Patient-Reported Health-Related Quality of Life in KEYNOTE-604: Pembrolizumab or Placebo Added to Etoposide and Platinum as First-Line Therapy for Extensive-Stage SCLC

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ABSTRACT

Introduction: In the phase 3 KEYNOTE-604 study (NCT03066778), pembrolizumab plus etoposide and platinum chemotherapy (EP) significantly ($p = 0.0023$) improved progression-free survival versus placebo plus EP in previously untreated extensive-stage SCLC (ES-SCLC). We present health-related quality of life (HRQoL) results from KEYNOTE-604.

Methods: Patients with stage IV SCLC were randomized 1:1 to pembrolizumab 200 mg or placebo every 3 weeks for 35 cycles plus four cycles of EP. Secondary end points included mean change from baseline to week 18 in the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire—Core 30 (QLQ-C30) global health status/quality of life (GHS/QoL) scale and time to deterioration in the composite outcome of cough, chest pain, or dyspnea from QLQ-C30 and QLQ—Lung Cancer Module 13. Two-sided, nominal p values are reported.

Results: A total of 439 patients completed at least one QLQ-C30 and QLQ—Lung Cancer Module 13 assessment (pembrolizumab + EP, n = 221; placebo + EP, n = 218). GHS/QoL scores improved from baseline to week 18: least squares mean (95% confidence interval [CI]) changes were 8.7 (5.3–12.1) for pembrolizumab plus EP and 4.2 (0.9–7.5) for placebo plus EP. Between-group differences in least squares mean scores were improved for pembrolizumab plus EP (4.4 [95% CI: 0.2–8.7], $p = 0.040$]). Median time to deterioration for the composite end point was not reached and 8.7 (95% CI: 5.9–not reached) months, respectively (hazard ratio = 0.80 [95% CI: 0.56–1.14], $p = 0.208$).

Conclusions: First-line pembrolizumab plus EP therapy maintained HRQoL in patients with ES-SCLC and may be associated with greater improvement than placebo plus EP. Together with the efficacy and safety findings in KEYNOTE-604, HRQoL data support the benefit of pembrolizumab in ES-SCLC.

Keywords: Pembrolizumab; Chemotherapy; Extensive-stage small-cell lung cancer; Health-related quality of life; Patient-reported outcomes

Introduction

SCLC is initially sensitive to chemotherapy and radiotherapy, but the disease often recurs.[1] Extensive-stage SCLC (ES-SCLC), in which distant metastases have developed, is generally considered incurable, and its treatment is primarily palliative, with few patients achieving durable treatment responses.[1,2] With disease progression, symptoms usually increase in severity and are associated with reduced health-related quality of life (HRQoL), including impairments in activities of daily living, reduced work activity, and negative impact on physical and social functioning.[3] Therefore, any treatment for ES-SCLC should also be evaluated for effects on patient HRQoL. To better understand changes in patient health status and HRQoL, patient-reported outcome (PRO) instruments are often used in clinical trials as a complement to objective measures of cancer status.[3,4]

The phase 3, randomized, double-blind KEYNOTE-604 study (NCT03066778) evaluated pembrolizumab plus etoposide and platinum chemotherapy (EP) versus placebo plus EP in patients with previously untreated ES-SCLC.[5] In KEYNOTE-604, progression-free survival (PFS) was significantly improved with pembrolizumab plus EP (median [95% confidence interval (CI)]: 4.5 [4.3–5.4] mo) versus placebo plus EP (4.3 [4.2–4.4] mo; hazard ratio [HR] = 0.75 [95% CI: 0.61–0.91], $p = 0.0023$).[5] Estimated 12-month PFS rates were 13.6% and 3.1%, respectively. The median (95% CI) overall survival (OS) with pembrolizumab plus EP was 10.8 (9.2–12.9) months compared with 9.7 (8.6–10.7) months with placebo plus EP (HR [95% CI]: 0.80 [0.64–0.98], $p = 0.0164$), which did not meet the threshold for statistical significance for OS.[5] Estimated 24-month OS rates were 22.5% and 11.2%, respectively. The incidence and severity of adverse events (AEs) were similar between patients in the pembrolizumab plus EP group and the placebo plus EP group, with no unanticipated toxicities.

In addition to assessing efficacy and safety, KEYNOTE-604 used PRO instruments to evaluate changes in HRQoL from baseline. These analyses included change from baseline in global health status and quality of life (GHS/QoL) and time to deterioration (TTD) with confirmation in lung cancer symptoms as protocol-specified end points. Here, we report the results of these HRQoL analyses.

