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Patient-reported outcomes with first-line durvalumab plus platinum-etoposide versus platinum-etoposide in extensive-stage small-cell lung cancer (CASPIAN): a randomized, controlled, open-label, phase III study

Jonathan W. Goldman [a,*], Marina Chiara Garassino [b], Yuanbin Chen [c], Mustafa Özgüroğlu [d], Mikhail Dvorkin [e], Dmytro Trukhin [f], Galina Statsenko [g], Katsuyuki Hotta [h], Jun Ho Ji [i], Maximilian J. Hochmair [j], Oleksandr Voitko [k], Libor Havel [l], Artem Poltoratskiy [m], György Losonczy [n], Niels Reinmuth [o], Nikunj Patel [p], Peter J. Laud [q], Norah Shire [p], Haiyi Jiang [p], Luis Paz-Ares [r]

[a] David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[b] Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[c] Cancer & Hematology Centers of Western Michigan, Grand Rapids, MI, USA
[d] Istanbul University–Cerrahpaşa, Cerrahpaşa School of Medicine, Istanbul, Turkey
[e] BHI of Omsk Region Clinical Oncology Dispensary, Omsk, Russia
[f] Odessa National Medical University, Odessa, Ukraine
[g] Omsk Regional Cancer Center, Omsk, Russian Federation
[h] Okayama University Hospital, Okayama, Japan
[i] Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Republic of Korea
[j] Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Klinik Floridsdorf, Vienna, Austria
[k] Kyiv City Clinical Oncological Centre, Kiev, Ukraine
[l] Thomayer Hospital, First Faculty of Medicine, Charles University, Prague, Czech Republic
[m] Petrov Research Institute of Oncology, St Petersburg, Russian Federation
[n] Semmelweis University, Budapest, Hungary
[o] Asklepios Lung Clinic, Munich-Gauting, Germany
[p] AstraZeneca, Gaithersburg, MD, USA
[q] Statistical Services Unit, University of Sheffield, Sheffield, UK
[r] Hospital Universitario 12 de Octubre, H120-CNIO Lung Cancer Unit, Universidad Complutense and Ciberonc, Madrid, Spain

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ABSTRACT

Objectives: In the phase III CASPIAN study, first-line durvalumab plus etoposide in combination with either cisplatin or carboplatin (EP) significantly improved overall survival (primary endpoint) versus EP alone in patients with extensive-stage small-cell lung cancer (ES-SCLC) at the interim analysis. Here we report patient-reported outcomes (PROs).

Materials and methods: Treatment-naïve patients with ES-SCLC received 4 cycles of durvalumab plus EP every 3 weeks followed by maintenance durvalumab every 4 weeks until progression, or up to 6 cycles of EP every 3 weeks. PROs, assessed with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) version 3 and its lung cancer module, the Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13), were prespecified secondary endpoints. Changes from baseline to disease progression or 12 months in prespecified key disease-related symptoms (cough, dyspnea, chest pain, fatigue, appetite loss) were analyzed with a mixed model for repeated measures. Time to deterioration (TTD) of symptoms, functioning, and global health status/quality of life (QoL) from randomization was analyzed.

Results: In the durvalumab plus EP and EP arms, 261 and 260 patients were PRO-evaluable. Patients in both arms experienced numerically reduced symptom burden over 12 months or until progression for key symptoms. For

* Corresponding author at: David Geffen School of Medicine at UCLA, 10833 Le Conte Ave, Los Angeles, CA, 90095, USA.
E-mail address: jwgoldman@mednet.ucla.edu (J.W. Goldman).

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the improvements from baseline in appetite loss, the between-arm difference was statistically significant, favoring durvalumab plus EP (difference, −4.5; 99% CI: −9.04, −0.04; nominal $p = 0.009$). Patients experienced longer TTD with durvalumab plus EP versus EP for all symptoms (hazard ratio [95% CI] for key symptoms: cough 0.78 [0.600–1.026]; dyspnea 0.79 [0.625–1.006]; chest pain 0.76 [0.575–0.996]; fatigue 0.82 [0.653–1.027]; appetite loss 0.70 [0.542–0.899]), functioning, and global health status/QoL.
Conclusion: Addition of durvalumab to first-line EP maintained QoL and delayed worsening of patient-reported symptoms, functioning, and global health status/QoL compared with EP.

1. Introduction

Approximately two-thirds of patients who present with small-cell lung cancer (SCLC) have extensive-stage SCLC (ES-SCLC), reflecting the highly aggressive nature of this tumor and its tendency for early, widespread metastasis [1,2]. Less than 5% of patients with ES-SCLC remain alive at 2 years after diagnosis [3]. Progress in improving outcomes for patients with ES-SCLC has been limited until recently. Standard first-line treatment has consisted of etoposide in combination with either carboplatin or cisplatin (EP) for more than three decades [4–6]. However, the addition of immunotherapy targeting the programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathway to platinum-based chemotherapy has been shown to prolong overall survival (OS) in patients with ES-SCLC [7,8].

