



# 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

Luis Paz-Ares, Mikhail Dvorkin, Yuanbin Chen, Niels Reinmuth, Katsuyuki Hotta, Dmytro Trukhin, Galina Statsenko, Maximilian J Hochmair, Mustafa Özgüroğlu, Jun Ho Ji, Oleksandr Voitko, Artem Poltoratskiy, Santiago Ponce, Francesco Verderame, Libor Havel, Igor Bondarenko, Andrzej Kazarnowicz, György Losonczy, Nikolay V Conev, Jon Armstrong, Natalie Byrne, Norah Shire, Haiyi Jiang, Jonathan W Goldman, for the CASPIAN investigators\*

## Summary

**Background** Most patients with small-cell lung cancer (SCLC) have extensive-stage disease at presentation, and prognosis remains poor. Recently, immunotherapy has demonstrated clinical activity in extensive-stage SCLC (ES-SCLC). The CASPIAN trial assessed durvalumab, with or without tremelimumab, in combination with etoposide plus either cisplatin or carboplatin (platinum–etoposide) in treatment-naïve patients with ES-SCLC.

**Methods** This randomised, open-label, phase 3 trial was done at 209 sites across 23 countries. Eligible patients were adults with untreated ES-SCLC, with WHO performance status 0 or 1 and measurable disease as per Response Evaluation Criteria in Solid Tumors, version 1.1. Patients were randomly assigned (in a 1:1:1 ratio) to durvalumab plus platinum–etoposide; durvalumab plus tremelimumab plus platinum–etoposide; or platinum–etoposide alone. All drugs were administered intravenously. Platinum–etoposide consisted of etoposide 80–100 mg/m<sup>2</sup> on days 1–3 of each cycle with investigator's choice of either carboplatin area under the curve 5–6 mg/mL per min or cisplatin 75–80 mg/m<sup>2</sup> (administered on day 1 of each cycle). Patients received up to four cycles of platinum–etoposide plus durvalumab 1500 mg with or without tremelimumab 75 mg every 3 weeks followed by maintenance durvalumab 1500 mg every 4 weeks in the immunotherapy groups and up to six cycles of platinum–etoposide every 3 weeks plus prophylactic cranial irradiation (investigator's discretion) in the platinum–etoposide group. The primary endpoint was overall survival in the intention-to-treat population. We report results for the durvalumab plus platinum–etoposide group versus the platinum–etoposide group from a planned interim analysis. Safety was assessed in all patients who received at least one dose of their assigned study treatment. This study is registered at ClinicalTrials.gov, NCT03043872, and is ongoing.

**Findings** Patients were enrolled between March 27, 2017, and May 29, 2018. 268 patients were allocated to the durvalumab plus platinum–etoposide group and 269 to the platinum–etoposide group. Durvalumab plus platinum–etoposide was associated with a significant improvement in overall survival, with a hazard ratio of 0.73 (95% CI 0.59–0.91;  $p=0.0047$ ); median overall survival was 13.0 months (95% CI 11.5–14.8) in the durvalumab plus platinum–etoposide group versus 10.3 months (9.3–11.2) in the platinum–etoposide group, with 34% (26.9–41.0) versus 25% (18.4–31.6) of patients alive at 18 months. Any-cause adverse events of grade 3 or 4 occurred in 163 (62%) of 265 treated patients in the durvalumab plus platinum–etoposide group and 166 (62%) of 266 in the platinum–etoposide group; adverse events leading to death occurred in 13 (5%) and 15 (6%) patients.

**Interpretation** First-line durvalumab plus platinum–etoposide significantly improved overall survival in patients with ES-SCLC versus a clinically relevant control group. Safety findings were consistent with the known safety profiles of all drugs received.

**Funding** AstraZeneca.

**Copyright** © 2019 Elsevier Ltd. All rights reserved.

## Introduction

Small-cell lung cancer (SCLC) accounts for 13–17% of all diagnosed cases of lung cancer and is characterised by rapid proliferation, high growth fraction, and early development of widespread metastases.<sup>1,2</sup> Less than 7% of patients with SCLC remain alive at 5 years after

diagnosis.<sup>2,3</sup> Extensive-stage SCLC (ES-SCLC) accounts for about two-thirds of all cases of SCLC.<sup>1</sup> For more than three decades, the standard first-line treatment has consisted of etoposide plus either cisplatin or carboplatin (platinum–etoposide), with few alternatives.<sup>4–7</sup> Despite initial response rates of up to 78% for patients treated

**Lancet 2019; 394: 1929–39**

Published Online  
October 4, 2019  
[https://doi.org/10.1016/S0140-6736\(19\)32222-6](https://doi.org/10.1016/S0140-6736(19)32222-6)

See **Editorial** page 1880

See **Comment** page 1884

\*A complete list of investigators who enrolled patients in CASPIAN is provided in the appendix (pp 2–3)

Department of Medical Oncology, Hospital Universitario 12 de Octubre, H120-CNIO Lung Cancer Unit, Universidad Complutense and Ciberonc, Madrid, Spain (Prof L Paz-Ares MD, S Ponce MD); BHI of Omsk Region Clinical Oncology Dispensary, Omsk, Russia (M Dvorkin MD); Cancer and Hematology Centers of Western Michigan, Grand Rapids, MI, USA (Y Chen MD); Asklepios Lung Clinic, Munich-Gauting, Germany (N Reinmuth MD); Okayama University Hospital, Okayama, Japan (Prof K Hotta MD); Odessa National Medical University, Odessa, Ukraine (D Trukhin MD); Omsk Regional Cancer Center, Omsk, Russia (G Statsenko MD); Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Krankenhaus Nord, Vienna, Austria (M J Hochmair MD); Istanbul University–Cerrahpaşa, Cerrahpaşa School of Medicine, Istanbul, Turkey (Prof M Özgüroğlu MD); Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, South Korea (J H Ji MD); Kyiv City Clinical Oncological Centre, Kiev, Ukraine (O Voitko MD); Petrov Research Institute of Oncology, St Petersburg, Russia (A Poltoratskiy MD);

AO Ospedali Riuniti PO  
Vincenzo Cervello, Palermo,  
Italy (F Verderame MD);  
Thomayer Hospital,  
First Faculty of Medicine,  
Charles University, Prague,  
Czechia (L Havel MD);  
Dnipropetrovsk Medical  
Academy, Dnipro, Ukraine  
(Prof I Bondarenko MD);  
Tuberculosis and Lung Disease  
Hospital, Olsztyn, Poland  
(A Kazarnowicz MD);  
Semmelweis University,  
Budapest, Hungary  
(Prof G Losonczy MD); Clinic of  
Medical Oncology, UMHAT  
St Marina, Varna, Bulgaria  
(N V Conev MD); AstraZeneca,  
Cambridge, UK  
(J Armstrong MSc, N Byrne BSc);  
AstraZeneca, Gaithersburg,  
MD, USA (N Shire PhD,  
H Jiang MD); and David Geffen  
School of Medicine at UCLA,  
Los Angeles, CA, USA  
(J W Goldman MD)

Correspondence to:  
Prof Luis Paz-Ares, Department  
of Medical Oncology, Hospital  
Universitario 12 de Octubre,  
Madrid 28041, Spain  
lpazares@seom.org

See Online for appendix

## Research in context

### Evidence before this study

We searched PubMed on July 8, 2019, for clinical trials published in English with the terms “PD-1” OR “PD-L1” OR “pembrolizumab” OR “nivolumab” OR “atezolizumab” OR “durvalumab” OR “avelumab” AND “extensive-disease” OR “extensive-stage” AND “first-line” OR “previously untreated” OR “treatment-naïve” AND “small-cell lung cancer” OR “SCLC”, selecting relevant publications published within the past 5 years (Jan 1, 2014, to July 8, 2019). We also searched the abstracts from the 2018 and 2019 American Society of Clinical Oncology Annual Meetings, the 2018 European Society for Medical Oncology Congress, and the 2018 World Conference on Lung Cancer using the same search terms. We identified one study of atezolizumab plus carboplatin-etoposide (IMpower133), which indicated the therapeutic value of immunotherapy targeting the programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) pathway to treat patients with extensive-stage small-cell lung cancer (ES-SCLC) in the first-line setting.

