Combination lurbinectedin and doxorubicin versus physician's choice of chemotherapy in patients with relapsed small-cell lung cancer (ATLANTIS) a multicentre, randomised, open-label, phase 3 trial

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Summary

Background Lurbinectedin is a synthetic marine-derived anticancer agent that acts as a selective inhibitor of oncogenic transcription. Lurbinectedin monotherapy (3·2 mg/m² every 3 weeks) received accelerated approval from the US Food and Drug Administration on the basis of efficacy in patients with small-cell lung cancer (SCLC) who relapsed after first-line platinum-based chemotherapy. The ATLANTIS trial assessed the efficacy and safety of combination lurbinectedin and the anthracycline doxorubicin as second-line treatment for SCLC.

Methods In this phase 3, open-label, randomised study, adult patients aged 18 years or older with SCLC who relapsed after platinum-based chemotherapy were recruited from 135 hospitals across North America, South America, Europe, and the Middle East. Patients were randomly assigned (1:1) centrally by dynamic allocation to intravenous lurbinectedin 2·0 mg/m² plus doxorubicin 40·0 mg/m² administered on day 1 of 21-day cycles or physician's choice of control therapy (intravenous topotecan 1·5 mg/m² on days 1–5 of 21-day cycles; or intravenous cyclophosphamide 1000 mg/m², doxorubicin 45·0 mg/m², and vincristine 2·0 mg on day 1 of 21-day cycles [CAV]) administered until disease progression or unacceptable toxicity. Primary granulocyte-colony stimulating factor prophylaxis was mandatory in both treatment groups. Neither patients nor clinicians were masked to treatment allocation, but the independent review committee, which assessed outcomes, was masked to patients' treatment allocation. The primary endpoint was overall survival in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT02566993, and with EudraCT, 2015-001641-89, and is complete.

Findings Between Aug 30, 2016, and Aug 20, 2018, 613 patients were randomly assigned to lurbinectedin plus doxorubicin (n=307) or control (topotecan, n=127; CAV, n=179) and comprised the intention-to-treat population; safety endpoints were assessed in patients who had received any partial or complete study treatment infusions (lurbinectedin plus doxorubicin, n=303; control, n=289). After a median follow-up of 24·1 months (95% CI 21·7–26·3), 303 patients in the lurbinectedin plus doxorubicin group and 289 patients in the control group had discontinued study treatment; progressive disease was the most common reason for discontinuation (213 [70%] patients in the lurbinectedin plus doxorubicin group *vs* 152 [53%] in the control group). Median overall survival was 8·6 months (95% CI 7·1–9·4) in the lurbinectedin plus doxorubicin group versus 7·6 months (6·6–8·2) in the control group (stratified log-rank p=0·90; hazard ratio 0·97 [95% CI 0·82–1·15], p=0·70). 12 patients died because of treatment-related adverse events: two (<1%) of 303 in the lurbinectedin plus doxorubicin group and ten (3%) of 289 in the control group. 296 (98%) of 303 patients in the lurbinectedin plus doxorubicin group had treatment-emergent adverse events compared with 284 (98%) of 289 patients in the control group; treatment-related adverse events occurred in 268 (88%) patients in the lurbinectedin plus doxorubicin group and 266 (92%) patients in the control group. Grade 3 or worse haematological adverse events were less frequent in the lurbinectedin plus doxorubicin group than the control group (anaemia, 57 [19%] of 302 patients in the lurbinectedin plus doxorubicin group *vs* 110 [38%] of 288 in the control group; neutropenia, 112 [37%] *vs* 200 [69%]; thrombocytopenia, 42 [14%] *vs* 90 [31%]). The frequency of treatment-related adverse events leading to treatment discontinuation was lower in the lurbinectedin plus doxorubicin group than in the control group (26 [9%] of 303 patients in the lurbinectedin plus doxorubicin group *vs* 47 [16%] of 289 in the control group).

Interpretation Combination therapy with lurbinectedin plus doxorubicin did not improve overall survival versus control in patients with relapsed SCLC. However, lurbinectedin plus doxorubicin showed a favourable haematological safety profile compared with control.

Funding PharmaMar.

Introduction

Small-cell lung cancer (SCLC) is an aggressive disease that accounts for approximately 13% of all lung cancers and is associated with poor long-term survival (5-year survival <10%).[1–3] Treatment is rarely curative, even in patients with limited-stage SCLC at diagnosis who are treated with first-line platinum-based chemotherapy plus radiotherapy.[4] In extensive-stage SCLC, the addition of atezolizumab or durvalumab to platinum-based chemotherapy has improved survival in the first-line setting.[5,6] However, relapse usually occurs within 1 year and 40% to 50% of patients will receive subsequent therapies.

As a monotherapy, lurbinectedin (3·2 mg/m² every 3 weeks) received accelerated approval by the US Food and Drug Administration (FDA) in June, 2020, for adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy[7] and has subsequently been approved in the United Arab Emirates (July, 2021) and in Australia, Canada, and Singapore (September, 2021). Other systemic therapeutic options for patients who relapse after first-line treatment are limited; before the approval of lurbinectedin, topotecan was the only FDA-approved therapy in the USA for SCLC that progressed after first-line chemotherapy.[7,8] However, treatment with topotecan is associated with modest efficacy and severe haematological toxicities that often necessitate dose reductions and treatment delays.[9,10] In the UK and European Union, cyclophosphamide, doxorubicin, and vincristine (CAV) is also used for second-line SCLC treatment and is included in US and European guidelines for the treatment of relapsed SCLC.[2,11] For patients with platinum-sensitive disease, US and European guidelines recommend rechallenge with the original chemotherapy regimen, with US guidelines also recommending treatment with oral or intravenous topotecan and lurbinectedin for subsequent systemic therapy.[2,11]

SCLC is a transcription-addicted disease, with high levels of dysregulated transcription factors that contribute to tumour initiation and progression.[12] Lurbinectedin is a synthetic marine-derived anticancer agent that acts as a selective inhibitor of oncogenic transcription, resulting in immunogenic cell death.[13–15] Preclinical studies have also shown that lurbinectedin modifies the tumour immune-suppressive microenvironment.[16]

Approval of lurbinectedin monotherapy as second-line therapy in metastatic SCLC was based on results from a phase 2, single-arm basket trial.[17] In the SCLC cohort, lurbinectedin monotherapy at a dose of 3·2 mg/m² every 3 weeks showed an overall response rate of 35%, with a 5·3-month duration of response by investigator assessment and a median overall survival of 9·3 months. The safety profile of lurbinectedin monotherapy was acceptable and manageable, with the most common grade 3 to 4 adverse events being haematological.

Before the start of the basket trial, lurbinectedin was investigated in combination with doxorubicin, an

Research in context

Evidence before this study

Small-cell lung cancer (SCLC) is an aggressive disease with a poor prognosis. Treatment is rarely curative, and few treatment options exist for patients with disease relapse after first-line platinum-based chemotherapy. We searched PubMed for clinical trials and randomised controlled trials published in English from database inception to Aug 10, 2021, using the search terms "((extensive stage SCLC) OR (relapsed SCLC)) AND second line". Although several agents have been investigated as potential second-line therapies in phase 1 and 2 studies, few have been evaluated in phase 3 trials. Lurbinectedin monotherapy (3·2 mg/m² every 3 weeks) showed clinical benefit as second-line therapy in patients with SCLC who relapsed after platinum-based chemotherapy in a phase 2 basket trial. Preclinical and phase 1 studies suggest synergistic effects when lurbinectedin is administered with doxorubicin, with encouraging results in relapsed SCLC.