Materials and Methods

Study Design and Participants

The methods of the randomized, double-blind, phase 3 KEYNOTE-604 study were previously described.[5] In brief, the study enrolled patients with stage IV SCLC per the American Joint Committee on Cancer seventh edition criteria[6] and measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 who had received no prior systemic therapy and had Eastern Cooperative Oncology Group performance status of 0 or 1, adequate organ function, and a life expectancy at least 3 months. Patients with brain metastases were required to complete the treatment (e.g., radiation therapy) at least 14 days before the first dose of the study drug, have no evidence of new or enlarging brain metastases, and remain neurologically stable after discontinuing corticosteroid treatment at least 7 days before the first dose of the study drug.

The study was conducted in accordance with the Declaration of Helsinki, the International Council on Harmonisation Good Clinical Practice guidelines, and all applicable local and national regulations. The study protocol and amendments were approved by the institutional review board or independent ethics committee at each study site before enrolling the first patient. All patients provided written informed consent to participate.

Treatment

Patients were randomized 1:1 to receive pembrolizumab 200 mg intravenously (IV) or saline placebo every 3 weeks for 35 cycles or until disease progression, intolerable toxicity, or physician or patient decision. Patients also received four cycles of etoposide 100 mg/m^2 IV on days 1, 2, and 3 and investigator's choice of IV carboplatin (area under the plasma drug concentration-time curve of 5) or cisplatin (75 mg/m^2) on day 1 of each 3-week cycle. Patients who achieved a complete or partial response after cycle 4 could receive up to 25 Gy of prophylactic cranial irradiation (PCI) in 10 fractions at the investigator's discretion. Randomization was stratified by choice of platinum chemotherapy (carboplatin versus cisplatin), Eastern Cooperative Oncology Group performance status (0 versus 1), and baseline lactate dehydrogenase concentration ($\leq$upper limit of normal versus $>$upper limit of normal).

Health-Related Quality-of-Life Assessments

Health-related quality-of-life assessments used the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire—Core 30 (QLQ-C30)[7] and the 13-item EORTC QLQ—Lung Cancer Module (LC13).[8] The QLQ-C30 includes a GHS/QoL scale, five scales that assess functioning, and eight scales that assess symptoms. The QLQ-LC13 is a 13-item supplement to the QLQ-C30 that includes multi- and single-item measures of disease symptoms and side effects of chemotherapy and radiation. The QLQ-C30 and LC13

instruments were administered electronically before study-related procedures at cycles 1 to 9, then at every other cycle to cycle 17, at treatment discontinuation, and at the 30-day safety follow-up (i.e., baseline, every 3 wk from wk 3 to wk 24, and every 6 wk from wk 30 to wk 48).

Health-Related Quality-of-Life End Points

The protocol-specified secondary end points included mean change from baseline to week 18 in the EORTC QLQ-C30 GHS/QoL scale (items 29 and 30) and TTD in the composite outcome of QLQ-C30 and QLQ-LC13 cough (QLQ-LC13 item 1), chest pain (QLQ-LC13 item 10), or dyspnea (QLQ-C30 item 8). The prespecified primary PRO analysis time point of week 18 was selected because it was the time most patients were expected to complete EP and PCI, if administered, and a time point when completion and compliance rates were expected to be at least 60% and 80%, respectively. Protocol-specified exploratory HRQoL end points included the mean change in score from baseline to week 18 in the QLQ-C30 physical functioning scale (items 1–5), TTD for the QLQ-C30 GHS/QoL and physical functioning scales, and the proportion of patients reporting improvements or stability in the QLQ-C30 GHS/QoL and physical functioning scales.

Statistical Analyses

Health-related quality-of-life analyses included all randomized patients who received at least one dose of the study treatment and completed at least one PRO assessment. The completion rate for the PRO instruments was defined as the percentage of patients who completed at least one questionnaire item, divided by the number of randomized patients at each time point. Because the completion rate was anticipated to decrease as patients discontinued treatment, the study also assessed PRO compliance rates, defined as the percentage of patients who completed at least one item, divided by the number of patients who were expected to complete the PRO assessment. For analysis purposes, relative visit days were mapped onto the analysis visits.

The mean change in scores for each continuous end point defined was analyzed using a constrained longitudinal data analysis method, as described by Liang and Zeger.[9] This method assumed a common mean across treatment groups at baseline and a different mean for each treatment at each postbaseline time point. Time was treated as a categorical variable. The analysis model included PRO score as the response variable, with covariates including treatment by study visit interaction. Group-wise comparisons were reported as the least squares (LS) mean change from baseline, with a 95% CI and nominal two-sided p value at week 18. Missing data were treated as missing at random.