### Added value of this study

The phase 3, randomised, open-label CASPIAN study showed a statistically significant improvement in overall survival (primary study endpoint) with first-line durvalumab and etoposide plus

either cisplatin or carboplatin (platinum-etoposide) versus platinum-etoposide alone in patients with ES-SCLC at a planned interim analysis. To our knowledge, this is the first phase 3 study of anti-PD-1 or anti-PD-L1 in patients with ES-SCLC that permitted the use of investigator's choice of either cisplatin or carboplatin as the platinum component in platinum-etoposide and that allowed up to six cycles of platinum-etoposide (consistent with routine clinical practice) in the control group, compared with four cycles in the durvalumab plus platinum-etoposide group.

### Implications of all the available evidence

In CASPIAN, the addition of durvalumab to platinum-etoposide as first-line treatment for patients with ES-SCLC resulted in consistent and durable clinical benefit across overall survival, progression-free survival, and objective response, compared with a clinically relevant control group that is reflective of current global clinical practice for this challenging-to-treat disease. Our results align with those from the IMpower133 trial of atezolizumab plus carboplatin-etoposide, while providing significant progress in offering the flexibility of platinum choice in combination with immunotherapy, expanding treatment options for patients and physicians.

with platinum-etoposide,<sup>8,9</sup> most patients relapse within 6 months of completing initial treatment and median overall survival is about 10 months.<sup>4,8,10</sup> Outside of Japan, the current standard-of-care treatment in the second-line setting is topotecan,<sup>5,6</sup> which is associated with poor outcomes (response rates of 5% and a 1-year survival rate of 9% in patients with platinum-refractory disease),<sup>11</sup> emphasising the significant unmet need for improved first-line therapies.

Immunotherapy targeting the programmed cell death 1 (PD-1, also known as PDCD1) and programmed cell death ligand 1 (PD-L1, also known as CD274) pathway has demonstrated clinical activity for patients with ES-SCLC, including as first-line treatment.<sup>12</sup> Durvalumab, a selective, high-affinity human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80,<sup>13</sup> is indicated for the treatment of patients with unresectable, stage 3 non-small-cell lung cancer following platinum-based chemoradiotherapy.<sup>14–17</sup> In early-phase clinical trials, durvalumab, both as monotherapy and in combination with the anti-cytotoxic T lymphocyte-associated antigen-4 antibody, tremelimumab, showed durable clinical activity and a manageable safety profile in patients with pretreated ES-SCLC, including those with relapsed or refractory disease.<sup>18–20</sup>

In CASPIAN, we assessed the efficacy and safety of durvalumab, with or without tremelimumab, in combination with platinum-etoposide for the first-line treatment of patients with ES-SCLC. We report results from a planned interim analysis of overall survival for

durvalumab plus platinum-etoposide versus platinum-etoposide alone; the durvalumab plus tremelimumab plus platinum-etoposide versus platinum-etoposide alone comparison is proceeding to final analysis.

## Methods

### Study design

This randomised, open-label, sponsor-blind, phase 3 trial was performed at 209 sites in 23 countries across Europe, Asia, North America, and South America. The study was done 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.

### Patients

Eligible patients were aged at least 18 years (20 years in Japan) with treatment-naïve histologically or cytologically documented ES-SCLC (American Joint Committee on Cancer, 7th edition, stage IV [T any, N any, M1a or M1b], or T3–4 due to multiple lung nodules that are too extensive or tumour or nodal volume that is too large to be encompassed in a tolerable radiation plan). Other eligibility criteria were a WHO performance status score of 0 or 1; measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; life expectancy of at least 12 weeks from the

study start; bodyweight of at least 30 kg; suitability for first-line platinum-based chemotherapy; adequate organ and marrow function; and negative pregnancy test for pre-menopausal women. Patients with brain metastases were eligible provided they were asymptomatic or treated and stable off steroids and anticonvulsants for at least 1 month before study entry.

Key exclusion criteria were history of radiotherapy to the chest or planned consolidation chest radiotherapy; active or previous autoimmune or inflammatory disorders; paraneoplastic syndrome of autoimmune nature requiring systemic treatment; history of active primary immunodeficiency; and uncontrolled, concurrent illness or active infections. Complete eligibility criteria are in the appendix (pp 6–10). All patients provided written informed consent for participation.

### Randomisation and masking

Patients were randomly assigned using an interactive voice-response or web-response system in a 1:1:1 ratio to receive durvalumab plus platinum–etoposide, durvalumab plus tremelimumab plus platinum–etoposide, or platinum–etoposide alone (appendix p 4). Randomisation was stratified according to planned platinum (carboplatin or cisplatin). Treatment was allocated in blocks of six in each stratum via a schedule generated by Parexel (Waltham, MA, USA) who used a computerised randomised list generator. The study was open-label and allocation was unmasked to investigators and patients. However, the sponsor was masked to all aggregated efficacy and safety data.

### Procedures

All drugs were administered intravenously. Across all three study groups, chemotherapy consisted of etoposide 80–100 mg/m<sup>2</sup> (administered on days 1–3 of each 21-day cycle), with investigator's choice of either carboplatin area under the curve 5–6 mg/mL per min or cisplatin 75–80 mg/m<sup>2</sup> (administered on day 1 of each cycle). Patients in the immunotherapy groups received up to four cycles of platinum–etoposide plus durvalumab 1500 mg with or without tremelimumab 75 mg every 3 weeks followed by maintenance durvalumab 1500 mg every 4 weeks. Patients in the platinum–etoposide group could receive an additional two cycles of platinum–etoposide (up to six cycles total) and prophylactic cranial irradiation (PCI) after chemotherapy at the investigator's discretion. Patients continued treatment until disease progression per investigator assessment, unacceptable toxicity, or other discontinuation criteria were met. Continuation of study treatment after disease progression was permitted if there was evidence of clinical benefit (appendix p 4). In-study crossover from the platinum–etoposide to the immunotherapy plus platinum–etoposide groups was not allowed.

Tumour imaging was performed every 6 weeks for the first 12 weeks, and every 8 weeks thereafter, until confirmed objective disease progression. Survival was

assessed every 2 months after treatment discontinuation. Adverse events were graded according to National Cancer Institute common terminology criteria for adverse events, version 4.03.