Added value of this study

This is the first phase 3 trial of lurbinectedin combination therapy as second-line treatment in patients with relapsed SCLC. Lurbinectedin in combination with doxorubicin did not show superiority in overall survival compared with control (intravenous topotecan or cyclophosphamide, doxorubicin, and vincristine [CAV]) in patients with SCLC who relapsed after platinum-based chemotherapy. The tolerability profile of lurbinectedin plus doxorubicin was acceptable and manageable, with no new safety signals relative to previous studies of lurbinectedin. Additionally, lurbinectedin plus doxorubicin showed favourable safety and tolerability compared with control, including fewer grade 3 or worse drug-related adverse events, deaths due to adverse events, haematological toxicities, dose reductions, red blood cell or platelet transfusions, and treatment discontinuations because of adverse events.

Implications of all the available evidence

Lurbinectedin, in combination with doxorubicin, did not improve survival in patients with SCLC who relapsed after platinum-based chemotherapy, but was associated with reduced haematological toxicity, fewer treatment-related dose reductions and delays, and numerically fewer transfusions compared with control therapy (intravenous topotecan or CAV). On the basis of these results, at present there is no intention to develop this combination in relapsed SCLC.

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anthracycline, on the basis of preclinical evidence of potential synergistic effects.[18] In a phase 1 study in 19 patients with SCLC treated at the recommended dose for the combination of lurbinectedin (4·0 mg flat dose every 3 weeks) with doxorubicin (50·0 mg/m² every 3 weeks) in the second-line setting, 65% of patients had an overall response, with a median duration of response of 6·7 months.[19] However, 88% of patients treated at this recommended dose had grade 3 to 4 neutropenia.[19] In an effort to reduce the incidence of severe myelosuppression, the combination was further evaluated in an expansion cohort of 28 patients with the reduced dose of lurbinectedin 2·0 mg/m² (converted from the flat dose) and doxorubicin 40·0 mg/m². Overall response was seen in 36% of patients, with a median overall survival of 7·9 months (overall response 46% and overall survival 10·2 months in 22 patients who had a chemotherapy-free interval >30 days).[20] Notably, the use of prophylactic granulocyte-colony stimulating factor (G-CSF) was recommended in both the phase 1 study and expansion cohort to reduce myelosuppression.

The findings from the phase 1 study of lurbinectedin plus doxorubicin formed the rationale for the phase 3 ATLANTIS study, which compared the efficacy of combination lurbinectedin 2·0 mg/m² and doxorubicin 40·0 mg/m² versus physician's choice of either intravenous topotecan or CAV with mandatory G-CSF prophylaxis in both groups in patients with SCLC who relapsed after one previous platinum-containing chemotherapy regimen.[21]

Methods

Study design and participants

ATLANTIS was an international, randomised, open-label, phase 3 trial. The study was done in 135 centres across the USA, Canada, Europe (Austria, Belgium, Bulgaria, Czech Republic, France, Germany, Greece, Hungary, Italy, Netherlands, Poland, Portugal, Romania, Spain, and UK), South America (Argentina, Brazil), and Lebanon (appendix pp 2–6). The study design and rationale have previously been published[21] and are summarised briefly here. The study protocol was approved by the independent ethics committee or institutional review board at all participating study centres, and the trial was done in accordance with the Declaration of Helsinki and Good Clinical Practice.

See Online for appendix

Full details of the inclusion and exclusion criteria are presented in the appendix (pp 18–19). Patients were eligible to participate if they were aged 18 years or older with Eastern Cooperative Oncology Group (ECOG) performance status 0–2, pathologically confirmed limited-stage SCLC or extensive-stage SCLC with relapse after one previous platinum-containing chemotherapy regimen, and chemotherapy-free interval of 30 days or longer; patients who had received previous treatment with a programmed death-1 (PD-1) or programmed death-ligand-1 (PD-L1) inhibitor (including as a separate therapy line) were also eligible.

Patients were excluded if they had received more than one previous chemotherapy-containing regimen (including rechallenge with the same initial regimen); no previous treatment with platinum-based chemotherapy for SCLC; previous treatment with lurbinectedin, topotecan, or anthracyclines; limited-stage SCLC and were candidates for local or regional therapy; symptomatic or steroid-requiring or progressive central nervous system (CNS) involvement for 4 weeks or more before randomisation. All participants provided written informed consent.

Randomisation and masking

Lurbinectedin plus doxorubicin (experimental group) was compared with physician's choice of topotecan or CAV (control group). Patients were randomly assigned centrally (1:1) to lurbinectedin plus doxorubicin or control; crossover between treatment groups was not permitted. An interactive web-response system with a computer-generated dynamic random-sequence program was implemented. The study was initially designed to cap recruitment in the control group when one of the treatment options reached 55% of the target patient enrolment; however, this capping requirement was removed in a protocol amendment dated May 3, 2018. Randomisation was stratified by ECOG performance status (0 *vs* 1–2), chemotherapy-free interval after first-line SCLC treatment (≥180 days *vs* 90–179 days *vs* <90 days), baseline CNS involvement (yes *vs* no), previous PD-1 or PD-L1 therapy (yes *vs* no), and physician's choice of topotecan or CAV. The study was open label; therefore, neither patients nor clinicians were masked to treatment allocation, although the independent review committee (IRC), which assessed outcomes, was masked to patients' treatment allocation.

Procedures

In the lurbinectedin plus doxorubicin group, patients received intravenous doxorubicin 40·0 mg/m² on day 1, followed by intravenous lurbinectedin 2·0 mg/m² on day 1 of each 21-day cycle. In the control group, patients received either intravenous topotecan 1·5 mg/m² daily on days 1 to 5 of a 21-day cycle (with dose reductions for patients with creatinine clearance <60 mL/min) or the combination of intravenous cyclophosphamide 1000 mg/m², doxorubicin 45·0 mg/m², and vincristine 2·0 mg total on day 1 of each 21-day cycle. In both treatment groups, a maximum of ten cycles of doxorubicin-containing regimens was permitted; patients in the lurbinectedin plus doxorubicin group could receive maintenance lurbinectedin at a dose of 3·2 mg/m² (2·6 mg/m² if dose reduction occurred while on combination therapy; 2·0 mg/m² if two dose reductions occurred while on combination therapy) on day 1 of each 21-day cycle. All patients in both groups received prophylactic G-CSF subcutaneously; the type, dose, and

regimen could vary according to institutional practices. The schedule of study visits and assessments is included in the appendix (pp 19–21). Treatment continued until disease progression, unacceptable toxicity, investigator decision, or patient withdrawal of consent.

Criteria for dose reductions included grade 3 or worse treatment-related non-haematological toxicity, febrile neutropenia, neutropenic infection, or sepsis; grade 4 thrombocytopenia or neutropenia; treatment-related dose delays of more than 5 days or frequent, shorter dose delays; treatment-related, non-optimally treated grade 3 nausea or vomiting; grade 3 fatigue or asthenia lasting less than 3 days; grade 3 diarrhoea lasting for up to 2 days or not optimally treated; and non-clinically relevant isolated biochemical abnormalities. Dose reductions in vincristine also occurred for patients assigned to CAV if their total bilirubin concentrations were 1·25–1·5 times the upper limit of normal (ULN) or bilirubin concentrations were abnormally high before the start of a new cycle; patients assigned to CAV who had grade 2 or worse neuropathy also had to stop receiving vincristine until neuropathy resolved to grade 1 or lower.

