
Change from baseline*			
Included in analysis	402	200	..
Least-squares mean score (95% CI)	1·0 (−1·3 to 3·2)	−2·6 (−5·8 to 0·5)	3·6 (−0·1 to 7·2); p=0·053†
Week 21			
Completed questionnaire	248	91	..
Mean score (SD)	67·0 (19·4)	62·6 (24·1)	..
Change from baseline*			
Included in analysis	402	200	..
Least-squares mean score (95% CI)	1·3 (−1·2 to 3·6)	−4·0 (−7·7 to −0·3)	5·3 (1·1 to 9·5); p=0·014†

Data are n unless otherwise stated. QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Based on a constrained longitudinal data analysis model with QLQ-C30 global health status/quality of life scores as the response variable and treatment-by-study-visit interaction and randomisation stratification factors as covariates. †p values are two sided and nominal.

Table 2: **Mean changes from baseline in QLQ-C30 global health status/quality of life score**

functional scales represent better GHS/QOL and functioning, whereas higher scores for symptom scales represent worse symptoms. We did all statistical analyses using SAS (version 9.4).

This ongoing study is registered with ClinicalTrials.gov, number NCT02578680.

Role of the funding source

This study was designed by the academic authors in conjunction with representatives of the study funder. All data were collected by the investigators and their site personnel, and were analysed and interpreted by senior academic authors and representatives of the funder. All authors had full access to the data. A medical writer contracted by the sponsor provided assistance in preparing the report. All authors were responsible for the decision to submit the manuscript for publication.

Results

Of 965 patients screened between Feb 26, 2016, and March 6, 2017, 616 were enrolled in the KEYNOTE-189 study; 410 were randomly assigned to the pembrolizumab plus pemetrexed–platinum group and 206 to the placebo plus pemetrexed–platinum group (figure 1). As of data cutoff on Nov 8, 2017, median follow-up was 10·5 months (range 0·2–20·4). As previously reported,[5] baseline characteristics for enrolled patients were similar between the groups, except for a slightly higher proportion of men in the pembrolizumab plus pemetrexed–platinum group (254 [62%] of 410 *vs* 109 [53%] of 206; appendix p 1).