Durvalumab is a selective, high-affinity human immunoglobulin G1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80 [9]. The phase III CASPIAN study (NCT03043872) is assessing the efficacy and safety of first-line durvalumab, with or without the anti-cytotoxic T lymphocyte-associated antigen-4 antibody tremelimumab, in combination with EP versus EP alone in patients with ES-SCLC [8]. At the planned interim analysis, durvalumab plus EP significantly prolonged OS compared with EP (hazard ratio [HR]: 0.73; 95% confidence interval [CI]: 0.59–0.91; $p = 0.0047$) [8]. Median OS was 13.0 months in the durvalumab plus EP arm versus 10.3 months in the EP arm. The survival benefit was observed across all prespecified, clinically relevant patient subgroups. Median progression-free survival (PFS) was 5.1 months in the durvalumab plus EP arm versus 5.4 months in the EP arm (HR: 0.78; 95% CI: 0.65–0.94); 12-month PFS rates were 18% versus 5%. A recent updated analysis demonstrated the OS improvement with durvalumab plus EP versus EP was sustained after a median follow-up of more than 2 years (HR: 0.75; 95% CI: 0.62–0.91; nominal $p = 0.0032$) [10]. Safety findings were consistent with the known safety profiles of both durvalumab and EP.

Prolonged survival is most meaningful if patients' quality of life (QoL) is not unduly compromised; as such, patient-reported outcomes (PROs) were an important secondary endpoint of the CASPIAN study. PROs provide the patient's perspective of their symptoms, functioning, and health-related QoL (HRQoL), and therefore complement objective investigator-assessed efficacy and safety endpoints. Patients diagnosed with SCLC typically present with a broad range of symptoms encompassing disease-related symptoms such as cough, dyspnea, chest pain, fatigue, and appetite loss, and signs of psychological distress such as anxiety and depression [11]. These symptoms may be more severe in patients who present with extensive-stage disease compared with earlier stages of disease, and can have a substantial impact on physical, cognitive, emotional, and social functioning. Patients with SCLC have worse HRQoL and PROs compared with the general population [12,13]. Furthermore, a systematic literature review has suggested that the impact of SCLC on HRQoL may be greatest in patients with treatment-naïve extensive-stage disease [13].

Here, we present PRO data from the interim analysis of the CASPIAN study, to assess the effect of adding durvalumab to EP as first-line treatment for ES-SCLC on patients' symptoms, functioning, and HRQoL.

2. Methods

2.1. Study design and patients

CASPIAN is a randomized, open-label, sponsor-blind, multicenter, global phase III study. Efficacy and safety results from this interim analysis (data cutoff: March 11, 2019) have been reported previously, and the study methodology is described in detail in the primary report [8]. Briefly, eligible patients were aged ≥18 years and had treatment-naïve histologically or cytologically documented ES-SCLC, World Health Organization (WHO) performance status score of 0 or 1, and measurable disease according to Response Evaluation Criteria in Solid Tumors, version 1.1 [14]. Patients with brain metastases were eligible provided they were asymptomatic or treated and stable and had been off steroids and anticonvulsants for at least 1 month prior to study entry.

The study was conducted in accordance with the International Conference on Harmonisation good clinical practice guidelines, the Declaration of Helsinki, and applicable local regulations with approval from an independent ethics committee or institutional review boards. The protocol and all modifications were approved by relevant ethics committees and regulatory authorities.

2.2. Treatment

Patients were randomized in a 1:1:1 ratio to receive durvalumab plus EP, durvalumab plus tremelimumab plus EP, or EP. Randomization was stratified by planned platinum agent (carboplatin or cisplatin). All drugs were administered intravenously. EP in each arm consisted of etoposide 80–100 mg/m^2, administered on days 1–3 of each 21-day cycle, and investigator's choice of either carboplatin area under the curve 5–6 mg/mL/min or cisplatin 75–80 mg/m^2, administered on day 1 of each cycle. Patients in the immunotherapy arms received EP plus durvalumab 1500 mg, with or without tremelimumab 75 mg, every 3 weeks for 4 cycles, followed by maintenance durvalumab 1500 mg every 4 weeks. Immunotherapies were administered on day 1 of each cycle. Patients in the EP arm could receive an additional 2 cycles of EP (up to 6 cycles in total) as well as prophylactic cranial irradiation (PCI) post-EP at the investigator's discretion. Patients continued treatment until disease progression per investigator assessment, unacceptable toxicity, or other discontinuation criteria were met. Patients could continue study treatment beyond disease progression if the investigator judged them to be deriving clinical benefit.

2.3. Endpoints and assessments

The primary endpoint was OS. Secondary endpoints included PFS, objective response rate, safety and tolerability, as well as PROs (the focus of this article). Prespecified secondary PRO endpoints comprised measurement of symptoms, functioning, and HRQoL. The symptoms of appetite loss, constipation, diarrhea, dyspnea, fatigue, nausea or vomiting, pain, and insomnia; functioning (physical, cognitive, emotional, role, and social); and global health status/QoL were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) 30-item core Quality of Life Questionnaire, version 3 (QLQ-C30 v3) [15]. Additional lung cancer-associated symptoms of cough, dyspnea, hemoptysis, arm or shoulder pain, chest pain, and other pain were

assessed using the EORTC 13-item lung cancer module (QLQ-LC13) [16]. Cough, dyspnea, and chest pain from QLQ-LC13, and fatigue and appetite loss from QLQ-C30 were predefined as primary measures of interest (key disease-related symptoms) based on a review of the literature and qualitative interviews with clinicians and patients to discuss their experiences related to ES-SCLC and its treatment [11]. Data regarding the financial difficulties item from the QLQ-C30 questionnaire and side-effects from conventional chemoradiotherapy (sore mouth, dysphagia, peripheral neuropathy, and alopecia) from the QLQ-LC13 module will not be reported.

The two questionnaires were administered to patients independently on a handheld electronic device during clinic visits, before any other study procedures. Questions could not be skipped on the device and thus it was not possible to submit a partially completed form. The questionnaires were completed at baseline and on the first day of each treatment cycle, or (for patients who discontinued treatment before progression) every 4 weeks, until disease progression. As disease progression often precipitates a deterioration in patient HRQoL, patients were also required to complete questionnaires on day 28 after progression, and thereafter every 8 weeks until second progression or death (whichever came first).

