

Research Paper

Durvalumab plus platinum-etoposide in the first-line treatment of extensive-stage small cell lung cancer (CANTABRICO): A single-arm clinical trial



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ABSTRACT

Background: Immunotherapy trials involving patients with extensive-stage small cell lung cancer (ES-SCLC) from real-world clinical practice are needed. We aimed to evaluate the safety and effectiveness of durvalumab plus platinum-etoposide as a first-line treatment in a real-world population of patients with ES-SCLC.

Patients and methods: A prospective, single-arm study was conducted in adult patients who had histologically or cytologically confirmed ES-SCLC and a WHO/ECOG PS of 0–2 (a maximum of 30 % of patients with a PS of 2 were allowed). Patients received durvalumab plus platinum-etoposide for up to 6 cycles, followed by durvalumab every 4 weeks as a single agent. The primary outcomes included the incidence of grade ≥ 3 adverse events (AEs) and immune-mediated AEs (imAEs).

Results: Between December 2020 and April 2021, 101 patients were included in this trial. Grade 3 or higher AEs occurred in 77 patients (76.2 %) and were considered treatment-related in 58 patients (57.4 %). Thirty-eight patients (37.6 %) reported at least one imAE, all of which were considered treatment related. Among the 82 imAEs reported during the study, 68 (82.9 %) were grade 1–2. The median overall survival was 9.6 months (95 % CI, 7.8 to 11.3), and the 12-month and 24-month overall survival rates were 40.7 % (31.1 % to 50.3 %) and 25.4 % (95 % CI, 16.8 % to 34.0 %), respectively.

Conclusions: This phase 3B trial suggests that first-line treatment of patients with ES-SCLC with an initial regimen of up to six cycles of durvalumab plus platinum-etoposide followed by maintenance with durvalumab is feasible providing more options in daily clinical practice for the management of these patients depending on their characteristics.

Trial registration: NCT04712903.

1. Introduction

Extensive-stage small cell lung cancer (ES-SCLC) accounts for more than two-thirds of SCLC cases at the time of diagnosis and is associated with poor prognosis, with a 5-year overall survival (OS) rate of < 5 % [1,2]. On the basis of the results of the IMpower133 [3] and CASPIAN [4] studies, standard treatment with carboplatin and etoposide plus immunotherapy (atezolizumab or durvalumab) followed by maintenance immunotherapy is recommended as first-line treatment for these patients [2,5,6].

CASPIAN demonstrated that the combination of durvalumab and platinum-etoposide as first-line treatment for patients with ES-SCLC significantly prolonged OS compared with platinum-etoposide alone, without increasing the frequency of grade 3–4 adverse events (AEs) or adverse events leading to death [4]. An updated analysis of the CASPIAN study revealed that the 3-year survival rate was 3-fold higher than that with placebo (17.6 % versus 5.8 %) [7]. The benefit of this combination does not appear to be dependent on cell death ligand-1 (PD-L1) expression or the tissue mutational burden of the tumor [8].

All immunotherapy trials in this setting were performed in patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, limiting the generalizability of the results. Data from real-world studies, including those with durvalumab, suggest that over one-third of patients with ES-SCLC have a PS ≥ 2 [9,10], and over 70 % of the patients would not have been eligible for those trials [11]. In addition, in contrast to clinical practice, in the CASPIAN study, chemotherapy in the durvalumab arm was limited to a maximum of four cycles, and patients who had progressed to limited disease were not included in the trial. Therefore, clinical trials involving patients in real-world clinical practice, including those with poor PS, are needed [11].

This clinical trial aimed to evaluate the safety and efficacy of durvalumab plus platinum-etoposide as first-line treatment in a real-world population of patients with ES-SCLC.

2. Material and methods

This prospective, phase 3b, single-arm study was conducted at 31 sites in Spain. The study was conducted according to the ethical principles of the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical

Guidelines and the applicable International Conference on Harmonization Good Clinical Practice (GCP) guidelines. This study was approved by the ethics committee of the Hospital Universitario 12 de Octubre (Madrid, Spain). Written informed consent was obtained from all participants. This trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (identifier: NCT04712903).