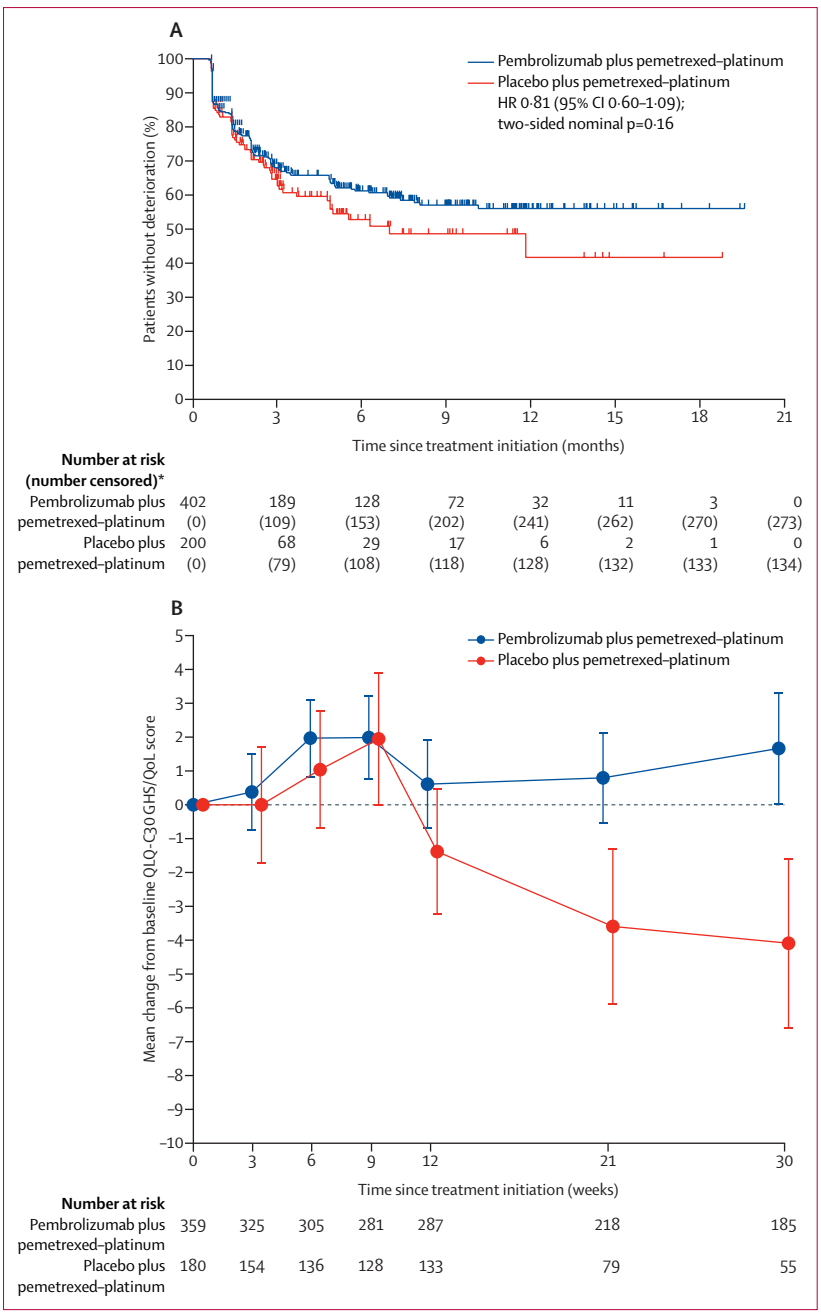

***Figure 2*: Kaplan-Meier curves of time to deterioration in the composite endpoint of cough, chest pain, or dyspnoea (A) and mean change from baseline in QLQ-C30 GHS/QOL scores (B)**

(A) Time to deterioration in the composite endpoint of cough, chest pain, or dyspnoea, based on relevant items in the QLQ-LC13 and QLQ-C30. HR=hazard ratio. QLQ-LC13=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 items. QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Post-baseline assessments were not available for 56 patients in the pembrolizumab plus pemetrexed–platinum group and 33 patients in the placebo plus pemetrexed–platinum group. (B) Mean change from baseline in QLQ-C30 GHS/QOL scores by visit. Error bars indicate SEs around the mean. GHS/QOL=global health status/quality of life.

405 patients in the pembrolizumab plus pemetrexed–platinum group and 202 patients in the placebo plus pemetrexed–platinum group received at least one dose of their assigned treatment (figure 1). The PRO analysis population (patients who completed at least one PRO assessment) comprised 402 (99%) of 405 patients in the pembrolizumab plus pemetrexed–platinum group and 200 (99%) of 202 patients in the placebo plus pemetrexed–platinum group. The proportion of patients who completed the QLQ-C30 and QLQ-LC13 was lower at week 21 than at baseline or week 12, partly because of patients missing from the analysis by design (ie, because they had discontinued treatment as a result of disease progression, adverse event, withdrawn consent, physician decision, no scheduled visit, death, or other unspecified reasons; table 1). At baseline, 359 (89%) of 402 patients in the pembrolizumab plus pemetrexed–platinum group and 180 (90%) of 200 patients in the placebo plus pemetrexed–platinum group were compliant with QLQ-C30; at week 12, 319 (90%) of 354 and 149 (89%) of 167 patients, respectively, were compliant; and at week 21, 249 (76%) of 326 and 91 (64%) of 143 patients, respectively, were compliant. Compliance with the QLQ-LC13 was similar (table 1). Compliance was higher than completion at all timepoints in both groups because the population for assessment of completion included all patients at each timepoint, whereas the compliance was assessed for patients expected to complete at each timepoint.

Baseline mean GHS/QOL scores were similar between treatment groups (table 2). Relative to baseline, scores at week 12 were maintained in both the pembrolizumab plus pemetrexed–platinum group (least-squares [LS] mean change: 1·0 point [95% CI –1·3 to 3·2] increase) and in the placebo plus pemetrexed–platinum group (–2·6 points [–5·8 to 0·5] decrease; table 2), with a between-group LS mean difference of 3·6 points (–0·1 to 7·2; p=0·053). At week 21, GHS/QOL score was improved by 1·3 points (95% CI –1·2 to 3·6) in the pembrolizumab plus pemetrexed–platinum group, whereas it had worsened by –4·0 points (–7·7 to –0·3) in the placebo plus pemetrexed–platinum group (table 2), with a between-group LS mean difference of 5·3 points (1·1 to 9·5; p=0·014).