2.4. Statistical analysis

Summary statistics were compiled for overall compliance and compliance over time for both questionnaires. Scores for the QLQ-30 and QLQ-LC13 questionnaires were calculated according to published scoring manuals or the developer's guidelines. Raw scores from scales in both questionnaires are standardized by linear transformation so that they range from 0 to 100. Higher scores for symptom items indicate greater symptom severity, while higher scores for function and global health status/QoL items indicate better function and health status/QoL. For both questionnaires, a clinically meaningful change was prespecified as an absolute change in score from baseline of ≥10 points (either deterioration or improvement) [17].

For the five key disease-related symptoms (cough, dyspnea, and chest pain [QLQ-LC13], and fatigue and appetite loss [QLQ-C30]), changes at each visit from baseline to disease progression or 12 months (whichever came first) were analyzed using a mixed model for repeated measures (MMRM) to derive an overall adjusted mean change from baseline, reflecting the average treatment effect over visits. The model assumes PROs were collected at multiple visits per patient and that data are missing at random. Visits with >75% missing data were excluded from the analysis. The MMRM included treatment, age at randomization (<65 vs ≥65 years), sex, smoking history (smoker vs non-smoker), visit, and treatment-by-visit interaction as fixed factors, and baseline score as a covariate; the model further adjusted for baseline score-by-visit interaction. PROs were not part of the multiple-testing procedure in CASPIAN and, as such, no alpha was allocated to the analysis of PRO endpoints and all *p*-values reported are nominal. However, the overall type I error (5% 2-sided) was controlled across the MMRM analysis for each of the five key symptoms using a Bonferroni adjusted 1% significance level and 99% CIs.

Time to deterioration (TTD) was assessed in patients whose baseline scores were ≥10 for functioning and global health status/QoL and ≤90 for symptoms. TTD was defined as the time from randomization to the first clinically meaningful deterioration (≥10-point increase from baseline for symptoms; ≥10-point decrease from baseline for function and global health status/QoL) that was confirmed at a subsequent assessment, or death from any cause in the absence of clinically meaningful deterioration. Patients with a single deterioration and no further assessments were treated as deteriorated. The Kaplan-Meier method was used to estimate TTD, which was analyzed using a stratified log-rank test adjusting for planned platinum therapy (carboplatin or cisplatin), with HRs and 95% CIs calculated using a stratified Cox proportional hazards model.

PRO analyses were to be performed in all randomized patients (i.e. the intent-to-treat [ITT] population). However, patients randomized at one site were excluded from these analyses as their PRO data could not be verified, and therefore the PRO-evaluable population consisted of the ITT population minus the patients randomized at this site.

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

3. Results

3.1. Patients

In total, 972 patients were enrolled into the study between March 2017 and May 2018, with 805 patients randomized to durvalumab plus EP (n = 268), durvalumab plus tremelimumab plus EP (n = 268), or EP alone (n = 269) [8] (Supplementary Fig. 1). The ITT population at this interim analysis included all 537 patients randomized to the durvalumab plus EP and EP arms. As previously reported, baseline demographics and disease characteristics were well balanced between treatment arms [8]. In the durvalumab plus EP and EP arms, 261 and 260 patients were evaluable for PRO analyses; this represents the ITT population minus 16 patients at one site who were excluded specifically from PRO analyses as their PRO data could not be verified.

3.2. QLQ-C30 and QLQ-LC13 compliance and baseline scores

Baseline QLQ-C30 data were available for 245 patients (94%) in each arm, and baseline QLQ-LC13 data were available for 244 patients (93%) in the durvalumab plus EP arm and 245 patients (94%) in the EP arm. For both questionnaires, compliance rates were >60% for up to cycle 23 in the durvalumab plus EP arm and up to cycle 7 in the EP arm (Supplementary Fig. 2A and B). Compliance during post-progression follow-up was more variable, but generally better in the durvalumab plus EP arm, compared with the EP arm (Supplementary Fig. 2C and D).

Baseline QLQ-C30 and QLQ-LC13 scores for global health status/QoL, functioning, and symptoms were generally comparable between treatment arms (Supplementary Fig. 3). Mean baseline scores for global health status/QoL were 56.0 in the durvalumab plus EP arm and 54.1 in the EP arm; for physical functioning, the scores were 72.2 and 70.7, respectively. In terms of symptoms, mean baseline scores with durvalumab plus EP and EP were 28.4 and 29.5 for pain, and 24.2 and 25.6 for appetite loss. The most severe symptoms at baseline (mean score ≥30) were cough (41.5 in the durvalumab plus EP arm and 40.5 in the EP arm), dyspnea (QLQ-C30: 36.5 and 38.5; QLQ-LC13: 30.7 and 31.8), fatigue (35.3 and 37.1), and insomnia (29.7 and 33.9). Low baseline values (mean score <10) were reported for diarrhea (4.9 and 5.6), nausea or vomiting (5.6 and 6.9), and hemoptysis (6.3 and 5.3). Baseline scores on the QLQ-C30 functioning scales from patients in both treatment arms were comparable to available reference values for patients with ES-SCLC; however, baseline scores for lung cancer-associated symptoms (cough, dyspnea, arm or shoulder pain, chest pain, other pain) from QLQ-LC13 in both arms were worse compared with a normative sample of patients with SCLC [12].