2.1. Patients

To be included, patients had to be aged ≥ 18 years, with histologically or cytologically confirmed ES-SCLC (stage IV [T any, N any, M1a/b/c] or with T3-4 disease due to multiple lung nodules that were too extensive or had a tumor/nodal volume that was too large to be encompassed in a tolerable radiation plan, according to the American Joint Committee on Cancer Stage, 8th edition); patients who had received chemoradiotherapy for LS-SCLC and had experienced a treatment-free interval of at least 6 months since the last chemotherapy, radiotherapy, or chemoradiotherapy cycle could be included under the investigator criteria. Patients were included if they either did not have brain metastases or had brain metastases that were asymptomatic or had been treated for at least 2 weeks prior to study treatment and were receiving 10 mg/day or less prednisone or equivalent at the time of study entry. Additional inclusion criteria were as follows: being considered suitable for receiving a platinum-based chemotherapy regimen; having a WHO/ECOG PS of 0–2 (a maximum of 30 % of patients with a PS of 2 were allowed); having at least one lesion that was not previously irradiated and could be accurately measured at baseline as ≥ 10 mm in the longest diameter (except for lymph nodes that must have a short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI), which was suitable for accurate repeated measurements as per RECIST 1.1 guidelines; having no prior exposure to immunotherapy for cancer; having adequate hematologic and organ function; having evidence of postmenopausal status or a negative pregnancy test; and having a life expectancy of at least 12 months. Patients were excluded if they had active or previously documented autoimmune or inflammatory disorders, uncontrolled intercurrent illness, a history of active primary immunodeficiency, active infection, prior systemic treatment for ES-SCLC, or planned consolidation chest radiation therapy. The exclusion criteria are shown in [Supplemental Table 1](#).

2.2. Treatment

All the treatments were administered in 21-day cycles. Intravenous chemotherapy consisted of etoposide 80–100 mg/m² administered on Days 1 to 3 (maximum total dose 300 mg/m²) every 3 weeks in combination with the investigator's choice of either carboplatin area under the curve 5–6 mg on Day 1 every 3 weeks or cisplatin 75–80 mg/m² on Day 1 every 3 weeks. The patients could receive up to six cycles of intravenous chemotherapy. Durvalumab was administered intravenously at 1500 mg every 3 weeks in combination with chemotherapy for 4–6 cycles and then at 1500 mg every 4 weeks as a single agent. Prophylactic cranial irradiation (PCI) was permitted at the discretion of the investigator. Durvalumab treatment was continued until clinical progression or RECIST 1.1-defined radiological progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

2.3. Assessments and outcomes

Safety assessments included clinical laboratory assessments, physical examinations, vital signs, and recording of AEs, which were elicited using an open-ended questionnaire and graded according to the NCI CTCAE version 5.0. Tumor imaging assessments were performed according to local standards but with a recommendation of every 9 ± 1 weeks during the first 12–18 weeks of chemotherapy and a maximum interval of 12 weeks thereafter until RECIST-defined radiological progression with an additional follow-up scan 4–8 weeks later. Survival assessments were performed every two months after treatment discontinuation. Global health status and quality of life were evaluated using the European Organisation for Research and Treatment of Cancer (EORTC) 30-item core Quality of Life Questionnaire, version 3 (QLQ-C30 v3) [12]. Additionally, lung cancer symptoms were evaluated with the EORTC 13-item lung cancer module (QLQ-LC 13) [13]. In both questionnaires, a change equal to or greater than 10 points in either direction for any item is considered clinically relevant.

The primary outcomes included the incidence of grade ≥ 3 AEs and immune-mediated AEs (imAEs). The secondary efficacy outcomes included progression-free survival (PFS), defined as the time from the first date of treatment until the date of objective disease progression or death (by any cause in the absence of progression); the PFS rate at 6 months and at 1 year; the objective response rate (ORR) based on investigator – assessed response to treatment of complete or partial response as per RECIST1.1; the duration of response (DoR), defined as the time from the date of first documented response per RECIST1.1 until the first date of documented progression per RECIST1.1 or death in the absence of disease progression; the DoR at 1 year; the time to treatment discontinuation (TTD) as a continuous variable; overall survival (OS), defined as the time from the first date of treatment until death due to any cause; and the OS rate at 6, 12, and 18 months.

