Durvalumab, with or without tremelimumab, plus platinum–etoposide versus platinum–etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial

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

Summary

Background First-line durvalumab plus etoposide with either cisplatin or carboplatin (platinum–etoposide) showed a significant improvement in overall survival versus platinum–etoposide alone in patients with extensive-stage small-cell lung cancer (ES-SCLC) in the CASPIAN study. Here we report updated results, including the primary analysis for overall survival with durvalumab plus tremelimumab plus platinum–etoposide versus platinum–etoposide alone.

Methods CASPIAN is an ongoing, open-label, sponsor-blind, randomised, controlled phase 3 trial at 209 cancer treatment centres in 23 countries worldwide. Eligible patients were aged 18 years or older (20 years in Japan) and had treatment-naive, histologically or cytologically documented ES-SCLC, with a WHO performance status of 0 or 1. Patients were randomly assigned (1:1:1) in blocks of six, stratified by planned platinum, using an interactive voice-response or web-response system to receive intravenous durvalumab plus tremelimumab plus platinum–etoposide, durvalumab plus platinum–etoposide, or platinum–etoposide alone. In all groups, patients received etoposide 80–100 mg/m² on days 1–3 of each cycle with investigator's choice of either carboplatin area under the curve 5–6 mg/mL/min or cisplatin 75–80 mg/m² on day 1 of each cycle. Patients in the platinum–etoposide group received up to six cycles of platinum–etoposide every 3 weeks and optional prophylactic cranial irradiation (investigator's discretion). Patients in the immunotherapy groups received 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. The two primary endpoints were overall survival for durvalumab plus platinum–etoposide versus platinum–etoposide and for durvalumab plus tremelimumab plus platinum–etoposide versus platinum–etoposide in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of study treatment. This study is registered at ClinicalTrials.gov, NCT03043872.

Findings Between March 27, 2017, and May 29, 2018, 972 patients were screened and 805 were randomly assigned (268 to durvalumab plus tremelimumab plus platinum–etoposide, 268 to durvalumab plus platinum–etoposide, and 269 to platinum–etoposide). As of Jan 27, 2020, the median follow-up was 25·1 months (IQR 22·3–27·9). Durvalumab plus tremelimumab plus platinum–etoposide was not associated with a significant improvement in overall survival versus platinum–etoposide (hazard ratio [HR] 0·82 [95% CI 0·68–1·00]; p=0·045); median overall survival was 10·4 months (95% CI 9·6–12·0) versus 10·5 months (9·3–11·2). Durvalumab plus platinum–etoposide showed sustained improvement in overall survival versus platinum–etoposide (HR 0·75 [95% CI 0·62–0·91]; nominal p=0·0032); median overall survival was 12·9 months (95% CI 11·3–14·7) versus 10·5 months (9·3–11·2). The most common any-cause grade 3 or worse adverse events were neutropenia (85 [32%] of 266 patients in the durvalumab plus tremelimumab plus platinum–etoposide group, 64 [24%] of 265 patients in the durvalumab plus platinum–etoposide group, and 88 [33%] of 266 patients in the platinum–etoposide group) and anaemia (34 [13%], 24 [9%], and 48 [18%]). Any-cause serious adverse events were reported in 121 (45%) patients in the durvalumab plus tremelimumab plus platinum–etoposide group, 85 (32%) in the durvalumab plus platinum–etoposide group, and 97 (36%) in the platinum–etoposide group. Treatment-related deaths occurred in 12 (5%) patients in the durvalumab plus tremelimumab plus platinum–etoposide group (death, febrile neutropenia, and pulmonary embolism [n=2 each]; enterocolitis, general physical health deterioration and multiple organ dysfunction syndrome, pneumonia, pneumonitis and hepatitis, respiratory failure, and sudden death [n=1 each]), six (2%) patients in the durvalumab plus platinum–etoposide group (cardiac arrest, dehydration, hepatotoxicity, interstitial lung disease, pancytopenia, and sepsis [n=1 each]), and two (1%) in the platinum–etoposide group (pancytopenia and thrombocytopenia [n=1 each]).

Lancet Oncol 2020

Published Online December 4, 2020 https://doi.org/10.1016/S1470-2045(20)30539-8

*CASPIAN investigators are listed in the appendix (pp 2–6)

David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA (J W Goldman 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 Regional Oncological Dispensary, Odessa, Ukraine** (D Trukhin MD); **Omsk Regional Cancer Centre, Omsk, Russia** (G Statsenko MD); **Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Klinik Floridsdorf, 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); **Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy** (M C Garassino MD); **Kyiv City Clinical Oncological Centre, Kiev, Ukraine** (O Voitko MD); **Petrov Research Institute of Oncology, St Petersburg, Russia** (A Poltoratskiy MD);

Interpretation First-line durvalumab plus platinum–etoposide showed sustained overall survival improvement versus platinum–etoposide but the addition of tremelimumab to durvalumab plus platinum–etoposide did not significantly improve outcomes versus platinum–etoposide. These results support the use of durvalumab plus platinum–etoposide as a new standard of care for the first-line treatment of ES-SCLC.

Funding AstraZeneca.

Department of Medical Oncology, Hospital Universitario 12 de Octubre, H120-CNIO Lung Cancer Unit, Universidad Complutense and Ciberonc, Madrid, Spain (S Ponce MD, Prof L Paz-Ares MD); **Azienda Ospedaliera Ospedali Riuniti PO Vincenzo Cervello, Palermo, Italy** (F Verderame MD); **Thomayer Hospital, First Faculty of Medicine, Charles University, Prague, Czech Republic** (L Havel MD); **Dnipropetrovsk Medical Academy, Dnipro, Ukraine** (Prof I Bondarenko MD); **Tuberculosis and Lung Disease Hospital, Olsztyn, Poland** (A Każarnowicz MD); **Department of Pulmonology, Semmelweis University, Budapest, Hungary** (Prof G Losonczy MD); **Clinic of Medical Oncology, University Multiprofile Hospital for Active Treatment St Marina, Varna, Bulgaria** (N V Conev MD); **AstraZeneca, Cambridge, UK** (J Armstrong MSc, N Byrne BSc, P Thiyagarajah MD); **AstraZeneca, Gaithersburg, MD, USA** (H Jiang MD)

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

See Online for appendix

Introduction

Small-cell lung cancer (SCLC) accounts for approximately 15% of all diagnosed lung cancers and is pathologically and clinically distinct from non-small-cell lung cancer (NSCLC).[1,2] Characterised by a rapid doubling time and early, widespread metastases, SCLC is the most aggressive form of lung cancer.[3] About two-thirds of patients with SCLC are diagnosed with extensive-stage (ES) disease.[1] Prognosis for patients with ES-SCLC is particularly poor, with a 2-year survival rate of less than 5% typically reported with platinum-doublet chemotherapy regimens.[3]

Checkpoint inhibitors have emerged as a standard first-line treatment option for many tumour types, including NSCLC and melanoma.[4–8] After many decades of minimal progress towards improving treatment outcomes in SCLC, recent clinical trials have shown longer overall survival for patients with ES-SCLC treated with an immune checkpoint inhibitor, specifically the PD-L1 inhibitors durvalumab and atezolizumab, representing substantial progress in this challenging to treat disease.[9,10] Another immune checkpoint protein that is being targeted in cancer treatment is CTLA-4, a co-inhibitory

Research in context

Evidence before this study

We searched PubMed on May 22, 2020, for clinical trials published in English with the terms "PD-1" OR "PD-L1" OR "CTLA-4" OR "pembrolizumab" OR "nivolumab" OR "atezolizumab" OR "durvalumab" OR "avelumab" OR "ipilimumab" OR "tremelimumab" AND "extensive-disease" OR "extensive-stage" AND "first-line" OR "previously untreated" OR "treatment-naive" AND "small-cell lung cancer" OR "SCLC", selecting relevant publications published within the past 5 years (Jan 1, 2015, to May 22, 2020). We also searched the abstracts from the 2019 and 2020 American Society of Clinical Oncology Annual Meetings, the 2019 European Lung Cancer Congress, the 2019 European Society for Medical Oncology Congress, and the 2019 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 PD-L1 pathway to treat patients with extensive-stage small-cell lung cancer (ES-SCLC) in the first-line setting, and a study of first-line pembrolizumab plus etoposide plus either cisplatin or carboplatin (platinum–etoposide; KEYNOTE-604) that did not show significant survival benefit in ES-SCLC. In addition, we identified two phase 3 studies of CTLA-4 blockade in ES-SCLC: one evaluating maintenance nivolumab plus ipilimumab after chemotherapy (CheckMate 451) and one evaluating the addition of ipilimumab to first-line platinum–etoposide (NCT01450761), neither of which showed a survival benefit. There were no previous studies evaluating the combination of dual immune checkpoint blockade with platinum–etoposide in SCLC.

Added value of this study

To our knowledge, this is the first report of a phase 3 trial evaluating a novel treatment approach of dual checkpoint blockade in combination with chemotherapy in ES-SCLC. In the CASPIAN study, the addition of tremelimumab to first-line durvalumab and platinum–etoposide did not significantly improve outcomes in patients with ES-SCLC. The updated analysis, with more than 2 years of follow-up, showed a sustained improvement in overall survival with first-line durvalumab plus platinum–etoposide versus platinum–etoposide alone in patients with ES-SCLC. To our knowledge, this is the first pivotal trial in ES-SCLC to show a significant survival benefit with PD-1 or PD-L1 blockade in combination with etoposide and a choice of carboplatin or cisplatin chemotherapy.