### Outcomes

The primary endpoint was overall survival (time from randomisation to death from any cause). Secondary endpoints were progression-free survival (time from randomisation to the date of objective disease progression or death from any cause in the absence of progression); objective response (unconfirmed; proportion of patients with a complete response or partial response on at least one visit); overall survival at 18 months, progression-free survival at 6 and 12 months, and safety. Progression-free survival and objective response were investigator-assessed according to RECIST, version 1.1. Other prespecified secondary endpoints were pharmacokinetics, immunogenicity, and symptoms and health-related quality of life assessments; these will be reported elsewhere. Although confirmation of objective response was not protocol defined, post-hoc analysis of confirmed objective response is also reported here in the interest of scientific rigor and to mitigate against the potential for bias. For confirmed responses, a confirmatory scan was required no sooner than 4 weeks after the initial complete or partial response. Duration of (confirmed) response and overall survival at 12 months were also analysed post hoc.

### Statistical analysis

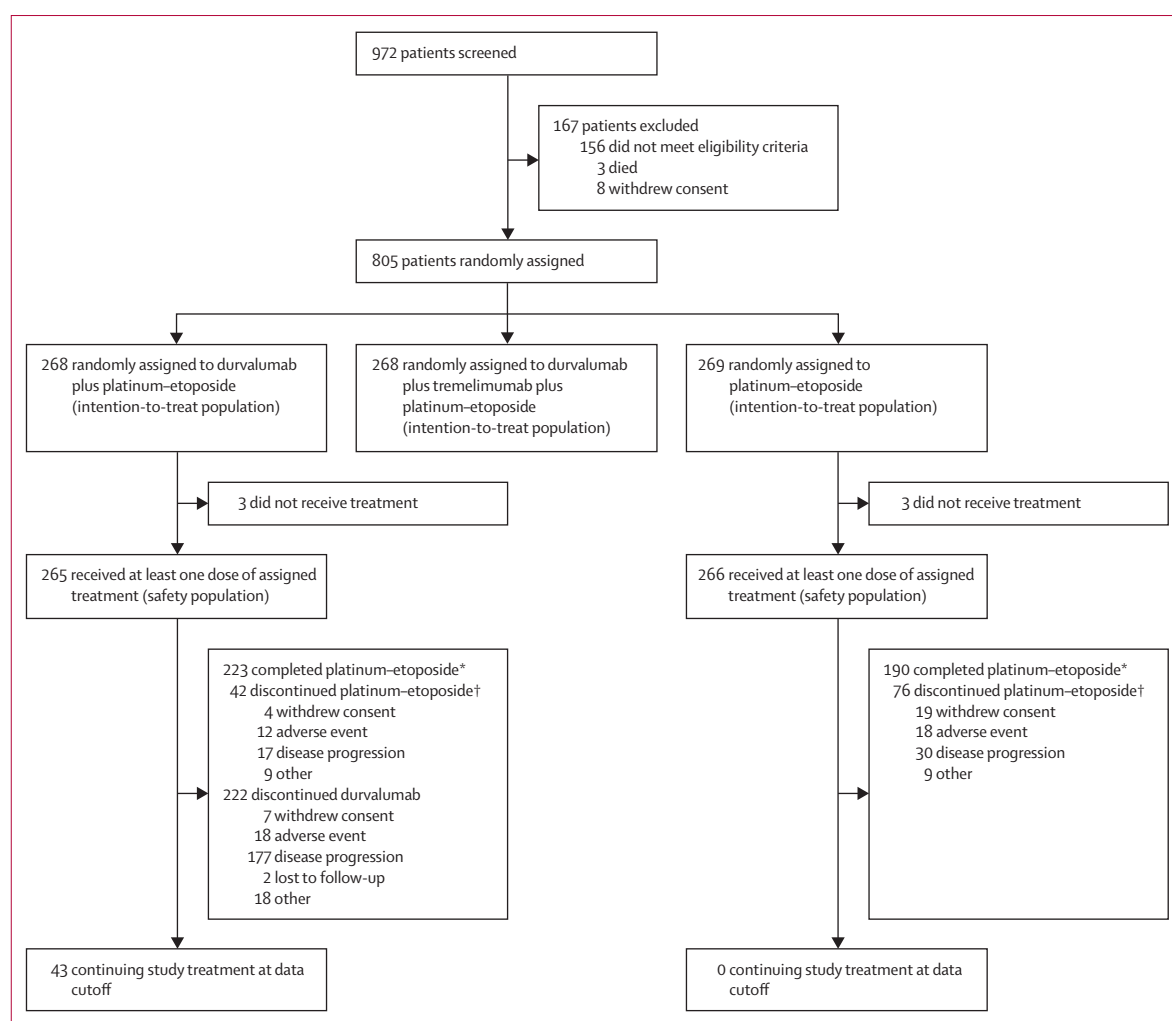
About 795 patients were needed for 1:1:1 randomisation to obtain 425 events in the durvalumab plus platinum–etoposide and platinum–etoposide groups combined and 425 events in the durvalumab plus tremelimumab plus platinum–etoposide and platinum–etoposide groups combined (80% maturity) for the final analysis of overall survival. Sample size assumptions are detailed in the appendix (p 11). The interim analysis of overall survival was planned when approximately 318 events had occurred both in the durvalumab plus platinum–etoposide and platinum–etoposide groups combined and in the durvalumab plus tremelimumab plus platinum–etoposide and platinum–etoposide groups combined (60% maturity). Based on an assumed overall survival hazard ratio (HR) of 0.71, we estimated that the trial would have 71% power to demonstrate statistical significance at the interim analysis with a two-sided significance level of 1.43% (for overall  $\alpha$  of 4%) for the comparison of durvalumab plus platinum–etoposide versus platinum–etoposide, although the actual  $\alpha$  spend was to be based on the observed number of events at data cutoff.

The study was considered to be positive if overall survival was significantly longer with either durvalumab plus platinum–etoposide versus platinum–etoposide or durvalumab plus tremelimumab plus platinum–etoposide versus platinum–etoposide. To control the type I error at

5% (two-sided), a hierarchical multiple-testing procedure with a gatekeeping strategy was used across the primary overall survival analyses and secondary progression-free survival analyses (appendix p 5). 4%  $\alpha$  was allocated to overall survival for durvalumab plus platinum–etoposide versus platinum–etoposide and 1%  $\alpha$  was allocated to overall survival for durvalumab plus tremelimumab plus platinum–etoposide versus platinum–etoposide. Progression-free survival was only to be formally tested within the multiple testing procedure if both overall survival primary analyses were significant.