3.3. Changes from baseline

The MMRM analysis of adjusted mean change from baseline to disease progression or 12 months averaged over visits showed that patients in both arms experienced a numerically reduced symptom burden for each of the key disease-related symptoms (Fig. 1). The improvement in appetite loss from baseline was significantly greater in the durvalumab plus EP arm as compared with the EP arm (adjusted mean change from baseline: −12.7 vs −8.2; estimated difference: −4.5; 99% CI: −9.04, −0.04; nominal $p = 0.009$). Adjusted mean changes from baseline were

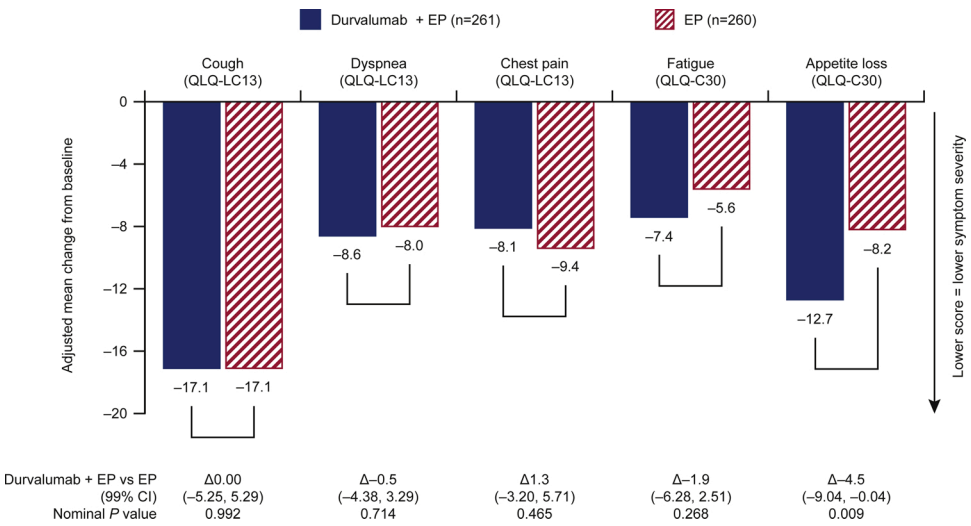

Fig. 1. MMRM analysis of adjusted mean change from baseline to disease progression or 12 months in prespecified key disease-related symptoms.
Presented are adjusted mean changes from baseline (bars), and between-arm differences (Δ), with 99% CIs. A negative difference (Δ) favors durvalumab plus EP versus EP alone. CI, confidence interval; EP, platinum-etoposide; ITT, intention-to-treat; MMRM, mixed model for repeat measures; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer 13.

similar across both arms for the other key symptoms of cough (−17.1 in the durvalumab plus EP arm and −17.1 in the EP arm), dyspnea (QLQ-LC13: −8.6 and −8.0), chest pain (−8.1 and −9.4), and fatigue (−7.4 and −5.6). Unadjusted mean changes from baseline over time in global health status/QoL, physical functioning, cognitive functioning, and the five prespecified key disease-related symptoms are shown in Supplementary Fig. 4.

3.4. Time to deterioration

Longer median TTD was observed for patients in the durvalumab plus EP arm compared with those in the EP arm for global health status/QoL and all functioning scales, as well as for all QLQ-C30 and QLQ-LC13 symptom scales (Fig. 2). HRs favored durvalumab plus EP versus EP, with upper bounds of 95% CIs <1 for all functioning domains, as well as for symptoms including appetite loss, constipation, diarrhea, dyspnea, and insomnia (QLQ-C30), and hemoptysis, arm or shoulder pain, chest pain, and other pain (QLQ-LC13). Kaplan-Meier curves for TTD in the key disease-related symptoms of cough, dyspnea, chest pain, fatigue, and appetite loss are shown in Fig. 3. Kaplan-Meier curves for TTD in global health status/QoL, functioning scales, and other symptoms are shown in Supplementary Figs. 5 and 6.

4. Discussion

First-line treatment with durvalumab plus EP was associated with a statistically significant and clinically meaningful improvement in OS compared with EP alone in patients with ES-SCLC, with an HR of 0.73 (95% CI: 0.59–0.91; $p = 0.0047$), as previously reported [8]. Clinical benefit with durvalumab plus EP was also observed across the secondary

QLQ-C30	Events/ patients, n	Median TTD, months Durvalumab + EP	EP	HR (95% CI)	Nominal *P* value
Global health status/QoL	240/470	8.4	7.2	0.81 (0.626–1.054)	0.1166
Cognitive functioning	261/486	8.4	6.0	0.61 (0.472–0.776)	<0.0001
Emotional functioning	216/481	12.9	7.3	0.61 (0.464–0.800)	0.0003
Physical functioning	246/483	8.5	6.5	0.75 (0.581–0.970)	0.0276
Role functioning	262/456	7.4	5.9	0.71 (0.550–0.904)	0.0059
Social functioning	264/472	7.6	6.2	0.70 (0.549–0.897)	0.0048
Appetite loss	251/454	8.3	6.6	0.70 (0.542–0.899)	0.0054
Constipation	225/468	11.1	7.3	0.65 (0.499–0.855)	0.0018
Diarrhea	208/487	14.6	7.7	0.59 (0.442–0.774)	0.0002
Dyspnea	220/442	9.0	7.4	0.75 (0.574–0.989)	0.0406
Fatigue	309/475	5.5	4.3	0.82 (0.653–1.027)	0.0835
Nausea/vomiting	260/488	8.4	6.6	0.80 (0.626–1.027)	0.0809
Pain	250/472	7.8	6.7	0.79 (0.615–1.021)	0.0718
Insomnia	220/435	8.6	7.3	0.75 (0.568–0.980)	0.0349
QLQ-LC13					
Cough	221/459	9.3	7.7	0.78 (0.600–1.026)	0.0747
Dyspnea	284/480	6.5	5.5	0.79 (0.625–1.006)	0.0578
Hemoptysis	165/487	18.3	10.5	0.64 (0.469–0.876)	0.0049
Arm/shoulder pain	224/478	9.9	7.5	0.70 (0.535–0.915)	0.0088
Chest pain	215/478	10.6	7.8	0.76 (0.575–0.996)	0.0464
Other pain	255/466	7.8	6.4	0.72 (0.558–0.923)	0.0096

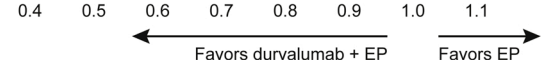

Fig. 2. Time to deterioration in global health status/QoL, functioning, and symptoms.
The analysis population includes patients with baseline scores ≥10 for the QLQ-C30 functional scales and global health status/QoL and patients with baseline scores ≤90 for the QLQ-C30 and QLQ-LC13 symptom scales/items. An HR < 1.0 indicates longer TTD with durvalumab plus EP versus EP alone. CI, confidence interval; EP, platinum-etoposide; HR, hazard ratio; OS, overall survival; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer 13; QoL, quality of life; TTD, time to deterioration.

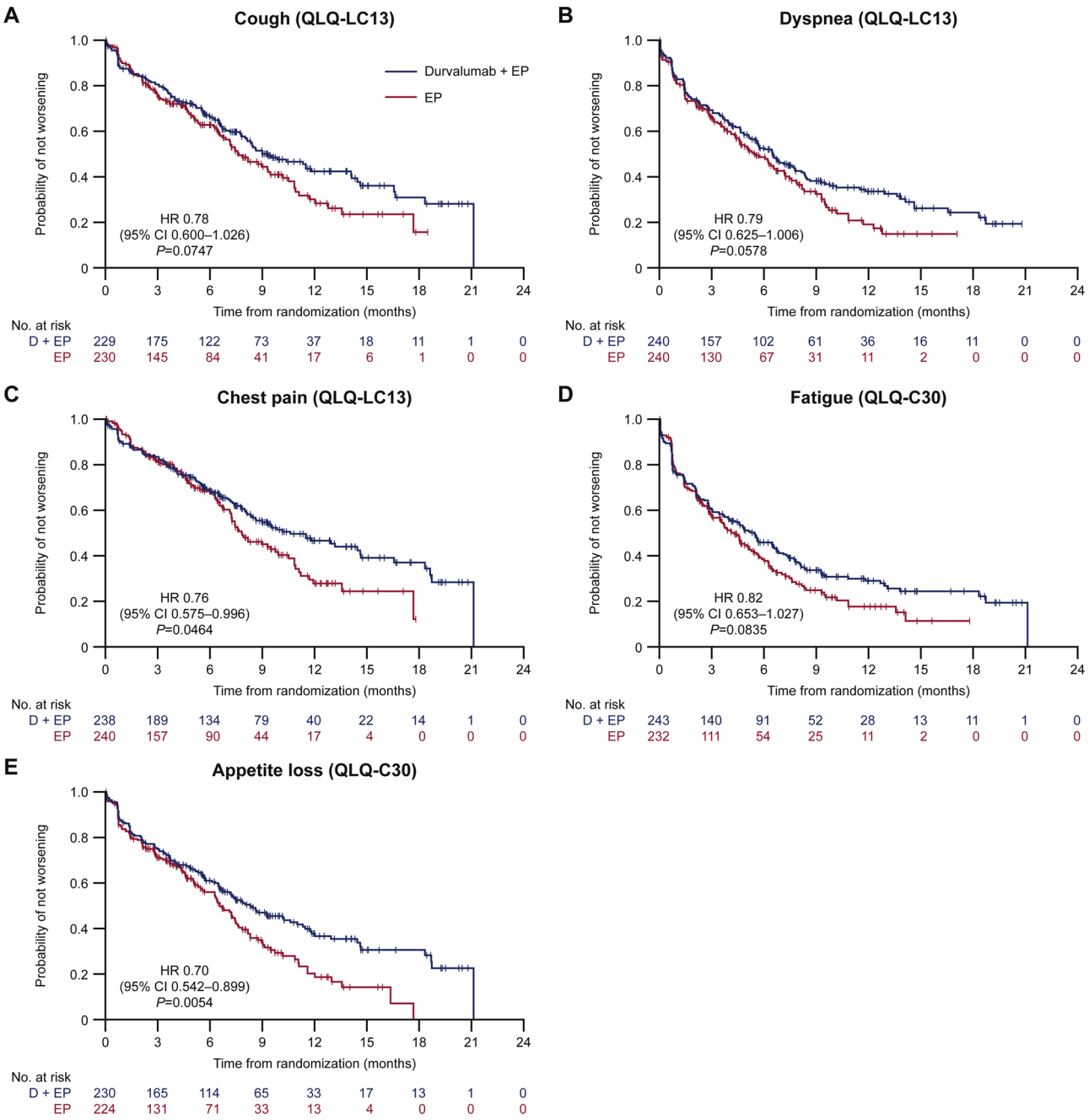

Fig. 3. Kaplan-Meier analysis of time to deterioration in prespecified key disease-related symptoms of (A) cough, (B) dyspnea, (C) chest pain, (D) fatigue, and (E) appetite loss.
The analysis population includes patients with baseline scores ≥10 for the QLQ-C30 functional scales and global health status/QoL and patients with baseline scores ≤90 for the QLQ-C30 and QLQ-LC13 symptom scales/items. An HR < 1.0 indicates longer TTD with durvalumab plus EP versus EP alone. *p*-values presented are nominal. CI, confidence interval; D, durvalumab; EP, platinum-etoposide; HR, hazard ratio; ITT, intention-to-treat; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer 13.

endpoints of PFS and objective response rate. Safety findings were consistent with the established safety profiles of both durvalumab and EP, and most immune-mediated adverse events (AEs) were low grade and manageable with standard treatment guidelines. In addition to efficacy, symptom control is an important element of therapeutic objectives in advanced lung cancer, where life expectancy is generally limited with potentially high symptom burden and low QoL [18]. We evaluated patient-reported symptoms, function, and HRQoL in the CASPIAN study to understand the impact of the disease and treatment from the patient perspective and ensure that clinical benefits do not come at the cost of impaired QoL.

In the CASPIAN study, the PRO results demonstrated that durvalumab plus EP maintained QoL while significantly improving OS in ES-SCLC. The MMRM analysis showed that patients treated with both durvalumab plus EP and EP alone experienced a numerically reduced symptom burden over a period of 12 months or until disease progression for the key disease-related symptoms of cough, dyspnea, chest pain, fatigue, and appetite loss. There was a statistically significant difference between arms in favor of durvalumab plus EP for the improvements from baseline in appetite loss, which may reflect improved tumor control without substantially increased toxicity. Consistent with efficacy outcomes, durvalumab plus EP delayed worsening of patient-reported

symptoms (including the five prespecified key disease-related symptoms), as well as all five patient functioning domains, and global health status/QoL, compared with EP.

The prolonged TTD observed with the addition of durvalumab to EP may reflect the longer OS, PFS, and duration of response observed in this arm in CASPIAN [8]. Similar to PFS, the TTD Kaplan-Meier curves separated between 4 cycles and 6 cycles across many PRO domains. This is consistent with the immediate expected effects of chemotherapy and the likely prolonged effects of immunotherapy on PROs. PROs were also collected beyond initial progression, up to second disease progression, to better characterize patient experience over a longer period. The TTD results suggest that treatment benefit with durvalumab plus EP compared to EP alone may be sustained beyond initial disease progression.

The analysis of changes from baseline in key disease-related symptoms showed an improvement in symptoms over time in both arms, but the effect was modest. This may be because patients enrolled in CASPIAN had a relatively good performance status (WHO performance status score of 0 or 1 was an eligibility criterion). Further, interpretation of the MMRM analysis of change from baseline was limited as the analysis model only accounted for data until initial disease progression, which occurred at ~5 months for over half of the patients.

In CASPIAN, PRO analyses were focused primarily on lung cancer symptoms, whereas investigator-assessed AEs were largely driven by treatment-related side-effects, so a direct relationship between PROs and safety is not necessarily anticipated. However, PROs complement physician-reporting of safety to better characterize treatment tolerability and its impact on QoL [19]. Safety data from CASPIAN showed the incidences of any AEs, grade 3 or 4 AEs, AEs leading to discontinuation, and AEs leading to death were similar across both treatment arms; the most common AEs were hematological toxicities associated with chemotherapy [8]. The incidence of serious AEs was slightly higher in the EP arm (36% of patients) compared with the durvalumab plus EP arm (31% of patients), possibly due to the increased number of cycles of EP received in the control arm. The type, incidence, and severity of AEs reported were consistent with the known safety profiles of both durvalumab and EP. As expected, immune-mediated AEs were more frequent in the durvalumab plus EP arm. However, the mainly low grade and manageable nature of these events, which were predominantly endocrine in nature, did not appear to have a clinically meaningful impact on PROs.

Despite the substantial symptom burden and poor outcomes associated with SCLC, the literature reporting PROs in this population is sparse [13]. To our knowledge, the IMpower133 study is the only other randomized study of immunotherapy targeting the PD-1/PD-L1 pathway for the treatment of patients with ES-SCLC from which PRO data are available [20]. Results of this double-blind, placebo-controlled study showed no increase in symptom burden with atezolizumab added to carboplatin-etoposide compared with placebo plus carboplatin-etoposide in patients with ES-SCLC. With the exception of dyspnea, improvements in TTD of lung cancer symptoms were not observed with the addition of atezolizumab [20]. Differences from CASPIAN in the study design, treatment, and schedule of PRO assessments should be considered when interpreting these results.

Potential limitations of the PRO analyses presented here include the open-label trial design, which could lead to reporting bias. However, symptoms and certain domains such as physical functioning that are directly impacted by disease physiology and treatment are likely to be less subject to open-label bias compared with domains such as emotional functioning that could be influenced by additional factors such as socioeconomic [21]. The PRO results are supported by other objective measures of efficacy, including the superior OS observed with durvalumab plus EP versus EP. The robustness of the findings is demonstrated by the consistent benefit observed in TTD with durvalumab plus EP versus EP across all symptoms and functioning domains.

Interpretation of the CASPIAN PROs data may also be limited by the divergence in compliance rates between the treatment arms. The sample size in the EP arm was markedly lower than that in the durvalumab plus EP arm from approximately week 24 onwards, and it is possible this indicates data are not missing at random. Reduced compliance in the EP arm is unsurprising due to the shorter duration of treatment in the EP arm compared with the durvalumab plus EP arm, in which patients received maintenance durvalumab post-EP. Following completion of study treatment, patients may have had a reduced level of engagement with study procedures and been less motivated to complete questionnaires. It is possible that the smaller amount of PRO data from the EP arm would bias the results in favor of the EP arm, if non-compliance was associated with declining function or increased symptom burden. Conversely, the larger amount of missing data on the EP arm could result in an opposite bias owing to under-representation of the EP arm during the later visits where scores are improved.

