Efficacy and safety of first-line maintenance therapy with lurbinectedin plus atezolizumab in extensive-stage small-cell lung cancer (IMforte): a randomised, multicentre, open-label, phase 3 trial

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Summary

Background Despite improved efficacy with first-line immune checkpoint inhibitors plus platinum-based chemotherapy for extensive-stage small-cell lung cancer (ES-SCLC), survival remains poor. In this study, we aimed to compare lurbinectedin plus atezolizumab and atezolizumab alone as maintenance therapies in patients with ES-SCLC without progression after induction therapy with atezolizumab, carboplatin, and etoposide.

Methods IMforte was a randomised, open-label, phase 3 trial done at 96 hospitals and medical centres in 13 countries (Belgium, Germany, Greece, Hungary, Italy, Mexico, Poland, South Korea, Spain, Taiwan, Türkiye, the UK, and the USA). Eligible patients were aged 18 years or older with treatment-naive ES-SCLC. Patients received four 21-day cycles of induction treatment (atezolizumab, carboplatin, and etoposide). After completing induction treatment, eligible patients without disease progression were randomly assigned (1:1) using permuted blocks (Interactive Voice/Web Response System) to receive maintenance treatment intravenously every 3 weeks with lurbinectedin (3·2 mg/m²; with granulocyte colony-stimulating factor prophylaxis) plus atezolizumab (1200 mg) or atezolizumab (1200 mg). The two primary endpoints were independent review facility-assessed (IRF) progression-free survival and overall survival, measured from randomisation into the maintenance phase. Efficacy endpoints were assessed in the full analysis set, which included all patients who were randomly assigned to maintenance phase treatment, regardless of whether they received their assigned study treatment. Safety was assessed in all patients who received at least one dose of lurbinectedin or atezolizumab, and was analysed according to the treatment received. This study is registered with ClinicalTrials.gov, NCT05091567, and is closed for recruitment.

Findings Between Nov 17, 2021, and Jan 11, 2024, 895 patients were screened for enrolment, of whom 660 (74%) were enrolled into the induction phase. Between May 24, 2022, and April 30, 2024, 483 (73%) of 660 patients entered the maintenance phase and were randomly assigned to lurbinectedin plus atezolizumab (n=242) or atezolizumab (n=241). At the data cutoff (July 29, 2024), IRF progression-free survival was longer in the lurbinectedin plus atezolizumab group than the atezolizumab group (stratified hazard ratio [HR] 0·54 [95% CI 0·43–0·67]; p<0·0001), as was overall survival (stratified HR 0·73 [0·57–0·95]; p=0·017). 92 (38%) of 242 patients in the lurbinectedin plus atezolizumab group and 53 (22%) of 240 patients in the atezolizumab group had grade 3–4 adverse events. The most common grade 3–4 events in the lurbinectedin plus atezolizumab group were anaemia (20 [8%] of 242 patients), decreased neutrophil count (18 [7%] patients), and decreased platelet count (18 [7%] patients) and the most common events in the atezolizumab group were hyponatremia (five [2%] of 240 patients), dyspnoea (four [2%] patients), and pneumonia (four [2%] patients). Grade 5 adverse events occurred in 12 (5%) of 242 patients in the lurbinectedin plus atezolizumab group and six (3%) of 240 patients in the atezolizumab group. The incidence of myelosuppressive toxicities (eg, neutropenia and leukopenia) was higher in the lurbinectedin plus atezolizumab group than the atezolizumab group.

Interpretation IRF progression-free survival and overall survival were longer in the lurbinectedin plus atezolizumab group than the atezolizumab group for patients with ES-SCLC, albeit with a higher incidence of adverse events. Lurbinectedin plus atezolizumab represents a novel therapeutic option for first-line maintenance treatment in this setting.

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Research in context

Evidence before this study

Extensive-stage small-cell lung cancer (ES-SCLC), which accounts for approximately 15% of lung cancers, is an aggressive and highly lethal disease. The current standard of care is induction therapy with a combination of etoposide, platinum chemotherapy, and immunotherapy, followed by maintenance therapy with the same immunotherapy agent, based on the findings from the IMpower133 and CASPIAN trials, which showed significant improvements in overall survival and progression-free survival with atezolizumab or durvalumab, respectively, compared with chemotherapy alone. IMforte was designed to improve patient outcomes using a novel treatment approach in the first-line maintenance therapy setting. We searched PubMed on Feb 28, 2025, for publications describing phase 3 studies of first-line maintenance therapy in ES-SCLC published in English between Jan 1, 2011, and Dec 31, 2021, using the combined search terms "extensive-stage small-cell lung cancer", "extensive-disease small-cell lung cancer", "maintenance", "first-line", "phase 3", and "phase III". Our search identified two phase 3 trials of maintenance therapy: CheckMate 451, involving maintenance therapy with nivolumab or nivolumab plus ipilimumab, and MERU, involving maintenance therapy with rovalpituzumab tesirine, an antibody-drug conjugate targeting delta-like ligand 3. Although progression-free survival was favourable compared with placebo in both studies, formal statistical testing was not done, and neither study was able to demonstrate significant improvement in overall survival with experimental treatment. MERU met futility for overall survival and was discontinued early.

Added value of this study

To our knowledge, IMforte is the first phase 3 trial to meet the primary endpoints of progression-free survival and overall survival in the first-line maintenance setting in ES-SCLC. In IMforte, compared with patients in the atezolizumab group, patients in the lurbinectedin plus atezolizumab group had statistically significant and clinically meaningful improvement in both independently-assessed progression-free survival and overall survival, with a 46% reduction in the risk of disease progression or death and a 27% reduction in the risk of death versus atezolizumab alone as the active comparator in first-line maintenance treatment. Although the incidence of adverse events was higher in the lurbinectedin plus atezolizumab group than the atezolizumab group, the safety profile of the combination was considered manageable and consistent with the known safety profiles of each agent, with no new safety signals identified. These findings build on the regimen of atezolizumab combined with platinum-based chemotherapy followed by atezolizumab maintenance therapy that was first established as a standard of care based on the results of IMpower133 in 2019.

Implications of all the available evidence

Due to the high attrition rate in ES-SCLC, effective first-line treatment strategies are crucial to improve the prognosis of this aggressive disease. Patients whose disease did not progress on induction therapy with atezolizumab, etoposide, and carboplatin and who were administered lurbinectedin plus atezolizumab in the maintenance phase had significantly longer independent review facility-assessed progression-free survival and overall survival compared with those given maintenance atezolizumab alone. When putting IMforte into context with previous trials that have shown significant improvement in study outcomes with experimental treatment in the first-line setting of ES-SCLC (eg, IMpower133 and CASPIAN) it is important to note that in IMforte, progression-free survival and overall survival were measured from randomisation into the maintenance phase rather than from the start of the induction phase, and patients randomly assigned to maintenance treatment had favourable outcomes from induction therapy (ie, without early disease progression and without significant toxicity from induction therapy). The clinical benefits observed in IMforte highlight the potential of lurbinectedin plus atezolizumab as a new first-line maintenance treatment for patients with ES-SCLC, a population for whom improved treatment outcomes are urgently needed.

Introduction

Immune checkpoint inhibitors transformed the treatment landscape of extensive-stage small-cell lung cancer (ES-SCLC) in 2019 and have since become the standard of care in the first-line setting.[1–3] Results from the phase 3 IMpower133 trial showed that first-line induction treatment with atezolizumab plus carboplatin and etoposide followed by atezolizumab maintenance treatment significantly improved overall survival and progression-free survival versus placebo plus carboplatin and etoposide,[1] leading to multiple regulatory approvals globally. Despite improved efficacy with first-line immune checkpoint inhibitors plus platinum-based chemotherapy, most patients eventually relapse and survival remains poor.[4–8]

The high attrition rate in ES-SCLC (ie, the proportion of patients unable to receive subsequent lines of treatment) highlights the importance of developing effective treatment strategies in the first-line setting to improve the prognosis of patients with this aggressive and difficult-to-treat disease.[9] ES-SCLC is initially highly responsive to treatment, with response rates ranging from 50–70%.[1–3] However, a significant proportion of patients progress early after the end of induction therapy. Thus, more effective therapy in the maintenance phase before progression represents an opportunity to improve clinical outcomes in the first-line setting.