Implications of all the available evidence

The significant improvement in overall survival and durable benefit from the addition of durvalumab to platinum–etoposide is particularly noteworthy in this aggressive disease setting where, historically, it has been difficult to show long-term survival benefit with platinum–etoposide. The flexibility in choice of platinum in CASPIAN represents an important advance in treatment options for patients and physicians given that up to 42% of patients with previously untreated ES-SCLC are reported to be treated with cisplatin in routine clinical practice globally. The absence of any additional benefit with the addition of tremelimumab to durvalumab plus platinum–etoposide and the absence of a significant difference versus platinum–etoposide suggests, along with other studies, that CTLA-4 blockade might not have a substantial role in unselected patients with ES-SCLC.

receptor that represses T-cell activity. CTLA-4 blockade prevents this downregulation of T cells, thereby releasing a brake on T-cell activation and enhancing immune function.[11] The simultaneous blockade of both non-redundant immune checkpoint pathways by combining antibodies that target PD-1 or PD-L1 with anti-CTLA-4 might have additive or synergistic effects on antitumour T-cell responses,[12] and has been shown to be an effective therapeutic approach in some tumour types, including NSCLC.[6,13,14] Combining chemotherapy with immunotherapy might further enhance tumour antigenicity, and the combination of dual checkpoint blockade with chemotherapy is a novel treatment approach that has not been previously explored in SCLC.

The aim of the phase 3 CASPIAN trial was to assess the efficacy and safety of durvalumab, a selective human IgG1 monoclonal antibody directed against PD-L1,[15] with or without tremelimumab, a human monoclonal IgG2 antibody targeting CTLA-4,[11] in combination with etoposide plus either cisplatin or carboplatin (platinum–etoposide) for the first-line treatment of patients with ES-SCLC. At the planned interim analysis (data cutoff March 11, 2019; 62·6% maturity), durvalumab plus platinum–etoposide treatment was associated with a significant and clinically meaningful improvement in overall survival versus platinum–etoposide alone, with a hazard ratio (HR) of 0·73 (95% CI 0·59–0·91; p=0·0047), meeting one of the two primary endpoints.[9] Median overall survival was 13·0 months versus 10·3 months for durvalumab plus platinum–etoposide versus platinum–etoposide alone and an overall survival benefit was observed across all prespecified patient subgroups. These benefits were observed in the context of a clinically relevant and robust control group that permitted up to six cycles of platinum–etoposide (compared with four cycles in the immunotherapy group) and prophylactic cranial irradiation at the investigator's discretion. On the basis of these results, durvalumab was approved as first-line treatment for patients with ES-SCLC in combination with platinum–etoposide.[16]

In this paper, we report the primary analysis for durvalumab plus tremelimumab plus platinum–etoposide versus platinum–etoposide alone, and the prespecified updated analysis of overall survival for durvalumab plus platinum–etoposide versus platinum–etoposide alone from the CASPIAN trial with an additional 11 months of follow-up.

Methods

Study design and participants

CASPIAN, an open-label, sponsor-blind, randomised, controlled, phase 3 study, was done at 209 cancer treatment centres in 23 countries worldwide (appendix pp 2–6). The study design has been previously reported.[9] Briefly, eligible patients were aged 18 years or older (20 years in Japan) with treatment-naive, histologically or cytologically documented ES-SCLC that was American Joint Committee on Cancer (7th edition) stage IV (any T-stage, any N-stage, M-stage M1a or M1b), or T-stage T3–4 due to multiple lung nodules that are too extensive or a tumour or nodal volume that is too large to be encompassed in a tolerable radiotherapy 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; a life expectancy of at least 12 weeks from the start of the study; a bodyweight of more than 30 kg; adequate organ and bone marrow function; and suitability for first-line platinum-based chemotherapy. Pre-menopausal women had to have a negative pregnancy test. Patients with brain metastases were eligible provided they were either asymptomatic or treated and stable off steroids and anticonvulsants for at least 1 month before study entry. Collection of tumour tissue was mandated at screening, if available. There were no requirements concerning PD-L1 expression at 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 10–11). All patients provided written informed consent for participation.

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 is available online, and the protocol and all amendments were approved by relevant ethics committees and regulatory authorities.

For the **protocol** see https://astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=24635

Randomisation and masking

Patients were randomly assigned (1:1:1) using an interactive voice-response or web-response system to receive durvalumab plus tremelimumab plus platinum–etoposide, durvalumab plus platinum–etoposide, or platinum–etoposide alone. Randomisation was stratified according to planned platinum agent (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 principal investigator or a suitably trained delegate enrolled the patients at each study site. The study was open-label and allocation was unmasked to investigators and patients, although the sponsor was masked.

Procedures

All drugs were administered intravenously. Across all three study groups, chemotherapy consisted of etoposide 80–100 mg/m² (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/min or cisplatin 75–80 mg/m² (administered on day 1 of each cycle). Patients in the immunotherapy groups received 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 durvalumab plus tremelimumab plus platinum–etoposide group received one additional dose of tremelimumab 75 mg after platinum–etoposide (up to five doses in total). Patients in the platinum–etoposide group could receive an additional two cycles of platinum–etoposide (up to six cycles in total) and optional prophylactic cranial irradiation after chemotherapy at the investigator's discretion (prophylactic cranial irradiation was not permitted in the immunotherapy groups before discontinuation of all study treatment). Patients continued treatment until disease progression per investigator assessment, unacceptable toxicity, or other discontinuation criteria were met. In the durvalumab plus tremelimumab plus platinum–etoposide group, patients who met the criteria for discontinuation of immunotherapy due to a treatment-related adverse event had to discontinue both durvalumab and tremelimumab. Continuation of study treatment following disease progression was permitted if there was evidence of clinical benefit.[9] Dose reductions were not permitted for immunotherapy; however, dose interruptions were allowed for management of toxicity. Dose reductions and interruptions for platinum–etoposide were at the investigator's discretion per local prescribing information. Patients were allowed to switch between carboplatin and cisplatin at the investigator's discretion. In-study crossover from the platinum–etoposide group to the immunotherapy plus platinum–etoposide groups was not allowed.

Tumour imaging by CT (preferred) or MRI was done every 6 weeks for the first 12 weeks, and every 8 weeks thereafter, until confirmed objective disease progression. Survival was assessed every 2 months following treatment discontinuation. Laboratory assessments, including clinical chemistry, haematology, and urinalysis, were done at screening and each cycle during the treatment period. Further clinical chemistry and haematology assessments were done at 28 days, 2 months, and 3 months after discontinuation of treatment. Adverse events were recorded continuously from the first dose to 90 days after the last dose of study treatment and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Periodic safety monitoring and interim efficacy assessments were done by an independent data monitoring committee.

Outcomes

The two primary endpoints were overall survival (time from randomisation to death from any cause) for durvalumab plus platinum–etoposide versus platinum–etoposide and for durvalumab plus tremelimumab plus platinum–etoposide versus platinum–etoposide. 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), unconfirmed objective response (proportion of patients with a complete or partial response on at least one visit), overall survival at 18 months, progression-free survival at 6 months and 12 months, and safety. Progression-free survival and objective response were investigator-assessed according to RECIST, version 1.1. Other secondary endpoints were pharmacokinetics, immunogenicity, and symptoms and health-related quality of life assessments; these endpoints will be reported elsewhere.

Statistical analysis

Approximately 795 patients were needed for 1:1:1 randomisation to obtain 425 events across the durvalumab plus platinum–etoposide and platinum–etoposide groups combined and 425 events across the durvalumab plus tremelimumab plus platinum–etoposide and platinum–etoposide groups combined (80% maturity) for the final analysis of overall survival. Sample size assumptions have been reported previously.[9] One planned interim analysis of overall survival was done at approximately 60% maturity. The α values at the interim and final analysis were adjusted using the Lan-DeMets spending function that approximates an O'Brien-Fleming approach to account for multiple comparisons.[17]

The study was considered to be positive if overall survival was significantly longer with either durvalumab plus platinum–etoposide or durvalumab plus tremelimumab plus platinum–etoposide versus platinum–etoposide alone. At the time of the previously published planned interim analysis of overall survival,[9] the independent data monitoring committee recommended that the durvalumab plus platinum–etoposide group and the platinum–etoposide group be unmasked to the sponsor, because this comparison met the predefined threshold for statistical significance. The previous analysis is therefore considered as the final result in terms of formal statistical testing for durvalumab plus platinum–etoposide versus platinum–etoposide, although follow-up continues. 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 remained masked to this group until the final overall survival analysis, described here.