Overall survival and progression-free survival were analysed using a stratified log-rank test adjusting for planned platinum (carboplatin or cisplatin), with HRs and 95% CIs estimated using a Cox proportional hazards model. The Kaplan-Meier method was used to estimate overall survival, progression-free survival, and duration of

response. A prespecified subgroup analysis of overall survival was done to establish the consistency of the treatment effect according to predefined baseline characteristics of planned platinum (carboplatin vs cisplatin), age (<65 years vs  $\geq 65$  years), sex (women vs men), WHO performance status (0 vs 1), smoking status (smoker vs non-smoker), brain or CNS metastases (yes vs no), disease stage at diagnosis (stage III vs stage IV), race (Asian vs non-Asian), and region (Asia vs Europe vs North and South America). HRs and 95% CIs for patient subgroups were calculated using an unstratified Cox proportional hazards model with treatment as the only covariate. Sensitivity analyses for overall survival included assessment of the effect of additional predefined covariates (the same as those included in the subgroup analysis) on the HR estimate. A further sensitivity analysis of overall survival was done to examine the censoring patterns to



**Figure 1: Trial profile**

Data cutoff was March 11, 2019. Platinum–etoposide=etoposide plus either cisplatin or carboplatin. \*Patients who completed platinum–etoposide reported the maximum cycle of chemotherapy reached for any platinum–etoposide component on the electronic case report form. †A patient was considered to have discontinued platinum–etoposide when both etoposide and platinum were discontinued; if different reasons for discontinuation were collected, the last discontinuation reason by date was selected.

identify potential attrition bias, using a Kaplan-Meier plot of time to censoring, where the censoring indicator of overall survival was reversed. Odds ratios and 95% CIs for comparing the proportion of patients with an objective response between treatment groups were calculated using a logistic regression model, adjusted for planned platinum. Efficacy data were analysed on an intention-to-treat basis including all randomised patients, regardless of whether they received treatment. All patients who received at least one dose of study treatment were included in safety analyses.

Periodic safety monitoring and interim efficacy assessments were done by an independent data monitoring committee. This trial is registered with ClinicalTrials.gov, NCT03043872, and is ongoing.

### Role of the funding source

The funder of the study participated in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access

to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between March 27, 2017, and May 29, 2018, 972 patients were screened, of whom 167 were excluded and 805 were randomly assigned to durvalumab plus platinum-etoposide (n=268), durvalumab plus tremelimumab plus platinum-etoposide (n=268), and platinum-etoposide alone (n=269; figure 1). At the time of the planned interim overall survival analysis, the independent data monitoring committee recommended that the durvalumab plus platinum-etoposide and platinum-etoposide groups be unmasked to the sponsor because this comparison met the predefined threshold for statistical significance. The durvalumab plus tremelimumab plus platinum-etoposide group had not met the predefined statistical significance threshold at the time of the interim analysis and therefore the sponsor remains masked to this group, which is continuing to the planned final overall survival analysis. Thus, here we report the results of the durvalumab plus platinum-etoposide group and platinum-etoposide group. Important protocol deviations, defined as those that could substantially affect the completeness, accuracy, or reliability of the study data, or a patient's rights, safety, or wellbeing, were reported in 19 (4%) of 537 randomised patients: 11 in the durvalumab plus platinum-etoposide group and eight in the platinum-etoposide group (appendix p 12). Baseline demographics and

	Durvalumab plus platinum-etoposide (n=268)	Platinum-etoposide (n=269)
Median age, years	62 (58–68)	63 (57–68)
Age group, years		
<65	167 (62%)	157 (58%)
≥65	101 (38%)	112 (42%)
Sex		
Men	190 (71%)	184 (68%)
Women	78 (29%)	85 (32%)
Race		
White	229 (85%)	221 (82%)
Asian	36 (13%)	42 (16%)
Black or African American	2 (1%)	3 (1%)
Other or missing	1 (<1%)	3 (1%)
Disease stage		
III	28 (10%)	24 (9%)
IV	240 (90%)	245 (91%)
WHO performance status		
0	99 (37%)	90 (33%)
1	169 (63%)	179 (67%)
Smoking history		
Never smoker	22 (8%)	15 (6%)
Former smoker	126 (47%)	128 (48%)
Current smoker	120 (45%)	126 (47%)
Brain or CNS metastases		
Yes	28 (10%)	27 (10%)
No	240 (90%)	242 (90%)
Liver metastases		
Yes	108 (40%)	104 (39%)
No	160 (60%)	165 (61%)

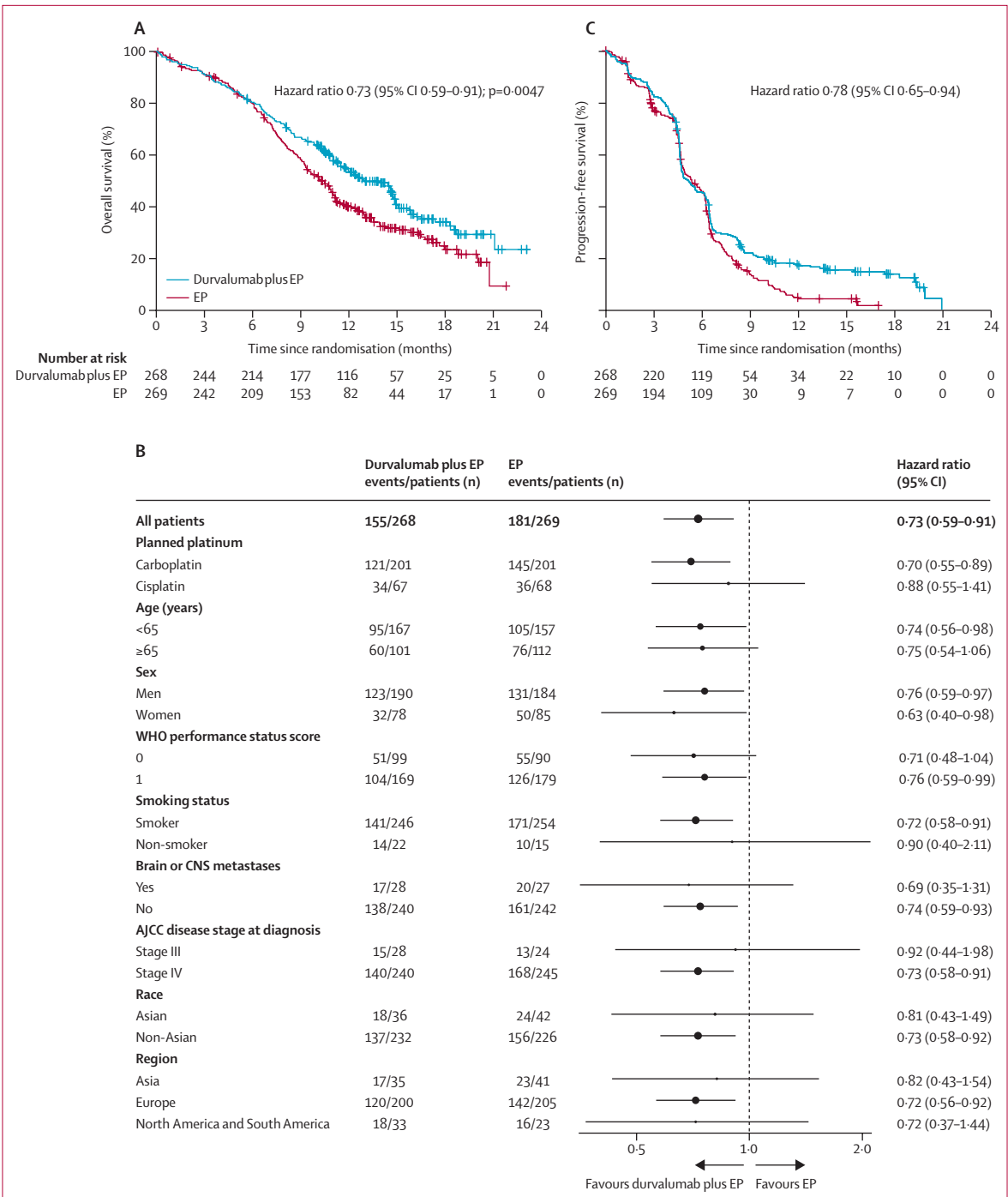
Data are median (IQR) or n (%). Data cutoff was March 11, 2019. Platinum-etoposide=etoposide plus either cisplatin or carboplatin.