Median time to deterioration in cough, chest pain, or dyspnoea was not reached (95% CI 10·2 months to not reached) in the pembrolizumab plus pemetrexed–platinum group versus 7·0 months (4·8 to not reached) in the placebo plus pemetrexed–platinum group (HR 0·81 [95% CI 0·60–1·09], p=0·16; figure 2A). The Kaplan-Meier curves began to separate after 3 months of follow-up. Deterioration in the composite of these symptoms occurred in 129 (32%) of 402 patients in the pembrolizumab plus pemetrexed–platinum group and 66 (33%) of 200 patients in the placebo plus pemetrexed–platinum group.

Mean QLQ-C30 GHS/QOL scores improved from baseline to week 9 in both treatment groups (figure 2B). Although scores subsequently declined in both groups, those in the pembrolizumab plus pemetrexed–platinum group remained above baseline, whereas those in the

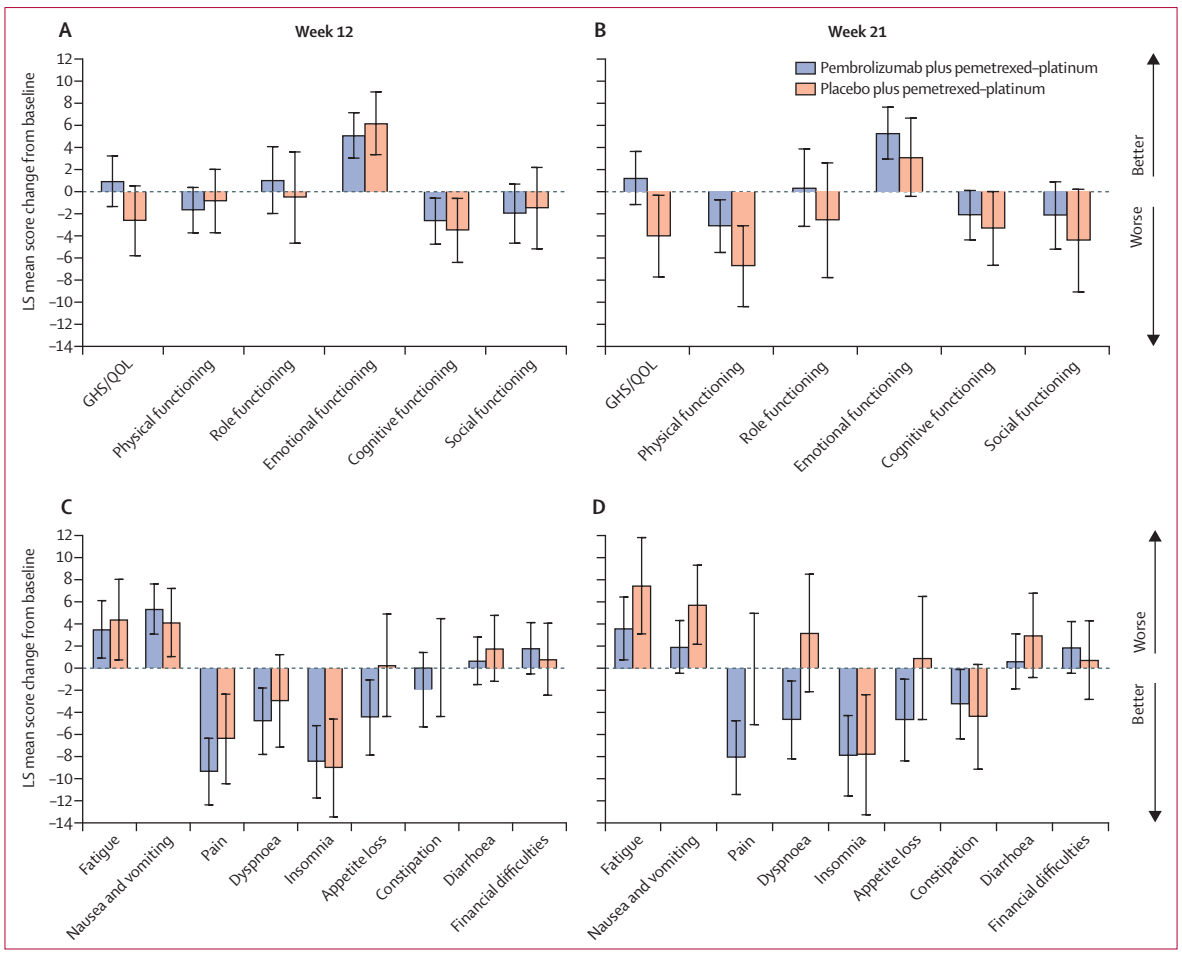

Figure 3: **Changes from baseline in QLQ-C30 GHS/QOL and functional subscale scores, and in QLQ-C30 symptom subscale scores**
Changes from baseline in QLQ-C30 GHS/QOL and functional subscale scores at week 12 (A) and week 21 (B), and in QLQ-C30 symptom subscale scores at week 12 (C) and week 21 (D). Higher GHS/QOL scores represent better GHS/QOL and higher functional subscale scores represent better functioning, whereas higher symptom subscale scores represent increased symptoms. Error bars indicate 95% CIs. GHS/QOL=global health status/quality of life. LS= least-squares. QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