To control the type I error at 5% (two-sided), a hierarchical multiple testing procedure with an α-exhaustive recycling strategy[18] was used across the primary overall survival analyses and secondary progression-free survival analyses (appendix p 7). Initially, 4% α was allocated to the primary endpoint of overall survival for durvalumab plus platinum–etoposide versus platinum–etoposide alone and 1% α was allocated to the primary endpoint of overall survival for

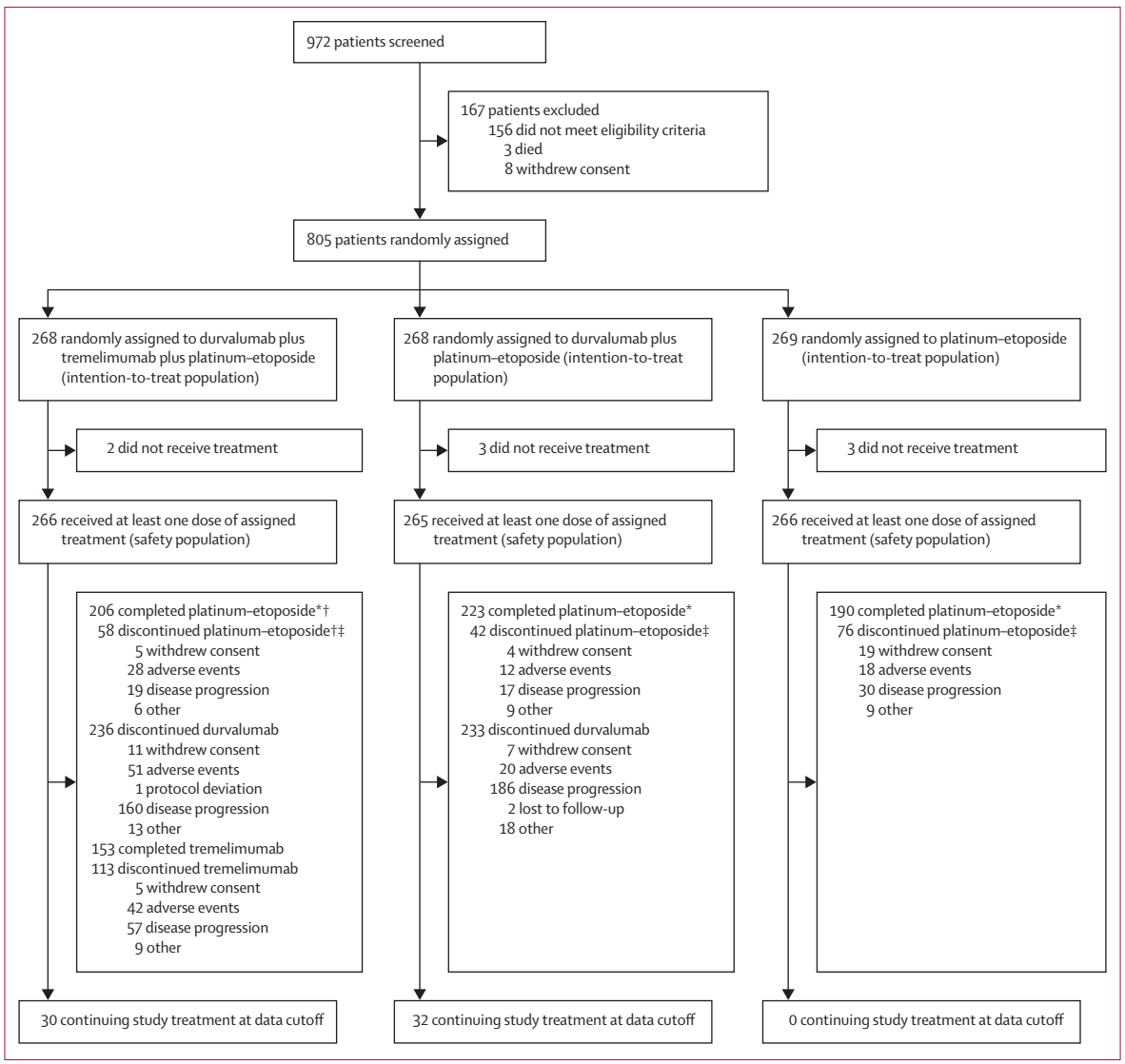


Figure 1: **Trial profile**

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. †Two patients in the durvalumab plus tremelimumab plus platinum–etoposide group discontinued due to adverse events during the immunotherapy infusions before receiving any platinum–etoposide. ‡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.

durvalumab plus tremelimumab plus platinum–etoposide versus platinum–etoposide.[9] Because durvalumab plus platinum–etoposide met the primary endpoint of improved overall survival versus platinum–etoposide at the interim analysis, 4% α was recycled to the final analysis of overall survival for the durvalumab plus tremelimumab plus platinum–etoposide versus platinum–etoposide comparison, which was therefore tested at the 5% level, and no α was allocated to the comparison of durvalumab plus platinum–etoposide versus platinum–etoposide at the final analysis. Based on an assumed overall survival HR of 0·69, it was estimated that the trial would have 96% power to show significance at the final analysis with a two-sided significance level of 4·43% (for overall α of 5%) for the comparison of durvalumab plus tremelimumab plus platinum–etoposide versus platinum–etoposide. However, the actual α spend was to be based on the observed number of events at data cutoff. 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 proportional hazards assumption was

	Durvalumab plus tremelimumab plus platinum–etoposide (n=268)	Durvalumab plus platinum–etoposide (n=268)	Platinum–etoposide (n=269)
Median age, years	63 (58–68)	62 (58–68)	63 (57–68)
<65	154 (57%)	167 (62%)	157 (58%)
≥65	114 (43%)	101 (38%)	112 (42%)
Sex			
Male	202 (75%)	190 (71%)	184 (68%)
Female	66 (25%)	78 (29%)	85 (32%)
Race			
White	215 (80%)	229 (85%)	221 (82%)
Asian	47 (18%)	36 (13%)	42 (16%)
Black or African American	1 (<1%)	2 (1%)	3 (1%)
Other or missing data	5 (2%)	1 (<1%)	3 (1%)
Disease stage*			
III	18 (7%)	28 (10%)	24 (9%)
IV	250 (93%)	240 (90%)	245 (91%)
WHO performance status			
0	109 (41%)	99 (37%)	90 (33%)
1	159 (59%)	169 (63%)	179 (67%)
Smoking history			
Never smoker	15 (6%)	22 (8%)	15 (6%)
Former smoker	141 (53%)	126 (47%)	128 (48%)
Current smoker	112 (42%)	120 (45%)	126 (47%)
Brain or CNS metastases			
Yes	38 (14%)	28 (10%)	27 (10%)
No	230 (86%)	240 (90%)	242 (90%)
Liver metastases			
Yes	117 (44%)	108 (40%)	104 (39%)
No	151 (56%)	160 (60%)	165 (61%)

Data are median (IQR) or n (%). Platinum–etoposide=etoposide plus either cisplatin or carboplatin. *All patients were confirmed as having extensive-stage small-cell lung cancer

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

assessed by examining plots of complementary log–log (event times) versus log (time) and by fitting a time-dependent covariate to test the extent to which this represented random variation. The Kaplan-Meier method was used to estimate overall survival, progression-free survival, and duration of response. We did prespecified exploratory subgroup analyses of overall survival by planned platinum, age, sex, WHO performance status, smoking status, brain or CNS metastases, disease stage at diagnosis, race, and region. Analysis of overall survival according to liver metastases was post hoc. HRs and 95% CIs for patient subgroups were calculated using an unstratified Cox proportional hazards model with treatment as the only covariate. Odds ratios (ORs) 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. Although confirmation of objective response was not protocol-defined, confirmed objective response was analysed post hoc to minimise the potential for bias. Duration of (confirmed) response, overall survival at 12 months and 24 months, and progression-free survival at 24 months were also analysed post hoc. Analysis of the best percentage change from baseline in target lesion size was prespecified for supportive purposes.

Efficacy was assessed in all randomly assigned patients, regardless of whether the treatment was received (intention-to-treat population). Safety was assessed in all patients who received at least one dose of study treatment. SAS (version 9.2 or higher) was used for all analyses. This trial is registered with ClinicalTrials.gov, NCT03043872.

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 tremelimumab plus platinum–etoposide (n=268), durvalumab plus platinum–etoposide (n=268), and platinum–etoposide alone (n=269; figure 1).[9] 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 33 (4%) of 805 randomly assigned patients: 15 in the durvalumab plus tremelimumab plus platinum–etoposide group; ten in the durvalumab plus platinum–etoposide group; and eight in the platinum–etoposide group (appendix p 12). Baseline demographics were generally well balanced across the groups (table 1). Across all groups, the median age was 63 years (IQR 57–68) and most patients were male (576 [72%] of 805), current or former smokers (753 [94%]), and had stage IV disease at diagnosis (735 [91%]).

Two patients in the durvalumab plus tremelimumab plus platinum–etoposide group and three patients each in the durvalumab plus platinum–etoposide group and the platinum–etoposide only group did not receive study treatment. A further two patients in the durvalumab plus tremelimumab plus platinum–etoposide group received immunotherapy but discontinued before receiving platinum–etoposide. Of the 795 patients who received chemotherapy, 618 (78%) received carboplatin and 198 (25%) received cisplatin. The median duration of treatment with chemotherapy was 12·3 weeks (IQR 12·0–13·5) in the durvalumab plus tremelimumab plus platinum–etoposide group, 12·1 weeks (12·0–13·1) in the durvalumab plus platinum–etoposide group, and 19·0 weeks (12·6–20·3) in the platinum–etoposide group (appendix p 13). More than 80% of patients in each