Time to deterioration was defined as the time to first 10-point or greater worsening from baseline with confirmation under a right-censoring rule. The primary approach for TTD analysis was based on the assumption of noninformative censoring. Patients who did not have deterioration on the last date of evaluation were censored. Nonparametric Kaplan-Meier analyses were used to estimate the deterioration curve for each treatment group and provide median (95% CI) TTD. Treatment differences in TTD were assessed using the stratified log-rank test. The magnitude of treatment difference (HR) was assessed using a stratified Cox proportional hazard model that used the Efron method of tie-handling and a single-treatment covariate.

Improvement or stability in PRO scores was defined as an improvement or less than 10-point worsening in score from baseline to any analytical time point during the study, which was required to be confirmed at the next consecutive visit. The stratified Miettinen and Nurminen method was used for comparison of the overall improvement and stability rate between the treatment groups. The difference in overall improvement and stability rate and its 95% CI from the stratified Miettinen and Nurminen method, with strata weighting by sample size, was provided.

The same stratification factors as used in the stratified analyses of efficacy end points were applied to the analysis of the mean change in scores by the constrained longitudinal data analysis model, TTD analysis by stratified log-rank test, and the overall improvement and stability by the stratified Miettinen and Nurminen method. All p values were nominal and two sided. No multiplicity adjustment was performed.

Results

Patients

Between May 15, 2017, and July 30, 2018, 453 patients were randomly assigned to pembrolizumab plus EP (n = 228) or placebo plus EP (n = 225). The median time from randomization to data cutoff (December 2, 2019) was 21.6 (range: 16.1–30.6) months. As reported previously, baseline characteristics were similar between the groups.[5]

With the exception of four patients in the pembrolizumab plus EP group and three in the placebo plus EP group, all enrolled patients received at least one dose of the assigned study treatment. Of the patients who received at least one dose of the study treatment, the PRO analysis population comprised 439 patients (pembrolizumab + EP, n = 221; placebo + EP, n = 218) who completed at least one QLQ-C30 and at least one QLQ-LC13 assessment. Compliance and completion rates

Table 1. Change From Baseline to Week 18 in the EORTC QLQ-C30 GHS/QoL Scale

Visit	Pembrolizumab Plus EP (n = 221)	Placebo Plus EP (n = 218)
Baseline, n[a]	208	207
Mean (SD) score	60.54 (22.644)	58.37 (20.552)
Week 18, n[a]	145	161
Mean (SD) score	69.94 (19.526)	65.37 (20.467)
Change from baseline, n[b]	221	218
LS mean score (95% CI)	8.66 (5.26-12.06)	4.23 (0.93-7.52)
Between-group difference in LS mean (95% CI)	4.43 (0.21-8.66) $p = 0.040$	

[a]n represents the number of patients in each treatment group with nonmissing assessments at the specific time point.
[b]n represents the number of patients in the analysis population in each treatment group.
CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; EP, etoposide and platinum; GHS, global health status; LS, least squares; QLQ-C30, Quality-of-Life Questionnaire—Core 30; QoL, quality of life.

with the QLQ-C30 were each ≥94% in both treatment groups at baseline (Supplementary Table 1). Compliance rates remained at or above 91% in both treatment groups at week 18. Completion rates decreased over time to 65% in the pembrolizumab plus EP group and 74% in the placebo plus EP group at week 18. Similar compliance and completion rates were observed for the QLQ-LC13.

Key Patient-Reported Outcome End Points

Protocol-Specified Secondary End Points. Baseline mean (SD) QLQ-C30 GHS/QoL scores were 60.5 (22.6) points in the pembrolizumab plus EP group and 58.4 (20.6) points in the placebo plus EP group. At week 18, LS mean (95% CI) change in QLQ-C30 GHS/QoL score from baseline was 8.7 (5.3–12.1) points in the pembrolizumab plus EP group and 4.2 (0.9–7.5) points in the placebo plus EP group (Table 1). The LS mean (95% CI) difference in scores between the treatment groups was 4.4 (0.2–8.7) points ($p = 0.040$). Scores for all QLQ-C30 functional scales also increased (indicative of better functioning) or remained unchanged from baseline to week 18 in the pembrolizumab plus EP group, whereas patients receiving placebo plus EP reported reductions or smaller increases in scores in functioning across all scales (Fig. 1).