Outcomes

The primary efficacy endpoint was the comparison of overall survival (from the date of randomisation to the date of death or last contact) between the lurbinectedin plus

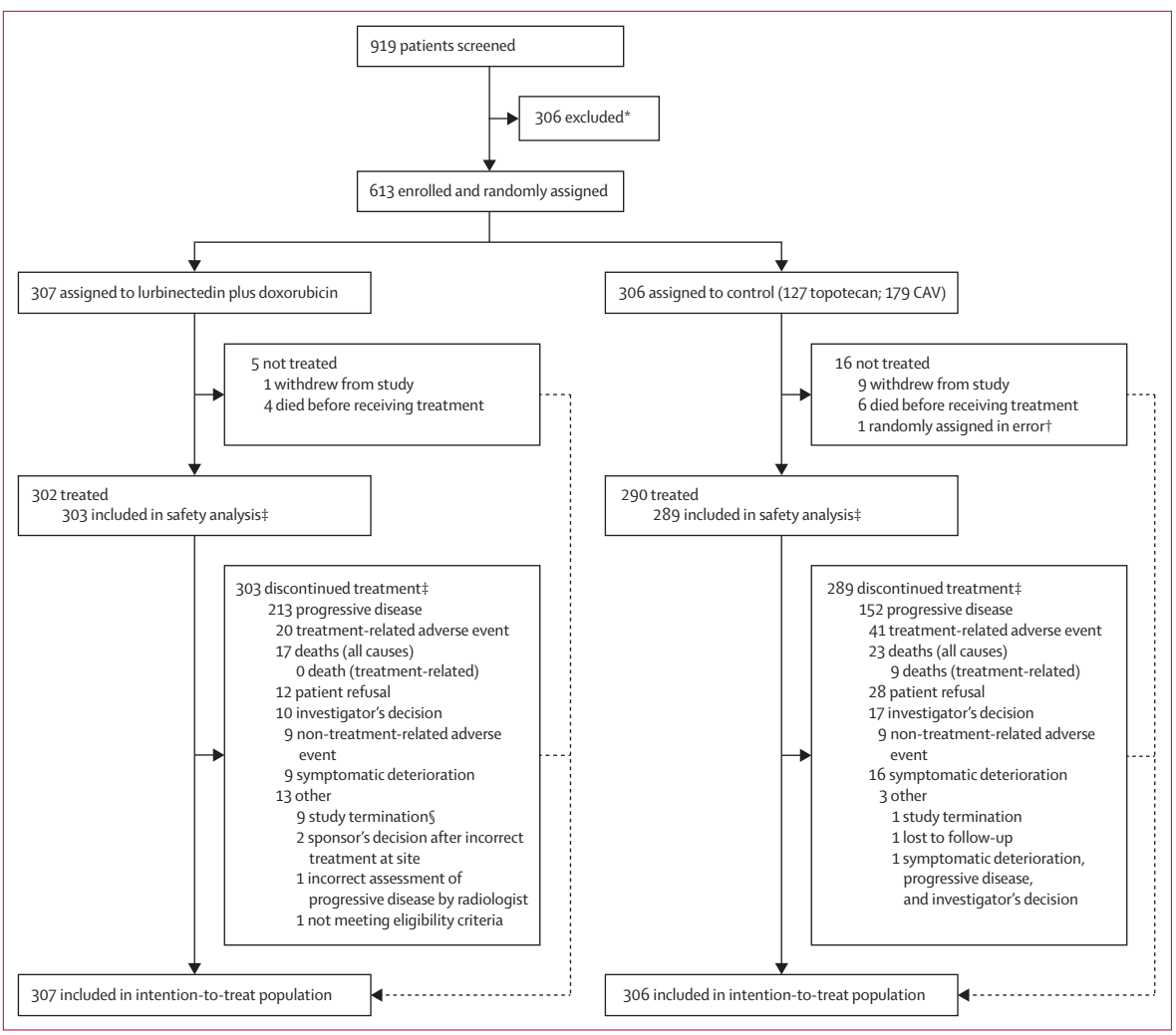

Figure 1: **Trial profile**

CAV=cyclophosphamide, doxorubicin, and vincristine. ULN=upper limit of normal. *For a list of reasons for exclusion, see appendix p 7. †Inclusion criteria (total bilirubin ≤1·5 × ULN or direct bilirubin ≤ULN) was not fulfilled. ‡One patient randomly assigned to receive topotecan in the control group was treated with lurbinectedin in cycle 1 because of a mistake at a study site. This was considered a major protocol deviation, and treatment was discontinued after cycle 1. For the purpose of efficacy and safety data analysis, this patient has been moved to the lurbinectedin plus doxorubicin group; therefore, the safety population comprised 303 patients in the lurbinectedin plus doxorubicin group and 289 patients in the control group. For the intention-to-treat primary endpoint analysis, each patients' initial treatment assignment was used for the comparison (ie, 307 patients in the lurbinectedin plus doxorubicin group and 306 patients in the control group). §Includes five patients who were moved to compassionate use after study termination.

doxorubicin group and the control group, and was assessed in the intention-to-treat population. Landmark analyses of overall survival were done at 12, 18, and 24 months.

Secondary and tertiary endpoints included the comparison of overall survival between lurbinectedin plus doxorubicin and topotecan or CAV individually; progression-free survival (centrally assessed by IRC) in the intention-to-treat population; overall survival and progression-free survival according to prespecified subgroups at baseline (baseline stratification factors and other potential prognostic factors, as widely recognised by the scientific community; full details are in the appendix pp 21–22); and tumour response and response duration as per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria (by IRC).

Safety endpoints were assessed in patients who had received any partial or complete study treatment infusions and included treatment-emergent and treatment-related adverse events (as per National Cancer Institute Common Terminology Criteria for Adverse Events version 4) and dose reductions and discontinuations because of treatment-related adverse events.

Statistical analysis

Sample size was calculated based on a one-sided 2·5% significance level, with at least 90% power to detect a 25% reduction in the risk of death with lurbinectedin plus doxorubicin relative to the control group. Median overall survival with topotecan or CAV was estimated to be 7·5 months based on a previous study of topotecan versus amrubicin.[22] This equated to 508 death events, requiring a sample size of approximately 600 patients. Efficacy analyses were done in the intention-to-treat population, which consisted of all randomly assigned patients. Only if the result of the primary endpoint analysis was significant would a hierarchical procedure be used to test secondary efficacy endpoints.

During the prespecified interim safety analysis, the independent data monitoring committee did not choose to review efficacy data; therefore, as per the protocol, no adjustments to the significance levels were needed to preserve an overall false-positive rate of 0·005 (one-sided).

Overall survival, progression-free survival, and duration of response were analysed according to the Kaplan-Meier method, and overall survival was compared using the stratified log-rank test (primary analysis; with CNS and chemotherapy-free interval as stratification factors); unstratified log-rank tests were also calculated as supportive analyses.

Cox regression was used to calculate the risk reduction for overall survival, progression-free survival, and duration of response and to determine any influence of the stratification variables and other potential prognostic factors (as previously noted) on time-to-event efficacy analyses. Forest plots were produced for patient subgroups according to baseline stratification factors, with their hazard ratios (HRs) and corresponding CIs. Counts and percentages, with their corresponding exact 95% CIs, were calculated for response rates. Statistical analyses were done with SAS version 9.4.

An independent data monitoring committee oversaw the conduct of the study. This study is registered with ClinicalTrials.gov, NCT02566993, and with EudraCT, 2015-001641-89.

Role of the funding source

This study was designed by the sponsor and the study investigators. Data were collected by the investigators and analysed by the sponsor. Reporting of the clinical study, including the interpretation of results, was the responsibility of the sponsor.

Results

Between Aug 30, 2016, and Aug 20, 2018, 919 patients were screened and 613 patients were randomly assigned to lurbinectedin plus doxorubicin (n=307) or control (n=306; topotecan, n=127; CAV, n=179; figure 1). 21 patients did not receive study treatment (lurbinectedin plus doxorubicin, n=5; control, n=16), and the safety population therefore included 592 patients. One patient randomly assigned to receive topotecan in the control group was treated with lurbinectedin in cycle 1 because of a mistake at a study site—this was considered a major protocol deviation, and treatment was discontinued after cycle 1. For the analysis of safety data, this patient was moved to the lurbinectedin plus doxorubicin group; therefore, the safety population comprised 303 patients in the lurbinectedin plus doxorubicin group and 289 patients in the control group. For the intention-to-treat primary endpoint analysis, each patients' initial treatment assignment was used for the comparison (ie, 307 patients in the lurbinectedin plus doxorubicin group and 306 patients in the control group).