**Table 1: Baseline patient demographics and disease characteristics**

	Durvalumab plus platinum-etoposide (n=265)	Platinum-etoposide (n=266)
Median number of durvalumab doses	7 (6–11)	..
Patients receiving 12 or more durvalumab doses	64 (24%)	..
Median total duration of durvalumab, weeks	28.0 (20.0–43.1)	..
Platinum received*		
Carboplatin	208 (78%)	208 (78%)
Cisplatin	65 (25%)	67 (25%)
Median number of cycles of platinum-etoposide†	4 (4–4)	6 (4–6)
Patients receiving four or more cycles of platinum-etoposide†	230 (87%)	225 (85%)
Patients receiving five or more cycles of platinum-etoposide†	3 (1%)	167 (63%)
Patients receiving six cycles of platinum-etoposide†	1 (<1%)	151 (57%)
Median total duration of platinum-etoposide, weeks†	11.9 (11.7–12.9)	18.7 (12.3–20.0)

Platinum-etoposide=etoposide plus either cisplatin or carboplatin. Data are median (IQR) or n (%). Data cutoff was March 11, 2019. \*Patients were allowed to switch between carboplatin and cisplatin at the investigator's discretion. †Based on etoposide exposure.

**Table 2: Treatment exposure (safety population)**



**Figure 2: Overall survival and investigator-assessed progression-free survival in the intention-to-treat population**  
(A) Kaplan-Meier graph of overall survival in the intention-to-treat population. (B) Forest plot of subgroup analysis of overall survival. (C) Kaplan-Meier graph of progression-free survival in the intention-to-treat population. Data cutoff was March 11, 2019. AJCC=American Joint Committee on Cancer. EP=etoposide plus either cisplatin or carboplatin.

disease characteristics were well balanced between the durvalumab plus platinum–etoposide and platinum–etoposide groups (table 1). The median age was 63 years (IQR 57–68) and most patients were men (374 [70%] of 537), current or former smokers (500 [93%]), and had stage IV disease at diagnosis (485 [90%]); at baseline, 55 (10%) patients had brain or CNS metastases and 212 (39%) patients had liver metastases.



Three patients in each group did not receive at least one dose of study treatment. Of the 531 patients who did receive treatment, 416 (78%) received carboplatin and 132 (25%) received cisplatin. In the durvalumab plus platinum–etoposide group, the median number of durvalumab doses received was 7 (IQR 6–11); 64 (24%) of 265 treated patients received 12 or more doses (table 2). In the durvalumab plus platinum–etoposide group, 230 patients (87%) received the planned maximum of four cycles of platinum–etoposide. In the platinum–etoposide group, 225 (85%) of 266 treated patients received at least four cycles of platinum–etoposide, and 151 patients (57%) received the maximum six cycles (table 2). As of March 11, 2019 (data cutoff), 43 patients in the durvalumab plus platinum–etoposide group and none in the platinum–etoposide group remained on study treatment. 113 (42%) of 268 patients in the durvalumab plus platinum–etoposide group and 119 (44%) of 269 in the platinum–etoposide group received at least one subsequent systemic anticancer therapy, with nearly all receiving chemotherapy; a small proportion of patients received subsequent immunotherapy (five [2%] in the durvalumab plus platinum–etoposide group and 14 [5%] in the platinum–etoposide group; appendix p 13). 21 (8%) of 269 patients in the platinum–etoposide group received PCI after chemotherapy.

At data cutoff, the median duration of follow-up for overall survival in censored patients was 14·2 months (IQR 11·7–17·0). There were 336 deaths across the durvalumab plus platinum–etoposide and platinum–etoposide groups (62·6% maturity); 155 (58%) patients had died in the durvalumab plus platinum–etoposide group and 181 (67%) had died in the platinum–etoposide group. The multiplicity-adjusted, two-sided  $\alpha$  spent at this interim analysis was 1·78% (ie, a  $p$  value less than 0·0178 was considered statistically significant). Overall survival was significantly longer in the durvalumab plus platinum–etoposide group than the platinum–etoposide group, with an HR of 0·73 (95% CI 0·59–0·91;  $p=0·0047$ ; figure 2A). Median overall survival was 13·0 months (95% CI 11·5–14·8) with durvalumab plus platinum–etoposide versus 10·3 months (9·3–11·2) with platinum–etoposide; the post-hoc 12-month overall survival rates were 54% (47·4–59·5) versus 40% (33·7–45·8); and the prespecified 18-month overall survival rates were 34% (26·9–41·0) versus 25% (18·4–31·6).

The overall survival benefit with durvalumab plus platinum–etoposide was consistently observed across prespecified patient subgroups defined by baseline clinical and demographic characteristics (figure 2B) and across the prespecified sensitivity analysis of the effect of additional covariates on the HR estimate (data not shown). The sensitivity analysis examining censoring patterns to identify potential attrition bias indicated that there was more early censoring in the platinum–etoposide group than in the durvalumab plus platinum–etoposide group.

	Durvalumab plus platinum–etoposide (n=268)	Platinum–etoposide (n=269)
Unconfirmed objective response*	213 (79%)	189 (70%)
Odds ratio (95% CI)†	1·64 (1·11–2·44)	..
Confirmed objective response*	182 (68%)	155 (58%)
Odds ratio (95% CI)†	1·56 (1·10–2·22)	..
Best objective response		
Complete response	6 (2%)	2 (1%)
Partial response	176 (66%)	153 (57%)
Stable disease for at least 6 weeks	20 (7%)	42 (16%)
Progressive disease	32 (12%)	31 (12%)
Not evaluable	3 (1%)	8 (3%)
Median (IQR) duration of response, months‡	5·1 (3·4–10·4)	5·1 (3·7–6·8)
Remaining in response‡		
6 months	39% (32–46)	34% (26–42)
12 months	23% (17–29)	6% (3–11)

Data are n (%) unless otherwise stated. Data cutoff was March 11, 2019. Data included are for confirmed responses except where otherwise specified. Platinum–etoposide=etoposide plus either cisplatin or carboplatin. \*Objective response by investigator review per Response Evaluation Criteria in Solid Tumors, version 1.1, is defined as patients with complete response or partial response on at least one visit (unconfirmed responses); for confirmed responses, a confirmatory scan was required no sooner than 4 weeks after the initial response. †Odds ratios and 95% CIs for comparing the proportion of patients with an objective response between treatment groups were calculated using a logistic regression model adjusted for planned platinum (carboplatin or cisplatin). ‡Estimated using the Kaplan–Meier method.