Deterioration in the composite end point of cough, chest pain, or dyspnea was observed in 57 patients (25.8%) in the pembrolizumab plus EP group and 71 patients (32.6%) in the placebo plus EP group. The median (95% CI) TTD (time to first ≥10-point worsening from baseline with confirmation at the next consecutive visit) for the composite end point was not reached (not reached–not reached) with pembrolizumab plus EP and 8.7 months (5.9 months–not reached) with

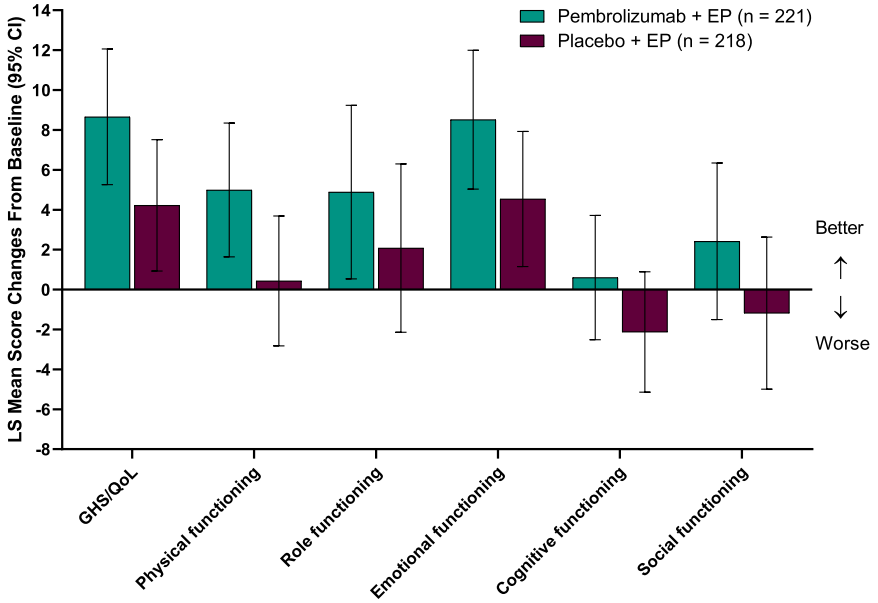

Figure 1. Mean change from baseline for EORTC QLQ-C30 GHS/QoL and functional scales at week 18. CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; EP, etoposide and platinum; GHS, global health status; LS, least squares; QLQ-C30, Quality-of-Life Questionnaire—Core 30; QoL, quality of life.

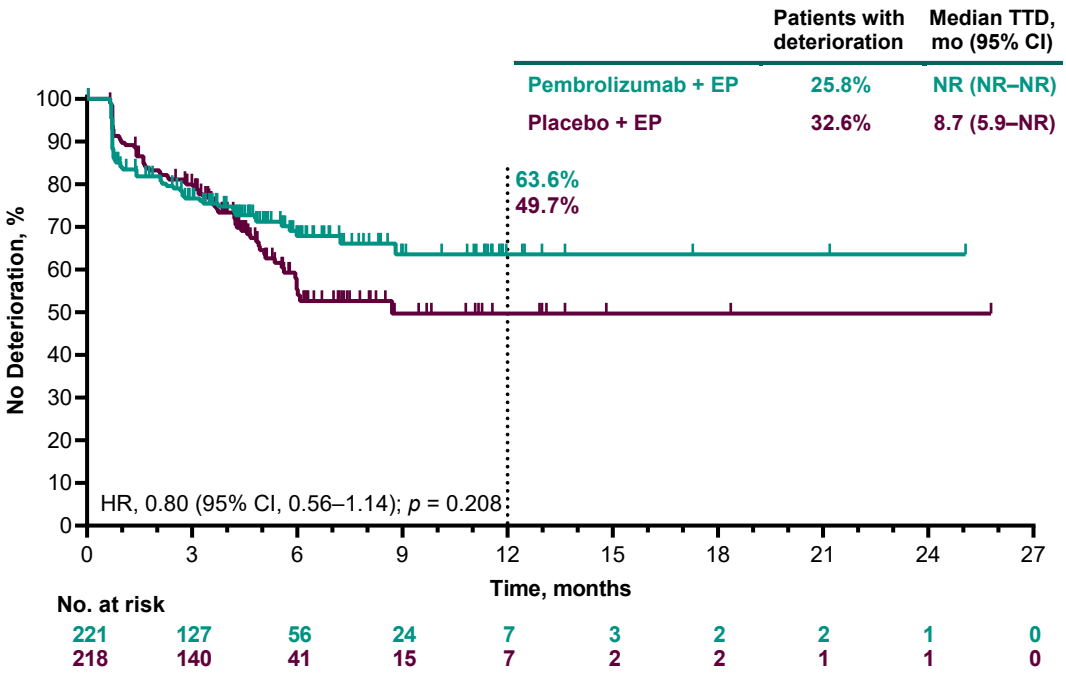

Figure 2. Time to deterioration in EORTC QLQ-C30 and QLQ-LC13 composite of cough, chest pain, or dyspnea. CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; EP, etoposide and platinum; HR, hazard ratio; LC13, Lung Cancer Module 13; NR, not reached; QLQ-C30, Quality-of-Life Questionnaire—Core 30; TTD, time to deterioration.

placebo plus EP (HR [95% CI]: 0.80 [0.56–1.14], $p = 0.208$) (Fig. 2). The estimated percentage of patients who were alive and did not deteriorate at 12 months was 63.6% in the pembrolizumab plus EP group and 49.7% in the placebo plus EP group.