Baseline characteristics in the lurbinectedin plus doxorubicin and control groups are shown in table 1; baseline characteristics according to physician's choice of therapy in the control group are shown in the appendix (pp 8–9). 560 (91%) of 613 patients had extensive-stage SCLC at study entry; most had widespread metastases including the liver, lymph nodes, adrenal glands, and bone; 95 (15%) had evidence of CNS involvement, and 36 (6%) had received previous immunotherapy with a PD-1 or PD-L1 inhibitor. Two-thirds (415 [68%]) of patients had achieved a partial or complete response to first-line chemotherapy, with a median time to progression of 7·4 months (IQR 5·5–10·0) in the lurbinectedin plus doxorubicin group and 7·4 months (IQR 5·6–9·5) in the control group, and median chemotherapy-free interval of 115·0 days (IQR 68·0–206·0) in the lurbinectedin plus doxorubicin group versus 120·5 days (IQR 71·0–201·0) in the control group.

303 patients in the lurbinectedin plus doxorubicin group and 289 patients in the control group discontinued study treatment. Progressive disease was the reason for

	Lurbinectedin plus doxorubicin (n=307)	Control (topotecan or CAV; n=306)
Sex		
Male	176 (57%)	173 (57%)
Female	131 (43%)	133 (44%)
Age (years)	63 (58–69)	63 (58–68)
>65 years	130 (42%)	127 (42%)
Ethnic origin		
White	266 (87%)	265 (87%)
Black or African American	1 (<1%)	1 (<1%)
Asian	0	1 (<1%)
Other	2 (<1%)	2 (<1%)
Not available*	38 (12%)	37 (12%)
ECOG performance status		
0	95 (31%)	95 (31%)
1	197 (64%)	204 (67%)
2	15 (5%)	7 (2%)
Smoking status		
Former	197 (64%)	199 (65%)
Current	91 (30%)	89 (29%)
Never	19 (6%)	18 (6%)
Time from first diagnosis to randomisation (months)	9·3 (7·1–11·9)	9·1 (7·2–11·8)
Disease stage at initial diagnosis		
Limited stage	25 (8%)	28 (9%)
Extensive stage	282 (92%)	278 (91%)
Disease involvement at baseline		
Lung	240 (78%)	260 (85%)
Lymph nodes	208 (68%)	209 (68%)
Liver	104 (34%)	102 (33%)
Adrenal	79 (26%)	80 (26%)
Bone	62 (20%)	67 (22%)
CNS	46 (15%)	49 (16%)
(Continued from previous column)		
LDH†	0·95 (0·76–1·32)	0·94 (0·77–1·18)
≤ULN	167 (54%)	179 (58%)
>ULN	135 (44%)	121 (40%)
Missing	5 (2%)	6 (2%)
Previous lines of anticancer therapy	1 (1–1)	1 (1–1)
One line	298 (97%)	302 (99%)
Two lines	9 (3%)	4 (1%)
Best response to previous chemotherapy		
Complete response	17 (6%)	15 (5%)
Partial response	192 (63%)	191 (62%)
Stable disease	71 (23%)	63 (21%)
Progressive disease	17 (6%)	21 (7%)
Not evaluable or not known	10 (3%)	16 (5%)
Time to progression on first-line chemotherapy (months)	7·4 (5·5–10·0)	7·4 (5·6–9·5)
Previous PD-1 or PD-L1 inhibitor therapy	19 (6%)	17 (6%)
Chemotherapy-free interval (days)	115·0 (68·0–206·0)‡	120·5 (71·0–201·0)§
<90 days	99 (32%)	101 (33%)
90–179 days	115 (38%)	116 (38%)
≥180 days	93 (30%)	89 (29%)

Data are n (%) or median (IQR). CAV=cyclophosphamide, doxorubicin, and vincristine. CNS=central nervous system. ECOG=Eastern Cooperative Oncology Group. LDH=lactate dehydrogenase. PD-1=programmed death-1. PD-L1=programmed death-ligand 1. ULN=upper limit of normal. *Some countries did not permit collection of data concerning race. †Data are median (range) × ULN. ‡Eight patients treated with lurbinectedin plus doxorubicin had a chemotherapy-free interval of less than 30 days. §One patient treated with topotecan and one patient treated with CAV had a chemotherapy-free interval of less than 30 days.

Table 1: **Baseline characteristics of the intention-to-treat population**

discontinuation in most patients (figure 1). Of patients who discontinued treatment, 145 (48%) of 303 in the lurbinectedin plus doxorubicin group and 134 (46%) of 289 in the control group received subsequent medical therapy (appendix p 10). Roughly twice as many patients in the control group discontinued treatment because of study treatment-related adverse events than did patients in the lurbinectedin plus doxorubicin group (41 [14%] of 289 patients in the control group *vs* 20 [7%] of 303 in the lurbinectedin plus doxorubicin group).

A total of 2159 treatment cycles were administered to patients receiving lurbinectedin plus doxorubicin, with a median of five treatment cycles (IQR 2–8) per patient and median time on treatment of 18·2 weeks (IQR 8·6–29·1). 61 patients received single-agent lurbinectedin, including 50 patients who completed ten cycles of lurbinectedin plus doxorubicin combination therapy and then switched to lurbinectedin monotherapy, and 11 patients who started single-agent lurbinectedin before completing ten cycles of lurbinectedin plus doxorubicin combination therapy. In the control group, 631 cycles of topotecan and 883 cycles of CAV were administered, with a median of five treatment cycles of topotecan per patient (IQR 2–6) and median time on treatment of 16·9 weeks (IQR 8·7–22·9), and a median of four cycles of CAV per patient (IQR 2–7) were administered with a median time on treatment of 14·3 weeks (IQR 8·2–21·3).

At data cutoff (Feb 24, 2020), median follow-up for overall survival was 24·1 months (95% CI 21·7–26·3) when a total of 522 deaths had occurred: 268 (87%) of 307 in the lurbinectedin plus doxorubicin group and 254 (83%) of 306 in the control group. Median overall survival was 8·6 months (95% CI 7·1–9·4) in patients randomly assigned to lurbinectedin plus doxorubicin versus 7·6 months (6·6–8·2) in patients randomly assigned to control treatment, which was not a statistically significant difference (stratified log-rank p=0·90; HR 0·97 [95% CI 0·82–1·15], p=0·70; table 2; figure 2).