Table 3: Summary of tumour response

Early censoring (>10 weeks before data cutoff) occurred in two (1%) of 268 patients for durvalumab plus platinum–etoposide compared with eight (3%) of 269 patients for platinum–etoposide. Most of these cases (nine of ten) were because of withdrawal of consent.

At the time of data cutoff, 226 (84%) of 268 patients in the durvalumab plus platinum–etoposide group and 233 (87%) of 269 patients in the platinum–etoposide group had disease progression or died. Although progression-free survival could not be tested for significance within the multiple-testing procedure at the time of the interim analysis because of the design of the study, an HR of 0·78 (95% CI 0·65–0·94) for the comparison was recorded (figure 2C). Median progression-free survival was 5·1 months (95% CI 4·7–6·2) with durvalumab plus platinum–etoposide versus 5·4 months (4·8–6·2) with platinum–etoposide; the 6-month progression-free survival rates were 45% (39·3–51·3) versus 46% (39·3–51·7); and the 12-month progression-free survival rates were 18% (13·1–22·5) versus 5% (2·4–8·0).

The proportion of patients with an investigator-assessed unconfirmed objective response was higher with durvalumab plus platinum–etoposide than with platinum–etoposide; 213 (79%) of 268 patients had an objective response in the durvalumab plus platinum–etoposide

	Durvalumab plus platinum-etoposide (n=265)		Platinum-etoposide (n=266)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any event	260 (98%)	163 (62%)	258 (97%)	166 (62%)
Any serious event	82 (31%)	57 (22%)	96 (36%)	70 (26%)
Any event leading to discontinuation*	25 (9%)	7 (3%)	25 (9%)	7 (3%)
Any event leading to death†	13 (5%)	..	15 (6%)	..
Adverse events with an incidence of at least 10% in any grade category or events of grade 3 or 4 with an incidence of at least 2% in either group‡				
Neutropenia	111 (42%)	64 (24%)	124 (47%)	88 (33%)
Anaemia	102 (38%)	24 (9%)	125 (47%)	48 (18%)
Nausea	89 (34%)	1 (<1%)	89 (33%)	5 (2%)
Alopecia	83 (31%)	3 (1%)	91 (34%)	2 (1%)
Constipation	44 (17%)	2 (1%)	51 (19%)	0
Decreased appetite	48 (18%)	2 (1%)	46 (17%)	2 (1%)
Thrombocytopenia	41 (15%)	15 (6%)	53 (20%)	25 (9%)
Fatigue	48 (18%)	4 (2%)	45 (17%)	3 (1%)
Vomiting	39 (15%)	0	44 (17%)	3 (1%)
Asthenia	40 (15%)	5 (2%)	40 (15%)	3 (1%)
Leucopenia	40 (15%)	17 (6%)	32 (12%)	14 (5%)
Dyspnoea	31 (12%)	5 (2%)	28 (11%)	3 (1%)
Neutrophil count decreased	26 (10%)	17 (6%)	31 (12%)	17 (6%)
Diarrhoea	26 (10%)	3 (1%)	30 (11%)	3 (1%)
Cough	33 (12%)	2 (1%)	18 (7%)	0
Hyponatraemia	26 (10%)	10 (4%)	12 (5%)	7 (3%)
Febrile neutropenia	17 (6%)	14 (5%)	17 (6%)	17 (6%)
White blood cell count decreased	14 (5%)	4 (2%)	17 (6%)	6 (2%)
Platelet count decreased	16 (6%)	4 (2%)	14 (5%)	6 (2%)
Pneumonia	11 (4%)	5 (2%)	18 (7%)	9 (3%)
Hypertension	15 (6%)	8 (3%)	7 (3%)	1 (<1%)
Lipase increased	12 (5%)	9 (3%)	7 (3%)	4 (2%)
Amylase increased	11 (4%)	6 (2%)	2 (1%)	1 (<1%)

Data cutoff was March 11, 2019. Listed are all adverse events that occurred during the treatment period and up to 90 days after the last dose of durvalumab or platinum-etoposide or up to the start of any subsequent therapy (whichever occurred first). Platinum-etoposide=etoposide plus either cisplatin or carboplatin. \*Includes patients who permanently discontinued at least one study drug. †Adverse events of any cause leading to death in the durvalumab plus platinum-etoposide group were sudden death in two patients, and acute respiratory failure, aspiration, cardiac arrest, dehydration, hepatotoxicity, hypoxia, pancytopenia, pulmonary artery thrombosis, pulmonary embolism, sepsis, and septic shock in one patient each; adverse events of any cause leading to death in the platinum-etoposide group were pneumonitis and death in two patients each, and acute cardiac failure, acute respiratory failure, cardiac arrest, cardiopulmonary failure, cerebrovascular accident, haematotoxicity, pancytopenia, pneumonia, sudden cardiac death, sudden death, and thrombocytopenia and haemorrhage (in the same patient) in one patient each. ‡The events are listed in descending order of frequency across both treatment groups.

**Table 4: Adverse events of any cause (safety population)**

group compared with 189 (70%) of 269 patients in the platinum-etoposide group (odds ratio [OR] 1.64 [95% CI 1.11–2.44]). Confirmed responses were analysed post hoc; 182 (68%) of 268 patients had a confirmed objective response in the durvalumab plus platinum-etoposide group compared with 155 (58%) of 269 patients in the platinum-etoposide group (OR 1.56 [1.10–2.22; table 3). Six (2%) patients in the durvalumab plus platinum-etoposide group and two (1%) patients in the platinum-etoposide group achieved a confirmed complete response. The median duration of (confirmed) response was the same for both groups. Of the patients with a confirmed

response, the estimated percentage remaining in response at 12 months was higher with durvalumab plus platinum-etoposide than with platinum-etoposide.

Adverse events of any cause and grade occurred in 260 (98%) of 265 patients treated with durvalumab plus platinum-etoposide and 258 (97%) of 266 patients treated with platinum-etoposide (table 4). Grade 3 or 4 adverse events occurred in 163 (62%) patients in the durvalumab plus platinum-etoposide group and 166 (62%) patients in the platinum-etoposide group and adverse events leading to discontinuation occurred in 25 (9%) patients in each group. The most common grade 3 or 4 adverse events were neutropenia and anaemia. Deaths due to adverse events of any cause occurred in 13 (5%) patients in the durvalumab plus platinum-etoposide group and 15 (6%) patients in the platinum-etoposide group (table 4). Treatment-related adverse events, serious adverse events, and adverse events leading to discontinuation are described in the appendix (pp 14–19).

Immune-mediated adverse events (imAEs) were reported in 52 (20%) of 265 patients treated with durvalumab plus platinum-etoposide and seven (3%) of 266 patients treated with platinum-etoposide (appendix pp 20–21). Most of these events were grade 1 or 2; grade 3 or 4 imAEs occurred in 12 patients (5%) in the durvalumab plus platinum-etoposide group and one patient (<1%) in the platinum-etoposide group. Deaths due to imAEs occurred in one (<1%) patient in each group; causes of death were hepatotoxicity in the durvalumab plus platinum-etoposide group and pneumonitis in the platinum-etoposide group. The most common imAEs were hypothyroid events (occurring in 24 [9%] patients in the durvalumab plus platinum-etoposide group and two [1%] patients in the platinum-etoposide group) and hyperthyroid events (occurring in 14 [5%] and none), which were all grade 1 or 2 in severity.