Protocol-Specified Exploratory End Points. Baseline mean (SD) QLQ-C30 physical functioning scores were 72.6 (23.4) points in the pembrolizumab plus EP group and 71.6 (22.2) points in the placebo plus EP group. The mean (SD) scores in each treatment group were 79.6 (20.5) and 75.6 (21.9), respectively, at week 18. The LS mean (95% CI) change in QLQ-C30 physical functioning scores from baseline to week 18 was 5.0 (1.6–8.4) points in the pembrolizumab plus EP group and 0.4 (−2.8 to 3.7) points in the placebo plus EP group. The LS mean (95% CI) difference in scores between the treatment groups was 4.6 (0.3–8.9) points ($p = 0.038$).

Deterioration in QLQ-C30 GHS/QoL scores was observed in 43 patients (19.5%) in the pembrolizumab plus EP group and 52 patients (23.9%) in the placebo plus EP group. Median (95% CI) TTD was not reached (not reached–not reached) in the pembrolizumab plus EP group and not reached (10.2 mo–not reached) in the placebo plus EP group (HR [95% CI]: 0.78 [0.52–1.18]; $p = 0.238$) (Fig. 3). The estimated percentage of patients who were alive and did not deteriorate at 12 months was 66.6% in the pembrolizumab plus EP group and 61.5% in the placebo plus EP group. Overall, 168 patients (76.0%) in the pembrolizumab plus EP group and 170 (78.0%) in the placebo plus EP group had QLQ-C30 GHS/QoL scores that improved or remained stable relative to the baseline score (defined by an improvement or less than 10-point worsening in score from baseline). The between-group difference in the proportion of patients with improved or stable GHS/QoL score was −2.1% (95% CI: −9.9% to 5.8%; $p = 0.605$).

Similar proportions of patients in the pembrolizumab plus EP (19.9% [44 of 221]) and placebo plus EP (21.1% [46 of 218]) treatment groups experienced deterioration in QLQ-C30 physical functioning. The median TTD in physical functioning was not reached in either treatment group (HR [95% CI]: 0.97 [0.64–1.47]; $p = 0.868$). In addition, 162 patients (73.3%) in the pembrolizumab plus EP group and 162 (74.3%) in the placebo plus EP group had QLQ-C30 physical functioning scores that improved or remained stable relative to baseline (as defined by an improvement or less than 10-point worsening in score from baseline). This was associated with a between-group difference of −1.1 points (95% CI: −9.3 to 7.2; $p = 0.796$).

Supportive Patient-Reported Outcomes Analyses

Changes in the QLQ-C30 GHS/QoL scores over time are found in Figure 4. Overall, study treatment was associated with similar or better scores compared with baseline for patients in both treatment groups across the time period. Toward the latter end of the follow-up