	Lurbinectedin plus doxorubicin (n=307)	Control (topotecan or CAV; n=306)	HR (95% CI) or difference (%)*
Overall survival			
Deaths	268 (87%)	254 (83%)	..
Censored	39 (13%)	52 (17%)	..
Median overall survival, months (95% CI)	8·6 (7·1–9·4)	7·6 (6·6–8·2)	HR 0·97 (0·82–1·15)†
12-month overall survival, % (95% CI)	31% (26–36)	28% (23–33)	Difference 3%
18-month overall survival, % (95% CI)	16% (12–20)	16% (12–21)	Difference <–1%
24-month overall survival, % (95% CI)	9% (6–13)	10% (6–13)	Difference <–1%
Progression-free survival by IRC			
Progression-free survival events	244 (80%)	234 (77%)	..
Censored	63 (21%)	72 (24%)	..
Median progression-free survival, months (95% CI)	4·0 (2·8–4·2)	4·0 (3·0–4·1)	HR 0·83 (0·69–1·00)
6-month progression-free survival, % (95% CI)	31% (26–37)	24% (19–30)	Difference 7%
12-month progression-free survival, % (95% CI)	11% (7–15)	4% (1–7)	Difference 6%‡
RECIST responses by IRC			
Complete response§	8 (3%)	4 (1%)	..
Partial response§	89 (29%)	87 (28%)	..
Stable disease	111 (36%)	116 (38%)	..
Progressive disease	74 (24%)	52 (17%)	..
Unknown	25 (8%)	47 (15%)	..
Overall response, % (95% CI)	32% (26–37)	30% (25–35)	..
Duration of response by IRC¶			
Events	68 (70%)	74 (81%)	..
Censored	29 (30%)	17 (19%)	..
Median duration of response, months (95% CI)	5·7 (4·1–7·1)	3·8 (2·8–4·3)	HR 0·58 (0·42–0·81)

Data are n (%), unless otherwise stated. CAV=cyclophosphamide, doxorubicin, and vincristine. HR=hazard ratio. IRC=independent review committee. RECIST=Response Evaluation Criteria in Solid Tumours. ··=not applicable. *Because the primary endpoint was not met, no formal statistical comparisons were performed for secondary endpoints. †Stratified log-rank p=0·90; unstratified log-rank p=0·70; p value for HR p=0·70. ‡Due to rounding of values for each treatment group. §Includes both confirmed and unconfirmed responses. ¶Lurbinectedin plus doxorubicin, n=97; control (topotecan or CAV), n=91.

Table 2: **Efficacy outcomes in the intention-to-treat population**

Overall survival at 12, 18, and 24 months was similar between the lurbinectedin plus doxorubicin and control groups.

Because the primary endpoint was not met, no formal statistical comparisons were performed for secondary endpoints. Median progression-free survival by IRC did not differ between the two groups (4·0 months for both groups; table 2). There was a numerical reduction in the risk of progression or death in the lurbinectedin plus doxorubicin group relative to the control group (HR 0·83, 95% CI 0·69–1·00; figure 2). 12-month progression-free survival by IRC was 11% (95% CI 7–15) in patients randomly assigned to lurbinectedin plus doxorubicin and 4% (1–7) in patients randomly assigned to control.

Partial or complete responses (including unconfirmed responses and those confirmed by IRC) were seen in 97 (32%) of 307 patients in the lurbinectedin plus doxorubicin group and 91 (30%) of 306 patients in the control group (table 2). The median duration of response was 5·7 months (95% CI 4·1–7·1) in the lurbinectedin plus doxorubicin group and 3·8 months (2·8–4·3) in the control group (HR 0·58, 95% CI 0·42–0·81).

In general, in subgroup analyses stratified by baseline patient characteristics and selected prognostic factors, overall survival and progression-free survival were broadly similar between the lurbinectedin plus doxorubicin group and the control group, with some exceptions (appendix pp 14–17). In patients older than 65 years, median overall survival was 8·9 months (95% CI 7·7–10·3) in the lurbinectedin plus doxorubicin group versus 5·9 months (5·2–7·6) in the control group (HR 0·75, 95% CI 0·57–1·00), and median progression-free survival was 4·2 months (3·3–5·4) in the lurbinectedin plus doxorubicin group versus 3·0 months (2·7–4·0) in the control group (HR 0·65, 95% CI 0·48–0·88). Median overall survival in patients with baseline lactate dehydrogenase (LDH) concentration less than or equal to the ULN was 11·4 months (95% CI 9·9–12·6) in the lurbinectedin plus doxorubicin group compared with 9·4 months (8·0–11·1) in the control group (HR 0·82, 95% CI 0·65–1·03), but similar between groups in patients with LDH greater than the ULN (5·2 months [4·0–6·1] in the lurbinectedin plus doxorubicin group *vs* 5·3 months [4·4–5·9] in the control group; HR 1·11, 95% CI 0·86–1·44). Median progression-free survival for patients with baseline LDH concentration less than or equal to the ULN was 5·4 months (95% CI 4·2–6·9) in the lurbinectedin plus doxorubicin group compared with 4·2 months (4·0–5·3) in the control group (HR 0·69, 95% CI 0·54–0·89). In patients with a chemotherapy-free interval of 180 days or longer, median overall survival was 12·7 months (95% CI 10·6–16·0) in the lurbinectedin plus doxorubicin group versus 9·8 months (7·6–13·3) in the control group (HR 0·85, 95% CI 0·61–1·19), and median progression-free survival was 8·2 months (5·3–9·7) in the lurbinectedin plus doxorubicin group versus 4·5 months (3·7–5·6) in the control group (HR 0·47, 95% CI 0·33–0·67); median overall survival and progression-free survival were similar in those with a chemotherapy-free interval of less than 180 days. In patients who had previously received a PD-1 or PD-L1 inhibitor, median progression-free survival by IRC was 6·9 months (95% CI 1·9–not estimable) in the lurbinectedin plus doxorubicin group compared with 4·2 months (4·0–7·0) in the control group (HR 0·55, 95% CI 0·25–1·20); median progression-free survival by IRC was lower in both groups for patients who had not received these treatments (3·5 months [2·8–4·1] *vs* 3·7 months [2·9–4·1]; HR 0·86, 95% CI 0·71–1·03). In patients with CNS involvement at baseline, median overall survival and progression-free survival by IRC were similarly poor in the lurbinectedin plus doxorubicin group and the control group. In patients without CNS