Lurbinectedin is a synthetic alkylating agent that promotes cancer cell death by inhibiting the binding of

oncogenic transcription factors to their recognition sequences.[10] In a phase 2 basket trial, lurbinectedin monotherapy had encouraging clinical activity,[11] which led to multiple regulatory approvals globally for metastatic SCLC following disease progression on or after platinum-based chemotherapy. A confirmatory phase 3 trial of lurbinectedin in patients with relapsed SCLC is ongoing (LAGOON; NCT05153239) after ATLANTIS, a phase 3 trial in relapsed SCLC with lurbinectedin plus doxorubicin, did not demonstrate improved overall survival when compared with a chemotherapy control.[12] Preclinical studies have shown that lurbinectedin modifies the tumour microenvironment[13] and synergises with immune checkpoint inhibitors.[14] Studies in the immunocompetent murine SCLC model with Rb1/Trp53 loss suggest that lurbinectedin plus PD-L1 inhibition act synergistically to achieve high rates of tumour regression and induce long-term T-cell memory.[15,16] In the first phase of 2SMALL, a trial in patients with relapsed ES-SCLC without previous exposure to cancer immunotherapy, the combination of the standard monotherapy dose of lurbinectedin (3·2 mg/m² every 3 weeks) with standard dose of atezolizumab (1200 mg every 3 weeks) was generally well tolerated without unexpected toxicities.[17] Consistent with preclinical findings, the combination demonstrated promising clinical activity (objective response rate [ORR] 57·7% and median progression-free survival of 4·9 months [range 3·4–7·7]) in a cohort of 26 patients. In a phase 2 study (LUPER; NCT04358237) of lurbinectedin and pembrolizumab in 28 patients with relapsed SCLC and no previous exposure to cancer immunotherapy, an ORR of 46·4% was achieved with median progression-free survival of 4·6 months (95% CI 2·7–6·0) and median overall survival of 10·5 months (95% CI 6·9–17·6).[18]

We hypothesised that the addition of lurbinectedin to standard-of-care atezolizumab maintenance treatment could improve first-line treatment outcomes without the addition of clinically significant toxicity. In IMforte, we aimed to compare the efficacy and safety of lurbinectedin combined with atezolizumab versus atezolizumab for the maintenance treatment of ES-SCLC in patients whose disease had not progressed after first-line induction treatment with atezolizumab, carboplatin, and etoposide.

Methods

Study design and participants

IMforte is a randomised, multicentre, open-label phase 3 study of lurbinectedin plus atezolizumab versus atezolizumab as maintenance therapy in patients with ES-SCLC after standard first-line induction therapy with atezolizumab, carboplatin, and etoposide, done at 96 sites in 13 countries (Belgium, Germany, Greece, Hungary, Italy, Mexico, Poland, South Korea, Spain, Taiwan, Türkiye, the UK, and the USA).

Patients aged 18 years or older were eligible to enrol in the induction phase if they had histologically or cytologically confirmed ES-SCLC per the Veterans Administration Lung Study Group staging system,[19] measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had not received previous systemic treatment for ES-SCLC. Key exclusion criteria for the induction phase were a history of autoimmune disease, previous treatment with immune checkpoint blockade therapies, and the presence or history of CNS metastases. Patients with CNS metastases were excluded on the basis of preclinical and exploratory clinical data suggesting limited activity of lurbinectedin in patients with CNS disease.[12]

Patients were eligible for the maintenance phase if they had an ongoing response or stable disease per RECIST (version 1.1) as assessed by the investigator after completing all four cycles of induction treatment and had an ECOG performance status of 0 or 1. Patients were not required to have measurable disease per RECIST (version 1.1) to be eligible for the maintenance phase. Patients were excluded from the maintenance phase if they had developed CNS metastases or if they had received consolidative thoracic radiation.

Sex, race, and ethnicity data were self-reported by patients.

IMforte was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. An independent data monitoring committee reviewed safety data at regular intervals. The protocol was approved by the institutional review board or ethics committee at each site. The protocol and statistical analysis plan are in the appendix (p 30). This trial is registered with ClinicalTrials.gov, NCT05091567.

Randomisation and masking

Patients were randomly assigned (1:1) to maintenance treatment using a permuted-block randomisation method (block size of four) with an interactive voice–web response system. Randomisation was stratified by ECOG performance status at maintenance baseline (0 or 1), lactate dehydrogenase level at maintenance baseline (≤ upper limit of normal [ULN] or >ULN), presence of liver metastases at induction baseline (yes or no), and previous receipt of prophylactic cranial irradiation (yes or no). Patients were required to be randomly assigned within 5 weeks from the last dose of induction treatment or within 9 weeks from the last dose of induction treatment if they received prophylactic cranial irradiation. The study was open label, therefore patients and investigators were not masked to treatment; however, assignments were withheld from sponsor personnel, including the study's medical monitor, statistician, statistical programmer, and data manager.

See Online for appendix

Procedures

During the induction phase, patients received four 21-day cycles of atezolizumab, carboplatin, and etoposide unless they experienced unacceptable toxic effects or disease progression per RECIST (version 1.1). 1200 mg intravenous atezolizumab was administered every 3 weeks. Carboplatin and etoposide were administered per institutional practice (appendix p 30). Patients could receive prophylactic cranial irradiation at the investigator's discretion per local standard of care after completing induction therapy and before randomisation.

After completing four cycles of induction therapy, eligible patients were randomly assigned to receive maintenance therapy with lurbinectedin (3·2 mg/m²) plus atezolizumab (1200 mg) or atezolizumab (1200 mg), administered intravenously every 3 weeks until the occurrence of unacceptable toxic effects, disease progression (per RECIST [version 1.1]), or withdrawal of consent. Study treatment beyond disease progression was not permitted per protocol. Unless contraindicated, patients receiving lurbinectedin plus atezolizumab also received prophylactic granulocyte colony-stimulating factor (G-CSF) and anti-emetic premedication per institutional guidelines. For lurbinectedin, up to two dose reductions were allowed (from 3·2 to 2·6 mg/m², then to 2·0 mg/m²); re-escalation was not permitted. Atezolizumab dose modifications were not permitted. If study treatment in the lurbinectedin plus atezolizumab group had to be temporarily interrupted or permanently discontinued to manage toxicity, lurbinectedin and atezolizumab could be interrupted or discontinued independently from each other. Crossover between treatment groups was not permitted. Patients who were not randomly assigned to the maintenance phase left the study and were managed according to the local standard of care.

Outcomes

The two primary endpoints were IRF progression-free survival (defined as the time from randomisation into the maintenance phase to disease progression per RECIST [version 1.1] as assessed by the IRF or death from any cause, whichever occurred first) and overall survival (defined as the time from randomisation into the maintenance phase to death from any cause). Secondary efficacy endpoints were investigator-assessed progression-free survival, confirmed ORR (proportion of patients with measurable disease at maintenance baseline and a complete or partial response on two consecutive occasions ≥4 weeks apart after randomisation into the maintenance phase, per RECIST [version 1.1]), and duration of response (defined as the time from the first occurrence of confirmed objective response after randomisation until disease progression per RECIST [version 1.1], or death from any cause, whichever occurred first), both assessed by the IRF and per investigator, and rates of progression-free survival at 6 and 12 months and overall survival at 12 and 24 months after randomisation. To assess the effect of experimental treatment on tumour response during the maintenance phase, tumour response was compared against the maintenance baseline (or nadir during the maintenance phase), not against the induction baseline. Exploratory subgroup analyses of progression-free survival and overall survival were assessed according to prespecified baseline characteristics. Additionally, immunogenicity of atezolizumab with and without lurbinectedin was assessed as a secondary outcome and will be reported separately. The effect of treatment on health-related quality of life was also assessed as a secondary endpoint and will be reported separately. Exploratory patient-reported outcome measures, pharmacokinetics, immunogenicity, and biomarker assessments will be reported separately.