2.4. Statistical analysis

A convenience sample size of 85 patients was estimated on the basis of the expected accrual, which could be increased if recruitment was extended. It was estimated that assuming a sample size of up to 85 and a 70 % incidence of grade ≥ 3 adverse events, the estimated precision would be no wider than 10 %. The safety population included patients who received at least one dose of the study medication. Safety and binary efficacy outcomes are presented with absolute and relative frequencies. Time-to-event data were analyzed using the Kaplan–Meier method. Survival rates, as estimated using the Kaplan–Meier method, are presented with their corresponding 95 % confidence intervals.

A post hoc analysis of patients who achieved long-term benefit (LTB) was performed using data from a post-trial access program in which investigators requested medication every two months when treatment was considered beneficial for the patient. Patients with long-term

benefit were defined as those who lived for at least 24 months after inclusion. Patients who were censored before 24 months were excluded from the analysis. Key safety parameters were estimated for those with and without LTB. In addition, a bivariate analysis of potential factors associated with LTB was performed. The following baseline factors were included in this analysis: age (categorized as < 65 years and ≥ 65 years), sex, smoking status, ECOG PS, presence of brain/central nervous system metastases, presence of comorbidities (i.e., at least one comorbidity included in the Charlson index, hypertension or dyslipidemia), presence of high tumor burden (defined as patients with at least one of the following criteria: sum of longest diameters ≥ 60 mm, 2 or more metastatic locations, LDH over the upper limit of normal) and the type of platinum.

Binary outcomes are presented as absolute and relative frequencies and corresponding 95 % confidence intervals (CIs). Continuous outcomes are presented as medians and interquartile ranges. All analyses were performed using SAS v.9.4.

3. Results

3.1. Patient disposition and characteristics

Between December 2020 and April 2021, 126 patients were screened, 101 (80.8 %) of whom were included in the study and received at least one dose of the study medication (Fig. 1). The main reasons for screening failure were that the patients did not have adequate hematologic and organ function (n = 6) or did not have histologically or cytologically confirmed ES-SCLC (stage IV [T any, N any, M1a/b/c] or with T3-4 (n = 5)); one additional patient did not meet both criteria. Two patients were excluded because they had a WHO/ECOG PS score ≥ 3. The median age was 65 years (56 % were ≥ 65 years). Most patients were male (n = 68; 67.3 %), and most had stage IV disease (n = 87; 86.1 %). Six patients (5.9 %) had a PS of 2, 11 (10.9 %) had brain metastases, 10 (9.9 %) had progressed from a previously limited disease, and 33 (32.7 %) had liver metastases (Table 1).

3.2. Treatment exposure and safety

The median number (interquartile range) of durvalumab doses was 8 (5–11). During the chemotherapy phase, 39 patients (38.6 %) received 5 or more doses of durvalumab, and during the entire study period, 24 patients (23.8 %) received 12 or more doses (Table 2). Eighty-seven patients (86.1 %) received carboplatin therapy. The median number (interquartile range) of platinum-etoposide doses was 4 (4–6). In total, 40 (39.6 %) patients received five or more cycles of platinum-etoposide, and 33 (32.7 %) patients received six or more cycles of platinum-etoposide (Table 2).

Adverse events of any grade occurred in 100 patients (99 %) (Table 3). The most common adverse events were asthenia, anemia, neutropenia, dyspnea, constipation, alopecia, cough, and diarrhea. Grade ≥ 3 AEs occurred in 77 patients (76.2 %) and were considered treatment-related in 58 patients (57.4 %). The most frequent grade ≥ 3 AEs were anemia (n = 25; 24.8 %), neutropenia (n = 22; 21.8 %), and thrombocytopenia (n = 9; 8.9 %). Fifty-seven patients (56.4 %) experienced at least one serious AE. Eight patients (7.9 %) experienced an AE leading to death, including two patients with sepsis and one patient each with respiratory tract infection, pneumonia, hemoptysis, cardiorespiratory arrest, intracranial hemorrhage, and an immune-mediated neurological disorder. Eighteen patients (17.8 %) experienced AEs that led to treatment discontinuation, most frequently due to hematological toxicity, including neutropenia (n = 3), thrombocytopenia (n = 2), and anemia (n = 2).