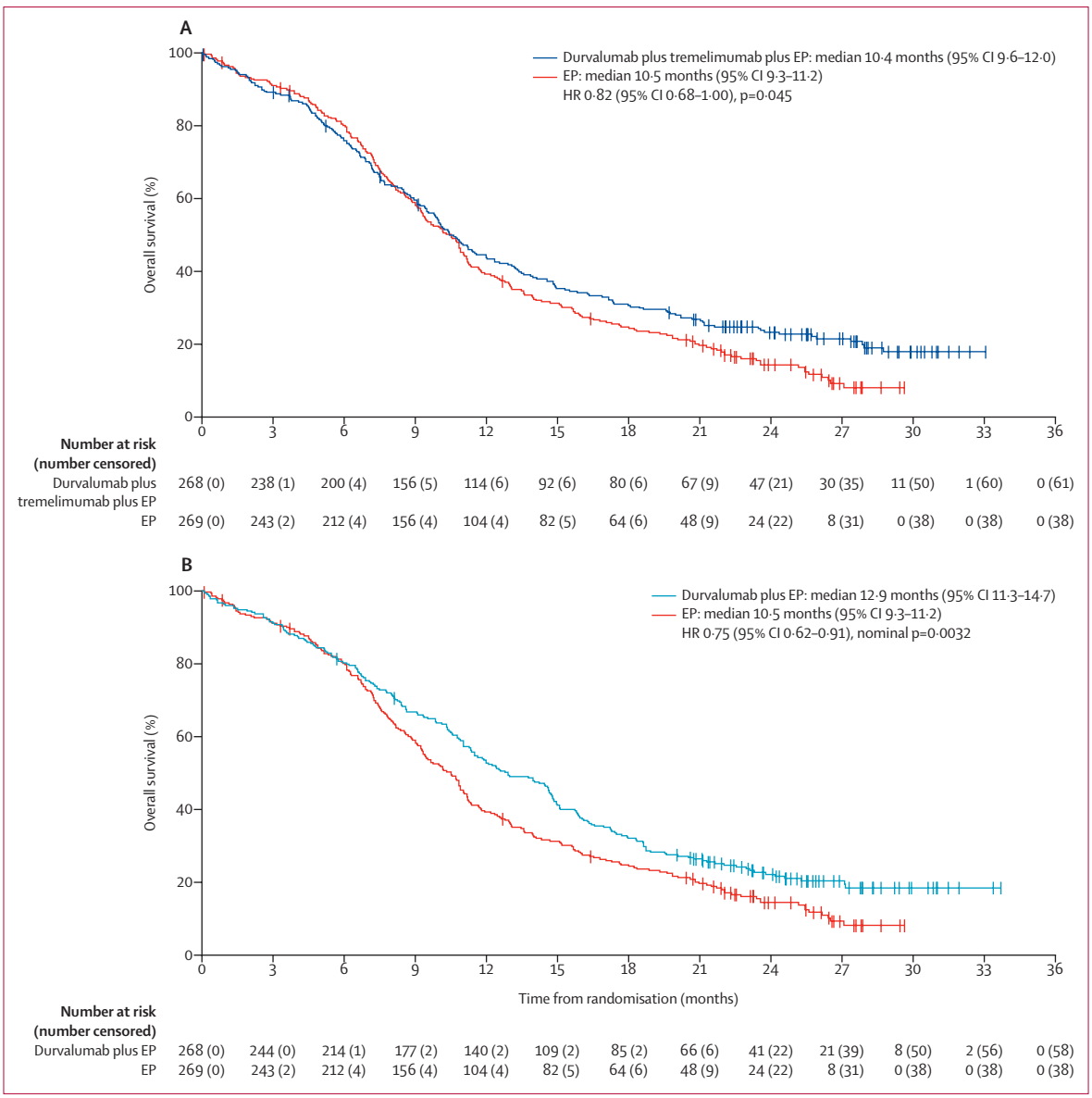


***Figure 2*: Overall survival in the intention-to-treat population**
(A) Kaplan-Meier graph of overall survival for durvalumab plus tremelimumab plus EP versus EP. (B) Kaplan-Meier graph of overall survival for durvalumab plus EP versus EP. EP=etoposide plus either cisplatin or carboplatin. HR=hazard ratio.

treatment group received at least four cycles of chemotherapy. The median duration of treatment with durvalumab was 23·1 weeks (IQR 14·1–38·3) in the durvalumab plus tremelimumab plus platinum–etoposide group and 28·0 weeks (20·0–43·9) in the durvalumab plus platinum–etoposide group (appendix p 13). The median number of durvalumab doses was six (IQR four to ten) in the durvalumab plus tremelimumab plus platinum–etoposide group and seven (six to 11) in the durvalumab plus platinum–etoposide group. 161 (61%) of 266 treated patients in the durvalumab plus tremelimumab plus platinum–etoposide group received the planned five doses of tremelimumab.

As of Jan 27, 2020 (data cutoff), the median follow-up for overall survival in censored patients was 25·1 months (IQR 22·3–27·9), reflecting an additional 11 months of follow-up compared with the interim analysis. 30 (11%) of 268 patients in the durvalumab plus tremelimumab plus platinum–etoposide group and 32 (12%) of 268 patients in the durvalumab plus platinum–etoposide group (compared with 43 [16%] patients at interim analysis) were continuing durvalumab treatment at the data cutoff. 117 (44%) of 268 patients in the durvalumab plus tremelimumab plus platinum–etoposide group, 123 (46%) of 268 in the durvalumab plus platinum–etoposide group, and 125 (46%) of 269 in the platinum–etoposide group

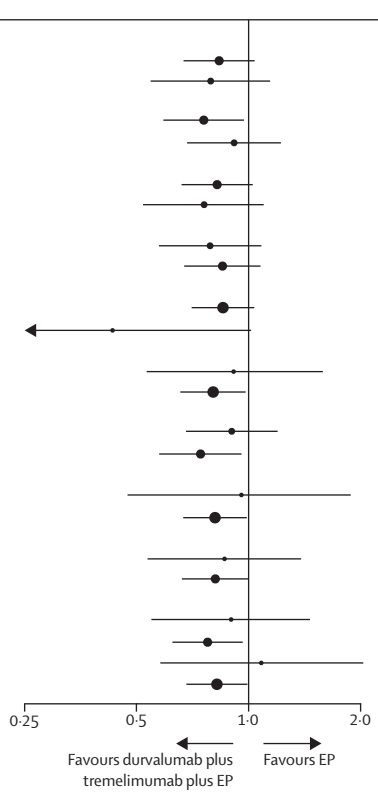
received at least one subsequent systemic anticancer therapy, with nearly all receiving chemotherapy (appendix p 14). In the durvalumab plus tremelimumab plus platinum–etoposide group, 31 (12%) patients received two or more subsequent lines of systemic anticancer therapy compared with 51 (19%) patients in the durvalumab plus platinum–etoposide group and 49 (18%) patients in the platinum–etoposide group. 22 (8%) of 269 patients in the platinum–etoposide group received prophylactic cranial irradiation after chemotherapy. In addition, prophylactic cranial irradiation use after discontinuation of study treatment was reported in seven (3%) of 268 patients in the durvalumab plus tremelimumab plus platinum–etoposide group (and none of the patients in the durvalumab plus platinum–etoposide group).

At the final analysis data cutoff, there were 438 deaths across the durvalumab plus tremelimumab plus platinum–etoposide group and the platinum–etoposide group (data maturity 81·6%); 207 (77%) of 268 patients in the durvalumab plus tremelimumab plus platinum–etoposide group and 231 (86%) of 269 patients in the platinum–etoposide group had died. Based on the observed number of events at data cutoff, the multiplicity-adjusted, two-sided α spent at the final analysis of overall survival for durvalumab plus tremelimumab plus platinum–etoposide versus platinum–etoposide was 4·18% (ie, a p value less than 0·0418 was considered significant). Durvalumab plus tremelimumab plus platinum–etoposide was not associated with a significant improvement in overall survival versus platinum–etoposide per the prespecified statistical plan: HR 0·82 (95% CI 0·68–1·00; p=0·045; figure 2A). Median overall survival was 10·4 months (95% CI 9·6–12·0) with durvalumab plus tremelimumab plus platinum–etoposide versus 10·5 months (9·3–11·2) with platinum–etoposide. A plot of the complementary log–log (event times) versus log (time) showed non-parallelism between the durvalumab plus tremelimumab plus platinum–etoposide curve and the platinum–etoposide curve, indicating evidence of non-proportional hazards (data not shown). Formal testing by fitting a time-dependent covariate in the proportional hazards model provided a p value of 0·0035.

At the final analysis data cutoff, there were 441 deaths across the durvalumab plus platinum–etoposide and platinum–etoposide groups (82·1% maturity); 210 (78%) of 268 patients in the durvalumab plus platinum–etoposide group and 231 (86%) of 269 patients in the

A

	Events/patients (n)		Hazard ratio (95% CI)
	Durvalumab plus tremelimumab plus EP	EP	
Planned platinum			
Carboplatin	154/200	169/201	0·84 (0·67–1·04)
Cisplatin	53/68	62/68	0·79 (0·55–1·15)
Age, years			
<65	118/154	135/157	0·76 (0·59–0·97)
≥65	89/114	96/112	0·92 (0·69–1·22)
Sex			
Male	160/202	161/184	0·83 (0·66–1·03)
Female	47/66	70/85	0·76 (0·52–1·10)
WHO performance status score			
0	81/109	75/90	0·79 (0·58–1·09)
1	126/159	156/179	0·87 (0·69–1·10)
Smoking status			
Smoker	197/253	217/254	0·86 (0·70–1·04)
Non-smoker	10/15	14/15	0·43 (0·17–1·02)
Brain or CNS metastases			
Yes	32/38	23/27	0·91 (0·53–1·59)
No	175/230	208/242	0·81 (0·66–0·98)
Liver metastases*			
Yes	99/117	95/104	0·90 (0·68–1·20)
No	108/151	136/165	0·74 (0·58–0·96)
AJCC disease stage at diagnosis			
Stage III	14/18	20/24	0·96 (0·47–1·88)
Stage IV	193/250	211/245	0·81 (0·67–0·99)
Race			
Asian	36/47	36/42	0·86 (0·53–1·38)
Non-Asian	171/221	194/226	0·81 (0·66–1·00)
Region			
Asia	33/43	35/41	0·90 (0·55–1·46)
Europe	153/199	177/205	0·78 (0·62–0·96)
North America and South America	21/26	19/23	1·08 (0·58–2·03)
All patients	**207/268**	**231/269**	**0·82 (0·68–1·00)**



(Figure 3 continues on next page)