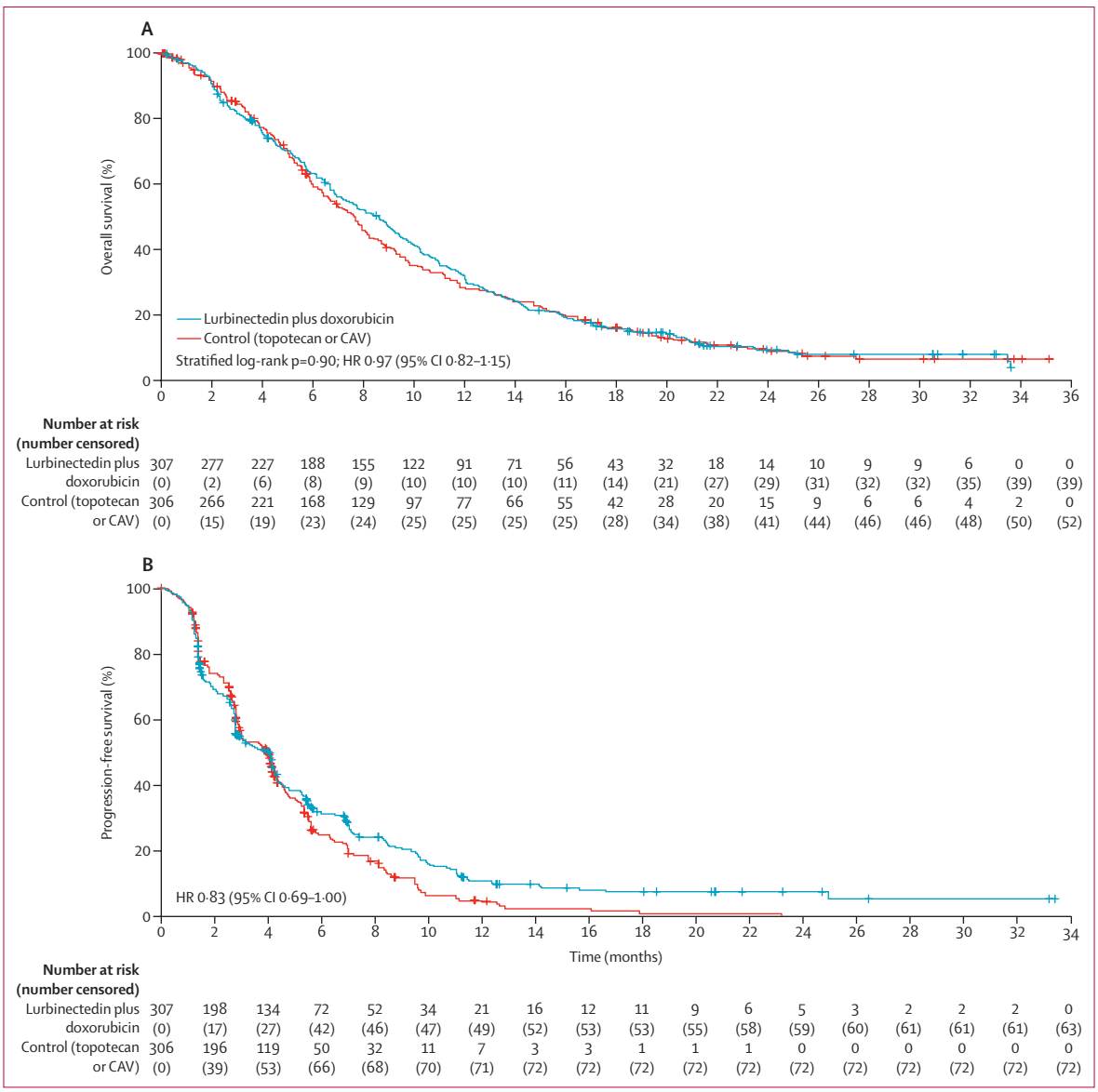

Figure 2: **Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival by IRC in the intention-to-treat population**
CAV=cyclophosphamide, doxorubicin, and vincristine. HR=hazard ratio. IRC=independent review committee.

involvement at baseline, median overall survival was 9·1 months (95% CI 8·1–10·2) in the lurbinectedin plus doxorubicin group and 7·7 months (6·7–8·6) in the control group (HR 0·92, 95% CI 0·76–1·11); progression-free survival was 4·2 months (3·7–4·8) in the lurbinectedin plus doxorubicin group versus 4·1 months (3·1–4·3) in the control group (HR 0·79, 95% CI 0·65–0·96).

After completing ten treatment cycles of lurbinectedin plus doxorubicin, 50 non-progressing patients with a tumour assessment by IRC continued to receive lurbinectedin monotherapy per the protocol. After discontinuation of doxorubicin, all three patients who achieved a complete response to lurbinectedin plus doxorubicin maintained their complete response on lurbinectedin monotherapy. Of 26 patients with a partial response to lurbinectedin plus doxorubicin who moved on to lurbinectedin monotherapy, three (12%) patients improved from partial response to complete response and 15 (58%) maintained their partial response. After discontinuation of doxorubicin, of 19 patients with stable disease on lurbinectedin plus doxorubicin, one (5%) patient improved to complete response and two (11%) patients improved to partial response, while eight (42%) maintained stable disease (appendix p 11).

296 (98%) of 303 patients in the lurbinectedin plus doxorubicin group had treatment-emergent adverse events compared with 284 (98%) of 289 patients in the control group; treatment-related adverse events occurred

	Lurbinectedin plus doxorubicin (n=303)		Control (topotecan or CAV; n=289)	
	Any adverse events	Treatment-related adverse events	Any adverse events	Treatment-related adverse events
Any adverse event	296 (98%)	268 (88%)	284 (98%)	266 (92%)
Grade ≥3 adverse event	200 (66%)	145 (48%)	250 (87%)	218 (75%)
Grade ≥4 adverse event	77 (25%)	50 (17%)	174 (60%)	160 (55%)
Any serious adverse event	126 (42%)	42 (14%)	141 (49%)	88 (30%)
Grade ≥3 serious adverse event	111 (37%)	38 (13%)	128 (44%)	83 (29%)
Grade ≥4 serious adverse event	42 (14%)	14 (5%)	68 (24%)	48 (17%)
Deaths associated with adverse events	19 (6%)	2 (<1%)*	22 (8%)	10 (4%)*
Treatment discontinuations because of adverse events	39 (13%)	26 (9%)	62 (21%)	47 (16%)
Dose reductions because of adverse events	75 (25%)	66 (22%)	142 (49%)	138 (48%)
Dose delays because of adverse events	111 (37%)	79 (26%)	128 (44%)	99 (34%)
Most common treatment-emergent adverse events (any grade)				
Fatigue	167 (55%)	136 (45%)	146 (51%)	120 (42%)
Nausea	124 (41%)	109 (36%)	90 (31%)	75 (26%)
Decreased appetite	86 (28%)	62 (21%)	60 (21%)	44 (15%)
Vomiting	74 (24%)	58 (19%)	48 (17%)	38 (13%)
Weight decreased	64 (21%)	17 (6%)	38 (13%)	5 (2%)
Cough	61 (20%)	8 (3%)	49 (17%)	2 (<1%)
Constipation	59 (20%)	29 (10%)	55 (19%)	28 (10%)
Dyspnoea	58 (19%)	4 (1%)	50 (17%)	10 (4%)
Alopecia	34 (11%)	32 (11%)	36 (13%)	35 (12%)
Diarrhoea	44 (15%)	26 (9%)	50 (17%)	30 (10%)
Haematological adverse events†				
Anaemia grade ≥3	..	57 (19%)	..	110 (38%)
Neutropenia grade ≥3	..	112 (37%)	..	200 (69%)
Febrile neutropenia grade ≥3	..	12 (4%)	..	24 (8%)
Thrombocytopenia grade ≥3	..	42 (14%)	..	90 (31%)

Data are n (%). CAV=cyclophosphamide, doxorubicin, and vincristine. NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events. ..=not applicable. *Causes of treatment-related deaths in the lurbinectedin plus doxorubicin group were pneumonia (n=1) and respiratory failure (n=1). Causes of treatment-related deaths in the control group were respiratory failure (n=1), respiratory-tract infection (n=1), interstitial lung disease (n=1), septic shock (n=5), sepsis (n=1), and neutropenic colitis (n=1; appendix p 12). †Based on laboratory parameters. One patient in each group had no haematological assessment; lurbinectedin plus doxorubicin group, n=302; control group, n=288.

Table 3: **NCI-CTCAE adverse events**

in 268 (88%) patients in the lurbinectedin plus doxorubicin group and 266 (92%) patients in the control group (table 3). The frequency of treatment-related adverse events leading to treatment discontinuation was lower in the lurbinectedin plus doxorubicin group than in the control group (26 [9%] patients in the lurbinectedin plus doxorubicin group *vs* 47 [16%] in the control group). Dose reductions because of adverse events were required in 75 (25%) patients in the lurbinectedin plus doxorubicin group compared with 142 (49%) patients in the control group. 12 patients died because of treatment-related adverse events: two (<1%) in the lurbinectedin plus doxorubicin group and ten (3%) in the control group (appendix p 12). The most frequently occurring non-haematological treatment-related adverse event of grade 3 or worse was fatigue (26 [9%] in the lurbinectedin plus doxorubicin group *vs* 31 [11%] in the control group; appendix p 13).

With respect to treatment-related haematological toxicities, anaemia of any grade occurred in 286 (95%) of 302 patients in the lurbinectedin plus doxorubicin group and in 278 (97%) of 288 patients in the control group (one patient in each group did not have haematological assessment). The proportions of patients with grade 3 or worse anaemia (57 [19%] patients in the lurbinectedin plus doxorubicin group *vs* 110 [38%] in the control group), neutropenia (112 [37%] *vs* 200 [69%]), febrile neutropenia (12 [4%] *vs* 24 [8%]), and thrombocytopenia (42 [14%] *vs* 90 [31%]) were all lower in the lurbinectedin plus doxorubicin group than the control group (table 3). Grade 3 or worse anaemia, neutropenia, and thrombocytopenia occurred in fewer patients assigned to lurbinectedin plus doxorubicin than in patients assigned to either topotecan or CAV individually (appendix p 13).