## Discussion

The CASPIAN trial met its primary endpoint of overall survival for durvalumab plus platinum-etoposide versus platinum-etoposide at the planned interim analysis. Durvalumab plus platinum-etoposide demonstrated a statistically significant and clinically meaningful improvement in overall survival versus platinum-etoposide alone, with an HR of 0.73 (95% CI 0.59–0.91;  $p=0.0047$ ). Overall survival benefit was observed across all clinically relevant patient subgroups. Consistent with the results for overall survival, progression-free survival (assessed without formal statistical significance testing) was also in favour of durvalumab plus platinum-etoposide, as were both unconfirmed and confirmed objective response. Overall survival benefit was durable for durvalumab plus platinum-etoposide, as evidenced by the tail of the Kaplan-Meier curve; in the durvalumab plus platinum-etoposide group, more patients were alive at 12 months and 18 months (prespecified endpoint) than in the



platinum–etoposide group. Sustained clinical benefit was also observed across progression-free survival and tumour response with durvalumab plus platinum–etoposide, with a higher 12-month progression-free survival rate and more patients remaining in response at 12 months in the durvalumab plus platinum–etoposide group than in the platinum–etoposide group. These clinical benefits were observed in the context of a clinically relevant control group that permitted up to six cycles of platinum–etoposide (compared with four cycles in the immunotherapy group) and PCI at the investigator's discretion. Furthermore, in both groups, the platinum component of platinum–etoposide included either carboplatin or cisplatin, as chosen by the investigator.

Our results, which align with those from the recent IMpower133 trial<sup>12</sup> of atezolizumab plus carboplatin–etoposide, represent progress in clinical outcomes for patients with ES-SCLC treated in the first-line setting. However, some notable study design differences between CASPIAN and IMpower133 exist, including the use of up to six cycles of platinum–etoposide in the control group of CASPIAN (up to four cycles were permitted in the control group of IMpower133), as well as the use of investigator's choice of platinum (carboplatin or cisplatin) across both groups. For the platinum–etoposide group of CASPIAN, median overall survival was consistent with previous reports,<sup>8,10,12</sup> whereas the median progression-free survival was longer than that observed in the control group in IMpower133.<sup>12</sup> Although the scan schedule in CASPIAN was the same for both treatment groups, it differed slightly from that in IMpower133. The better early performance in the control group of CASPIAN might be driven by the fact that more than half of the patients in the platinum–etoposide group of CASPIAN received six cycles of platinum–etoposide, compared with the maximum of four cycles in the control group of IMpower133.<sup>12</sup> Notably, the addition of durvalumab to platinum–etoposide in CASPIAN did not compromise the number of cycles of platinum–etoposide received, because a similar majority of patients received at least four cycles in each group (87% in the durvalumab plus platinum–etoposide group and 85% in the platinum–etoposide group). At the time of designing the CASPIAN study, the guidelines recommended between four and six cycles of platinum–etoposide, because no evidence supported that six cycles of platinum–etoposide would result in a better outcome than four cycles. Additionally, safety data were scarce for the combination of chemotherapy and immunotherapy in SCLC. Therefore, platinum–etoposide was limited to the minimum recommended number of cycles (ie, four) in the immunotherapy groups, whereas up to six cycles of platinum–etoposide were allowed in the control group to reflect current clinical practice.

Although the treatment effect with durvalumab plus platinum–etoposide versus platinum–etoposide was well

sustained over the study period, longer follow-up is required to ascertain the long-term survival benefit in patients who responded to durvalumab plus platinum–etoposide. Use of PD-1 or PD-L1 inhibitors has resulted in a significant proportion of long-term survivors among patients with different stages of non-small-cell lung cancer;<sup>21–23</sup> however, the extent of long-term survival benefit with immunotherapy remains to be demonstrated in SCLC. Further study to identify patients with SCLC who might derive long-term survival benefit is warranted, including analyses of biomarkers such as PD-L1 expression and tumour mutation burden. A better understanding of the underlying biology is important to discover which patients with this heterogeneous disease might derive greater treatment benefit, so that therapy may be tailored to the individual.

In patients with ES-SCLC, brain metastases are common and associated with poor clinical outcomes. The role of PCI in patients with ES-SCLC after treatment with platinum–etoposide remains controversial, with conflicting evidence regarding its potential survival benefit.<sup>24–26</sup> In CASPIAN, because no safety data were available regarding the use of PCI concurrently with immune checkpoint blockade targeting the PD-1 and PD-L1 pathway at the time of study start, PCI was only permitted in the platinum–etoposide group at the investigator's discretion; 21 (8%) patients in the control group received PCI. Further investigation is required to define the role of PCI in ES-SCLC, particularly with the use of immune checkpoint blockade targeting the PD-1 and PD-L1 pathway in combination with chemotherapy.

The overall safety profile in CASPIAN was similar between the two groups, with similar frequencies of grade 3 or 4 adverse events, adverse events leading to discontinuation, and adverse events leading to death. The most common adverse events were haematological toxicities, some of which were numerically higher in the platinum–etoposide group, potentially because of the greater number of platinum–etoposide cycles received in the control group than in the durvalumab plus platinum–etoposide group. Immune-mediated adverse events were mostly low grade and manageable with standard treatment guidelines and were numerically higher in the durvalumab plus platinum–etoposide group than the platinum–etoposide group, driven by thyroid endocrinopathies, and consistent with the known safety profile of durvalumab.<sup>27</sup>

A limitation of the study is its open-label design, which could potentially affect study conduct and secondary endpoints such as investigator assessment of response and progression, attribution of adverse events, and patient withdrawals. However, the primary study endpoint was overall survival, which is not subject to open-label bias. Furthermore, progression-free survival in the control group was in line with historical data, and safety regardless of cause was similar between the two groups,

suggesting that open-label bias was not a factor. Finally, although there was more early censoring in the platinum–etoposide group than in the durvalumab plus platinum–etoposide group, the patient numbers were small and are not considered to have affected the overall conclusions.

In conclusion, this randomised, open-label, phase 3 trial demonstrated that the addition of durvalumab to platinum–etoposide as first-line treatment for ES-SCLC resulted in significantly longer overall survival than with a control group reflective of current clinical practice worldwide.<sup>5–7</sup> The safety profile was consistent with previous reports of both durvalumab and platinum–etoposide. These results represent an important step forward in providing the flexibility of combining immunotherapy with different platinum-based regimens in ES-SCLC, expanding treatment options for both patients and physicians.

#### Contributors

LP-A, NB, NS, and HJ were involved in the conception, design, and planning of the study. LP-A, MD, YC, NR, KH, DT, GS, MJH, MÖ, JHJ, OV, AP, SP, FV, LH, IB, AK, GL, NVC, and JWG collected the data. JA did the statistical analysis. All authors reviewed the data analyses, contributed to data interpretation and writing of the report, and approved the final version of the submitted report.