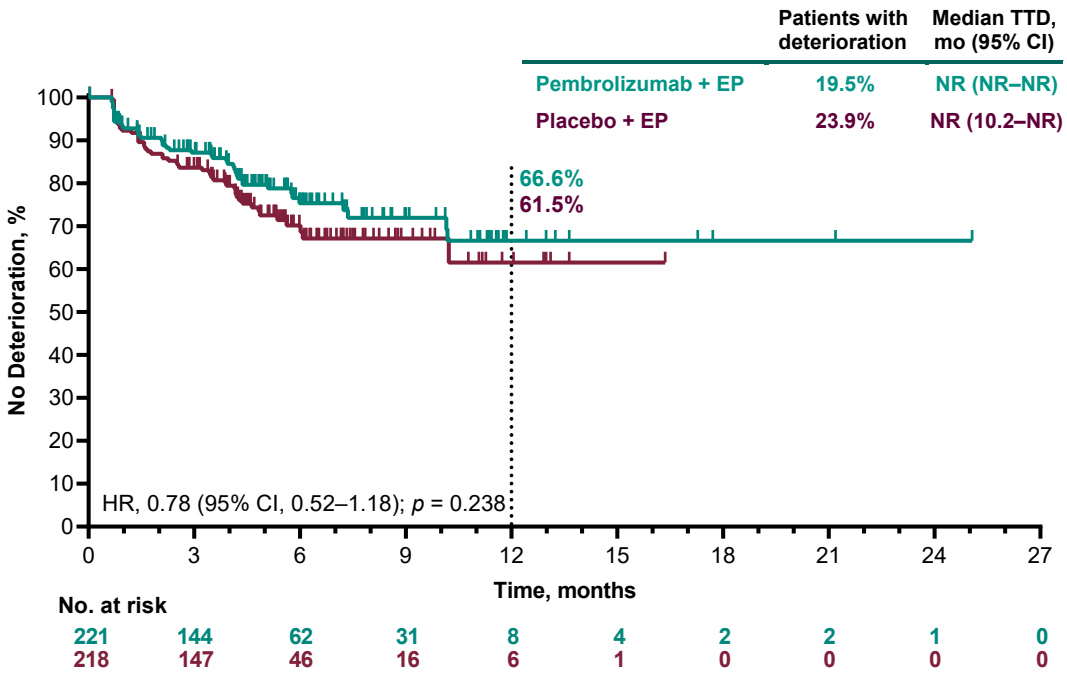

Figure 3. Time to deterioration in EORTC QLQ-C30 GHS/QoL scale. CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; EP, etoposide and platinum; GHS, global health status; HR, hazard ratio; LC13, Lung Cancer Module 13; NR, not reached; QLQ-C30, Quality-of-Life Questionnaire—Core 30; QoL, quality of life; TTD, time to deterioration.

period (approximately 36 wk), there were fewer assessable patients, and the SE was wider, precluding definitive conclusions.

QLQ-C30 physical functioning scores were substantially improved from baseline with pembrolizumab plus EP treatment, whereas minimal changes were observed for patients who received placebo plus EP. Nevertheless, the SEs were very wide and preclude definitive conclusions (Fig. 5).

Discussion

In the KEYNOTE-604 study, pembrolizumab plus EP significantly ($p = 0.0023$) improved PFS versus placebo plus EP, together with a manageable safety profile. In the

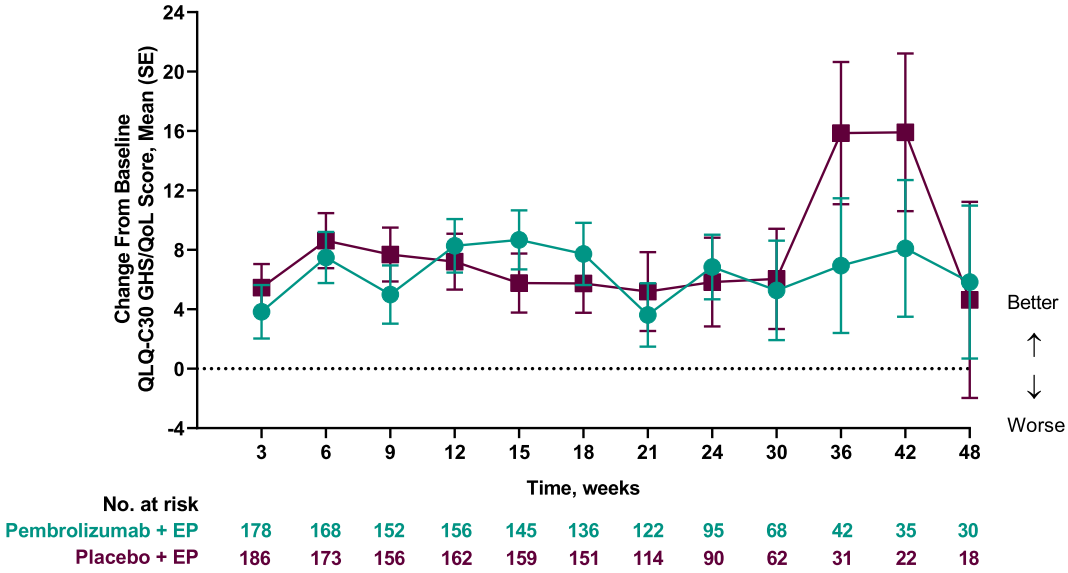

Figure 4. Mean change from baseline in EORTC QLQ-C30 GHS/QoL scores over time. EORTC, European Organisation for Research and Treatment of Cancer; EP, etoposide and platinum; GHS, global health status; QLQ-C30, Quality-of-Life Questionnaire—Core 30; QoL, quality of life.