Thirty-eight patients (37.6 %) reported at least one imAE, all of which were considered treatment related (Table 3). The most common imAEs were hypothyroidism (n = 14, 13.9 %), hyperthyroidism (n = 7, 6.9 %), diarrhea (n = 4, 4.0 %), pneumonitis (n = 4, 4.0 %), and rash (n

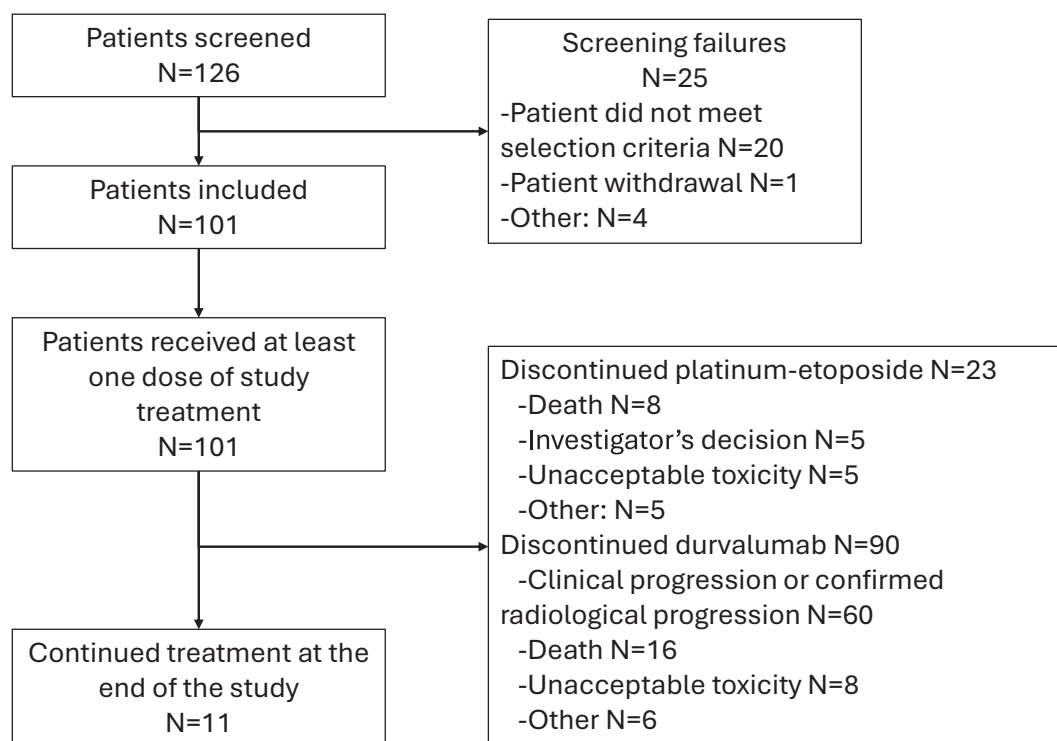


Fig. 1. Patient disposition.

Table 1
Demographic and clinical characteristics.

Characteristic ^a	
Age	
Median (years), median (IQR)	65 (62–71)
<65 years	44 (43.6)
≥65 years	57 (56.4)
Sex	
Female	33 (32.7)
Male	68 (67.3)
Race	
Caucasian	2 (2.0)
White	99 (98.0)
Smoking status	
Current smoker	46 (45.5)
Former smoker	53 (52.5)
Not available	2 (2.0)
Initial stage at diagnosis	
Extensive	91 (90.1)
Limited	10 (9.9)
Disease stage	
III	12 (11.9)
IV	87 (86.1)
Unknown	2 (2.0)
WHO performance status	
0	31 (30.7)
1	64 (63.4)
2	6 (5.9)
Brain metastases	
Yes	11 (10.9)
No	86 (85.2)
Unknown	4 (3.9)
Liver metastases	
Yes	33 (32.7)
No	64 (63.4)
Unknown	4 (3.9)

IQR = interquartile range.

^a All figures are No. (%) unless otherwise specified.

Table 2
Treatment exposure.

	Chemotherapy N = 101	Postchemotherapy N = 81	Total N = 101
Number of doses of durvalumab, median (IQR)	4 (4–6)	4 (2–9)	8 (5–11)
Patients receiving ≥ 4 doses of durvalumab, No. (%)	87 (86.1)	NA	NA
Patients receiving ≥ 5 doses of durvalumab, No. (%)	39 (38.6)	NA	NA
Patients receiving ≥ 6 doses of durvalumab, No. (%)	30 (29.7)	NA	NA
Patients receiving ≥ 12 doses of durvalumab, No. (%)	NA	17 (21.0)	24 (23.8)
Duration of durvalumab (weeks), median (IQR)	13.7 (12.0–18.0)	16 (8–38.3)	27 (19.7–42.9)
Platinum received, No. (%)			
Carboplatin	87 (86.1)	NA	NA
Cisplatin	11 (10.9)	NA	NA
Carboplatin plus cisplatin	3 (3.0)	NA	NA
Number of cycles of platinum-etoposide, median (IQR)	4 (4–6)	NA	NA
Patients receiving ≥ 4 cycles of platinum-etoposide, No. (%)	88 (87.1)	NA	NA
Patients receiving ≥ 5 cycles of platinum-etoposide, No. (%)	40 (39.6)	NA	NA
Patients receiving ≥ 6 cycles of platinum-etoposide, No. (%)	33 (32.7)	NA	NA
Duration of platinum-etoposide, median (IQR)	14.1 (12.3–18.3)	NA	NA

IQR = interquartile range.

Table 3
Summary of safety profiles.

	Adverse events		Treatment-related adverse events	
Key safety outcomes, No. (%)				
Any event	100 (99.0)		92 (91.1)	
Any event grade ≥ 3	77 (76.2)		58 (57.4)	
Any event leading to treatment discontinuation	18 (17.8)		12 (11.9)	
Any event leading to death	8 (7.9)		2 (2.0)	
Any SAE	57 (56.4)		26 (25.7)	
Any AESI	38 (37.6)		38 (37.6)	
Any imAE	38 (37.6)		38 (37.6)	
Grade 1–2	34 (33.7)		34 (33.7)	
Grade ≥ 3	12 (11.9)		12 (11.9)	
Adverse events that occurred with a frequency of at least 10 % (any grade)				
	Adverse events		Treatment-related adverse events	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Asthenia	63 (62.4)	6 (5.9)	49 (48.5)	4 (4.0)
Anemia	50 (49.5)	25 (24.8)	46 (45.5)	23 (22.8)
Neutropenia	36 (35.6)	22 (21.8)	32 (31.7)	19 (18.8)
Dyspnea	33 (32.7)	3 (3)	7 (6.9)	—
Constipation	27 (26.7)	1 (1)	12 (11.9)	—
Alopecia	24 (23.8)	—	24 (23.8)	—
Cough	22 (21.8)	—	2 (2.0)	—
Diarrhea	22 (21.8)	—	13 (12.9)	—
Thrombocytopenia	19 (18.8)	9 (8.9)	16 (15.8)	9 (8.9)
Nausea	18 (17.8)	—	10 (9.9)	—
Decreased appetite	18 (17.8)	1 (1.0)	12 (11.9)	1 (1.0)
Pyrexia	16 (15.8)	—	1 (1.0)	—
Back pain	16 (15.8)	—	—	—
Hypothyroidism	15 (14.9)	—	11 (10.9)	—
Arthralgia	14 (13.9)	1 (1.0)	6 (5.9)	1 (1.0)
Vomiting	13 (12.9)	2 (2.0)	6 (5.9)	2 (2.0)
Pruritus	12 (11.9)	—	9 (8.9)	—
Platelet count decreased	11 (10.9)	2 (2.0)	8 (7.9)	1 (1.0)

AESI, adverse event of special interest; imAE, immune-mediated adverse event; SAE, serious adverse event.

= 4, 4.0 %). Among the 82 imAEs reported during the study, 68 (82.9 %) were grades 1–2, whereas grade 3 imAEs were reported in 11 patients, with pneumonitis being the most common (n = 2). There was one case of a grade 5 immune-mediated neurological disorder.

3.3. Efficacy outcomes

The median (IQR) follow-up was 9.4 (6.1–22.5) months. The median PFS was 6.1 months (95 % CI 5.2 to 6.9), and the 12-month PFS rate was 21.0 % (13.0 % to 29 %). Fifty-five patients had an objective response, leading to an ORR of 54.5 % (95 % CI, 44.7 % to 64.2). The median OS was 9.6 months (95 % CI, 7.8 to 11.3), and the 12-month and 24-month OS rates were 40.7 % (95 % CI 31.1 % to 50.3 %) and 25.4 % (95 % CI, 16.8 % to 34.0 %), respectively. The efficacy outcomes are summarized in Table 4.

Table 4
Efficacy outcomes.

Outcome	
Progression-free survival	
Median, months (95 % CI)	6.1 (5.2 to 6.9)
6-month PFS rate, % (95 % CI)	53.0 % (43.2 % to 62.8 %)
12-month PFS rate, % (95 % CI)	21.0 % (13.0 % to 29 %)
Objective Response Rate, n (%; 95 % CI) ^a	55 (54.5 %; 44.7 % to 64.2)
Duration of response	
Median, months (95 % CI)	5.6 (4.7 to 6.5)
12-month duration of response rate, % (95 % CI)	35.7 % (23 % to 48.4 %)
Time to treatment discontinuation	
Median (IQR), months	6.2 (4.5–9.9)
Overall survival	
Median, months (95 % CI)	9.6 (7.8 to 11.3)
6-month OS rate, % (95 % CI)	75.2 % (66.8 % to 83.6 %)
12-month OS rate, % (95 % CI)	40.7 % (31.1 % to 50.3 %)
18-month OS rate, % (95 % CI)	31.6 % (22.4 % to 40.8 %)
24-months OS rate, % (95 % CI)	25.4 % (16.8 % – 34.0 %)

CI, confidence interval; IQR, interquartile range; OS, overall survival; PFS, progression-free survival.

^a Calculated for 101 patients (7 patients were not evaluable).

3.4. Patient-reported outcomes

According to the QLQ-C30, global health status shows clinically relevant deterioration at the end of the induction phase but not during maintenance (Supplementary Fig. 1). Among the five functional subscales, only the emotional scores showed clinically relevant worsening at certain timepoints during the induction and maintenance phases. With respect to symptoms, appetite loss showed clinically relevant improvement at most timepoints. The remaining symptoms showed no relevant changes except for insomnia, which showed clinically relevant improvements at several time points during the induction and maintenance phases.

The results of the disease-specific questionnaire, the QLQ-LC13, revealed clinically relevant improvements in cough at several timepoints during the induction and maintenance phases of cough (Supplementary Fig. 2). Alopecia and neuropathy showed clinically relevant worsening at several timepoints during the course of the treatment, especially during the induction phase.

3.5. Long-term benefit

Overall, 98 patients were included in this post hoc analysis, 24 (24.5 %) of whom were categorized as having LTB (four of these patients had a limited stage at diagnosis). The frequency of grade 3–4 treatment-related AEs was comparable between patients with and without LTB (55.1 % vs. 55.4 %), whereas no clinically meaningful differences were observed in the frequency of grade 3–4 immune-mediated AEs (12.5 % vs. 9.5 %). However, patients with LTB experienced a greater frequency of treatment-related AEs leading to discontinuation (25.0 % vs. 8.1 %). The ECOG PS at baseline was significantly better in patients with LTB than in those without LTB (ECOG PS 0.1 and 2 in 50 %, 50 % and 0 %, respectively, of the patients with LTB, compared with 24.3 %, 67.6 % and 8.1 %, respectively, of patients without LTB; p = 0.035). No other factors were significantly associated with LTB according to the bivariate analysis.

4. Discussion

Our study showed that first-line treatment with durvalumab plus platinum-etoposide in a sample of patients that better reflects the real-world population of patients with ES-SCLC with up to six cycles of induction therapy had a manageable toxicity profile. The efficacy results were consistent with those expected from previous studies in this setting.

Compared with the results of the combination arm of the CASPIAN study [14], we found an increased frequency of grade 3–5 AEs (76 % vs. 65 %) and a greater frequency of imAEs (38 % vs. 20 %), mostly grade 1–2. AEs leading to treatment discontinuation (18 % vs. 10 %), serious AEs (56 % vs. 32 %), and AEs leading to death (8 % vs. 5 %) were also more frequent than those reported in the CASPIAN study [14]. In addition to the greater exposure to durvalumab plus platinum-etoposide, the worse PS (6 % of the patients had a PS of 2) and older age (56 % of the patients were 65 years or older) of the patients in our study could partially explain these safety results because patients with ES-SCLC who are ≥ 65 years and/or have poorer PS are considered to be at higher risk of chemotherapy toxicity [15,16]. In a retrospective study of 63 patients with ES-SCLC with PS ≥ 2 who had received first-line carboplatin plus etoposide therapy, patients with a PS ≥ 3 showed a greater frequency of grade ≥ 3 hematologic events and dose modifications due to toxicity than those with a PS of 2 [15]. In a recently reported phase II study evaluating the safety and efficacy of durvalumab plus carboplatin-etoposide (up to 4 cycles of induction therapy) as a first-line treatment for patients with ES-SCLC with a poor performance status, grade ≥ 3 AEs were reported in 93 % of the patients with a PS of 2 and 100 % of those with a PS of 3, further supporting the role of PS in toxicity [17]. Moreover, the inclusion of patients who may have eligible for chemoradiotherapy for limited-stage SCLC could also have contributed to this increased toxicity.

Several observational studies have reported the use of durvalumab plus platinum-etoposide as a first-line treatment for patients with ES-SCLC in clinical practice [10,18–20]. In a single-center, retrospective study conducted in Japan among 40 patients who received the combination, 26 (65 %) reported grade ≥ 3 adverse events, 3 (7.5 %) experienced adverse events leading to treatment discontinuation, and 2 (5.0 %) experienced AEs leading to death, with a high frequency of grade ≥ 3 neutropenia ($n = 19$, 47.5 %) [10]. In another retrospective study conducted in five centers in Japan that included 234 patients and compared the combination of platinum etoposide with either atezolizumab or durvalumab, the incidences of grade ≥ 3 AEs (77.8 % and 70.4 %, respectively) and AEs leading to death (4.0 % and 5.6 %, respectively) were similar to those of both immunotherapies [18]. In a single-center, retrospective study undertaken in Japan among 20 patients treated with atezolizumab and 20 patients treated with durvalumab in combination with platinum-based chemotherapy, all patients in both groups experienced grade 4 hematologic toxicities; in addition, imAEs occurred in 4 (20 %) atezolizumab-treated patients and 7 (35 %) in the durvalumab-treated group, and treatment was discontinued because of treatment-related AEs in one patient in each treatment group [19]. Finally, in a single-center, retrospective study conducted in the U.S. in patients who received atezolizumab or durvalumab in combination with chemotherapy, Vince et al. reported that 22 of 46 patients (47.8 %) treated with atezolizumab and 18 of 55 (32.7 %) treated with durvalumab experienced imAEs (no information on toxicity severity was provided) [20]. Safety results from randomized clinical trials are difficult to compare with data from observational studies because, in observational studies, patients are less closely monitored for adverse events. Therefore, in our view, these studies tend to underestimate the frequency of adverse events. Despite this risk of underreporting, observational studies have the advantage of evaluating safety, which usually includes real-world patients who are not included in RCTs because of characteristics (e.g., older age, greater comorbidities, worse PS) that could negatively affect safety results. Although we must consider these differences, overall, we believe that our results are consistent with those reported in observational studies.