Tumour assessments were required at induction and maintenance screenings and were done every 6 weeks during the maintenance phase for the first 48 weeks starting from cycle 1 day 1 of the maintenance phase, and every 9 weeks thereafter until the occurrence of disease progression per RECIST (version 1.1). Patients without any radiographical evidence of disease progression 2 years after day 1 of cycle 1 of the maintenance phase underwent tumour assessments every 3 months or more frequently, if required per local standard.

Adverse events were assessed per National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) and encoded using the Medical Dictionary for Regulatory Activities (version 27.0); investigators determined relatedness to study treatment. Adverse events of special interest for lurbinectedin and atezolizumab were predefined by Jazz Pharmaceuticals (for lurbinectedin) and Roche (for atezolizumab), based on the mechanism of action of the respective agents and were independent of the causal relationship assigned by the investigator.

Statistical analysis

Efficacy was assessed in the full analysis set, which included all patients who were randomly assigned to maintenance phase treatment, regardless of whether they received their assigned study treatment. Safety was assessed in the safety analysis set, which comprised patients randomly assigned to the maintenance phase who received at least one dose of lurbinectedin or atezolizumab, and was analysed according to the treatment received.

The study was designed to randomise approximately 450 participants, with this sample size determined based on the number of events required to demonstrate efficacy with regards to overall survival in the full analysis set. The overall two-sided type I error rate of 0·05 was controlled using a group-sequential weighted Holm procedure[20,21] in which the two-sided

significance levels of 0·001 and 0·049 were allocated to the primary comparisons for IRF progression-free survival and overall survival, respectively. An α recycling between IRF progression-free survival and overall survival was conducted per the statistical analysis plan (appendix p 266). The Hwang–Shih–DeCani spending function[22] with the γ parameter of –1·5 was used to control the type I error for the planned overall survival interim and final analyses. One interim analysis for overall survival was planned at 68% of the information fraction (ie, when approximately 219 deaths had occurred in the full analysis set) or when the target sample size of 450 patients had completed a minimum follow-up of 5 months from randomisation into the maintenance phase, whichever occurred later. The study had approximately 85% power at the two-sided significance level of 0·049 to detect a hazard ratio (HR) of 0·71 for overall survival in the full analysis set. No interim analysis for IRF progression-free survival was planned and the primary analysis of IRF progression-free survival was performed at the same time as the overall survival interim analysis. It was estimated that, at the time of the overall survival interim analysis, approximately 392 IRF progression-free survival events would have occurred in the full analysis set. This would provide more than 99% power to detect an HR of 0·5 for IRF progression-free survival at a two-sided significance level of 0·001. The stopping boundary for overall survival at the interim analysis was determined by the Hwang–Shih–DeCani α spending function using the γ parameter of –1·5 and based on the actual number of overall survival events observed. If the overall survival results were statistically significant at the interim analysis, no further formal hypothesis testing with type I error control would be conducted for overall survival at the prespecified final analysis.

The efficacy endpoints were analysed according to the assigned treatment. Patients who were alive with no disease progression by the clinical cutoff date were censored for progression-free survival at the time of the last tumour assessment. Patients without tumour assessment after baseline who were alive at the clinical cutoff date were censored for progression-free survival at the date of randomisation. For overall survival, patients who were not reported as having died by the clinical cutoff

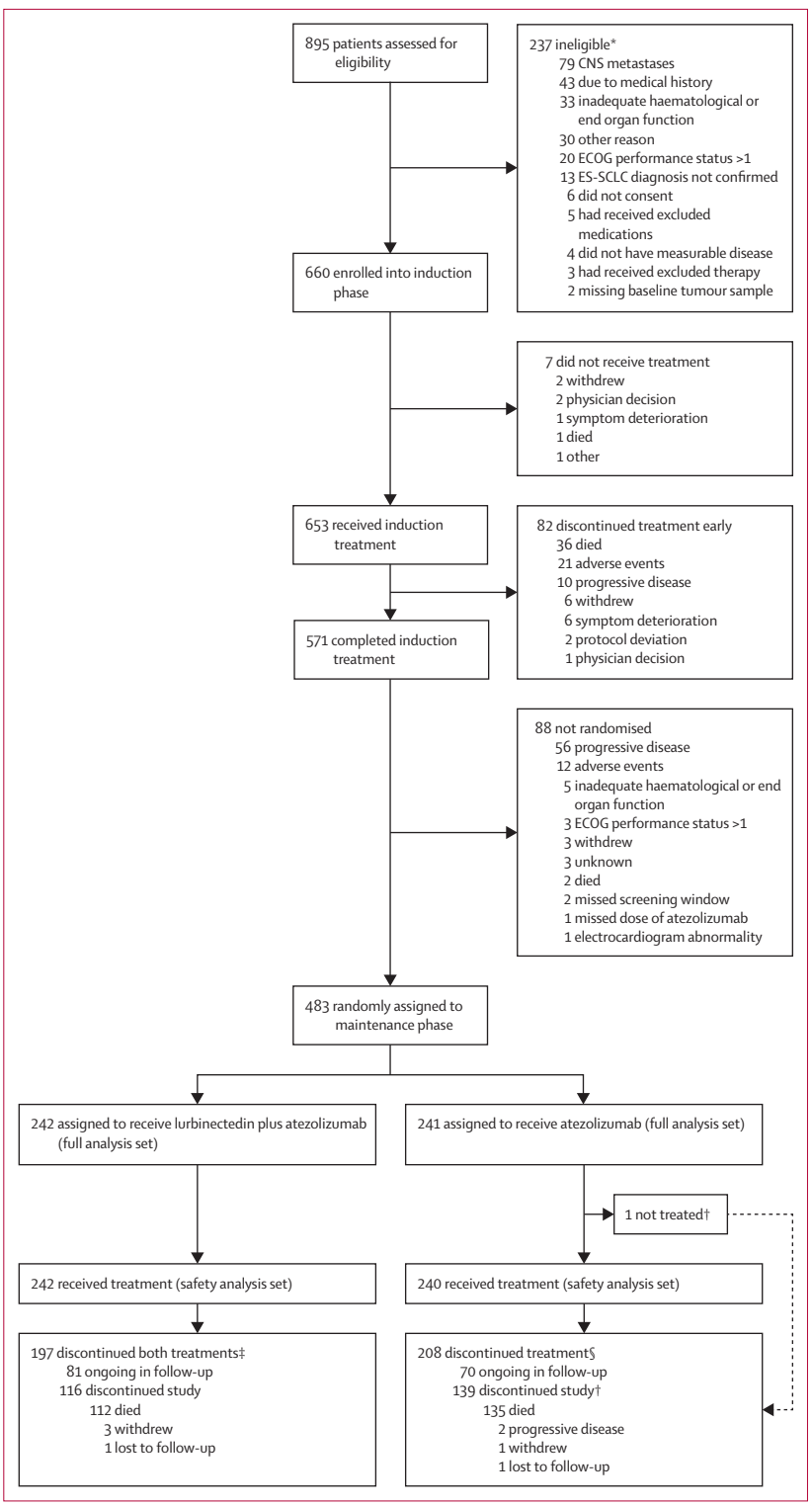


Figure 1: **Trial profile**
ECOG=Eastern Cooperative Oncology Group. ES-SCLC=extensive-stage small-cell lung cancer. *Two patients were enrolled after their second screening and were therefore counted as ineligible at screening and as enrolled. Additionally, one patient was deemed ineligible at screening twice. †One patient was not treated and had discontinued the study. ‡198 patients in the lurbinectedin plus atezolizumab group discontinued lurbinectedin and 197 patients in the lurbinectedin plus atezolizumab group discontinued atezolizumab. Reasons for discontinuation of lurbinectedin were progressive disease (n=155), death (n=16), adverse events (n=13), withdrawal (n=8), deterioration of symptoms (n=5), and physician's decision (n=1). Reasons for discontinuation of atezolizumab were progressive disease (n=160), death (n=16), adverse events (n=6), withdrawal (n=9), deterioration of symptoms (n=5), and physician's decision (n=1). §208 patients in the atezolizumab group discontinued treatment. Reasons for discontinuation of atezolizumab were progressive disease (n=185), death (n=6), adverse events (n=9), deterioration of symptoms (n=5), withdrawal (n=2), and physician's decision (n=1).