placebo plus pemetrexed–platinum group fell below baseline (figure 2B). The similarity between treatment groups in mean change from baseline to week 12 GHS/QOL score was consistent across QLQ-C30 functional and symptom subscales (figure 3A, 3C). At week 21, mean score changes from baseline were generally more favourable in the pembrolizumab plus pemetrexed–platinum group than in the placebo plus pemetrexed–platinum group for most functional and symptom scales (figure 3B, 3D). Notably, symptom scale scores for dyspnoea and pain improved in the pembrolizumab plus pemetrexed–platinum group and worsened or remained stable in the placebo plus pemetrexed–platinum group (figure 3D).

At week 21, deterioration in GHS/QOL was less frequent in patients in the pembrolizumab plus pemetrexed–platinum group (105 [26%] patients) than in the placebo plus pemetrexed–platinum group (75 [38%] patients), with similar results on all QLQ-C30 functional and symptom scales (figure 4). Conversely, improvement in GHS/QOL was recorded more frequently in patients in the pembrolizumab plus pemetrexed–platinum group (121 [30%] patients) than in the placebo plus pemetrexed–platinum group (45 [23%] patients), with greater proportions of patients in the pembrolizumab plus pemetrexed–platinum group also reporting improvements on most functional and symptoms scales (figure 4). Differences in the distribution of responses for improved, stable, and deteriorated scores at week 21 between the pembrolizumab plus pemetrexed–platinum and placebo plus pemetrexed–platinum groups were most pronounced for the two disease-related symptom scales: pain (173 [43%] of 402 *vs* 69 [35%] of 200 patients for improved, 130 [32%] *vs* 62 [31%] patients for stable, and 99 [25%] *vs* 69 [35%] patients for deteriorated) and dyspnoea (141 [35%] *vs* 57 [29%] patients for improved, 162 [40%] *vs* 68 [34%] patients for stable, and 99 [25%] *vs* 75 [38%] patients for deteriorated; figure 4). At week 12, similar results in the