B

	Events/patients (n)		Hazard ratio (95% CI)
	Durvalumab plus EP	EP	
Planned platinum			
Carboplatin	159/201	169/201	0·79 (0·63–0·98)
Cisplatin	51/67	62/68	0·67 (0·46–0·97)
Age, years			
<65	125/167	135/157	0·72 (0·56–0·91)
≥65	85/101	96/112	0·84 (0·62–1·12)
Sex			
Male	158/190	161/184	0·79 (0·63–0·99)
Female	52/78	70/85	0·65 (0·45–0·93)
WHO performance status score			
0	75/99	75/90	0·77 (0·56–1·06)
1	135/169	156/179	0·76 (0·60–0·96)
Smoking status			
Smoker	193/246	217/254	0·75 (0·62–0·91)
Non-smoker	17/22	14/15	0·83 (0·41–1·71)
Brain or CNS metastases			
Yes	23/28	23/27	0·79 (0·44–1·41)
No	187/240	208/242	0·76 (0·62–0·92)
Liver metastases*			
Yes	96/108	95/104	0·87 (0·66–1·16)
No	114/160	136/165	0·68 (0·53–0·88)
AJCC disease stage at diagnosis			
Stage III	21/28	20/24	0·83 (0·44–1·54)
Stage IV	189/240	211/245	0·75 (0·62–0·92)
Race			
Asian	29/36	36/42	0·86 (0·52–1·40)
Non-Asian	181/232	194/226	0·75 (0·61–0·92)
Region			
Asia	28/35	35/41	0·87 (0·53–1·43)
Europe	157/200	177/205	0·74 (0·60–0·92)
North America and South America	25/33	19/23	0·77 (0·42–1·43)
All patients	**210/268**	**231/269**	**0·75 (0·62–0·91)**

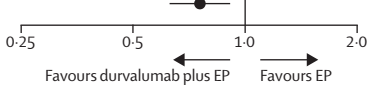


Figure 3: **Subgroup analysis of overall survival**

(A) Forest plot of subgroup analysis for overall survival for durvalumab plus tremelimumab plus EP versus EP. (B) Forest plot of subgroup analysis for overall survival for durvalumab plus EP versus EP. The size of circle in the forest plot is proportional to the number of events across both treatment groups. AJCC=American Joint Committee on Cancer. EP=etoposide plus either cisplatin or carboplatin. *Post-hoc analysis; all other subgroups were prespecified.

platinum–etoposide group had died. The overall survival benefit observed at the interim analysis for durvalumab plus platinum–etoposide compared with platinum–etoposide was sustained; in this updated analysis, the HR for overall survival was 0·75 (95% CI 0·62–0·91; nominal p=0·0032; figure 2B). Median overall survival was 12·9 months (95% CI 11·3–14·7) with durvalumab plus platinum–etoposide versus 10·5 months (9·3–11·2) with platinum–etoposide. A plot of the complementary log–log (event times) versus log (time) showed non-parallelism between the durvalumab plus platinum–etoposide curve and the platinum–etoposide alone curve, indicating evidence of non-proportional hazards (data not shown). Formal testing by fitting a time-dependent covariate in proportional hazards model provided a p value of 0·47.

Overall survival at 18 months was 30·7% (95% CI 25·2–36·4) in the durvalumab plus tremelimumab plus platinum–etoposide group and was 32·0% (26·5–37·7) in the durvalumab plus platinum-etoposide group versus 24·8% (19·7–30·1) in the platinum–etoposide group. The overall survival HRs for durvalumab plus tremelimumab plus platinum–etoposide versus platinum–etoposide alone across prespecified and post-hoc patient subgroups defined by baseline clinical and demographic characteristics were generally consistent with the overall population (figure 3A). The HRs for overall survival consistently favoured durvalumab plus platinum–etoposide versus platinum–etoposide across all prespecified patient subgroups, as observed at the interim analysis, as well as post-hoc subgroups defined by liver metastases at baseline (figure 3B).

At the time of data cutoff, 229 (85%) of 268 patients in the durvalumab plus tremelimumab plus platinum–etoposide group, 234 (87%) of 268 in the durvalumab plus platinum–etoposide group, and 236 (88%) of 269 in the platinum–etoposide group had disease progression or died. Median progression-free survival was similar for all groups (figure 4A, B). Progression-free survival at 6 months was 43·2% (95% CI 37·1–49·1) with durvalumab plus tremelimumab plus platinum–etoposide, 45·4% (39·3–51·3) with durvalumab plus platinum–etoposide, and 45·8% (39·5–51·9) with platinum–etoposide. At 12 months, progression-free survival was

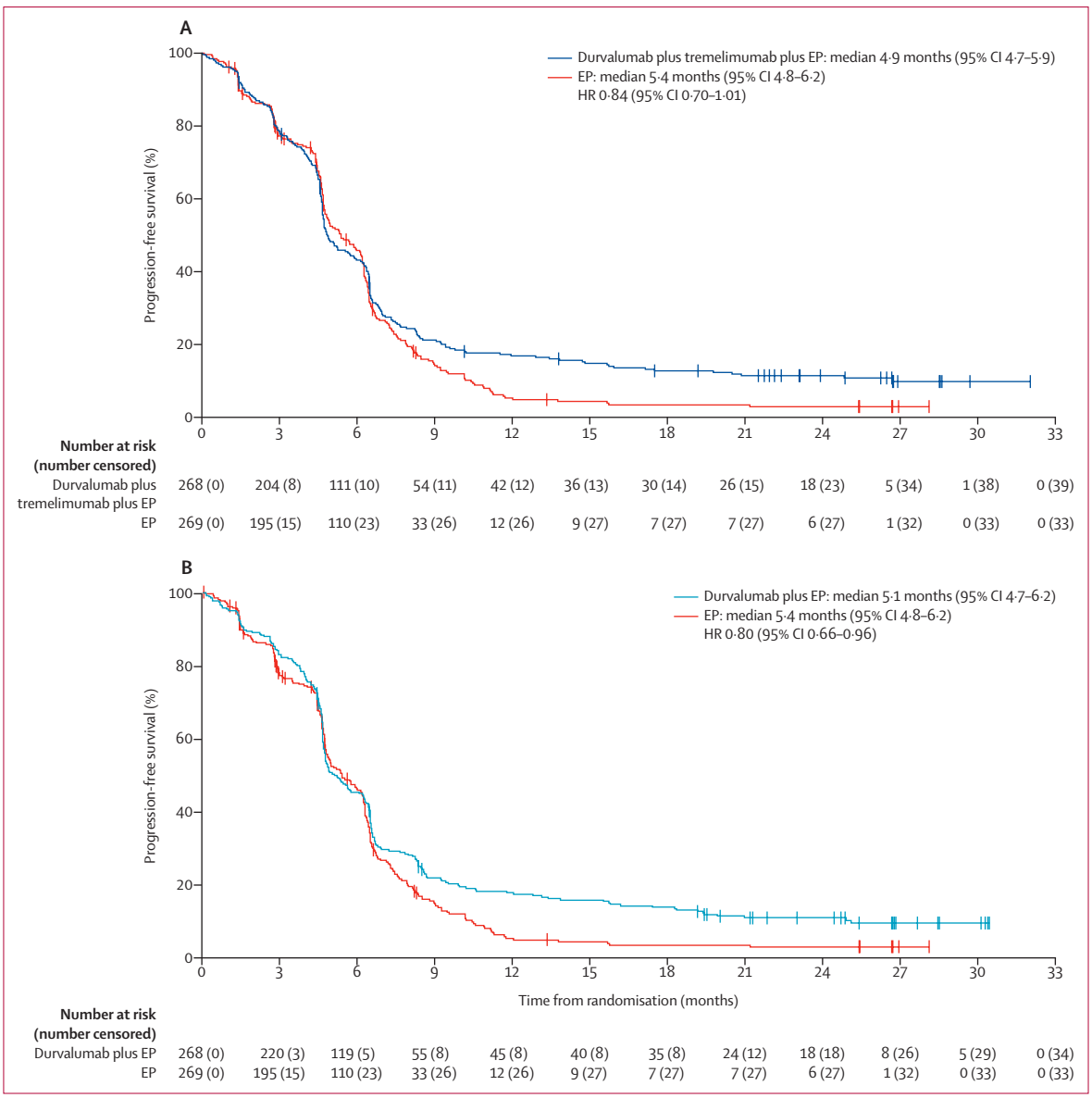


Figure 4: **Progression-free survival in the intention-to-treat population**
(A) Kaplan-Meier graph of progression-free survival for durvalumab plus tremelimumab plus EP versus EP. (B) Kaplan-Meier graph of progression-free survival for durvalumab plus EP versus EP. EP=etoposide plus either cisplatin or carboplatin. HR=hazard ratio.

16·9% (95% CI 12·6–21·7) with durvalumab plus tremelimumab plus platinum–etoposide, 17·9% (13·5–22·8) with durvalumab plus platinum–etoposide, and 5·3% (2·9–8·8) with platinum–etoposide.

The proportion of patients with an investigator-assessed unconfirmed objective response with durvalumab plus tremelimumab plus platinum–etoposide (198 [74%] of 267 patients) was similar to that with platinum–etoposide (190 [71%] of 269 patients); OR 1·19 (95% CI 0·82–1·75). Further details of unconfirmed response in all three treatment groups are reported in the appendix (p 15).

In a post-hoc analysis, the proportion of patients with a confirmed objective response in the durvalumab plus tremelimumab plus platinum–etoposide group (156 [58%] of 267 patients) was the same as in the platinum–etoposide group (156 [58%] of 269 patients); OR 1·02 (95% CI 0·72–1·44). The median best reduction from baseline in target lesion size was –59·3% (IQR –73·6 to –40·0) in the durvalumab plus tremelimumab plus platinum–etoposide group compared with –55·9% (–71·3 to –35·8) in the platinum–etoposide group. The depth of response is shown in the appendix (p 8).