	Lurbinectedin plus atezolizumab (n=242)	Atezolizumab (n=241)
Age, years	65·0 (60·0–71·0)	67·0 (61·0–72·0)
<65 years	118 (49%)	90 (37%)
≥65 years	124 (51%)	151 (63%)
Sex		
Male	151 (62%)	151 (63%)
Female	91 (38%)	90 (37%)
Region		
Asia–Pacific	30 (12%)	31 (13%)
Europe and Middle East	194 (80%)	190 (79%)
North America	14 (6%)	17 (7%)
Central and South America	4 (2%)	3 (1%)
Race		
White	195 (81%)	199 (83%)
Asian	31 (13%)	31 (13%)
Black or African American	3 (1%)	1 (<1%)
American Indian or Alaska Native	1 (<1%)	0
Not reported	12 (5%)	10 (4%)
Ethnicity		
Hispanic or Latino	16 (7%)	16 (7%)
Not Hispanic or Latino	206 (85%)	210 (87%)
Not reported	20 (8%)	15 (6%)
Tobacco use history		
Never	7 (3%)	5 (2%)
Current	88 (36%)	73 (30%)
Previous	147 (61%)	163 (68%)
Liver metastases at induction baseline*		
Yes	100 (41%)	94 (39%)
No	142 (59%)	147 (61%)
Previous prophylactic cranial irradiation*		
Yes	34 (14%)	37 (15%)
No	208 (86%)	204 (85%)
Eastern Cooperative Oncology Group performance status at maintenance baseline*		
0	105 (43%)	102 (42%)
1	137 (57%)	139 (58%)
Lactate dehydrogenase at maintenance baseline*		
≤ULN	176 (73%)	179 (74%)
>ULN	66 (27%)	62 (26%)
Time from day 1 of induction cycle 1 to randomisation, months	3·2 (2·9-3·5)	3·2 (3·0-3·5)
Response to induction therapy†		
Complete response or partial response	206/236 (87%)	213/240 (89%)
Stable disease	28/236 (12%)	25/240 (10%)
Progressive disease	2/236 (1%)	2/240 (1%)

Data are median (IQR), n (%), or n/N (%). ULN=upper limit of normal. *Data were obtained from electronic case-report forms. †Seven randomly assigned patients did not have a maintenance screening tumour assessment.

Table 1: **Baseline characteristics in the full analysis set (n=483)**

date were censored at the date when they were last known to be alive. Patients for whom no data were available after baseline were censored at the time of randomisation.

Each primary endpoint was compared between treatment groups based on the stratified log-rank test, using the same stratification factors as for randomisation into the maintenance phase. The HRs and 95% CIs for progression-free survival and overall survival were estimated using a stratified Cox regression model. Kaplan–Meier methodology was used to calculate the median progression-free survival and overall survival. The Brookmeyer and Crowley method was used to construct the 95% CI for the medians.[23] The medians and the corresponding 95% CIs for duration of response were calculated using the same methods as for progression-free survival and overall survival. The Clopper Pearson method was used to estimate the confirmed ORR 95% CIs for patients in the full analysis set who had measurable disease at the maintenance baseline.

Role of the funding source

The study funders collaborated with an academic steering committee on study design, data collection, data analysis, and data interpretation. The authors prepared all drafts and approved the submission of the manuscript.

Results

Between Nov 17, 2021, and Jan 11, 2024, 660 patients were enrolled into the induction phase at 96 sites in 13 countries (appendix p 2). Between May 24, 2022, and April 30, 2024, 483 (73%) of 660 patients were randomly assigned to maintenance treatment: lurbinectedin plus atezolizumab (n=242) or atezolizumab (n=241; figure 1).

At the clinical cutoff for the overall survival interim and IRF progression-free survival final analyses (July 29, 2024), median follow-up from randomisation was 15·0 months (IQR 8·6–18·3). Baseline characteristics were generally well balanced between treatment groups (table 1), with the exception of age, whereby there was a higher proportion of younger patients (age <65 years) in the lurbinectedin plus atezolizumab group (118 [49%] of 242 patients) than in the atezolizumab group (90 [37%] of 241 patients). At maintenance screening, 419 (88%) of 476 randomly assigned patients with a valid tumour assessment per investigator had an objective response to induction therapy, 53 (11%) of 476 patients had stable disease, and four (1%) had progressive disease following induction treatment and were inadvertently randomised in violation of the protocol (appendix p 10). Seven patients who were randomly assigned to maintenance treatment did not have a tumour response assessment between the last dose of induction treatment and randomisation into the maintenance phase and thus were excluded from tumour response assessments during the maintenance phase for this reason. The distribution of patients according to their response to induction therapy was balanced between groups (table 1).

At the clinical cutoff, 174 (72%) of 242 patients in the lurbinectedin plus atezolizumab group and 202 (84%) of 241 patients in the atezolizumab group had disease progression per IRF assessment or had died. The median