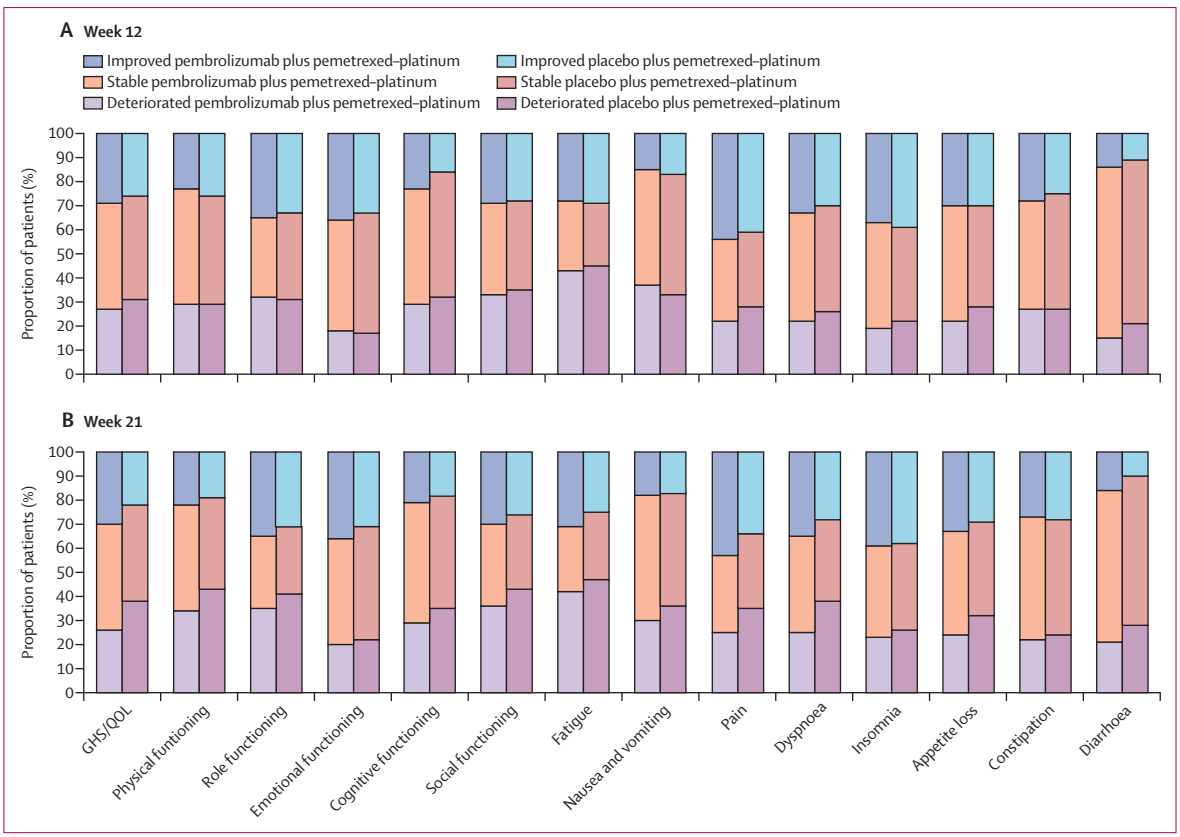

Figure 4: **Proportions of patients with improved, stable, and deteriorated QLQ-C30 GHS/QOL, functional subscale and symptom subscale scores at weeks 12 and 21**

GHS/QOL=global health status/quality of life. QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

distribution of responses on the GHS/QOL and functional and symptoms scales were observed between the two treatment groups (figure 4).

Analysis of the effect of disease progression on mean changes from baseline to weeks 12 and 21 in QLC-C30 GHS/QOL score showed that in patients with disease progression, there was little change in GHS/QOL in the pembrolizumab plus pemetrexed–platinum group, whereas there was a decline in GHS/QOL in the placebo plus pemetrexed–platinum group (appendix p 4). In patients without disease progression, changes from baseline to weeks 12 and 21 in GHS/QOL were small in both treatment groups.

Discussion

At week 21 after initiation of treatment, HRQOL (evaluated with the QLQ-C30) was maintained with pembrolizumab plus pemetrexed–platinum compared with baseline, with a better HRQOL score in the pembrolizumab plus pemetrexed–platinum group than in the placebo plus pemetrexed–platinum group at week 21 in patients with previously untreated metastatic non-squamous non-small-cell lung cancer without sensitising *EGFR* mutations or *ALK* translocations. Notably, minimal changes from baseline were observed in both treatment groups at week 12 (ie, a period during which pembrolizumab was administered in combination with pemetrexed and platinum compared with placebo plus pemetrexed and platinum), with no apparent between-group differences. However, HRQOL was maintained from baseline to week 21 with pembrolizumab plus pemetrexed–platinum, whereas HRQOL declined with placebo plus pemetrexed–platinum, with a significant between-group difference. A similar pattern of results was observed in patients with disease progression: at both weeks 12 and 21, HRQOL did not change (ie, it was maintained) in the pembrolizumab plus pemetrexed–platinum group, whereas it declined in the placebo plus pemetrexed–platinum group. The combination of these findings underscores the efficacy benefits previously observed and recorded with pembrolizumab plus pemetrexed–platinum in this study.