Of 94 cycles of treatment in the lurbinectedin plus doxorubicin group where there was a treatment-related dose reduction in either drug, 65 (69%) were related to haematological toxicity. By comparison, of 194 cycles of control treatment administered where there was a treatment-related dose reduction in either drug, 162 (84%) were due to haematological toxicity (topotecan, 75 [87%] of 86 dose reductions; CAV, 87 [81%] of 108 dose reductions).

Supportive care with respect to haematological function was required in fewer patients in the lurbinectedin plus doxorubicin group than in the control group (erythropoietin use, 22 [7%] of 303 patients in the lurbinectedin plus doxorubicin group *vs* 32 [11%] of 289 in the control group; red blood cell transfusions, 47 [16%] *vs* 87 [30%]; platelet transfusions, seven [2%] *vs* 22 [8%]).

Discussion

In the ATLANTIS trial, the combination of lurbinectedin and doxorubicin did not meet the primary endpoint of overall survival and did not show a statistical survival advantage compared with physician's choice of topotecan or CAV in patients with SCLC whose disease progressed after first-line platinum-based chemotherapy. Because the primary endpoint was not met, no formal statistical comparisons were performed for secondary endpoints. The secondary endpoints of progression-free survival and duration of treatment response were numerically longer with lurbinectedin plus doxorubicin versus control in the total study population and progression-free survival was numerically longer in some subgroups of clinical interest, including patients older than 65 years of age, patients with baseline LDH concentration less than or equal to the ULN, and patients with a chemotherapy-free interval of 180 days or longer. Notably, outcomes were similarly poorer in both treatment groups for patients with CNS metastases versus those without CNS metastases at

baseline; however, firm conclusions cannot be drawn from the present study regarding the activity of lurbinectedin plus doxorubicin in patients with CNS metastases because, although those with asymptomatic and non-progressive CNS lesions were eligible to participate, only 95 such patients were included. Additionally, because the primary endpoint was not reached, the results of these secondary endpoint and subgroup analyses can only be considered exploratory.[21] Lurbinectedin plus doxorubicin showed a more favourable safety and tolerability profile compared with control with respect to the incidence of haematological toxicities.

Progression-free survival in patients with a chemotherapy-free interval of 180 days or more was numerically longer in the lurbinectedin plus doxorubicin group than in the control group (8·2 months *vs* 4·5 months). A previous phase 3 trial reported a similar progression-free survival with topotecan (4·3 months) in patients with platinum-sensitive SCLC to that seen in the present study.[22] However, it should be noted that platinum-sensitive disease was defined as a chemotherapy-free interval of 90 days or longer in that study, which makes direct comparisons difficult.

Although the number of patients who had received previous immunotherapy for SCLC was small, there was a numerically longer median progression-free survival in the lurbinectedin plus doxorubicin group versus the control group (6·9 months *vs* 4·2 months). Improved results in patients previously exposed to PD-1 or PD-L1 inhibitors versus those who were not exposed were also seen in the phase 2 lurbinectedin single-agent trial.[17] This finding is of interest as immunotherapy is now standard of care in the first-line treatment setting of extensive-stage SCLC,[2,11] and the majority of patients receiving second-line treatment would be expected to have received these agents.

No new safety signals were observed in the lurbinectedin plus doxorubicin group, with the most frequent treatment-related adverse events including fatigue, nausea, and decreased appetite, which is consistent with those reported in the phase 1b study of lurbinectedin plus doxorubicin and the phase 2 study of single-agent lurbinectedin.[17,19] Additionally, the lurbinectedin plus doxorubicin combination showed a better safety profile compared with control in terms of severity of treatment-related adverse events (most were mild to moderate), serious adverse events, deaths, discontinuations, and dose modifications due to toxicity.

Patients in the lurbinectedin plus doxorubicin group had fewer haematological adverse events compared with patients in the control group, with fewer patients requiring erythropoietin support or red blood cell or platelet transfusions. Grade 3 or worse haematological adverse events were more common in the control group, driven primarily by topotecan toxicity, although grade 3 or worse neutropenia and febrile neutropenia were also more frequent in patients treated with CAV than in those treated with lurbinectedin plus doxorubicin; this finding is notable, because administration of G-CSF was mandatory in both treatment groups. Haematological toxicity was reflected in the requirement for dose reductions. Drug-related dose reductions were required for 86 (14%) of 631 topotecan treatment cycles, with 75 dose reductions associated with haematological toxicity; in the lurbinectedin plus doxorubicin group, treatment-related dose reduction was required for 94 (4%) of 2159 treatment cycles, with 65 due to haematological toxicity. CAV was the physician's choice of chemotherapy in 58% of patients in the control group, which might reflect its apparent more favourable toxicity profile relative to topotecan. Indeed, in a previous direct comparison of topotecan versus CAV, grade 3 or worse leukopenia, neutropenia, thrombocytopenia, and anaemia were all more common during treatment with topotecan,[9] and many clinicians have suggested a reduction in the standard topotecan dose to reduce excessive toxicity.[2]

Despite the haematological toxicity associated with topotecan, a topoisomerase I inhibitor, per guidelines from the National Comprehensive Cancer Network, oral or intravenous topotecan are still preferred regimens for patients with platinum-resistant SCLC.[2] Platinum-based rechallenge is a preferred second-line regimen for patients with SCLC and a chemotherapy-free interval of more than 6 months. Data from two phase 3 trials (carboplatin plus etoposide *vs* topotecan;[23] cisplatin plus etoposide plus irinotecan *vs* topotecan[24]) in patients with relapse after 90 days or more suggest a clinical benefit for rechallenge with a platinum-based regimen compared with topotecan. There are no head-to-head randomised controlled trials comparing lurbinectedin with platinum rechallenge. In a network meta-analysis, it was estimated that when single-agent lurbinectedin was compared with either oral or intravenous topotecan and platinum rechallenge in patients with platinum-sensitive SCLC (chemotherapy-free interval ≥90 days), the HR for overall survival favoured lurbinectedin.[25] However, this is an indirect treatment comparison, which has inherent assumptions and limitations in data availability that necessitate caution in interpreting these results.

Preclinical evidence suggested a potential synergistic effect of lurbinectedin in combination with doxorubicin and formed the basis for the clinical investigation of this combination. In a xenograft mouse model of SCLC, the combination of lurbinectedin and doxorubicin showed more robust antitumour activity versus either drug alone, with additive and sometimes synergistic effects observed.[18] However, because these data were derived from preclinical models, it is not known whether the effects of lurbinectedin plus doxorubicin at the doses used in ATLANTIS are synergistic or additive in patients with SCLC. Indeed, the role of doxorubicin itself in SCLC is debatable, because single-agent doxorubicin therapy has shown little to no efficacy in SCLC and is not a recommended regimen.[2,26]

The dose of lurbinectedin used in this study (2·0 mg/m²) concurrently with doxorubicin was 35% lower than the monotherapy dose used in the phase 2 basket trial (3·2 mg/m²) that formed the basis for FDA approval of lurbinectedin monotherapy.[17] The ATLANTIS study was initiated before the availability of the results from the phase 2 basket trial, and was therefore not designed as a confirmatory trial of monotherapy in patients with relapsed SCLC. However, patients who completed a maximum of ten cycles of lurbinectedin plus doxorubicin and continued to receive lurbinectedin monotherapy tended to maintain or improve their best response after discontinuation of doxorubicin.