The efficacy results were consistent with those reported in the CASPIAN study [14]. Thus, the median PFS in the CASPIAN study in the last update was 5.4 months, and the PFS rate was 45.4 % at 6 months and 17.9 % at 12 months [14]. However, in our study, the median PFS was 6.1 months, and the PFS rates were 53.0 % and 21.0 % at 6 and 12 months, respectively. In the CASPIAN study, the median OS was 12.9

months, and the 18-month survival rate was 32 % [14]. In our study, the corresponding figures were 9.6 months and 31.6 %, respectively. In a phase 2 study conducted in patients with ES-SCLC and poor performance status who received durvalumab plus carboplatin-etoposide (up to 4 cycles of induction therapy), the median PFS was 4.7 months and 5.1 months in patients with PS values of 2 and 3, respectively, and the median OS was 9.5 months and 5.1 months, respectively [17]. Our results are also consistent with those reported for immunotherapy in clinical practice. In an analysis of a cohort of 251 patients with ES-SCLC and ECOG PS of 0–1 treated with chemotherapy and immunotherapy in clinical practice in France, the median OS was 11.4 months (95 % CI 10.2 to 14.1) [21]. Similarly, in an observational study of atezolizumab plus chemotherapy in 518 patients with ES-SCLC, 89 % of whom had an ECOG PS of 0–1, the median OS was 11.3 months (95 % CI 10.1 to 12.4) [22].

In a post-analysis, we found that 24.5 % of the patients showed long-term benefit (i.e., patients lived for at least 24 months after inclusion), and the PS was the single factor associated with this long-term benefit. Gobbini et al in a large cohort of 3,150 patients with ES-SCLC treated between 2014 and 2021 in the real-world setting, 13 % were long-term survivors [23]. In this study, in addition to a better PS, being a woman, younger than 65 years old, having less than three metastatic sites, and being a never or former smoker were associated with long-term survival.

In addition to its noncomparative design, the main limitation of our study was that we included a small proportion of patients with a PS of 2. Although we met the initial assumptions, the sample size of our trial was relatively small. Therefore, further real-world data on this treatment regimen would be useful.

In conclusion, this phase 3b trial suggests that first-line treatment of patients with ES-SCLC with an initial regimen of up to 6 cycles of durvalumab plus platinum-etoposide followed by maintenance durvalumab is feasible providing more options in daily clinical practice for the management of these patients depending on their characteristics.

Declaration of generative AI and AI-assisted technologies in the writing process

Not applicable.

Data availability statement

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

Data for studies directly listed on Vivli can be requested through Vivli at <https://www.vivli.org>. Data for studies not listed on Vivli could be requested through Vivli at <https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/>. AstraZeneca Vivli member page is also available outlining further details: <https://vivli.org/ourmember/astrazeneca/>.

CRediT authorship contribution statement

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Declaration of competing interest

Dolores Isla has been advisory board member for Amgen, AstraZeneca, Bayer, BMS, Beigene, Boehringer Ingelheim, F. Hoffmann-La Roche, Johnson & Johnson, Lilly, Merck, MSD, Pfizer, Pharmamar, Sanofi, Takeda; has received speaker honorarium from Amgen, AstraZeneca, Bayer, BMS, F. Hoffmann-La Roche, Johnson & Johnson, Lilly, MSD, Pfizer, Pharmamar; has received research grants from AstraZeneca, BMS, F. Hoffmann-La Roche, GSK; has received consulting honorarium from Amgen, AstraZeneca, Bayer, BMS, Beigene, Boehringer Ingelheim, F. Hoffmann-La Roche, Johnson & Johnson, Lilly, Merck, MSD, Pfizer, Pharmamar; and has received travel grants from Amgen, AstraZeneca, BMS, F. Hoffmann-La Roche, Johnson & Johnson, MSD, Pfizer.

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Appendix A. Supplementary material

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