Time to deterioration in the composite endpoint of cough, chest pain, or dyspnoea was used to evaluate changes in lung cancer-specific symptoms that are likely to be affected by systemic anticancer treatment. This endpoint has been used in several previous clinical trials,[11–13] and its use here allows for direct comparison with these previous reports. With median follow-up of 10·5 months at data cutoff for these analyses, median

time to deterioration in the composite endpoint of increased cough, chest pain, or dyspnoea was not reached among patients in the pembrolizumab plus pemetrexed–platinum group and was 7·0 months among those in the placebo plus pemetrexed–platinum group. Although the 95% CI for HR for deterioration in this composite endpoint crossed 1, indicating a lack of statistical significance, the Kaplan-Meier curve began to separate at approximately 3 months and the results indicated a longer time to deterioration in the pembrolizumab plus pemetrexed–platinum group than in the placebo plus pemetrexed–platinum group. Notably, disease-related symptoms of cough, pain, and dyspnoea have been reported to have a substantial negative effect on lung cancer-specific QOL[1,2] and to significantly interact with changes in Eastern Cooperative Oncology Group performance status.[8] Thus, our finding that time to deterioration in these symptoms might be longer with pembrolizumab plus pemetrexed–platinum provides further support for a clinically meaningful HRQOL benefit with this combination treatment regimen. Another finding worth mentioning is that the two symptom scales with the most substantial change in distribution of responses for improved, stable, or deteriorated (based on a 10-point change in score) at week 21 were dyspnoea and pain (with a higher proportion of improved scores and a lower proportion of deteriorated scores in the pembrolizumab plus pemetrexed–platinum group than in the placebo plus pemetrexed–platinum group).

At week 12, similar proportions of patients in each treatment group had improved, stable, and deteriorated GHS/QOL, with the same pattern of results on the QLQ-C30 functional and symptoms subscales. Although the number of patients who remained on treatment and completed PRO questionnaires declined with longer follow-up, there was a notable change at week 21 (following the end of platinum therapy), with fewer patients in the pembrolizumab plus pemetrexed–platinum group than in the placebo plus pemetrexed–platinum group experiencing deterioration in GHS/QOL and similar results on all QLQ-C30 functional and symptoms scales.

The HRQOL benefit we observed with pembrolizumab plus pemetrexed–platinum in KEYNOTE-189 was similar to that observed with pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel in patients with previously untreated metastatic squamous non-small-cell lung cancer in the KEYNOTE-407 study,[14] in which the treatment difference for mean change in QLQ-C30 GHS/QOL score from baseline to week 18 was approximately 5 points, representing improvement in the pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel group and a decline in the placebo plus carboplatin and paclitaxel or nab-paclitaxel group. Our finding of a between-group difference in GHS/QOL score for pembrolizumab plus chemotherapy versus placebo plus chemotherapy at week 21 is also consistent with PROs in patients with metastatic non-small-cell lung cancer with a PD-L1 tumour proportion score of 50% or more and without sensitising *EGFR* or *ALK* alterations in the KEYNOTE-024 study,[15] which found a treatment difference for mean change in GHS/QOL score from baseline to week 15 of approximately 8 points with pembrolizumab versus chemotherapy. However, it is important to note that, by contrast with the current study, time to deterioration in the composite of cough, chest pain, or dyspnoea was significant (HR 0·66, 95% CI 0·44–0·97; p=0·029).

This study had some limitations. PROs were collected during treatment and at the 30-day visit following discontinuation of treatment; collection of PROs beyond 30 days was not feasible because there were no study visits beyond this time. Therefore, results must be interpreted as PROs while patients are on treatment and up until the point of disease progression, within each treatment group. Although the follow-up period for this study was quite long for assessing PROs on treatment, HRQOL effects can extend for long periods thereafter.[16] Thus, with a median follow-up of 10·5 months in the current study, it is unclear what effect combining pembrolizumab with pemetrexed and platinum might have on PROs with longer-term follow-up. Additionally, PROs were analysed in patients who completed assessments according to the PRO assessment schedule during the study, and thus do not reflect PROs beyond treatment discontinuation. A complete comparison between treatment groups was therefore not possible. However, it is unlikely that treatment effects were overestimated given the higher proportions of patients in the control group with early discontinuations due to disease progression and adverse events, both of which might adversely affect QOL. Notably, PRO assessments are inherently dependent on a patient's own experience of their quality of life and symptoms, and concordance with clinician assessments has been shown to be moderate at best for many symptoms commonly associated with cancer therapies.[17,18] Importantly, PRO assessments provide a means to capture additional information directly from patients regarding such symptoms, and complement the overall assessment of drug tolerability.[19] Finally, a recent study[20] identified patient-reported and genetic risk factors that were associated with chemotherapy-induced nausea and vomiting; currently, it is uncertain how such risk factors might affect these symptoms during treatment with pembrolizumab plus pemetrexed and platinum.