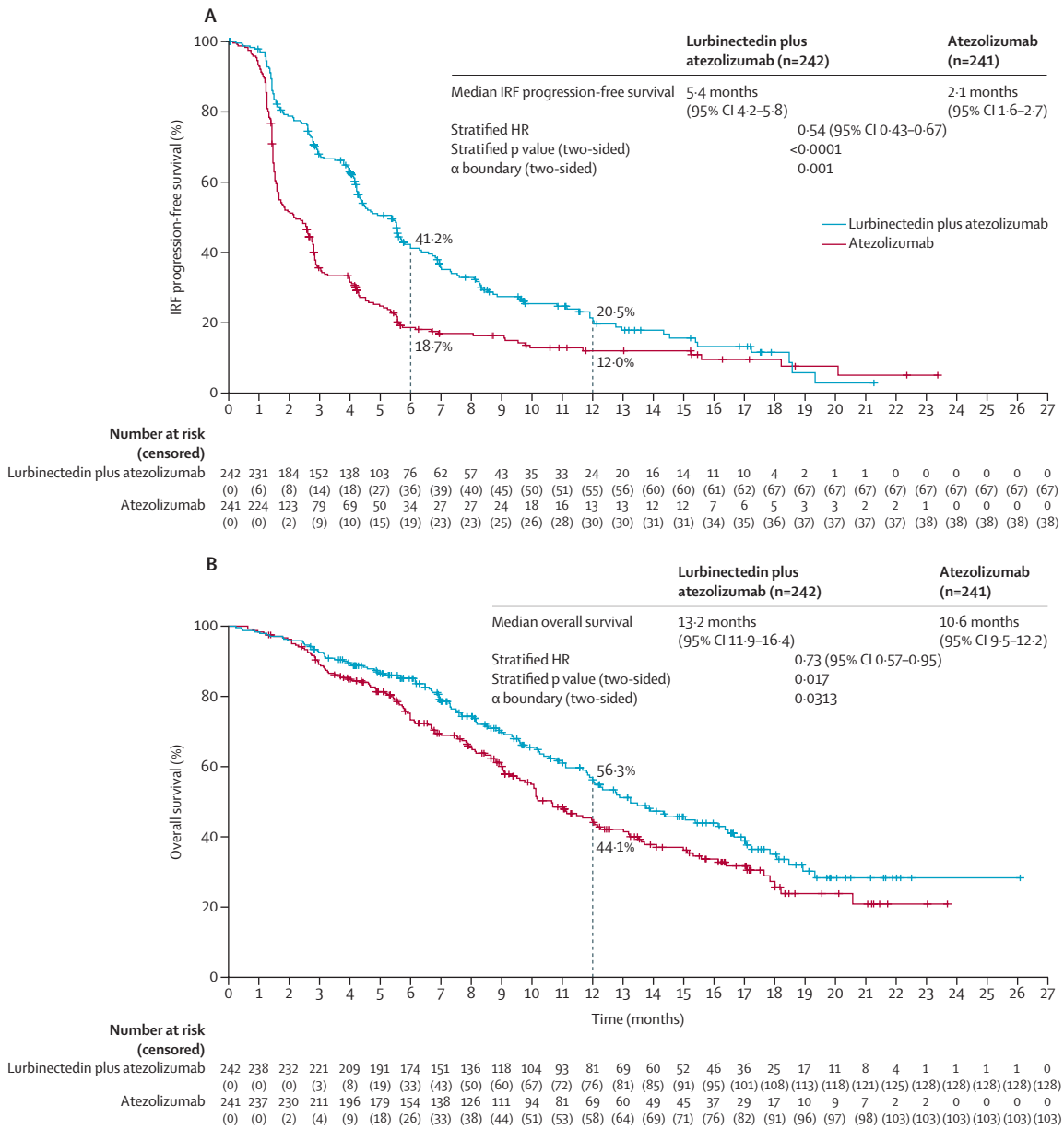


Figure 2: **IRF progression-free survival and overall survival from randomisation into the maintenance phase in the full analysis set**
Kaplan–Meier estimates of IRF progression-free survival (A) and overall survival (B) in the full analysis set. Stratification factors included in the stratified p value and Cox model are the same stratification factors used for randomisation. Censored events are indicated with a + symbol. HR=hazard ratio. IRF=independent review facility–assessed.

IRF progression-free survival from randomisation into the maintenance phase was longer in the lurbinectedin plus atezolizumab group (5·4 months [95% CI 4·2–5·8]) than in the atezolizumab group (2·1 months [1·6–2·7]; stratified HR 0·54 [95% CI 0·43–0·67]; p<0·0001; figure 2A). The stratified log-rank p value was less than 0·0001 compared with the two-sided α boundary of 0·001 and therefore statistically significant. The 6-month IRF progression-free survival rate was 41·2% in the lurbinectedin plus atezolizumab group and 18·7% in the atezolizumab group; the respective 12-month IRF progression-free survival rates were 20·5% and 12·0%.

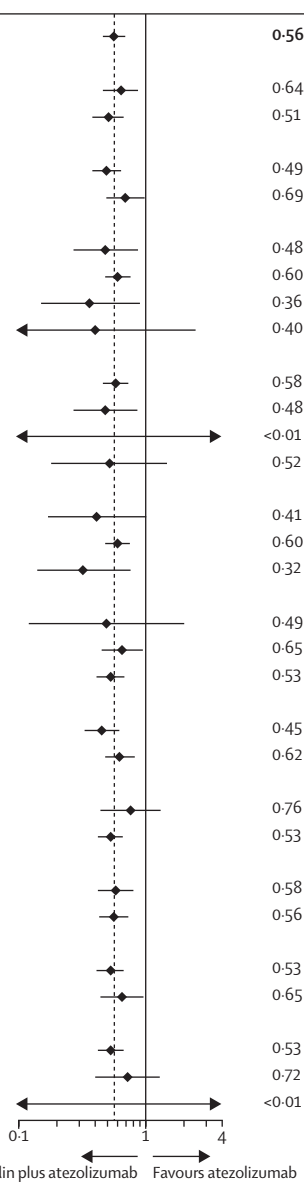
At the planned interim analysis of overall survival, 113 (47%) of 242 patients in the lurbinectedin plus atezolizumab group and 136 (56%) of 241 patients in the atezolizumab group had died (overall survival event rate 52% [249 of 483 patients]). Median overall survival from randomisation into the maintenance phase was longer in the lurbinectedin plus atezolizumab group (13·2 months [95% CI 11·9–16·4]) than in the

atezolizumab group (10·6 months [9·5–12·2]; stratified HR 0·73 [95% CI 0·57–0·95]; p=0·017; figure 2B). The stratified log-rank p value was 0·017 compared with the two-sided α boundary of 0·0313 and therefore statistically significant at this overall survival interim analysis; hence, no formal hypothesis testing will be performed at the prespecified overall survival final analysis. The 12-month overall survival rate was 56·3% in the lurbinectedin plus atezolizumab group and 44·1% in the atezolizumab group. The absolute risk reduction for overall survival at 12 months was 12·1% (95% CI 1·97–22·31).

IRF progression-free survival and overall survival were longer in the lurbinectedin plus atezolizumab group than the atezolizumab group across the majority of predefined subgroups, including sex, race, and ethnicity,

A

	Total, n	Lurbinectedin plus atezolizumab (n=242)		Atezolizumab (n=241)		HR (95% CI)*
		n/N	Median progression-free survival, months	n/N	Median progression-free survival, months	
All patients	**483**	**174/242**	**5·4**	**202/241**	**2·1**	**0·56 (0·46–0·69)**
Age, years						
<65	208	86/118	5·4	73/90	1·8	0·64 (0·46–0·87)
≥65	275	88/124	5·5	129/151	2·5	0·51 (0·38–0·67)
Sex						
Male	302	110/151	5·5	131/151	1·8	0·49 (0·38–0·64)
Female	181	64/91	4·3	71/90	2·7	0·69 (0·49–0·98)
Region						
Asia–Pacific	61	21/30	6·3	26/31	1·8	0·48 (0·27–0·87)
Europe and Middle East	384	140/194	5·4	157/190	2·4	0·60 (0·48–0·76)
North America	31	10/14	3·1	16/17	2·1	0·36 (0·15–0·90)
Central and South America	7	3/4	5·1	3/3	1·5	0·40 (0·06–2·47)
Race						
White	394	140/195	4·7	167/199	2·1	0·58 (0·46–0·73)
Asian	62	22/31	6·3	26/31	1·8	0·48 (0·27–0·86)
Black or African American	4	3/3	8·3	1/1	1·4	<0·01 (0·00–NE)
Not reported	22	8/12	3·8	8/10	2·8	0·52 (0·18–1·47)
Ethnicity						
Hispanic or Latino	32	8/16	6·8	13/16	2·6	0·41 (0·17–1·01)
Not Hispanic or Latino	416	153/206	4·9	176/210	2·1	0·60 (0·48–0·75)
Not reported	35	13/20	5·4	13/15	1·8	0·32 (0·14–0·76)
Tobacco use history						
Never	12	6/7	5·8	4/5	1·4	0·49 (0·12–2·01)
Current	161	61/88	4·7	57/73	2·5	0·65 (0·45–0·95)
Previous	310	107/147	5·5	141/163	2·1	0·53 (0·41–0·68)
Liver metastases at induction baseline†						
Yes	194	75/100	4·4	87/94	1·6	0·45 (0·33–0·62)
No	289	99/142	5·6	115/147	2·8	0·62 (0·48–0·82)
Prior prophylactic cranial irradiation†						
Yes	71	25/34	4·1	29/37	2·9	0·76 (0·44–1·31)
No	412	149/208	5·5	173/204	2·1	0·53 (0·42–0·66)
Eastern Cooperative Oncology Group performance status at maintenance baseline†						
0	207	76/105	5·4	82/102	2·6	0·58 (0·42–0·80)
1	276	98/137	4·7	120/139	2·1	0·56 (0·43–0·73)
Lactate dehydrogenase at maintenance baseline†						
≤ULN	355	123/176	5·5	150/179	2·5	0·53 (0·41–0·67)
>ULN	128	51/66	4·0	52/62	1·6	0·65 (0·44–0·96)
Response to induction therapy‡						
Complete response or partial response	419	143/206	5·6	176/213	2·4	0·53 (0·42–0·67)
Stable disease	53	26/28	2·8	23/25	1·6	0·72 (0·40–1·29)
Progressive disease	4	2/2	11·3	2/2	1·4	<0·01 (0·00–NE)