#### Declaration of interests

LP-A reports leadership (himself) with Genomics and leadership (immediate family member) with the European Medicines Agency; travel, accommodation, or expenses from Roche, AstraZeneca, AstraZeneca Spain, Merck, Sharp and Dohme (MSD), Bristol-Myers Squibb (BMS), Lilly, and Pfizer; honoraria from Roche/Genentech, Lilly, Pfizer, Boehringer Ingelheim, BMS, MSD, AstraZeneca, Merck Serono, PharmaMar, Novartis, Celgene, Sysmex, Amgen, and Incyte; and fees (immediate family member) from Novartis, Ipsen, Pfizer, Servier, Sanofi, Roche, Amgen, and Merck, all outside the submitted work. YC reports personal fees from AstraZeneca, Genentech, BMS, Merck, Novartis, Takeda, Eli Lilly, Guardant Health, Pfizer, and Array BioPharma; and grants from AstraZeneca, ISPEN, Roche, and BMS, all outside the submitted work. NR reports personal fees and non-financial support from AstraZeneca, Boehringer Ingelheim, Hoffmann La-Roche, BMS, and Pfizer; non-financial support from AbbVie; and personal fees from MSD and Takeda, all outside the submitted work. KH reports grants and personal fees from AstraZeneca during the conduct of the study; grants and personal fees from Lilly and BMS outside the submitted work; and personal fees from MSD, Ono, Nipponkayaku, Taiho, Boehringer Ingelheim, and Chugai outside the submitted work. MÖ reports advisory board participation for Janssen, Sanofi, and Astellas; honoraria from Novartis, Roche, Janssen, Sanofi, and Astellas; and travel, accommodation, or expenses from BMS and Janssen. FV reports grants from AstraZeneca during the conduct of the study. JWG reports consulting or advisory role for AstraZeneca, Genentech, and Lilly; speakers' bureau for Merck; and research funding from AstraZeneca/MedImmune, Eli Lilly, Genentech, BMS, Array BioPharma, Celgene, and AbbVie. JA, NS, and HJ are full-time employees of and own stock in AstraZeneca. NB is a contractor for and owns stock in AstraZeneca. All other authors declare no competing interests.

#### Data sharing

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy.

#### Acknowledgments

The study was funded by AstraZeneca. The authors would like to thank the patients, their families and caregivers, and all investigators involved in this study, Alan Hatfield, formerly of AstraZeneca, and all members of the independent data monitoring committee for their contributions to the study. Medical writing support, which was in accordance with good

publication practice guidelines, was provided by Craig Turner and Samantha Holmes, of Cirrus Communications (Macclesfield, UK), an Ashfield company, and was funded by AstraZeneca.

#### References

- Oronsky B, Reid TR, Oronsky A, Carter CA. What's new in SCLC? A review. *Neoplasia* 2017; **19**: 842–47.
- Wang S, Tang J, Sun T, et al. Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages. *Sci Rep* 2017; **7**: 1339.
- Byers LA, Rudin CM. Small cell lung cancer: where do we go from here? *Cancer* 2015; **121**: 664–72.
- Pietanza MC, Byers LA, Minna JD, Rudin CM. Small cell lung cancer: will recent progress lead to improved outcomes? *Clin Cancer Res* 2015; **21**: 2244–55.
- Früh M, De Ruysscher D, Popat S, Crinò L, Peters S, Felip E. Small-cell lung cancer (SCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24** (suppl 6): vi99–105.
- Rudin CM, Ismaila N, Hann CL, 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* 2015; **33**: 4106–11.
- Japan Lung Cancer Society. Lung cancer clinical practice guidelines 2018 version III. Small cell lung cancer (in Japanese). <https://www.haigan.gr.jp/guideline/2018/1/3/180103020100.html> (accessed Aug 2, 2019).
- Farago AF, Keane FK. Current standards for clinical management of small cell lung cancer. *Transl Lung Cancer Res* 2018; **7**: 69–79.
- Fukuoka M, Furuse K, Saijo N, et al. Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. *J Natl Cancer Inst* 1991; **83**: 855–61.
- Rossi A, Di Maio M, Chiodini P, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. *J Clin Oncol* 2012; **30**: 1692–98.
- Horita N, Yamamoto M, Sato T, et al. Topotecan for relapsed small-cell lung cancer: systematic review and meta-analysis of 1347 patients. *Sci Rep* 2015; **5**: 15437.
- Horn L, Mansfield AS, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med* 2018; **379**: 2220–29.
- Stewart R, Morrow M, Hammond SA, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. *Cancer Immunol Res* 2015; **3**: 1052–62.
- AstraZeneca. Imfinzi (durvalumab) prescribing information. August, 2019. <https://www.azpicentral.com/imfinzi/imfinzi.pdf#page=1> (accessed Aug 2, 2019).
- AstraZeneca. Imfinzi (durvalumab) summary of product characteristics. September, 2018. <https://www.medicines.org.uk/emc/product/9495/smpc> (accessed Aug 2, 2019).
- Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017; **377**: 1919–29.
- Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med* 2018; **379**: 2342–50.
- Cho DC, Mahipal A, Dowlati A, et al. Safety and clinical activity of durvalumab in combination with tremelimumab in extensive disease small-cell lung cancer (ED-SCLC). *Proc Am Soc Clin Oncol* 2018; **36** (suppl): abstr 8517.
- Goldman JW, Dowlati A, Antonia SJ, et al. Safety and antitumor activity of durvalumab monotherapy in patients with pretreated extensive disease small-cell lung cancer (ED-SCLC). *Proc Am Soc Clin Oncol* 2018; **36** (suppl): abstr 8518.
- Bondarenko I, Juan-Vidal O, Pajkos G, et al. Preliminary efficacy of durvalumab plus tremelimumab in platinum-refractory/resistant ED-SCLC from arm A of the phase II BALTIMORE study. *Ann Oncol* 2018; **29** (suppl 8): viii596–602 (abstr).
- Garon EB, Hellmann MD, Rizvi NA, et al. Five-year overall survival for patients with advanced non-small-cell lung cancer treated with pembrolizumab: results from the phase I KEYNOTE-001 study. *J Clin Oncol* 2019; **37**: 2518–27.

- 
- 22 Gray JE, Villegas AE, Daniel DB, et al. Three-year overall survival update from the PACIFIC trial. *Proc Am Soc Clin Oncol* 2019; **37** (suppl): abstr 8526.
- 23 Topalian SL, Hodi FS, Brahmer JR, et al. Five-year survival and correlates among patients with advanced melanoma, renal cell carcinoma, or non-small cell lung cancer treated with nivolumab. *JAMA Oncol* 2019; published online July 25. DOI:10.1001/jamaoncol.2019.2187.
- 24 Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007; **357**: 664–72.
- 25 Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2017; **18**: 663–71.
- 26 Nosaki K, Seto T, Shimokawa M, Takahashi T, Yamamoto N. Is prophylactic cranial irradiation (PCI) needed in patients with extensive-stage small cell lung cancer showing complete response to first-line chemotherapy? *Radiother Oncol* 2018; **127**: 344–48.
- 27 Antonia SJ, Balmanoukian A, Brahmer J, et al. Clinical activity, tolerability, and long-term follow-up of durvalumab in patients with advanced NSCLC. *J Thorac Oncol* 2019; **14**: 1794–806.