In conclusion, the combination of pembrolizumab and standard platinum-based chemotherapy maintained GHS/QOL in patients with previously untreated metastatic non-squamous non-small-cell lung cancer without sensitising *EGFR* mutations or *ALK* translocations, with improved GHS/QOL scores in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group at 21 weeks. These HRQOL findings complement the superior efficacy observed with

pembrolizumab plus pemetrexed–platinum over placebo plus pemetrexed–platinum in the KEYNOTE-189 study and support the use of pembrolizumab plus pemetrexed–platinum as first-line therapy for metastatic non-squamous non-small-cell lung cancer without sensitising *EGFR* mutations or *ALK* translocations.

Contributors

HGB and TB contributed to the conception or design of the study. All authors were involved in acquisition, analysis, or interpretation of the data; writing or reviewing and editing the manuscript; and approved the final version for submission.

Declaration of interests

MCG received grants and personal fees during the conduct of this study from Merck Sharp & Dohme (MSD) and has received grants and personal fees for clinical trials from AstraZeneca, Novartis, Bristol-Myers Squibb, Roche, Pfizer, Celgene, Bayer, and MSD; grants from Tiziana Life Sciences, Clovis, Merck Serono, GlaxoSmithKline, and Spectrum Pharmaceuticals; and personal fees from Eli Lilly, Boehringer Ingelheim, Otsuka Pharmaceuticals, Incyte, Inivata, Takeda, and Sanofi-Aventis. SG has received personal fees from AstraZeneca, Genentech/Roche, Takeda/Ariad, Boehringer Ingelheim, Novocure, Bristol-Myers Squibb, AbbVie, and Xcovery. EF has received personal fees as an adviser, consultant, or speaker from AbbVie, AstraZeneca, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Guardant Health, Janssen, Medscape, Merck KGaA, MSD, Novartis, Pfizer, Roche, Takeda, Touchtime, BerGenBio, and Samsung, and is an independent member of the board for Grífols. MD has received personal fees as an adviser or lecturer from AbbVie, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, MSD, Pfizer, and Roche. SP has received grants and research support to the institution from Merck; personal fees and research support to the institution from Bristol-Myers Squibb; and research support to the institution from Incyte, Genentech, Novartis, Pfizer, and Vyriad. NP has received grants, personal fees, or honoraria as an adviser from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, MSD, Novartis, Pfizer, Roche, NovellusDx, Foundation Medicine, and Gaurdant360. MR has received personal fees or honoraria for consultancy and lectures from Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Merck, MSD, Eli Lilly, Pfizer, AbbVie, Roche, and Novartis. RH has received personal fees for advisory boards or speaker honoraria from MSD, AstraZeneca, Bristol-Myers Squibb, Novartis, Roche, and Eli Lilly. EBG received grants and research support to the institution during the conduct of this study from Merck; has received grants from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Genentech, Merck, Novartis, Dynavax, Mirati Therapeutics, and Iovance Biotherapeutics; and has received payment for advisory boards or steering committees from Dracen Pharmaceuticals, EMD Serono, and Novartis. MB received grants and non-financial support from MSD during the conduct of this study; has received grants and non-financial support from AstraZeneca and Genentech/Roche; and has received grants from Bristol-Myers Squibb, Amgen, Pfizer, and Novartis. ZW and TB are full-time employees of MSD. MCP is a full-time employee of MSD and owns stock in Merck & Co. DR-A has received grants and personal fees as a consultant or adviser for Bristol-Myers Squibb and personal fees as a consultant or adviser for MSD, Genentech/Roche, AstraZeneca, Boehringer Ingelheim, Novartis, and Eli Lilly. All other authors declare no competing interests.

Data sharing

The data sharing policy, including restrictions, of Merck Sharp & Dohme, a subsidiary of Merck & Co (Kenilworth, NJ, USA) is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or by email to dataaccess@merck.com.

Acknowledgments

Funding for this research was provided by Merck Sharp & Dohme, a subsidiary of Merck & Co (Kenilworth, NJ, USA). We thank the patients and their families and caregivers for participating in this study, along with all investigators and site personnel. We thank Eli Lilly and Company (Indianapolis, IN, USA) for providing pemetrexed. Medical writing assistance was provided by Sheri Arndt of C4 MedSolutions (Yardley, PA, USA), a CHC Group company. This assistance was funded by Merck Sharp & Dohme.

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