(Figure 3 continues on next page)

B

	Total, n	Lurbinectedin plus atezolizumab (n=242)		Atezolizumab (n=241)		HR (95% CI)*
		n/N	Median overall survival, months	n/N	Median overall survival, months	
All patients	**483**	**113/242**	**13·2**	**136/241**	**10·6**	**0·74 (0·58–0·96)**
Age, years						
<65	208	53/118	15·4	49/90	12·2	0·77 (0·52–1·14)
≥65	275	60/124	12·9	87/151	10·1	0·76 (0·55–1·05)
Sex						
Male	302	75/151	12·9	88/151	10·1	0·72 (0·53–0·98)
Female	181	38/91	13·9	48/90	11·5	0·78 (0·51–1·19)
Region						
Asia–Pacific	61	12/30	16·5	14/31	12·2	0·81 (0·37–1·75)
Europe and Middle East	384	91/194	13·5	108/190	10·6	0·74 (0·56–0·97)
North America	31	8/14	7·7	11/17	9·0	1·08 (0·43–2·69)
Central and South America	7	2/4	NE	3/3	10·1	0·87 (0·14–5·51)
Race						
White	394	92/195	13·5	118/199	10·1	0·71 (0·54–0·94)
Asian	62	13/31	10·8	14/31	12·2	0·86 (0·40–1·84)
Black or African American	4	0/3	NE	0/1	NE	NE
Not reported	22	8/12	7·3	4/10	12·0	2·31 (0·68–7·82)
Ethnicity						
Hispanic or Latino	32	5/16	NE	9/16	10·2	0·45 (0·15–1·40)
Not Hispanic or Latino	416	99/206	13·2	121/210	10·2	0·75 (0·57–0·98)
Not reported	35	9/20	16·4	6/15	12·0	1·21 (0·43–3·39)
Tobacco use history						
Never	12	3/7	18·1	3/5	10·7	0·34 (0·06–2·12)
Current	161	38/88	13·2	39/73	10·7	0·79 (0·51–1·24)
Previous	310	72/147	13·5	94/163	10·6	0·76 (0·56–1·03)
Liver metastases at induction baseline†						
Yes	194	55/100	12·0	63/94	8·6	0·70 (0·48–1·00)
No	289	58/142	16·1	73/147	12·3	0·76 (0·54–1·07)
Prior prophylactic cranial irradiation†						
Yes	71	16/34	12·3	18/37	12·3	1·02 (0·52–2·00)
No	412	97/208	13·5	118/204	10·1	0·70 (0·53–0·92)
Eastern Cooperative Oncology Group performance status at maintenance baseline†						
0	207	51/105	15·0	53/102	12·0	0·88 (0·60–1·29)
1	276	62/137	12·3	83/139	10·0	0·66 (0·47–0·92)
Lactate dehydrogenase at maintenance baseline†						
≤ULN	355	72/176	16·1	97/179	10·7	0·66 (0·49–0·90)
>ULN	128	41/66	9·1	39/62	10·1	0·96 (0·62–1·50)
Response to induction therapy‡						
Complete response or partial response	419	92/206	13·9	115/213	11·1	0·76 (0·57–0·99)
Stable disease	53	17/28	10·8	18/25	8·8	0·62 (0·31–1·24)
Progressive disease	4	1/2	NE	2/2	8·3	0·39 (0·03–4·44)

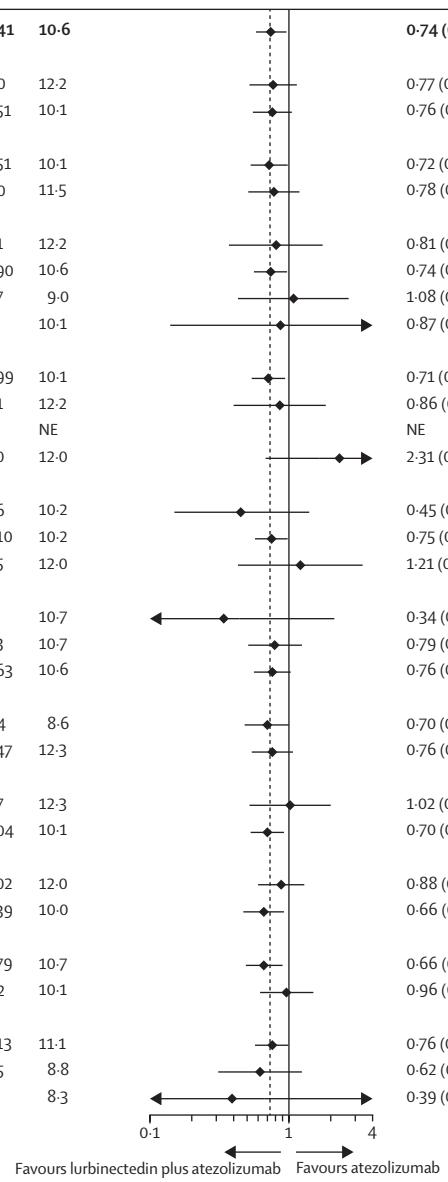


Figure 3: **Subgroup analysis of IRF progression-free survival (A) and overall survival (B)**
IRF=independent review facility–assessed. n=events. N=number of patients. HR=hazard ratio. NE=not estimable. ULN=upper limit of normal. *HRs are unstratified. †Data were determined from electronic case report forms. ‡Seven randomised patients did not have a maintenance screening tumour assessment.

with the exception of patients with lactate dehydrogenase concentrations above the upper limit of normal and patients who had received prophylactic cranial irradiation for overall survival (figure 3A, B). Investigator-assessed progression-free survival was consistent with IRF progression-free survival: median survival was 5·4 months (95% CI 4·3–6·6) in the lurbinectedin plus atezolizumab group and 2·7 months (2·5–2·8) in the atezolizumab group (stratified HR 0·55 [95% CI 0·45–0·68]; appendix p 29).

Per IRF assessment, 175 (72%) of 242 patients in the lurbinectedin plus atezolizumab group and 182 (76%) of

	Lurbinectedin plus atezolizumab (n=242)	Atezolizumab (n=240)
Patients with ≥1 adverse event	235 (97%)	194 (81%)
Treatment-related adverse events	202 (83%)	96 (40%)
Grade 3–4 adverse events	92 (38%)	53 (22%)
Treatment-related grade 3–4 adverse events	62 (26%)	14 (6%)
Grade 5 adverse events	12 (5%)	6 (3%)
Treatment-related grade 5 adverse events	2 (1%)	1 (<1%)
Serious adverse events	75 (31%)	41 (17%)
Treatment-related serious adverse events	28 (12%)	9 (4%)
Adverse events leading to treatment discontinuation of any study drug	15 (6%)	8 (3%)
Adverse events leading to dose interruption/ modification of any study drug	92 (38%)	33 (14%)
Adverse events of special interest for lurbinectedin	93 (38%)	62 (26%)
Grade 3–4	18 (7%)	12 (5%)
Grade 5	7 (3%)	4 (2%)
Serious	28 (12%)	16 (7%)
Adverse events of special interest for atezolizumab	76 (31%)	54 (23%)
Grade 3–4	15 (6%)	8 (3%)
Grade 5	0	0
Serious	10 (4%)	5 (2%)
Requiring corticosteroids	40 (17%)	18 (8%)

Data are n (%).