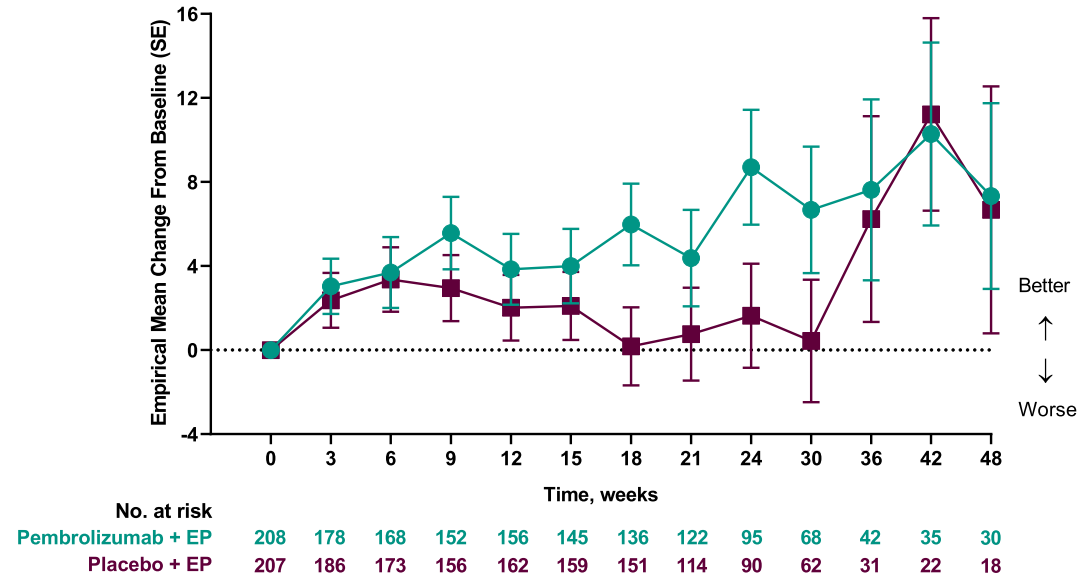

Figure 5. Empirical mean change from baseline in EORTC QLQ-C30 physical functioning score across time. EORTC, European Organisation for Research and Treatment of Cancer; EP, etoposide and platinum; QLQ-C30, Quality-of-Life Questionnaire—Core 30.

current analysis of PROs from the KEYNOTE-604 study, we provide a comprehensive assessment of global health including physical functioning, HRQoL, and disease-related symptoms. Our results suggest that HRQoL was not decreased in patients with ES-SCLC who received first-line treatment with pembrolizumab plus EP compared with those who received placebo plus EP. These findings are consistent with the manageable safety profile and low discontinuation rate of pembrolizumab plus EP that were previously reported.[5]

Compliance and completion rates were high at baseline in both treatment groups. As expected, completion rates decreased over time owing to an increase in numbers of patients who discontinued because of AEs, physician decision, disease progression, study withdrawal, or death, or who had no scheduled visit. At week 18 (the time point at which most patients were expected to have completed EP and PCI and PRO completion rates were expected to be high), a moderate improvement in HRQoL from baseline was observed in both treatment groups. Nevertheless, the magnitude of improvement in EORTC QLQ-C30 GHS/QoL was numerically greater with pembrolizumab plus EP than with placebo plus EP. Similar results were observed across all QLQ-C30 functioning scales, where pembrolizumab plus EP was associated with increased or unchanged scores from baseline to week 18 and placebo plus EP was associated with numerically smaller increases (physical, role, and emotional functioning) or decreased scores (cognitive and social functioning). There was also a longer TTD in symptoms of the composite end point of cough, chest pain, or dyspnea in the pembrolizumab plus EP group versus placebo plus EP group, although the between-group treatment differences did not reach statistical significance. The Kaplan-Meier curves indicated a continuous separation over time of the pembrolizumab plus EP curve from the placebo plus EP curve from approximately week 18. Similarly, prolonged TTD with pembrolizumab plus EP versus placebo plus EP was observed for the assessment of the GHS/QoL score. Supportive analyses were consistent with the key PRO end points indicating greater magnitude of improvement in the individual symptoms that comprised the composite end point with pembrolizumab plus EP versus placebo plus EP from baseline to week 18. Pembrolizumab plus EP was also associated with greater increases in mean change in QLQ-C30 physical functioning scores from baseline to week 48 versus placebo plus EP. The improvements in physical functioning observed at week 18 aligned with the observed median PFS of 4.5 months (previously reported) with pembrolizumab plus EP.[5] Taken together, our findings provide additional evidence to support the treatment benefits previously reported with pembrolizumab plus EP versus placebo plus EP, including prolonged PFS, longer median OS, and a manageable safety profile.[5]