A phase 3 confirmatory study comparing the FDA-approved dose of lurbinectedin either as monotherapy or in combination with irinotecan versus investigator's choice of irinotecan or topotecan is currently planned.[27] The inclusion of the combination group with irinotecan in this trial is based on promising preliminary antitumour activity of this combination in a phase 1b/2 trial of 21 patients with relapsed SCLC, in which the proportion of patients with overall response (partial response) was 62%, with a median progression-free survival of more than 6·2 months. These findings suggest potential synergy of lurbinectedin with topoisomerase I inhibitors.[28] Additionally, lurbinectedin combinations with other agents, including immunotherapies, are being actively investigated in ongoing and planned clinical trials.[27]

To optimise treatment strategies in SCLC, including lurbinectedin, there is a crucial need to better understand the underlying biology of SCLC and to identify predictive biomarkers. Four distinct molecular subtypes of SCLC have been proposed, each with its own therapeutic vulnerabilities.[29] Ultimately, more research is needed to better understand how to leverage these findings to optimise treatment with lurbinectedin monotherapy and potential novel combinations in patients with SCLC.

There were several limitations to this study. Mandatory prophylaxis with G-CSF in both groups could have reduced the observed haematological toxicity. As such, the reported rates of haematological toxicity in the current study might differ from what is observed in a real-world clinical practice setting, in which the use of supportive G-CSF is not mandatory for all patients but is instead generally recommended for consideration in patients with high ECOG performance status.[2] For example, the topotecan summary of product characteristics does not indicate that the use of primary prophylaxis with G-CSF is mandatory.[30] Moreover, although adverse events associated with G-CSF therapy are uncommon, few studies have examined the long-term use of G-CSF.[31] Furthermore, randomisation was not stratified by LDH concentration. There were slightly more patients with LDH concentrations higher than the ULN in the lurbinectedin plus doxorubicin group (44%) than in the control group (40%), which could have potentially affected the results to some degree in the intention-to-treat or subgroup analyses, because high LDH concentrations are associated with poor prognosis.[2] Comparison between the lurbinectedin plus doxorubicin and control groups could be complicated by the higher number of patients who received CAV than those who received topotecan. However, the preplanned subgroup analyses indicated that overall survival and progression-free survival were similar for lurbinectedin plus doxorubicin and either topotecan or CAV individually. Additionally, comparison between lurbinectedin plus doxorubicin and platinum rechallenge in patients with platinum-sensitive SCLC was not possible, because platinum rechallenge was not included as part of the control group.

In conclusion, the ATLANTIS study showed similar median overall survival for the combination of lurbinectedin plus doxorubicin versus physician's choice of topotecan or CAV in patients with SCLC who relapsed after one previous platinum-containing line. Although the primary endpoint was not met, lurbinectedin plus doxorubicin showed a better haematological safety profile, with less common severe (grade 3–4) haematological abnormalities, regardless of relation to treatment, and fewer subsequent complications and supportive care requirements compared with the standard of care therapy at the time this study was done. Together, these results support lurbinectedin monotherapy as a viable treatment option in relapsed SCLC, on the basis of the previously demonstrated clinical activity and tolerability in this setting. Other lurbinectedin combinations may be explored in the future.

Contributors

All authors had full access to the raw data and contributed to the interpretation of the data and the development, writing, approval of the final version of the manuscript, and had the final responsibility to submit for publication. LP-A wrote the first draft of the manuscript in conjunction with the sponsor. JG and ANi verified the underlying data.

Declaration of interests

SPA has received honoraria from Roche and Bristol Myers Squibb; has received support for attending meetings or travel from Roche; and has a patent for lurbinectedin plus atezolizumab. TEC reports consultant or advisory fees from Astellas Pharma, Janssen, Bristol Myers Squibb, Merck Serono, Amgen, Roche, Pfizer, Boehringer Ingelheim, Eli Lilly, AstraZeneca, Merck Sharp & Dohme, Sanofi, Novartis, Servier, and A&D Pharma; and travel support from Pfizer, Sanofi, Boehringer Ingelheim, Merck, Servier, Ipsen, Amgen, A&D Pharma, AstraZeneca, Genentech, Bristol Myers Squibb, Merck Sharp & Dohme Oncology, Eli Lilly, Janssen, Novartis, and Astellas Pharma. LB reports payment or honoraria from AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, and Roche; and participation on a data safety monitoring board or advisory board for AstraZeneca and Roche. EFS reports consulting fees paid to his institution from Merck and Eli Lilly; payment or honoraria to his institution from Boehringer Ingelheim, AstraZeneca, and Daiichi Sankyo; and participation on a data safety monitoring board or advisory board for Merck, AstraZeneca, and Merck Sharp & Dohme. AC reports payment or honoraria from Genentech, Takeda, Blueprint Medicines, and Amgen; participation on a data safety monitoring board or advisory board for Ipsen, Odonate Therapeutics, Jazz Pharmaceuticals, Aileron Therapeutics, Janssen, AstraZeneca, and Sanofi; and holds stock or stock options in Merck. IH reports personal payments and payments to her institution from Syneos Health UK. AFF reports a consultancy or advisory role with AstraZeneca, Syros, OncLive, Clinical Care Oncology,

Bayer, H3 Biomedicine, Pfizer, Medscape, PeerView, Genentech, Merck, Bristol Myers Squibb, and Boehringer Ingelheim; research funding to her institution from Bayer, Genentech, and AstraZeneca; was an employee and held stock or stock options in Novartis; and received support for this manuscript from PharmaMar. JAL-V, ANi, NV, JG, CK, and AZ are employees of PharmaMar and report stock or stock options in PharmaMar. MC-Y is an employee of PharmaMar. KS reports personal consulting fees from Roche, Bristol Myers Squibb, and Merck Sharp & Dohme; and consulting fees paid to his institution from Amgen. IB reports payment or honoraria from AstraZeneca, Amgen, Takeda, Bristol Myers Squibb, and Pfizer. CFW reports consulting fees from Viatris, Roche, and Alvotech; honoraria for lectures from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Takeda; meeting or travel support from Bristol Myers Squibb; and honoraria for advisory boards from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, and Merck Sharp & Dohme. OJ-V reports consulting fees from Boehringer Ingelheim, Merck Sharp & Dohme, AstraZeneca, Eli Lilly, and Takeda; payment or honoraria from Boehringer Ingelheim, Bristol Myers Squibb, Merck Sharp & Dohme, Roche, AstraZeneca, and Takeda; and meeting or travel support from Merck Sharp & Dohme and Roche. NR reports payment or honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Hoffmann-La Roche, Eli Lilly, Merck Sharp & Dohme, Merck, Pfizer, and Takeda; and meeting or travel support from AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Hoffmann-La Roche, Merck Sharp & Dohme, Pfizer, and Takeda. MD reports payment or honoraria for lectures and advisory boards from AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, Sanofi, and Roche. LP-A reports honoraria for scientific advice and speaker fees from Eli Lilly, Merck Sharp & Dohme, Bristol Myers Squibb, Roche, PharmaMar, Merck, AstraZeneca, Novartis, Servier, Amgen, Pfizer, Ipsen, Sanofi, Bayer, Mirati, GlaxoSmithKline, Janssen, and Takeda; participates as external member of the board of Genómica; is a founder and board member of Altum sequencing; and has received institutional support for contracted research from Merck Sharp & Dohme, Bristol Myers Squibb, AstraZeneca, and Pfizer. All other authors declare no competing interests.

Data sharing

Individual participant data are not publicly available since this requirement was not anticipated in the study protocol considering that this trial started patient enrolment in 2016. Posting of clinical trial summary results will be placed in the European Clinical Trials Database (EudraCT number 2015-001641-89; https://eudract.ema.europa.eu).

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