Table 2: **Adverse events during the maintenance phase (safety analysis set; n=482)**

241 patients in the atezolizumab group had measurable disease at the time of randomisation into the maintenance phase. Objective response during the maintenance phase was assessed in patients with measurable disease by comparing against the maintenance baseline tumour assessment at the time of randomisation after the completion of induction therapy. During the maintenance phase, 34 (19%) of 175 patients in the lurbinectedin plus atezolizumab group and 19 (10%) of 182 patients in the atezolizumab group had a confirmed objective response per IRF assessment compared with the maintenance baseline scan (between-group difference in ORR 9% [95% CI 1–17]; appendix p 13). The median duration of response as assessed by the IRF was 9·0 months (95% CI 5·5–not estimable [NE]) in the lurbinectedin plus atezolizumab group and 5·6 months (4·2–NE) in the atezolizumab group. Confirmed ORR and duration of response results per investigator assessment are in the appendix (p 15). At the clinical cutoff, 108 (45%) of 242 patients in the lurbinectedin plus atezolizumab group and 132 (55%) of 241 patients in the atezolizumab group had received follow-up systemic anticancer treatment, with the difference being driven by the proportion of patients receiving follow-up chemotherapy (37% [89 of 242 patients] in the lurbinectedin plus atezolizumab group *vs* 49% [119 of 241 patients] in the atezolizumab group; appendix p 17). No patients in the lurbinectedin plus atezolizumab group received follow-up lurbinectedin after discontinuation of both study drugs, whereas 22 (9%) of 241 patients in the atezolizumab group received follow-up lurbinectedin. Other follow-up systemic anticancer therapies were generally balanced between groups (appendix p 17).

242 patients in the lurbinectedin plus atezolizumab group and 240 patients in the atezolizumab group were included in the safety analysis set. In the maintenance phase, the median duration of treatment with lurbinectedin was 4·1 months (IQR 1·5–7·4) and patients received a median of seven (IQR 3–11) doses of lurbinectedin (appendix p 20). The median duration of treatment with atezolizumab was 4·2 months (2·0–7·6) in the lurbinectedin plus atezolizumab group and 2·1 months (0·8–4·2) in the atezolizumab group. A median of seven (3–11) atezolizumab doses were received in the lurbinectedin plus atezolizumab group and four (2–7) doses in the atezolizumab group. The median dose intensity of lurbinectedin was 98%. The median dose intensity of atezolizumab was similar between groups: 99% in the lurbinectedin plus atezolizumab group and 100% in the atezolizumab group.

All-cause adverse events were reported in 235 (97%) of 242 patients in the lurbinectedin plus atezolizumab group and 194 (81%) of 240 patients in the atezolizumab group (table 2). Adverse events considered related to any study treatment by the investigator occurred in 202 (83%) of 242 patients in the lurbinectedin plus atezolizumab group and 96 (40%) of 240 patients in the atezolizumab group (table 2). All-cause grade 3–4 adverse events occurred in 92 (38%) of 242 patients in the lurbinectedin plus atezolizumab group and 53 (22%) of 240 patients in the atezolizumab group. The most common grade 3–4 adverse events were haematological toxicities: anaemia (20 [8%] of 242 patients in the lurbinectedin plus atezolizumab group *vs* two [1%] of 240 patients in the atezolizumab group), decreased neutrophil count (18 [7%] of 242 patients *vs* none of 240 patients), decreased platelet count (17 [7%] of 242 patients *vs* none of 240 patients), neutropenia (11 [5%] of 242 patients *vs* one [<1%] of 240 patients), and thrombocytopenia (11 [5%] of 242 patients *vs* one [<1%] of 240 patients; table 3). Grade 3–4 treatment-related adverse events occurred in 62 (26%) of 242 patients in the lurbinectedin plus atezolizumab group and 14 (6%) of 240 patients in the atezolizumab group. Serious adverse events occurred in 75 (31%) of 242 patients in the lurbinectedin plus atezolizumab group versus 41 (17%) of 240 patients in the atezolizumab group. Serious adverse events that occurred in more than 1% of patients in either group were pneumonia (six [2%] of 242 patients in the lurbinectedin plus atezolizumab group; six [3%] of 240 patients in the atezolizumab group), dyspnoea (five [2%] of 242 patients *vs* four [2%] of 240 patients), respiratory tract infection (five [2%] of 242 patients *vs* one [<1%] of 240 patients), decreased platelet count (five [2%] of 242 patients *vs* none of 240 patients), and

febrile neutropenia (four [2%] of 242 patients *vs* none of 240 patients; appendix p 21). Treatment-related serious adverse events occurred in 28 (12%) of 242 patients in the lurbinectedin plus atezolizumab group and nine (4%) of 240 patients in the atezolizumab group (table 2).

Deaths due to adverse events occurred in 12 (5%) of 242 patients in the lurbinectedin plus atezolizumab group and in six (3%) of 240 patients in the atezolizumab group. Fatal adverse events in the lurbinectedin plus atezolizumab group included two myocardial infarctions and two cardiorespiratory arrests (appendix p 22). All other events in the lurbinectedin plus atezolizumab group were reported as single occurrences and included one suicide. The four fatal cardiac events were reported as unrelated to study treatment by the investigator. One patient who had a fatal myocardial infarction presented with a medical history of congestive heart failure and hypertension, the other patient had a history of multiple events of atherosclerosis and a stent placement. The two patients who died of cardiorespiratory arrest died at home with no further case details available; these events were considered by the investigator as related to the underlying disease and concurrent illness, respectively. Treatment-related grade 5 adverse events occurred in two (1%) of 242 patients in the lurbinectedin plus atezolizumab group (sepsis and febrile neutropenia, both considered related to lurbinectedin) and one (<1%) of 240 patients in the atezolizumab group (sepsis considered related to atezolizumab).

Adverse events resulting in dose modifications or interruptions of any study treatment occurred in 92 (38%) of 242 patients in the lurbinectedin plus atezolizumab group compared with 33 (14%) of 240 patients in the atezolizumab group (table 2). Adverse events leading to permanent treatment discontinuation occurred in 15 (6%) of 242 patients in the lurbinectedin plus atezolizumab group and eight (3%) of 240 patients in the atezolizumab group.

Adverse events of special interest for lurbinectedin occurred in 93 (38%) of 242 patients in the lurbinectedin plus atezolizumab group and 62 (26%) of 240 patients in the atezolizumab group (appendix p 24). The most common adverse event of special interest in both groups was infection without concomitant neutropenia (87 [36%] of 242 patients in the lurbinectedin plus atezolizumab group and 59 [25%] of 240 patients in the atezolizumab group). Grade 5 adverse events of special interest for lurbinectedin occurred in seven (3%) of 242 patients in the lurbinectedin plus atezolizumab group (febrile neutropenia [n=1], sepsis [n=1], septic shock [n=1], COVID-19 pneumonia [n=1], pneumonia [n=1], viral pneumonia [n=1], and vascular device infection [n=1]). In the atezolizumab group, four (2%) of 240 patients died due to adverse events categorised as adverse events of special interest for lurbinectedin (pneumonia [n=2], sepsis [n=1], and intestinal abscess [n=1]).

	Lurbinectedin plus atezolizumab (n=242)	Atezolizumab (n=240)
Anaemia	20 (8%)	2 (1%)
Decreased neutrophil count	18 (7%)	0
Decreased platelet count	17 (7%)	0
Neutropenia	11 (5%)	1 (<1%)
Thrombocytopenia	11 (5%)	1 (<1%)
Fatigue	8 (3%)	3 (1%)
Nausea	6 (2%)	2 (1%)
Increased alanine transaminase	6 (2%)	1 (<1%)
Dyspnoea	5 (2%)	4 (2%)
Pneumonia	5 (2%)	4 (2%)
Hypokalaemia	5 (2%)	3 (1%)
Decreased white blood cell count	5 (2%)	0
Hyponatremia	3 (1%)	5 (2%)

Data are n (%). All events that occurred in at least 2% of patients in either group are shown.

Table 3: **Grade 3–4 adverse events**

Adverse events of special interest for atezolizumab occurred in 76 (31%) of 242 patients in the lurbinectedin plus atezolizumab group and 54 (23%) of 240 patients in the atezolizumab group (appendix p 27). No grade 5 adverse events of special interest for atezolizumab occurred in either group. The most common adverse events of special interest for atezolizumab were hepatitis in the lurbinectedin plus atezolizumab group (25 [10%] of 242 patients) and rash and hypothyroidism in the atezolizumab group (18 [8%] of 240 patients for each). Additional details on adverse events are provided in the appendix (pp 21–28).