In a post-hoc analysis, the proportion of patients with an investigator-assessed confirmed objective response remained higher with durvalumab plus platinum–etoposide (182 [68%] of 268 patients) than with

	Durvalumab plus tremelimumab plus platinum–etoposide (n=266)				Durvalumab plus platinum–etoposide (n=265)				Platinum–etoposide (n=266)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any event	68 (26%)	112 (42%)	57 (21%)	27 (10%)*	89 (34%)	116 (44%)	42 (16%)	13 (5%)*	85 (32%)	107 (40%)	51 (19%)	15 (6%)*
Neutropenia	30 (11%)	52 (20%)	33 (12%)	0	47 (18%)	38 (14%)	26 (10%)	0	36 (14%)	58 (22%)	30 (11%)	0
Anaemia	66 (25%)	32 (12%)	2 (1%)	0	78 (29%)	24 (9%)	0	0	77 (29%)	47 (18%)	1 (<1%)	0
Nausea	81 (30%)	5 (2%)	0	0	88 (33%)	1 (<1%)	0	0	84 (32%)	5 (2%)	0	0
Alopecia	78 (29%)	1 (<1%)	0	0	81 (31%)	3 (1%)	0	0	89 (33%)	2 (1%)	0	0
Decreased appetite	52 (20%)	5 (2%)	0	0	46 (17%)	2 (1%)	0	0	44 (17%)	2 (1%)	0	0
Constipation	53 (20%)	1 (<1%)	0	0	43 (16%)	2 (1%)	0	0	51 (19%)	0	0	0
Thrombocytopenia	30 (11%)	13 (5%)	11 (4%)	0	26 (10%)	11 (4%)	4 (2%)	0	27 (10%)	14 (5%)	11 (4%)	1 (<1%)
Fatigue	50 (19%)	3 (1%)	0	0	44 (17%)	4 (2%)	0	0	42 (16%)	3 (1%)	0	0
Asthenia	33 (12%)	5 (2%)	0	0	37 (14%)	5 (2%)	0	0	37 (14%)	3 (1%)	0	0
Vomiting	32 (12%)	4 (2%)	0	0	39 (15%)	0	0	0	41 (15%)	3 (1%)	0	0
Leucopenia	17 (6%)	13 (5%)	3 (1%)	0	23 (9%)	17 (6%)	0	0	18 (7%)	14 (5%)	0	0
Diarrhoea	37 (14%)	7 (3%)	0	0	25 (9%)	4 (2%)	0	0	27 (10%)	3 (1%)	0	0
Dyspnoea	19 (7%)	5 (2%)	1 (<1%)	0	27 (10%)	5 (2%)	0	0	25 (9%)	4 (2%)	0	0
Cough	27 (10%)	1 (<1%)	0	0	33 (12%)	2 (1%)	0	0	19 (7%)	0	0	0
Pyrexia	36 (14%)	0	0	0	22 (8%)	0	0	0	17 (6%)	1 (<1%)	0	0
Back pain	30 (11%)	0	0	0	22 (8%)	2 (1%)	0	0	17 (6%)	1 (<1%)	0	0
Pruritus	40 (15%)	0	0	0	21 (8%)	0	0	0	10 (4%)	0	0	0
Headache	28 (11%)	1 (<1%)	0	0	16 (6%)	1 (<1%)	0	0	22 (8%)	0	0	0
Neutrophil count decreased	0	4 (2%)	7 (3%)	0	9 (3%)	9 (3%)	8 (3%)	0	14 (5%)	8 (3%)	9 (3%)	0
Hyponatraemia	12 (5%)	7 (3%)	7 (3%)	0	16 (6%)	7 (3%)	3 (1%)	0	5 (2%)	6 (2%)	1 (<1%)	0
Rash	33 (12%)	3 (1%)	0	0	16 (6%)	0	0	0	10 (4%)	0	0	0
Hyperthyroidism	27 (10%)	1 (<1%)	0	0	26 (10%)	0	0	0	1 (<1%)	0	0	0
Pneumonia	12 (5%)	9 (3%)	0	5 (2%)	6 (2%)	5 (2%)	0	0	8 (3%)	9 (3%)	0	1 (<1%)
Febrile neutropenia	1 (<1%)	11 (4%)	3 (1%)	2 (1%)	3 (1%)	13 (5%)	1 (<1%)	0	0	14 (5%)	3 (1%)	0
White blood cell count decreased	1 (<1%)	6 (2%)	2 (1%)	0	10 (4%)	3 (1%)	1 (<1%)	0	11 (4%)	4 (2%)	2 (1%)	0
Hypertension	8 (3%)	6 (2%)	1 (<1%)	0	8 (3%)	8 (3%)	0	0	6 (2%)	1 (<1%)	0	0
Platelet count decreased	3 (1%)	2 (1%)	1 (<1%)	0	12 (5%)	3 (1%)	1 (<1%)	0	8 (3%)	3 (1%)	3 (1%)	0
Lipase increased	4 (2%)	5 (2%)	1 (<1%)	0	3 (1%)	8 (3%)	1 (<1%)	0	3 (1%)	3 (1%)	1 (<1%)	0
Amylase increased	5 (2%)	1 (<1%)	0	0	5 (2%)	5 (2%)	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
Pulmonary embolism	3 (1%)	3 (1%)	1 (<1%)	2 (1%)	0	1 (<1%)	0	1 (<1%)	2 (1%)	1 (<1%)	0	0

Grade 1–2 events with an incidence of ≥10% in any treatment group and grade 3 or worse events with an incidence of ≥2% in any treatment group are shown. All grade 3–5 events are listed in the appendix (pp 16–21). Events are listed in descending order of frequency across all treatment groups. Includes adverse events that occurred during the treatment period and up to 90 days after the last dose of study treatment or up to the start of any subsequent therapy (whichever occurred first). Platinum–etoposide=etoposide plus either cisplatin or carboplatin. *Adverse events of any cause leading to death were death and pneumonia in four patients each, febrile neutropenia, pulmonary embolism, and sudden death in two patients each, and acute respiratory failure, brain oedema, cardiac arrest, choking, *Clostridium difficile* colitis, enterocolitis, general physical health deterioration and multiple organ dysfunction syndrome (in the same patient), inappropriate antidiuretic hormone secretion, pneumonia and loss of consciousness (in the same patient), pneumonitis, pneumonitis and hepatitis (in the same patient), pulmonary haemorrhage, and respiratory failure in one patient each in the durvalumab plus tremelimumab plus platinum–etoposide group; sudden death in two patients, and acute respiratory failure, aspiration, cardiac arrest, dehydration, hepatotoxicity, interstitial lung disease, pancytopenia, pulmonary artery thrombosis, pulmonary embolism, sepsis, and septic shock in one patient each in the durvalumab plus platinum–etoposide group; and 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 in the platinum–etoposide group.

Table 2: **Adverse events of any cause (safety population)**

platinum–etoposide alone (156 [58%] of 269 patients) in the updated analysis; OR 1·53 (95% CI 1·08–2·18; appendix p 15). The median best reduction from baseline in target lesion size was –60·4% (IQR –72·9 to –44·3) in the durvalumab plus platinum–etoposide group compared with –55·9% (–71·3 to –35·8) in the platinum–etoposide group. The depth of response is shown in the appendix (p 8).

In a post-hoc analysis, among patients with a confirmed response, the median duration of response was similar for all groups (appendix p 9). The estimated percentage of patients remaining in response at 12 months was 24·9% (95% CI 18·4–32·0) in the durvalumab plus tremelimumab plus platinum–etoposide group and 23·2% (17·3–29·7) in the durvalumab plus platinum–etoposide group versus 7·3% (3·8–12·4) in the platinum–etoposide group. At 24 months, the estimated percentage of patients remaining in response was 17·2% (11·4–24·0) in the durvalumab plus tremelimumab plus platinum–etoposide group and 13·5% (8·7–19·3) in the durvalumab

plus platinum–etoposide group versus 3·9% (1·4–8·4) in the platinum–etoposide group.

In post-hoc analyses, 12-month overall survival was 43·8% (95% CI 37·7–49·7) in the durvalumab plus tremelimumab plus platinum–etoposide group, 52·8% (46·6–58·5) in the durvalumab plus platinum–etoposide group, and 39·3% (33·4–45·1) in the platinum–etoposide group; 24-month overall survival was 23·4% (18·4–28·8), 22·2% (17·3–27·5), and 14·4% (10·3–19·2), respectively. 24-month progression-free survival was 11·5% (95% CI 7·9–15·8) with durvalumab plus tremelimumab plus platinum–etoposide, 11·0% (7·5–15·2) with durvalumab plus platinum–etoposide, and 2·9% (1·2–5·8) with platinum–etoposide.