Other limitations include a potential confounding effect of PCI, which was permitted only in the control arm. A prior phase III trial showed a short-term negative impact of PCI on selected HRQOL scales in patients with ES-SCLC [22]. However, as only 8% of patients in the EP arm in CASPIAN received PCI [8], any effect is likely to have been minimal. Finally, the EORTC QLQ-C30 and QLQ-LC13 questionnaires were designed in the era of chemotherapy and, although they have since been used in many clinical trials of immunotherapy in lung cancer, certain side effects of modern-day immunotherapy are not covered by them. They are, however, the most frequently used instruments in lung cancer research and have been extensively tested and validated [23].

In conclusion, the addition of durvalumab to EP in the CASPIAN trial appeared to have no additional detrimental impact on PROs. First-line durvalumab plus EP provided a meaningful patient-centered benefit by significantly prolonging survival in patients with ES-SCLC, while preserving their QoL and delaying worsening of patient-reported symptoms, functioning, and HRQoL compared with EP.

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CRediT authorship contribution statement

Jonathan W. Goldman: Investigation, Writing - review & editing. **Marina Chiara Garassino:** Investigation, Writing - review & editing. **Yuanbin Chen:** Investigation, Writing - review & editing. **Mustafa Özgüroğlu:** Investigation, Writing - review & editing. **Mikhail Dvorkin:** Investigation, Writing - review & editing. **Dmytro Trukhin:** Investigation, Writing - review & editing. **Galina Statsenko:** Investigation, Writing - review & editing. **Katsuyuki Hotta:** Investigation, Writing - review & editing. **Jun Ho Ji:** Investigation, Writing - review & editing. **Maximilian J. Hochmair:** Investigation, Writing - review & editing. **Oleksandr Voitko:** Investigation, Writing - review & editing. **Libor Havel:** Investigation, Writing - review & editing. **Artem Poltoratskiy:** Investigation, Writing - review & editing. **György Losonczy:** Investigation, Writing - review & editing. **Niels Reinmuth:** Investigation, Writing - review & editing. **Nikunj Patel:** Conceptualization, Methodology, Investigation, Writing - review & editing. **Peter J. Laud:** Formal analysis, Writing - review & editing. **Norah Shire:** Conceptualization, Methodology, Investigation, Writing - review & editing. **Haiyi Jiang:** Conceptualization, Methodology, Investigation, Writing - review & editing. **Luis Paz-Ares:** Conceptualization, Methodology, Investigation, Writing - review & editing.

Declaration of Competing Interest

Dr Goldman reports grants and personal fees from AstraZeneca during the conduct of the study; and grants and personal fees from Genentech outside the submitted work. Dr Garassino reports grants and personal fees from Eli Lilly, Otsuka Pharmaceutical, AstraZeneca,

Novartis, Bristol-Myers Squibb, Roche, Pfizer, Celgene, Incyte, Bayer, Merck Sharp and Dohme, GlaxoSmithKline, Spectrum Pharmaceuticals, and Blueprint Medicines; personal fees from Boehringer Ingelheim, Inivata, Takeda, Sanofi, Seattle Genetics, Daiichi-Sankyo, and Janssen; grants from Tiziana Life Sciences, Clovis, Merck Serono, United Therapeutics Corporation, Merck KGaA, Turning Point Therapeutics, Ipsen, and Exelisis; and non-financial support from Merck Sharp and Dohme, Pfizer, and Eli Lilly, all outside the submitted work. Dr Chen reports personal fees from AstraZeneca, Genentech, Bristol-Myers Squibb, Merck, Novartis, Takeda, Eli Lilly, Guardant Health, Pfizer, and Array Biopharma; and grants from AstraZeneca, Ipsen, Roche, and Bristol-Myers Squibb, all outside the submitted work. Dr Özgüroğlu reports advisory board participation for Janssen, Sanofi, and Astellas; honoraria from Novartis, Roche, Janssen, Sanofi, and Astellas; and travel, accommodation, or expenses from Bristol-Myers Squibb and Janssen. Dr Hotta reports grants and personal fees from AstraZeneca during the conduct of the study; grants and personal fees from Lilly and Bristol-Myers Squibb outside the submitted work; and personal fees from Merck Sharp and Dohme, Ono, Nipponkayaku, Taiho, Boehringer Ingelheim, and Chugai outside the submitted work. Dr Reinmuth reports personal fees and non-financial support from AstraZeneca, Boehringer Ingelheim, Hoffmann La-Roche, Bristol-Myers Squibb, and Pfizer; non-financial support from AbbVie; and personal fees from Merck Sharp and Dohme and Takeda, all outside the submitted work. Drs Patel, Shire, and Jiang are full-time employees of and own stock in AstraZeneca. Mr Laud is contracted to AstraZeneca from the Statistical Services Unit at the University of Sheffield, UK, which received funding from AstraZeneca. Dr Paz-Ares reports leadership with Genomica and Altum Sequencing; travel, accommodation, or expenses from Roche, AstraZeneca, AstraZeneca Spain, Merck Sharp and Dohme, Bristol-Myers Squibb, Lilly, and Pfizer; honoraria from Roche/Genentech, Lilly, Pfizer, Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp and Dohme, AstraZeneca, Merck Serono, PharmaMar, Novartis, Celgene, Sysmex, Bayer, Amgen, Blueprint Medicines, and Incyte; and fees (immediate family member) from Novartis, Ipsen, Pfizer, Servier, Sanofi, Roche, Amgen, and Merck, all outside the submitted work. Drs Dvorkin, Trukhin, Statsenko, Ji, Hochmair, Voitko, Havel, Poltoratskiy, and Losonczy declare no conflicts of interest.

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Appendix A. Supplementary data

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References

[1] B. Oronsky, T.R. Reid, A. Oronsky, C.A. Carter, What's new in SCLC? A review, Neoplasia 19 (2017) 842–847.
[2] S. Wang, J. Tang, T. Sun, et al., Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages, Sci Rep. 7 (2017) 1339.
[3] L.A. Byers, C.M. Rudin, Small cell lung cancer: where do we go from here? Cancer 121 (2015) 664–672.
[4] M. Früh, D. De Ruysscher, S. Popat, L. Crinò, S. Peters, E. Felip, Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann Oncol. 24 (suppl. 6) (2013) vi99–vi105.
[5] C.M. Rudin, N. Ismaila, C.L. Hann, et al., Treatment of small-cell lung cancer: American Society of Clinical Oncology endorsement of the American College of Chest Physicians guideline, J Clin Oncol. 33 (2015) 4106–4111.
[6] M.C. Pietanza, L.A. Byers, J.D. Minna, C.M. Rudin, Small cell lung cancer: will recent progress lead to improved outcomes? Clin Cancer Res. 21 (2015) 2244–2255.
[7] L. Horn, A.S. Mansfield, A. Szczęsna, L. Havel, M. Krzakowski, M.J. Hochmair, on behalf of the IMpower133 Study Group, et al., First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer, N Engl J Med. 379 (2018) 2220–2229.
[8] L. Paz-Ares, M. Dvorkin, Y. Chen, N. Reinmuth, K. Hotta, D. Trukhin, on behalf of the CASPIAN investigators, et al., Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial, Lancet 394 (2019) 1929–1939.
[9] R. Stewart, M. Morrow, S.A. Hammond, K. Mulgrew, D. Marcus, E. Poon, et al., Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody, Cancer Immunol Res. 3 (2015) 1052–1062.
[10] L. Paz-Ares, M. Dvorkin, Y. Chen, N. Reinmuth, K. Hotta, D. Trukhin, et al., Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): Updated results from the phase III CASPIAN study, J Clin Oncol 38 (15_suppl) (2020) (abstr. 9002).
[11] A. Rydén, S. Ollis, E. Love, A.L. Shields, H. Jiang, P. Dennis, Understanding the patient perspective of small cell lung cancer (SCLC), J Thorac Oncol. 13 (4S) (2018) S1–S139.
[12] N.W. Scott, P.M. Fayers, N.K. Aaronson, A. Bottomley, A. de Graeff, M. Groenvold, on behalf of the EORTC Quality of Life Group, et al., EORTC QLQ-C30 reference values manual, 2nd edn, EORTC Quality of Life Group, Brussels, Belgium, 2008. Available at: https://www.eortc.org/app/uploads/sites/2/2018/02/reference_values_manual2008.pdf (last accessed July 15, 2020).
[13] B.M. Bennett, J.R. Wells, C. Panter, Y. Yuan, J.R. Penrod, The humanistic burden of small cell lung cancer (SCLC): a systematic review of health-related quality of life (HRQoL) literature, Front Pharmacol. 8 (2017) 339.
[14] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur J Cancer. 45 (2009) 228–247.
[15] N.K. Aaronson, S. Ahmedzai, B. Bergman, M. Bullinger, A. Cull, N.J. Duez, et al., The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology, J Natl Cancer Inst. 85 (1993) 365–376.
[16] B. Bergman, N.K. Aaronson, S. Ahmedzai, S. Kaasa, M. Sullivan, The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life, Eur J Cancer. 30A (1994) 635–642.
[17] D. Osoba, G. Rodrigues, J. Myles, B. Zee, J. Pater, Interpreting the significance of changes in health-related quality-of-life scores, J Clin Oncol. 16 (1998) 139–144.
[18] M.J. Simoff, B. Lally, M.G. Slade, W.G. Goldberg, P. Lee, G.C. Michaud, et al., Symptom management in patients with lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines, Chest 143 (5 suppl) (2013) e455S–e497S.
[19] P.G. Kluetz, B. Kanapuru, S. Lemery, L.L. Johnson, M.H. Fiero, K. Arscott, et al., Informing the tolerability of cancer treatments using patient-reported outcome measures: summary of an FDA and Critical Path Institute workshop, Value Health 21 (2018) 742–747.
[20] A.S. Mansfield, A. Każarnowicz, N. Karaseva, et al., Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small-cell lung cancer (IMpower133): a randomized phase I/III trial, Ann Oncol. 31 (2020) 310–317.
[21] J.K. Roydhouse, M.H. Fiero, P.G. Kluetz, Investigating potential bias in patient-reported outcomes in open-label cancer trials, JAMA Oncol. 5 (2019) 457–458.
[22] B.J. Slotman, M.E. Mauer, A. Bottomley, et al., Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups, J Clin Oncol. 27 (2009) 78–84.
[23] Y.B. Bouazza, I. Chiairi, O. El Kharbouchi, et al., Patient-reported outcome measures (PROMs) in the management of lung cancer: a systematic review, Lung Cancer 113 (2017) 140–151.