Discussion

IMforte is the first phase 3 study of first-line maintenance treatment of ES-SCLC to show a statistically significant and clinically meaningful improvement in IRF progression-free survival and overall survival. IMforte builds on the standard of care of anti-PD-L1 therapy in combination with platinum-based chemotherapy first established in 2019.[1] The addition of the novel alkylating agent lurbinectedin to atezolizumab in the maintenance setting resulted in a reduction in the risk of disease progression or death by 46%. This translated into a survival benefit, with a 27% reduction in risk of death; the survival curves for overall survival separated approximately 2·5 months after randomisation into the maintenance phase and maintained their separation thereafter. The treatment benefit with lurbinectedin plus atezolizumab in terms of IRF progression-free survival was consistent across all predefined subgroups. For overall survival, the treatment benefit was consistent across the majority of predefined subgroups, with the exception of the groups of patients with ECOG performance score of 0, patients with lactate dehydrogenase concentrations above the upper limit of normal at the time of randomisation, and patients who

had received prophylactic cranial irradiation, where the HR was close to 1; however, it should be noted that these subgroup analyses were exploratory with wide confidence intervals and with some of the subgroups being small in sample size, thus limiting data interpretation.

The safety profile of lurbinectedin plus atezolizumab maintenance therapy was considered manageable, with no new safety signals identified relative to the known risks of both drugs. The incidence of adverse events was higher in the lurbinectedin plus atezolizumab group than in the atezolizumab group, which was not unexpected considering the addition of an alkylating agent to the regimen and longer treatment exposure. Median treatment duration in the lurbinectedin plus atezolizumab group was two times longer than the median treatment duration in the atezolizumab group. It is important to note that the majority of adverse events were grade 1–2 in severity in both groups. Furthermore, the proportion of patients who discontinued study treatment due to adverse events was low in both groups, but was slightly higher in the lurbinectedin plus atezolizumab group than the atezolizumab group (15 [6%] of 242 patients *vs* eight [3%] of 240 patients).

Although there was a higher incidence of fatal adverse events in the lurbinectedin plus atezolizumab group (12 [5%] of 242 patients) than the atezolizumab group (six [3%] of 240 patients), the majority of these events were assessed by the investigator as not related to study treatment or were confounded by the underlying medical history or the expected clinical course in this patient population. Fatal adverse events assessed as related to treatment by the investigator were rare in both groups (two events in the lurbinectedin plus atezolizumab group *vs* one event in the atezolizumab group).

A higher incidence of grade 3–4 adverse events was observed in the lurbinectedin plus atezolizumab group than in the atezolizumab group, with the difference being driven by adverse events consistent with the myelosuppressive nature of lurbinectedin. However, the incidence of these grade 3–4 myelosuppressive disorders (eg, neutropenia and leukopenia) were lower in the IMforte combination group than with lurbinectedin monotherapy in the B-005 study,[11] the findings of which formed the basis for regulatory approval of lurbinectedin in metastatic SCLC. Primary prophylaxis with G-CSF for patients in the lurbinectedin plus atezolizumab group in IMforte might have contributed to fewer myelosuppressive events when compared with B-005.

It is important to note that IMforte measured efficacy endpoints from the time of randomisation into the maintenance phase, rather than from the start of induction treatment, as was the case for the previous phase 3 studies of first-line treatment of ES-SCLC,[1,2] the results of which established the current standard of care. The IMforte study design selected for patients who had favourable clinical outcomes from induction treatment in contrast to previous studies of first-line ES-SCLC treatment that included the induction phase in their analyses. Therefore, the IMforte findings are not directly comparable with these previous studies since median survival in IMforte (13·2 months with lurbinectedin plus atezolizumab and 10·6 months with atezolizumab) did not include the induction treatment period (median time from start of induction treatment to randomisation of 3·2 months, both groups), and selected for patients without disease progression on or after induction treatment and without significant toxicity from induction treatment. While interpreting these study results, it is also important to consider that, at the time of this analysis, 22 (9%) of 241 patients in the atezolizumab group had received lurbinectedin as a follow-up treatment. Decisions regarding patient management after discontinuing study treatment were left to the discretion of the investigator and were per local standards of care. However, it is important to note that the combination of lurbinectedin plus atezolizumab demonstrated unequivocal clinically meaningful benefit in terms of progression-free survival that is not confounded by follow-up treatment.

To account for tumour response to induction treatment, measurable disease was not an eligibility criterion for randomisation into the maintenance phase, and 126 (26%) of 483 patients did not have measurable disease as per IRF assessment at the time of randomisation. The analyses of ORR and duration of response were done in a non-randomised subset of patients with measurable disease at randomisation and additionally, in the case of duration of response, among patients who achieved a confirmed objective response after randomisation. At the time of randomisation into the maintenance phase, 419 (88%) of 476 patients had already achieved an objective response to induction therapy, and 53 (11%) of 476 patients had achieved stable disease. Thus, the ORRs of 19% and 10%, respectively, achieved during the maintenance phase of IMforte reflects the proportion of patients achieving an additional objective response relative to their tumour burden at the time of randomisation after completion of induction therapy. As a result, the analysis of duration of response was done in a small sample size (34 and 19 patients, respectively; per IRF assessment), limiting data interpretability.

The findings from IMforte represent a clear and clinically meaningful improvement in both progression-free survival and overall survival compared with the current standard of care first-line treatment of ES-SCLC with atezolizumab anti-PD-L1 therapy in combination with platinum-based chemotherapy. Further investigation of predictive factors to identify patients who would benefit most or those unlikely to benefit will be important. Additionally, extended follow-up of the patients in IMforte will enable better understanding of the long-term outcomes of this novel combination.

Other promising novel first-line treatment approaches are currently being investigated. These strategies include targeting delta-like ligand 3 or B7 homolog 3,[24,25] or using personalised DNA vaccines to amplify the immune response (NCT04397003). Notably, the combination of tarlatamab with a PD-L1 inhibitor in the first-line maintenance setting demonstrated promising survival outcomes with a manageable safety profile.[26] A phase 3 study evaluating this approach in a randomised setting is ongoing.[27] Results from these studies are eagerly awaited and will determine whether more progress can be made for patients with this difficult-to-treat disease.

In conclusion, the addition of lurbinectedin to first-line atezolizumab maintenance therapy for ES-SCLC resulted in significant and clinically meaningful improvement in progression-free survival and overall survival. The safety profile of the combination was consistent with expectations and was considered manageable overall. These results highlight the potential of lurbinectedin plus atezolizumab as a promising novel treatment option in the first-line maintenance setting of ES-SCLC.

Contributors

LP-A, DC, RI, and VG conceptualised the study. Y-CL developed the methodology. Y-CL conducted the formal analysis. LP-A, HB, SVL, SP, RSH, KS, MM, MANS, GC, RBC, KHL, MLJ, NK, CG, SB, TC, JSA, RC, T-YY, YK, MR, VC, and VG participated in the investigation. LP-A, HB, KS, MM, MANS, GC, RBC, KHL, MLJ, NK, CG, SB, TC, JSA, RC, T-YY, YK, and MR provided resources. VC and VG wrote the original draft. LP-A, HB, SVL, SP, RSH, KS, MM, MANS, GC, RBC, KHL, MLJ, NK, CG, SB, TC, JSA, RC, T-YY, YK, MB, VC, VG, Y-CL, DC, KB, GC, RI, and MR critically reviewed and edited the manuscript. MB provided supervision. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. LP-A and Y-CL have directly accessed and verified the underlying data.

Declaration of interests

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Data sharing

Qualified researchers can request access to individual patient-level clinical data through the Vivli data request platform (https://vivli.org/ourmember/roche/). Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents is available online (https://go.roche.com/data_sharing). Anonymised records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

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