In the updated analysis, the safety profiles in the durvalumab plus platinum–etoposide group and the platinum–etoposide group were consistent with those previously reported.[9] Adverse events of any cause and grade occurred in 264 (99%) of 266 patients in the durvalumab plus tremelimumab plus platinum–etoposide group, 260 (98%) of 265 patients in the durvalumab plus platinum–etoposide group, and 258 (97%) of 266 patients in the platinum–etoposide group (table 2). The most common grade 3 or worse adverse events were neutropenia (85 [32%] in the durvalumab plus tremelimumab plus platinum–etoposide group, 64 [24%] in the durvalumab plus platinum–etoposide group, and 88 [33%] in the platinum–etoposide group) and anaemia (34 [13%], 24 [9%], and 48 [18%]), consistent with the interim analysis. Serious adverse events were reported in 121 (45%) patients in the durvalumab plus tremelimumab plus platinum–etoposide group, 85 (32%) patients in the durvalumab plus platinum–etoposide group, and 97 (36%) patients in the platinum–etoposide group (appendix pp 22–25). Adverse events leading to discontinuation of at least one study drug were reported in 57 (21%) patients in the durvalumab plus tremelimumab plus platinum–etoposide group, 27 (10%) patients in the durvalumab plus platinum–etoposide group, and 25 (9%) patients in the platinum–etoposide group (appendix p 26). Deaths due to adverse events of any cause occurred in 27 (10%) patients in the durvalumab plus tremelimumab plus platinum–etoposide group (12 [5%] were related to treatment: death, febrile neutropenia, and pulmonary embolism [n=2 each], and enterocolitis, general physical health deterioration and multiple organ dysfunction syndrome, pneumonia, pneumonitis and hepatitis, respiratory failure, and sudden death [n=1 each]), 13 (5%) patients in the durvalumab plus platinum–etoposide group (six [2%] related to treatment: cardiac arrest, dehydration, hepatotoxicity, interstitial lung disease, pancytopenia, and sepsis [n=1 each]), and 15 (6%) patients in the platinum–etoposide group (two [1%] related to treatment: pancytopenia in one patient and thrombocytopenia and haemorrhage in one patient; table 2; appendix p 27). Of the total deaths in the intention-to-treat population, the majority were considered by the investigator to be related to the disease under investigation only: 166 (62%) of 268 patients in the durvalumab plus tremelimumab plus platinum-etoposide group, 189 (71%) of 268 patients in the durvalumab plus platinum-etoposide group, and 200 (74%) of 269 patients in the platinum-etoposide group. Treatment-related adverse events, treatment-related serious adverse events, and treatment-related adverse events leading to discontinuation are shown in the appendix (pp 27–29).

Immune-mediated adverse events were reported in 96 (36%) of 266 patients in the durvalumab plus tremelimumab plus platinum–etoposide group, 53 (20%) of 265 patients in the durvalumab plus platinum–etoposide group, and seven (3%) of 266 patients in the platinum–etoposide group (appendix p 30). Grade 3 or 4 immune-mediated adverse events occurred in 36 (14%) patients in the durvalumab plus tremelimumab plus platinum–etoposide group, 13 (5%) patients in the durvalumab plus platinum–etoposide group, and one patient (<1%) in the platinum–etoposide group. Deaths due to immune-mediated adverse events occurred in three (1%) patients receiving durvalumab plus tremelimumab plus platinum–etoposide (enterocolitis, pneumonitis, and pneumonitis and hepatitis in the same patient), two (1%) patients receiving durvalumab plus platinum–etoposide (hepatotoxicity and interstitial lung disease), and one patient (<1%) receiving platinum–etoposide (pneumonitis). The most common immune-mediated adverse events were hypothyroid events and hyperthyroid events, most of which were grade 1 or 2 in severity. Diarrhoea or colitis and dermatitis or rash immune-mediated adverse events were also common in the durvalumab plus tremelimumab plus platinum–etoposide group (appendix p 30).

Discussion

To our knowledge, this is the first report of a phase 3 trial evaluating dual immune checkpoint blockade in combination with chemotherapy in ES-SCLC. Durvalumab plus tremelimumab plus platinum–etoposide was not associated with a significant improvement in overall survival versus platinum–etoposide (HR 0·82 [95% CI 0·68–1·00]; p=0·045). The updated analysis of the durvalumab plus platinum–etoposide group compared with platinum–etoposide showed a sustained overall survival benefit for first-line treatment with durvalumab plus platinum–etoposide after an additional 11 months of follow-up (HR 0·75 [95% CI 0·62–0·91]; nominal p=0·0032), which was consistent with the interim analysis (HR 0·73 [0·59–0·91]; p=0·0047).[9] Key secondary efficacy outcomes of progression-free survival and objective response continued to favour durvalumab plus platinum–etoposide over platinum–etoposide, and safety findings in this group were consistent with the previously reported safety profile.

The late separation of the Kaplan-Meier curves for each immunotherapy group versus platinum–etoposide shows evidence of non-proportionality of hazards for both overall survival and progression-free survival, which was further

supported by the complementary log–log (event times) versus log (time) plots for overall survival. Therefore, the HRs should be considered as an average estimate of the observed benefit and it is appropriate to include the landmarks as a component of the overall survival and progression-free survival assessment. Although there was no difference in median overall survival between the durvalumab plus tremelimumab plus platinum–etoposide and platinum–etoposide groups, notably, overall survival at 24 months was higher in the durvalumab plus tremelimumab plus platinum–etoposide group than in the platinum–etoposide group. Similarly, progression-free survival at both 12 months and 24 months was higher with durvalumab plus tremelimumab plus platinum–etoposide than with platinum–etoposide. There was no difference between the durvalumab plus tremelimumab plus platinum–etoposide group and the platinum–etoposide group in the proportion of patients with a confirmed objective response or in the median duration of response. However, the proportion of patients remaining in response was greater with durvalumab plus tremelimumab plus platinum–etoposide than with platinum–etoposide at both 12 months and 24 months.

Treatment with durvalumab plus tremelimumab plus platinum–etoposide was associated with a higher incidence of grade 3 or worse adverse events, serious adverse events, and adverse events leading to death or discontinuation than was durvalumab plus platinum–etoposide or platinum–etoposide, although results were consistent with the established safety profile of durvalumab plus tremelimumab and the individual chemotherapy agents. The higher toxicity was not driven by a single type of event; rather, the increase in adverse events was dispersed across several system organ classes. The increased toxicity observed with the addition of tremelimumab might have resulted in fewer patients having the intended exposure to all agents. Although the addition of tremelimumab to durvalumab plus platinum–etoposide did not affect the median duration of chemotherapy treatment, a lower proportion of patients received at least four cycles of chemotherapy in the tremelimumab-containing group than in the other two groups. In addition, only 61% of patients received the full five planned doses of tremelimumab. Importantly, patients in the durvalumab plus tremelimumab plus platinum–etoposide group had lower total exposure to durvalumab than the durvalumab plus platinum–etoposide group, which might have resulted from the requirement to discontinue both durvalumab and tremelimumab in the event of a treatment-related adverse event meeting criteria for discontinuation of immunotherapy. This reduced study drug exposure might have affected the proportion of patients with an objective response and ultimately median overall survival in the durvalumab plus tremelimumab plus platinum–etoposide group, and could have contributed to the absence of significant benefit compared with platinum–etoposide, although further investigation is required to confirm this hypothesis.

Although there were some minor differences in prognostic baseline characteristics between the durvalumab plus tremelimumab plus platinum–etoposide group and the platinum–etoposide group (eg, brain metastases, liver metastases, and performance status), it is unlikely that these would have affected the overall conclusions of the study. The proportion of patients who received second-line systemic anticancer therapy was similar across treatment groups. However, a smaller proportion of patients received third-line systemic anticancer therapy in the durvalumab plus tremelimumab plus platinum–etoposide group than the platinum–etoposide group, which might have contributed to the absence of significant improvement in overall survival with durvalumab plus tremelimumab plus platinum–etoposide versus platinum–etoposide.

Durvalumab plus platinum–etoposide met the primary endpoint of improved survival compared with platinum–etoposide alone at the planned interim analysis, which is therefore considered the final result. This updated analysis, with more than 2 years of median follow-up, showed a sustained overall survival improvement with durvalumab plus platinum–etoposide. The estimated proportion of patients alive was higher with durvalumab plus platinum–etoposide than with platinum–etoposide at all landmark timepoints and the separation of the Kaplan-Meier curves was maintained to the end of follow-up. The overall survival benefit with durvalumab plus platinum–etoposide versus platinum–etoposide was consistently shown across all patient subgroups, including patients treated with cisplatin and patients with brain metastases at baseline. In the updated analysis, progression-free survival remained in favour of durvalumab plus platinum–etoposide versus platinum–etoposide and progression-free survival at both 12 months and 24 months was higher with durvalumab plus platinum–etoposide than with platinum–etoposide. The proportion of patients with an objective response (based on either unconfirmed or confirmed responses) was higher with durvalumab plus platinum–etoposide versus platinum–etoposide, consistent with the interim analysis. Additionally, the proportion of patients remaining in response was greater with durvalumab plus platinum–etoposide than with platinum–etoposide at both 12 months and 24 months. After an additional year of follow-up, durvalumab plus platinum–etoposide continued to show a manageable safety profile that was consistent with the interim analysis and the established safety profiles of the individual agents.

Although durvalumab plus tremelimumab plus platinum–etoposide did not show a significant difference in overall survival compared with platinum–etoposide, the tails of the overall survival Kaplan-Meier curves for both immunotherapy groups were similar, with more than 20% of patients estimated to be alive at 24 months

in each group. Similarity between the immunotherapy groups was also seen in the tails of the progression-free survival Kapan-Meier curves. The observation that nearly 20% of patients were estimated to be progression free at 12 months across both durvalumab groups (compared with 5% in the platinum–etoposide group), and that many of these patients remained progression free even at 24 months, suggests that there is a proportion of patients with ES-SCLC who derive long-term clinical benefit with durvalumab plus platinum–etoposide. The sustained benefit is particularly noteworthy in this aggressive disease setting where, historically, it has been difficult to show long-term survival benefit.

Overall, there was no evidence of any additional benefit with the addition of tremelimumab to durvalumab plus platinum–etoposide in CASPIAN, even in the population of patients who seem to derive long-term clinical benefit. Although disappointing, this is consistent with findings from phase 3 studies of ipilimumab in ES-SCLC,[19,20] indicating that CTLA-4 blockade might not have a substantial role in an unselected patient population in this setting.