Health-related quality-of-life data are also available from two other phase 3 studies in patients with ES-SCLC who received a combination of anti–programmed cell death ligand 1 therapy plus EP.[10,11] In the double-blind, placebo-controlled, phase 3 IMpower133 study, the changes from baseline to week 54 in functioning and HRQoL scores were similar with atezolizumab plus carboplatin and etoposide versus placebo plus carboplatin

and etoposide in patients with chemotherapy-naive ES-SCLC.[10] The TTD of treatment-related symptoms was similar between the treatment groups.[10] Similarly, in the randomized, open-label, phase 3 CASPIAN study, there was no increase in symptom burden with the addition of durvalumab to EP in patients with ES-SCLC.[11] The median TTD with durvalumab plus EP was longer in the prespecified key disease-related symptoms of cough, dyspnea, chest pain, fatigue, and appetite loss.[11] Consistent with the IMpower133 and CASPIAN studies of anti–programmed cell death ligand 1 therapies, the addition of pembrolizumab, an anti–programmed cell death protein 1 monoclonal antibody, to EP as first-line therapy for ES-SCLC did not decrease HRQoL. Our findings for longer TTD in lung cancer symptoms of cough, chest pain, or dyspnea are also consistent with the CASPIAN study. Nevertheless, caution is warranted for any cross-trial comparisons, particularly given differences in individual study treatments, study designs, follow-up durations, and study populations.

The placebo-controlled, randomized, double-blind, phase 3 KEYNOTE-604 study provides a large and comprehensive data set of efficacy, safety, and PROs in patients with ES-SCLC who received treatment with anti–programmed cell death protein 1 combination therapy. There are, however, some limitations associated with the current PRO analysis. First, in this study, PRO data were collected up through the 30-day safety follow-up period; therefore, it is not possible to ascertain longer-term changes in HRQoL effects from this analysis. Second, as was expected for a patient population with an aggressive disease such as ES-SCLC, the PRO completion rates decreased over time, limiting data toward the later time points; however, compliance rates remained high throughout the study duration, suggesting that questionnaires were completed by most of the patients at the given time. Finally, all *p* values noted here are nominal and there were no adjustments for multiplicity.

In summary, the addition of pembrolizumab to EP as first-line therapy for patients with previously untreated ES-SCLC was not associated with reductions in GHS/QoL and functioning or disease symptoms. Although HRQoL was improved in both treatment groups at week 18 compared with baseline, pembrolizumab plus EP may be associated with a greater improvement than placebo plus EP. Along with the efficacy and safety observed in KEYNOTE-604, HRQoL data support the benefit of pembrolizumab and reveal the value of immunotherapy in SCLC.

CRediT Authorship Contribution Statement

Hye Ryun Kim: Full access to all data in the study and takes responsibility for the integrity and the accuracy of the data analysis; Investigation; Roles/Writing—original draft; Writing—review and editing.

Mark M. Awad: Investigation; Resources; Writing—review and editing.

Alejandro Navarro: Investigation; Resources; Writing—review and editing.

Maya Gottfried: Formal analysis; Writing—review and editing.

Solange Peters: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Roles/Writing—original draft; Writing—review and editing.

Tibor Csőszi: Conceptualization; Investigation; Methodology; Writing—review and editing.

Parneet K. Cheema: Investigation; Writing—review and editing.

Delvys Rodriguez-Abreu: Formal analysis; Investigation; Writing—review and editing.

Mirjana Wollner: Investigation; Writing—review and editing.

James Chih-Hsin Yang: Writing—review and editing.

Julien Mazieres: Investigation; Resources; Roles/Writing—original draft; Writing—review and editing.

Francisco J. Orlandi: Investigation; Resources; Writing—review and editing.

Alexander Luft: Investigation; Resources; Writing—review and editing.

Mahmut Gümüş: Investigation; Resources; Writing—review and editing.

Terufumi Kato: Investigation; Writing—review and editing.

Gregory P. Kalemkerian: Investigation; Resources; Writing—review and editing.

Yiwen Luo: Formal analysis; Writing—review and editing.

Melissa L. Santorelli: Conceptualization; Formal analysis; Methodology; Roles/Writing—original draft; Writing—review and editing.

M. Catherine Pietanza: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Roles/Writing—original draft; Writing—review and editing.

Charles M. Rudin: Investigation; Resources; Supervision; Writing—review and editing.

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Data-Sharing Statement

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (Merck Sharp & Dohme), 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. Merck Sharp & Dohme 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 Merck Sharp & Dohme data-sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of Merck Sharp & Dohme 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 Merck Sharp & Dohme before data access is granted. Data will be made available for request after product approval in the United States and European Union or after product development is discontinued. There are circumstances that may prevent Merck Sharp & Dohme 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 Merck Sharp & Dohme subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, Merck Sharp & Dohme will either 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.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100572.

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