To our knowledge, CASPIAN is the first pivotal trial in ES-SCLC to show a significant survival benefit with PD-1 or PD-L1 blockade in combination with etoposide and a choice of carboplatin or cisplatin chemotherapy. This represents an important therapeutic advance given that in recent years (2014–16) cisplatin-containing chemotherapy was used for 27–42% of patients in the first-line treatment of ES-SCLC in different regions of the world.[21] The overall survival benefit observed with durvalumab plus platinum–etoposide in CASPIAN aligns with findings from the IMpower133 trial of first-line atezolizumab plus carboplatin–etoposide for patients with ES-SCLC.[10,22] Like CASPIAN, the KEYNOTE-604 study permitted investigator's choice of platinum; although the addition of first-line pembrolizumab to platinum–etoposide significantly improved progression-free survival in patients with ES-SCLC, the other primary endpoint of improved overall survival was not met.[23] The phase 2 EA5161 trial of nivolumab plus platinum–etoposide versus platinum–etoposide alone as first-line therapy for ES-SCLC, which also permitted use of carboplatin or cisplatin, showed a significant improvement in the primary endpoint of progression-free survival.[24]

Additional work is needed to identify patient characteristics that might predict long-term benefit following treatment with first-line immunotherapy and chemotherapy in ES-SCLC. To date, most studies suggest that PD-L1 expression does not predict benefit with immune checkpoint inhibitors in SCLC,[22,25–27] although one single-arm, phase 2 study showed PD-L1 positivity enriched for response in patients with relapsed or refractory advanced SCLC.[28] Association of higher tumour mutational burden levels with improved outcomes in SCLC has only been observed in an early phase trial in patients with relapsed or refractory disease,[29] and subgroup analyses from IMpower133 showed no evidence of association of tumour mutational burden with outcomes.[10] Further biomarker analyses in this context are warranted, including the exploration of emerging biomarkers such as SCLC molecular subtypes.[30]

Limitations of the CASPIAN study have been previously described and include the open-label study design.[9] Although the primary endpoint of overall survival is not subject to open-label bias, secondary endpoints such as investigator assessment of progression and response could be affected. In addition, bias cannot be ruled out in the attribution of causality for adverse event reporting and, as such, we have focused on any-cause adverse events in this paper. A further limitation is that it was not possible to formally test progression-free survival for statistical significance within the multiple testing procedure at either the interim or final analysis.

In conclusion, updated results from this randomised, open-label, phase 3 trial show sustained overall survival benefit with the addition of durvalumab to platinum–etoposide in patients with ES-SCLC compared with a robust control group after a median follow-up of more than 2 years. The addition of tremelimumab to durvalumab plus platinum–etoposide did not significantly improve outcomes in this trial. Safety findings in all groups were consistent with the known safety profiles of the individual drugs. These results support the use of durvalumab plus platinum–etoposide as a new standard of care for the first-line treatment of ES-SCLC, offering the flexibility of platinum choice and an every-4-weeks maintenance dosing schedule that expands treatment options for patients and physicians.

Contributors

NB, HJ, and LP-A were involved in the conception, design, and planning of the study. JWG, MD, YC, NR, KH, DT, GS, MJH, MÖ, JHJ, MCG, OV, AP, SP, FV, LH, IB, AK, GL, NVC, and LP-A 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

JWG has received grants and personal fees from AstraZeneca during the conduct of the study; and grants and personal fees from Genentech outside the submitted work. YC has received personal fees from AstraZeneca, Genentech, Bristol Myers Squibb (BMS), Merck, Novartis, Takeda, Eli Lilly, Guardant Health, Pfizer, and Array Biopharma; and grants from AstraZeneca, Ipsen, Roche, and BMS, all outside the submitted work. NR has received 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 Merck Sharp and Dohme (MSD) and Takeda, all outside the submitted work. KH has received grants and personal fees from AstraZeneca during the conduct of the study; grants and personal fees from Lilly, AstraZeneca, BMS, MSD, and Chugai outside the submitted work; personal fees from Pfizer, Ono, Nipponkayaku, Taiho, Boehringer Ingelheim, Novartis, Daiichi-Sankyo, and Kyorin outside the submitted work; and grants from Astellas outside the submitted work. MÖ has participated in advisory boards for Janssen, Sanofi, and Astellas; has received honoraria from Novartis, Roche, Janssen, Sanofi, and Astellas; and has been reimbursed for travel, accommodation, or expenses from BMS and Janssen, all outside the submitted work. MCG has received grants and personal fees from Eli Lilly, Otsuka Pharmaceutical, AstraZeneca, Novartis, BMS,

Roche, Pfizer, Celgene, Incyte, Bayer, MSD, 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, Merck, Turning Point Therapeutics, Ipsen, and Exelisis; and non-financial support from MSD, Pfizer, and Eli Lilly, all outside the submitted work. SP has received grants from Roche and MSD; and lecture fees from Roche, BMS, AstraZeneca, and Pfizer, all outside the submitted work. FV has received grants from AstraZeneca during the conduct of this study. JA, PT, and HJ are full-time employees of and own stock in AstraZeneca. NB is a contractor for and owns stock in AstraZeneca. LP-A reports leadership with Genomica and Altum Sequencing; has been reimbursed for travel, accommodation, or expenses from Roche, AstraZeneca, AstraZeneca Spain, MSD, BMS, Lilly, and Pfizer; has received honoraria from Roche/Genentech, Lilly, Pfizer, Boehringer Ingelheim, BMS, MSD, 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. 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. We thank the patients, their families and caregivers, and all investigators involved in this study, April Franks 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 3 guidelines, was provided by Rebecca Douglas and Samantha Holmes of Cirrus Communications (Macclesfield, UK), an Ashfield company, and was funded by AstraZeneca.

References

1 Oronsky B, Reid TR, Oronsky A, Carter CA. What's new in SCLC? A review. *Neoplasia* 2017; **19:** 842–47.
2 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.
3 Byers LA, Rudin CM. Small cell lung cancer: where do we go from here? *Cancer* 2015; **121:** 664–72.
4 Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med* 2015; **372:** 2521–32.
5 Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without *BRAF* mutation. *N Engl J Med* 2015; **372:** 320–30.
6 Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015; **373:** 23–34.
7 Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016; **375:** 1823–33.
8 Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2019; **393:** 1819–30.
9 Paz-Ares L, Dvorkin M, Chen Y, 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* 2019; **394:** 1929–39.
10 Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med* 2018; **379:** 2220–29.
11 Tarhini AA. Tremelimumab: a review of development to date in solid tumors. *Immunotherapy* 2013; **5:** 215–29.
12 Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012; **12:** 252–64.
13 Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018; **378:** 1277–90.
14 Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non–small-cell lung cancer. *N Engl J Med* 2019; **381:** 2020–31.
15 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.
16 AstraZeneca. Imfinzi (durvalumab) prescribing information. March, 2020. https://www.azpicentral.com/imfinzi/imfinzi.pdf#page=1 (accessed April 1, 2020).
17 Lan K-KG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983; **70:** 659–63.
18 Burman CF, Sonesson C, Guilbaud O. A recycling framework for the construction of Bonferroni-based multiple tests. *Stat Med* 2009; **28:** 739–61.
19 Reck M, Luft A, Szczesna A, et al. Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. *J Clin Oncol* 2016; **34:** 3740–48.
20 Owonikoko TK, Kim HR, Govindan R, et al. Nivolumab (nivo) plus ipilimumab (ipi), nivo, or placebo (pbo) as maintenance therapy in patients (pts) with extensive disease small cell lung cancer (ED-SCLC) after first-line (1L) platinum-based chemotherapy (chemo): results from the double-blind, randomized phase 3 CheckMate 451 study. *Ann Oncol* 2019; **30** (suppl 2)**:** ii77–80 (abstr LBA1_PR).
21 DiBonaventura MD, Shah-Manek B, Higginbottom K, Penrod JR, Yuan Y. Adherence to recommended clinical guidelines in extensive disease small-cell lung cancer across the US, Europe, and Japan. *Ther Clin Risk Manag* 2019; **15:** 355–66.
22 Reck M, Liu SV, Mansfield AS, et al. IMpower133: updated overall survival (OS) analysis of first-line (1L) atezolizumab (atezo) + carboplatin + etoposide in extensive-stage SCLC (ES-SCLC). *Ann Oncol* 2019; **30** (suppl 5)**:** v710–717 (abstr 2374).
23 Rudin CM, Awad MM, Navarro A, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. *J Clin Oncol* 2020; **38:** 2369–79.
24 Leal T, Wang Y, Dowlati A, et al. Randomized phase II clinical trial of cisplatin/carboplatin and etoposide (CE) alone or in combination with nivolumab as frontline therapy for extensive-stage small cell lung cancer (ES-SCLC): ECOG-ACRIN EA5161. *Proc Am Soc Clin Oncol* 2020; **38** (suppl)**:** abstr 9000.
25 Paz-Ares L, Goldman JW, Garassino MC, et al. PD-L1 expression, patterns of progression and patient-reported outcomes (PROS) with durvalumab plus platinum-etoposide in ES-SCLC: results from CASPIAN. *Ann Oncol* 2019; **30** (suppl 5)**:** v851–934 (abstr 3837).
26 Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol* 2016; **17:** 883–95.
27 Ready N, Farago AF, de Braud F, et al. Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. *J Thorac Oncol* 2019; **14:** 237–44.
28 Chung HC, Lopez-Martin JA, Kao SC-H, et al. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158. *Proc Am Soc Clin Oncol* 2018; **36** (suppl)**:** abstr 8506.
29 Hellmann MD, Callahan MK, Awad MM, et al. Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in small-cell lung cancer. *Cancer Cell* 2018; **33:** 853–861.e4.
30 Rudin CM, Poirier JT, Byers LA, et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. *Nat Rev Cancer* 2019; **19:** 289–97.

For **AstraZeneca's data sharing policy** see https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure