ORIGINAL ARTICLE

Lurbinectedin Plus Pembrolizumab in Relapsed SCLC: The Phase I/II LUPER Study

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ABSTRACT

Introduction: SCLC has limited second-line treatment options after chemotherapy. We assessed the efficacy and safety of lurbinectedin combined with pembrolizumab in relapsed SCLC patients who had not received prior immunotherapy, aiming to prevent early progression and achieve sustained responses.

Methods: The LUPER trial (NCT04358237) is a phase I/II, single-arm, open-label, multicenter study. Phase I established the recommended phase II dose. The primary endpoint of phase II was the investigator-confirmed objective response rate. Secondary endpoints included duration of response, progression-free survival (PFS), overall survival (OS), and safety. Patients were categorized as platinum-sensitive (chemotherapy-free interval $\geq$ 90 d) or platinum-resistant (<90 d).

Results: The recommended phase II dose was 3.2 mg/m^2 lurbinectedin and 200 mg pembrolizumab IV every three weeks. Phase II included 28 patients, 50% of whom were platinum-resistant. The objective response rate was 46.4% (95% confidence interval: 27.5–66.1, $p < 0.001$), including three complete responses, with two complete metabolic responses post-treatment completion at 35 cycles. The median duration of response was 7.8 months, with 40% of patients maintaining responses for 12 months or longer. The median PFS was 4.6 months, and the median OS was 10.5 months. Platinum-sensitive patients had significantly better PFS (8.0 versus 2.8 mo, $p = 0.012$) and numerically superior OS (15.7 versus 7.1 mo, $p = 0.058$). Grade 3 or higher treatment-related adverse events occurred in 71.4% of patients, with transient neutropenia being the most common. Immune-related adverse events were consistent with prior pembrolizumab studies.

Conclusions: Lurbinectedin plus pembrolizumab reported promising efficacy in relapsed SCLC, particularly for

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platinum-sensitive patients, with a known and manageable safety profile. These results support further exploration of this combination in SCLC treatment.

Keywords: Lurbinectedin; Pembrolizumab; Phase II; Platinum-sensitive; SCLC

Introduction

SCLC is a highly aggressive malignancy linked to smoking that accounts for approximately 10% to 15% of all lung cancer cases.[1–3] Although initially responsive to first-line platinum-based chemotherapy, responses are not durable, with fewer than 3% of patients alive five years after diagnosis.[3,4] Treating SCLC after progression to first-line chemotherapy remains a significant challenge, with minimal patient survival improvements over the past two decades.[5] Current second-line treatments, including platinum-etoposide rechallenge, topoisomerase I inhibitors (e.g., topotecan or irinotecan), and anthracycline-based regimens, offer limited efficacy,[6,7] with tumor response rates of approximately 20% and median overall survival (OS) of eight months in patients with a chemotherapy-free interval (CTFI) of 90 days or longer. In platinum-resistant cases (CTFI $<$ 90 days), tumor responses are below 10%, with survival only extending a few weeks.

Promising phase I and II studies with immune checkpoint inhibitors, such as nivolumab[8] and pembrolizumab,[9] led to their accelerated approval by the United States Food and Drug Administration (FDA) as monotherapy for recurrent SCLC. These therapies reported tumor responses in up to 20% of patients, regardless of tumor PD-L1 expression, with some achieving long-term responses. In the first-line treatment of extensive-stage SCLC, new standards of care combining chemotherapy and immunotherapy were established on the basis of the modest improvements in progression-free survival (PFS) and OS reported in phase III clinical trials IMpower133 and CASPIAN, which evaluated the addition of anti–PD-L1–immunotherapy with platinum-etoposide chemotherapy.[10,11] Nevertheless, only a three-year OS rate of nearly 15% was reported compared with 5% in the control arm, and only a small subset of patients benefited from these combinations, with no predictive factors identified yet.

Despite early promise, the indication of nivolumab and pembrolizumab in treating relapsed SCLC was withdrawn after the failure of their phase III confirmatory trials.[12–14] Similarly, a phase II study evaluating single-agent atezolizumab for relapsed SCLC failed to show significant efficacy.[15] The underlying reasons for these failures remain unclear; however, the higher incidence of early progression in the immunotherapy arms than in chemotherapy suggests that combining these agents with active cytotoxic therapies could help prevent early disease progression.

Lurbinectedin, an alkylating drug that binds to guanine residues in the minor groove of DNA, selectively inhibits oncogenic transcription and induces apoptosis of cancer cells[16,17] and tumor-associated macrophages,[18] reducing inflammatory cytokine production. It also disrupts nucleotide excision repair,[19] a DNA repair mechanism associated with resistance to platinum-based chemotherapy.[19–21] In a phase II basket study, lurbinectedin monotherapy (3.2 mg/m^2 every three weeks) was evaluated as a second-line treatment in 105 patients with metastatic SCLC.[22], yielding a 35.2% response rate (95% confidence interval [CI]: 26.2–45.2) and a PFS of 3.4 months, with transient hematologic count decrease as the most common toxicity. In 2019, the European Medicines Agency designated lurbinectedin as an orphan drug for SCLC,[23] and the FDA granted accelerated approval in June 2020.[24]

Although the basket study reported promising results, the phase III ATLANTIS trial evaluating lurbinectedin with doxorubicin in relapsed SCLC failed to report an OS benefit compared with topotecan or anthracycline regimens.[25] Nevertheless, lurbinectedin was administered at a lower dose (2.0 mg/m^2) compared with the 3.2 mg/m^2 dose used in the basket trial. A post-hoc analysis revealed that patients who completed 10 cycles of this treatment and subsequently switched to full-dose lurbinectedin monotherapy (3.2 mg/m^2) generally maintained or improved tumor response, with favorable OS and duration of response (DoR).[26]

We hypothesized that combining lurbinectedin with pembrolizumab may yield additive effects on the basis of their complementary mechanism of action, improving response rates and prolonging survival in relapsed SCLC. The phase I/II LUPER study evaluated the efficacy and safety of this combination, with phase I focusing on dose determination and phase II expanding the efficacy and safety assessment.

Materials and Methods

Study Design and Participants

LUPER was a single-arm, open-label, multicenter phase I/II study performed across five sites in Spain (three sites during phase I) that recruited patients from September 2020 to February 2023.

The eligibility criteria included adult patients with histologically confirmed SCLC who experienced disease progression during or immediately after first-line chemotherapy (including those with platinum-refractory disease and CTFI $<$ 30 days), had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1), Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 to 1, and adequate organ function. Patients with previously treated, stable, and asymptomatic brain metastasis were also eligible. Patients were excluded if they had received prior treatment with immune checkpoint inhibitors or other immunotherapies, as these were not established as the standard of care when the trial was conducted. Detailed inclusion and exclusion criteria are provided in the Supplementary Materials.

This study adhered to the principles of the Declaration of Helsinki and was approved by the institutional review boards or independent ethics committees at each site. All patients provided written informed consent. This trial was registered with ClinicalTrials.gov (NCT04358237).

Procedures

In phase I, patients received intravenous pembrolizumab at its recommended fixed dose of 200 mg IV every three weeks and escalating doses of lurbinectedin on day 1 of every three-week cycle. Lurbinectedin dose escalation followed a 3+3 design, starting at 2.4 mg/m^2 (dose level [DL] 1) and increasing by approximately 33% in subsequent cohorts if no dose-limiting toxicity (DLT) occurred (Supplementary Materials for DLT definition). The maximum tolerated dose (MTD) was defined as the lowest DL in which at least one-third of the evaluable patients experienced a DLT in cycle 1. Dose escalation ceased when MTD or the last dose level (i.e., DL2, the FDA monotherapy-approved dose [3.2 mg/m^2]) was reached, whichever occurred first. If all DLTs occurring at a given DL were exclusively related to neutropenia, dose escalation was paused, and granulocyte colony-stimulating growth factor (G-CSF) prophylaxis was administered before resuming dose escalation at the lowest dose at which neutropenia-related DLTs were observed. An expansion cohort of at least six patients received the dose immediately below the MTD, or DL2 if the MTD was not reached. This DL was confirmed as the recommended phase II dose (RP2D) if less than one-third of the first six evaluable patients experienced any DLT during cycle 1. In addition, a safety-stopping rule was planned (Supplementary Materials).

Phase II included all patients from phase I treated at any DL, including the RP2D and additional patients receiving an intravenous infusion of pembrolizumab at a fixed dose of 200 mg followed by lurbinectedin infusion at the RP2D on day 1 every three weeks. Dose escalation was not allowed during this phase. If required, secondary G-CSF prophylaxis in cycle 1 was given according to standard institutional practice.

Regardless of the phase, treatment continued until disease progression, unacceptable toxicity, death, withdrawal of consent, or study completion, whichever occurred first. Pembrolizumab was administered for up to 35 cycles; thereafter, patients could continue lurbinectedin treatment if it reported a clinical benefit. Radiologic tumor assessments with computed tomography or magnetic resonance imaging of the chest, brain, abdomen, and pelvis were conducted at baseline, every six weeks, or before every second subsequent cycle during treatment. Patients who discontinued treatment without disease progression as per RECIST v1.1 were monitored with radiologic tumor assessments every six weeks until disease progression, initiation of new anti-cancer therapy, death, or end of study, whichever occurred first. After one year, evaluations were performed every nine weeks until the end of the study.

Patients who discontinued treatment after disease progression according to RECIST v1.1 or started new anti-cancer therapy were followed up for survival every 12 weeks until death or the end of the study, whichever occurred first. Nevertheless, patients who were clinically stable at the time of disease progression according to RECIST v1.1 could continue treatment until the next radiological assessment. If no disease progression according to immune RECIST (iRECIST) was observed at that time, treatment continued until disease progression was confirmed according to iRECIST.

Outcomes

In the phase I, the primary endpoints were MTD and RP2D of lurbinectedin plus pembrolizumab. Secondary endpoints included preliminary efficacy assessments as per RECIST v1.1.

In Phase II, the primary endpoint was confirmed objective response rate (ORR) by RECIST v1.1 assessed by the investigator. ORR (complete response [CR] or partial response [PR]) was confirmed by a tumor imaging assessment within four weeks after the initial observation of a response. Secondary endpoints were clinical benefit rate (CBR) as per RECIST v1.1, DoR, PFS, and OS. Exploratory endpoints included the time to next treatment (TTNT), TTNT failure, and efficacy association with baseline characteristics and prognostic factors, including CTFI, ECOG-PS, age, sex, central nervous system (CNS) involvement, liver metastasis, and baseline levels of interleukin-6 (IL-6), lactate dehydrogenase, and alpha-1 acid glycoprotein relative to the upper limit of

normal. Patients were classified on the basis of CTFI as "resistant" (CTFI $<$ 90 d) or "sensitive" (CTFI $\geq$ 90 d) as per the European Society for Medical Oncology Clinical Practice Guidelines.[6]

The secondary endpoints in both phases included safety, as per the Common Terminology Criteria for Adverse Events version 5.0, and the pharmacokinetics of lurbinectedin in combination with pembrolizumab.

The exploratory endpoints common to both phases were efficacy assessments according to iRECIST 1.1, including immune ORR, immune CBR, and immune PFS.

Pharmacokinetic Evaluation

Plasma concentration data from the 28 patients enrolled in this study were included in the pharmacokinetic analysis. Sampling timepoints were pre-infusion, five minutes before the end of infusion, one hour after the end of infusion, and seven days after the end of infusion. A previously validated model for lurbinectedin as a single agent[22] was used to estimate the individual pharmacokinetic parameters of lurbinectedin in this study.

Statistical Analysis

All treated patients were included in the efficacy and safety analyses. In phase I, the proportion of patients with DLTs was calculated with 95% Clopper-Pearson CIs. In phase II, the ORR was calculated with 95% Wilson score intervals. A sample size of 30 patients was estimated to test the null hypothesis that the ORR was 10% or lower against the alternative hypothesis that 35% or more would respond. The study was considered positive if the null hypothesis fell below the lower boundary of the 95% Wilson score intervals, with a one-sided p value of 0.025. The null hypothesis would be rejected if seven or more patients presented a confirmed objective response.

Two-sided p values were used for all secondary analyses in phase II. The PFS and OS were estimated using the Kaplan-Meier method, with median survival times and their respective 95% CIs reported.

For exploratory analysis, univariate Cox proportional hazards models were fitted to evaluate the association between efficacy (PFS and OS) and baseline characteristics. Safety data were summarized using descriptive statistics. The relative dose intensity (RDI) was calculated as a ratio comparing the amount of study drug administered to each patient to the amount scheduled according to the study protocol.[27,28]

Results

Between September 2020 and November 2021, 13 patients were enrolled in phase I, seven receiving DL1 (2.4 mg/m^2) and six DL2 (3.2 mg/m^2) of lurbinectedin. The median age was 66.0 years, nine patients (69.2%) had extensive disease at diagnosis, and six (46.2%) were resistant to platinum-based chemotherapy. CNS involvement was present in one patient (7.7%). Additional baseline characteristics are detailed in Supplementary Table 1.

One DLT (G3 fatigue) occurred in the DL1 group. One non-clinically relevant DLT (G4 afebrile neutropenia) was reported at each DL, both lasting less than one week and successfully resolved with G-CSF treatment. Phase I established the RP2D for lurbinectedin at 3.2 mg/m^2, and the MTD was not reached. At the data cut-off for phase I analysis (March 2022), the median treatment duration was 3.1 months (range: 0–14.6), with four patients (30.8%) still on treatment. The median RDI for lurbinectedin and pembrolizumab was 90.6% and 90.8%, respectively. Treatment-emergent adverse events (TEAEs) of any grade were reported in 11 patients (84.6%), with nine patients (69.3%) having G3 or higher TEAEs. The most frequent TEAEs were neutropenia in seven patients (53.9%) and fatigue in 10 patients (76.9%) (Supplementary Table 2). Preliminary efficacy was observed at both DLs, achieving an ORR of 30.8% (one CR and three PRs) (Supplementary Fig. 1) and a CBR of 53.8%. Median DoR was not reached; after nine months, 75% (95% CI: 42.6–100) of patients were responding.

Phase II included a total of 28 patients, 13 from phase I and 15 additional patients receiving RP2D (DL2). The median age was 65.5 years. All patients were current (10 [35.7%]) or former (18 [64.3%]) smokers, and 25 (89.3%) had extensive disease at diagnosis. Half of the patients (14) were resistant to first-line platinum-based chemotherapy, and six (21.4%) had CNS involvement. Additional baseline characteristics of participants are detailed in Table 1.

At the data cut-off (May 2024), the median follow-up was 10.5 months (range: 1.0–38.6). At the time of this analysis, the study remains ongoing, with two patients (7.4%) still receiving treatment—one continuing the full combination therapy, whereas the other transitioned to lurbinectedin monotherapy after completing the 35-cycle limit of pembrolizumab. A total of four patients are currently in the follow-up phase. The primary reason for treatment discontinuation was disease progression (19 [67.9%]), followed by patient death (six [21.4%]), and completion of pembrolizumab treatment after lurbinectedin discontinuation (one [3.7%]).

The primary endpoint was met, with an ORR of 46.4% (95% CI: 27.5–66.1) (Table 2). Three patients (10.7%) achieved CRs, all confirmed; and 10 patients (35.7%) had PRs, nine of which (32.1%) were confirmed. CBR was 60.7% (95% CI: 40.6–78.5). For patients with

Table 1. Baseline Patient Characteristics in Phase II

Baseline Characteristics	n (%) N = 28
Age; median (min; max) (y)	65.5 (41.0-78.0)
Sex	
Female[a]	13 (46.4)
Male	15 (53.6)
Disease stage at diagnosis	
Limited disease	3 (10.7)
Extensive disease	25 (89.3)
ECOG performance status	
0	10 (35.7)
1	18 (64.3)
Smoking status	
Former smoker	18 (64.3)
Current smoker	10 (35.7)
Never smoker	0 (0.0)
Platinum sensitivity	
Resistant, <90 d CTFI	14 (50.0)
Sensitive, ≥90 d CTFI	14 (50.0)
Previous PD-1/PD-L1 inhibitor therapy	
No	28 (100.0)
Yes	0 (0.0)
Central nervous system involvement	
Yes	6 (21.4)
No	22 (78.6)
Liver metastasis	
Yes	13 (46.4)
No	15 (53.6)
IL-6 levels	
≤ULN	12 (42.9)
>ULN	16 (57.1)
AAG levels	
≤ULN	20 (71.4)
>ULN	8 (28.6)
LDH levels	
≤ULN	17 (60.7)
>ULN	11 (39.3)

n (%): number of participants (percentage on the basis of N)
N: number of patients.
[a]All participating women were postmenopausal.
AAG, alpha-1 acid glycoprotein; CTFI, therapy-free interval; ECOG, Eastern Cooperative Oncology Group; IL-6, interleukin 6; LDH, lactate dehydrogenase; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; ULN, upper limit of normal.

platinum-sensitive disease, the ORR was 57.1% and the CBR was 78.6%, whereas patients with platinum-resistant disease had an ORR of 35.7% and a CBR of 42.9%. All CRs were reported in platinum-sensitive patients. A waterfall plot depicting the best overall response and tumor size changes by platinum sensitivity is presented in Figure 1. No statistically significant differences were observed in response rates between dose levels (28.6%, 95% CI: 3.7–71.0 for DL1; 47.6%, 95% CI: 25.7–71.2 for DL2) (Supplementary Table 3). Among patients with CNS involvement, five of the six (83.3%) had platinum-resistant disease, with three of the six (50.0%) showing unconfirmed ORR and CBR. The best overall responses included three PRs, one stable disease (<12 wk), and two progressive diseases. Intracranial responses included two CRs and four cases of non-CR/non-progressive disease over 12 weeks.

The median DoR to lurbinectedin plus pembrolizumab in the overall population was 7.8 months (95% CI: 2.8–19.1), 11.9 months (95% CI: 2.8–not achieved [NA]) in patients with platinum-sensitive disease, and 4.4 months (95% CI: 0.9–NA) in those with platinum-resistant disease (Fig. 2 and Supplementary Fig. 2). Notably, approximately 40% of patients continued to respond after 12 months of treatment, with seven patients showing durable responses over six months, six of whom had platinum-sensitive disease.

The median PFS was 4.6 months (95% CI: 2.7–6.0) (Fig. 3*A*) and the median OS was 10.5 months (95% CI: 6.9–17.6) (Fig. 3*C*) in the overall population. No significant differences in PFS or OS were observed according to lurbinectedin dose levels (Supplementary Fig. 3). Patients with platinum-sensitive disease had significantly longer PFS (8.0 mo, 95% CI: 2.7–15.2, $p = 0.012$) and numerically superior OS (15.7 mo, 95% CI: 7.7–NA, $p = 0.058$) than those with platinum-resistant disease (2.8 mo, 95% CI: 1.2–5.6 and 7.1 mo and 95% CI: 1.4–11.1, respectively) (Fig. 3*B* and *D*, and Supplementary Fig. 4). Exploratory analysis stratified by other factors reported a benefit in PFS and OS in patients with an ECOG-PS of 0 and baseline levels of IL-6 within or below the normal range (Supplementary Fig. 4).

Antitumor activity as per iRECIST yielded almost identical results, with 50.0% (95% CI: 30.6–69.4) immune ORR, 75.0% (95% CI: 55.1–89.3) immune CBR, and 5.4 months (95% CI: 3.0–7.4) median immune PFS (Supplementary Table 4).

Tumor progression included 28 de novo lesions and 20 recurrences, the most common site being the brain for de novo progressions (nine [18.8%]) and the liver for recurrences (five [10.4%]) (Supplementary Table 5). Nine patients (32.1%) received further anti-tumor therapy after tumor progression with lurbinectedin and pembrolizumab (Supplementary Table 6). The agents most frequently administered post-progression were topotecan (four [44.4%]) and irinotecan (three [33.3%]) for the third line of treatment and carboplatin plus paclitaxel (two [28.6%]) for the fourth line (N = 7). Up to six subsequent lines of treatment were documented in some cases. The overall time from initiating LUPER treatment to the next treatment (TTNT) was 7.1 months (range: 4.6–11.1), 11.2 months (95% CI: 4.6–NA; $p = 0.022$) in patients with platinum-sensitive disease, and 5.1 months (95% CI: 1.4–10.0) in those with platinum-resistant disease (Supplementary Fig. 5). In the subsequent lines post-LUPER treatment, the median TTNT failure was 3.7 months (95% CI: 1.4–NA) (Supplementary Fig. 6).

Table 2. Efficacy Analyses Per RECIST v1.1 Assessed by Investigators in Phase II

Tumor Response, n (%)	Platinum-Resistant (N = 14)	Platinum-Sensitive (N = 14)	Overall (N = 28)
Unconfirmed BOR			
CR	0 (0.0)	3 (21.4)	3 (10.7)
PR	5 (35.7)	5 (35.7)	10 (35.7)
SD ≥12w	1 (7.1)	3 (21.4)	4 (14.3)
SD <12w	2 (14.3)	2 (14.3)	4 (14.3)
PD	3 (21.4)	0 (0.0)	3 (10.7)
NE[a]	3 (21.4)	1 (7.1)	4 (14.3)
Unconfirmed ORR			
No	9 (64.3)	6 (42.9)	15 (53.6)
Yes	5 (35.7)	8 (57.1)	13 (46.4)
95% CI	(12.8; 64.9)	(28.9; 82.3)	(27.5; 66.1)
Unconfirmed CBR			
No	8 (57.1)	3 (21.4)	11 (39.3)
Yes	6 (42.9)	11 (78.6)	17 (60.7)
95% CI	(17.7; 71.1)	(49.2; 95.3)	(40.6; 78.5)
Confirmed BOR			
CR	0 (0.0)	3 (21.4)	3 (10.7)
PR	4 (28.6)	5 (35.7)	9 (32.1)
SD ≥12w	2 (14.3)	3 (21.4)	5 (17.9)
SD <12w	2 (14.3)	2 (14.3)	4 (14.3)
PD	3 (21.4)	0 (0.0)	3 (10.7)
NE	3 (21.4)	1 (7.1)	4 (14.3)
Confirmed ORR			
No	10 (71.4)	6 (42.9)	16 (57.1)
Yes	4 (28.6)	8 (57.1)	12 (42.9)
95% CI	(8.4-58.1)	(28.9-82.3)	(24.5-62.8)
Confirmed CBR			
No	8 (57.1)	3 (21.4)	11 (39.3)
Yes	6 (42.9)	11 (78.6)	17 (60.7)
95% CI	(17.7-71.1)	(49.2-95.3)	(40.6-78.5)

n (%): number of participants (percentage on the basis of N).
N: number of patients.
[a]Response evaluation is missing for four patients who died before the tumor assessment.
BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

The median RDI of lurbinectedin and pembrolizumab was 95.0% and 92.5%, respectively. All patients (100.0%) experienced TEAEs, 20 (71.4%) reported G3 or higher treatment-related adverse events, and 15 (53.6%) experienced serious TEAEs. No adverse events of clinical interest were observed (Supplementary Table 7). TEAEs led to five patients (17.9%) discontinuing treatment, two deaths unrelated to study treatment (coronavirus disease-19 infection and febrile infection with respiratory failure), and one death related to lurbinectedin (sepsis caused by *Pseudomonas aeruginosa*).

Of the 28 patients, 23 (82.1%) experienced hematologic toxicity, with neutropenia being the most common (67.9% any grade; 46.4% G ≥ 3) (Table 3). A weekly timeline for absolute neutrophil and platelet counts within cycle 1 is shown in Supplementary Figure 7. The most common non-hematologic TEAEs of any grade were fatigue (75.0%; 7.1% G3), nausea (46.4%; 0.0% G ≥ 3), decreased appetite (39.3%; 0.0% G ≥ 3), increased alanine aminotransferase (ALT) (39.3%; 14.3% G3), and increased aspartate aminotransferase (AST) (35.7%; 7.1% G3) (Table 3). Detailed safety evaluations by study drug are detailed in Supplementary Tables 8 and 9. The most common serious TEAEs of any grade were pneumonia (10.7%; 10.7% G3) and thrombocytopenia (7.1%; 3.6% G3) (Supplementary Table 10). Immune-related TEAEs (irTEAEs) occurred in 15 patients (53.6%), predominantly of grade 1 to 2 severity. The most frequently reported irTEAEs included increased ALT (39.3%), increased AST (35.7%), diarrhea (28.6%), arthralgia (21.4%), myalgia (17.9%), and hypothyroidism (14.3%). Grade 3 irTEAEs occurred in five patients (17.9%) (Supplementary Table 11).

Pharmacokinetic evaluation of the LUPER treatment combination revealed total plasma clearance of 9.9 liters/h, an apparent volume at a steady state of 476.8 L, and a median half-life of 51 hours. Additional

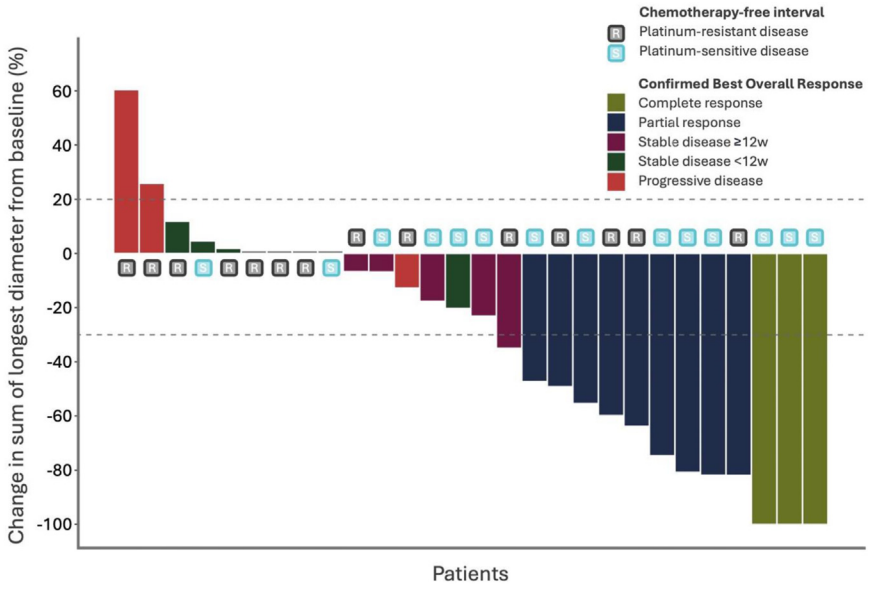

Figure 1. Waterfall plot of confirmed best overall response per RECIST v1.1 according to platinum sensitivity in phase II. The dotted lines indicate the thresholds for partial response (≥30% decrease) and disease progression (≥20% increase). RECIST v1.1, Evaluation Criteria in Solid Tumors version 1.1; w, weeks.

pharmacokinetic parameters are detailed in Supplementary Table 12. No statistically significant differences were observed compared with previous data for lurbinectedin alone or in combination with other agents (Supplementary Figs. 8 and 9).[29,30]

Discussion

In the LUPER phase I/II study, the combination of lurbinectedin and pembrolizumab reported promising efficacy and manageable safety as a second-line treatment for patients with SCLC who had not received prior immunotherapy.

The primary endpoint was met with an ORR of 46.4% and a median DoR of 7.8 months, surpassing the results with lurbinectedin monotherapy (ORR = 35.2% and DoR = 5.3 mo)[22] or in combination with doxorubicin (ORR = 31%)[25] in second-line treatment. Responses were notable, with a median tumor reduction of approximately 40% and 12 patients experiencing a tumor volume decrease of 50% or greater, including three CRs. Remarkably, 53.8% of responding patients had durable responses lasting at least six months, which compared favorably to the 16.2% (six out of 37 responders) with lurbinectedin monotherapy.[22] Moreover, two patients achieved metabolic CR by positron emission tomography-computed tomography scan after completing 35 cycles of therapy (data not shown). Intracranial responses were observed in two of six patients with CNS involvement, likely reflecting the cerebral activity of pembrolizumab given the limited activity of lurbinectedin in the CNS.[31,32]

In our study, the observed median PFS of 4.6 months with the combination of lurbinectedin and pembrolizumab exceeded the PFS for the treatments as monotherapies, 3.5 and 2.0 months for lurbinectedin and pembrolizumab, respectively.[22,33] This combination also surpassed the 4.0-month PFS observed with lurbinectedin plus doxorubicin.[25] A post-hoc analysis of the ATLANTIS trial indicated an incremental PFS benefit when escalating lurbinectedin doses from 2.0 mg/m^2 to 3.2 mg/m^2, suggesting a dose-response relationship. However, our study found no significant differences in PFS on the basis of lurbinectedin dosage, potentially because of the small sample size and the concurrent use of immunotherapy.

The median OS was 10.5 months, with 28.6% of patients not experiencing an OS event at 18 months, some achieving prolonged disease stability for over 20 months. These outcomes are promising compared with the OS of 9.3 months with lurbinectedin[22] and 9.1 months with pembrolizumab in the KEYNOTE-158 trial.[33] Moreover, most of the patients in our study had poor prognostic factors, including 64.3% with ECOG PS 1, 50.0% with a CTFI less than 90 days, 21.4% with CNS involvement, and 39.3% with high lactate dehydrogenase levels, making the observed efficacy outcomes more remarkable.[34] It is unlikely that subsequent treatments had an impact on OS, as only nine patients (32.1%) who progressed on the LUPER regimen received further treatment (mostly topotecan or irinotecan).

Subgroup analysis revealed that patients with platinum-sensitive disease had significantly better

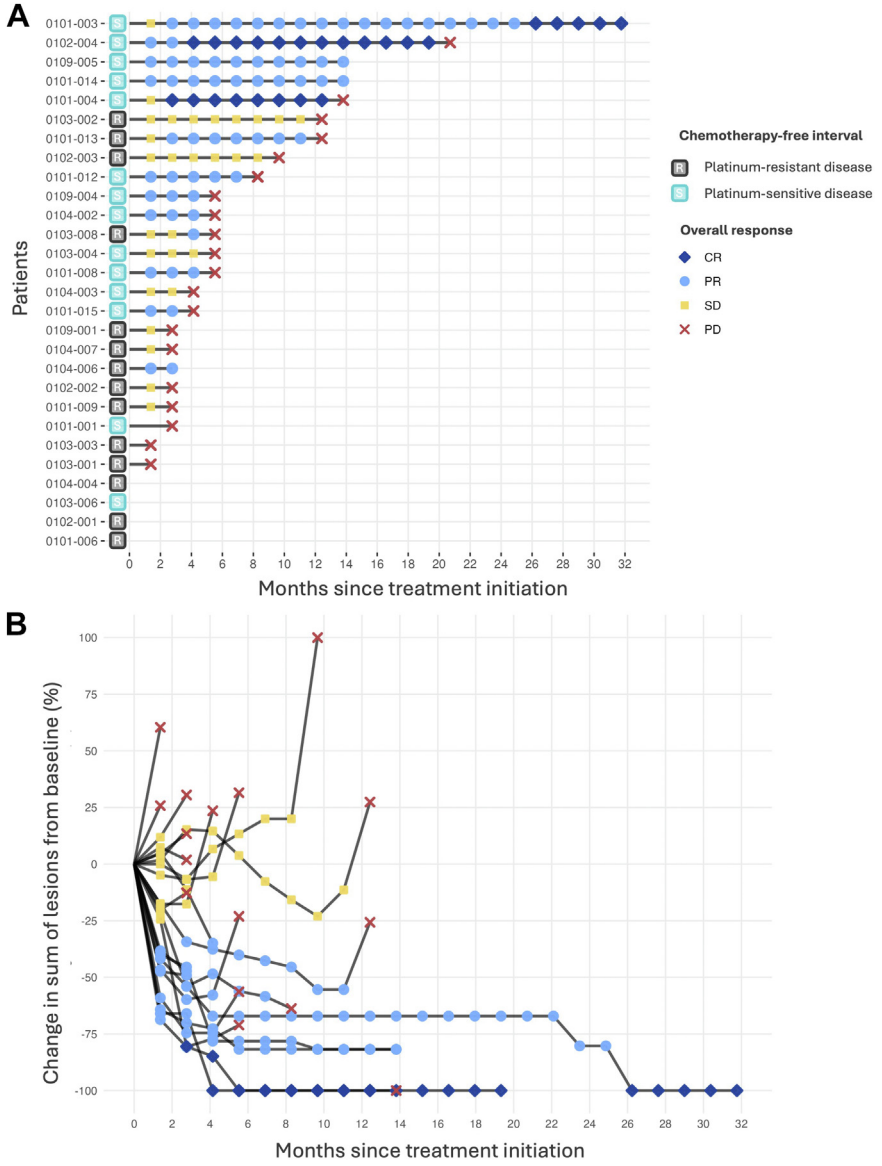

Figure 2. Duration of response *(A)* and change in the size of lesions according to response *(B)* in phase II. Four patients died before a post-baseline tumor assessment was performed. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

outcomes, with a higher ORR (57.1% versus 35.7%), longer PFS (8.0 versus 2.8 mo), and extended OS (15.7 versus 7.1 mo) than patients with platinum-resistant disease. Our exploratory subgroup analysis also identified ECOG-PS of 1 and elevated basal IL-6 concentration as other potential predictors of poor response to lurbinectedin and pembrolizumab. The latter observation aligns with the established association of IL-6 levels with immune activation and tumor progression[35] and its previously identified role as a circulating biomarker for clinical response to immunotherapy in SCLC patients.[36] Additional biomarker analyses, including transcriptomic profiling of cell-free RNA, spatial biology studies of tumor samples, and correlation analyses with non-invasive biomarkers, are planned to uncover patterns of treatment response and tumor microenvironment signatures, providing valuable insights to advance more personalized therapies for SCLC.

Overall, these outcomes highlight the notable long-term activity of combining lurbinectedin and pembrolizumab in relapsed SCLC, showing competitive activity compared with tarlatamab (a bispecific T-cell engager immunotherapy that targets delta-like ligand 3 on SCLC cells and CD3 on T-cells) in the DeLLphi-301 phase II trial, with an updated efficacy reported of ORR 40%, DoR 9.7 months, PFS 4.3 months, and OS 15.2 months.[37,38] Nevertheless, although comparisons with larger studies provide valuable context for

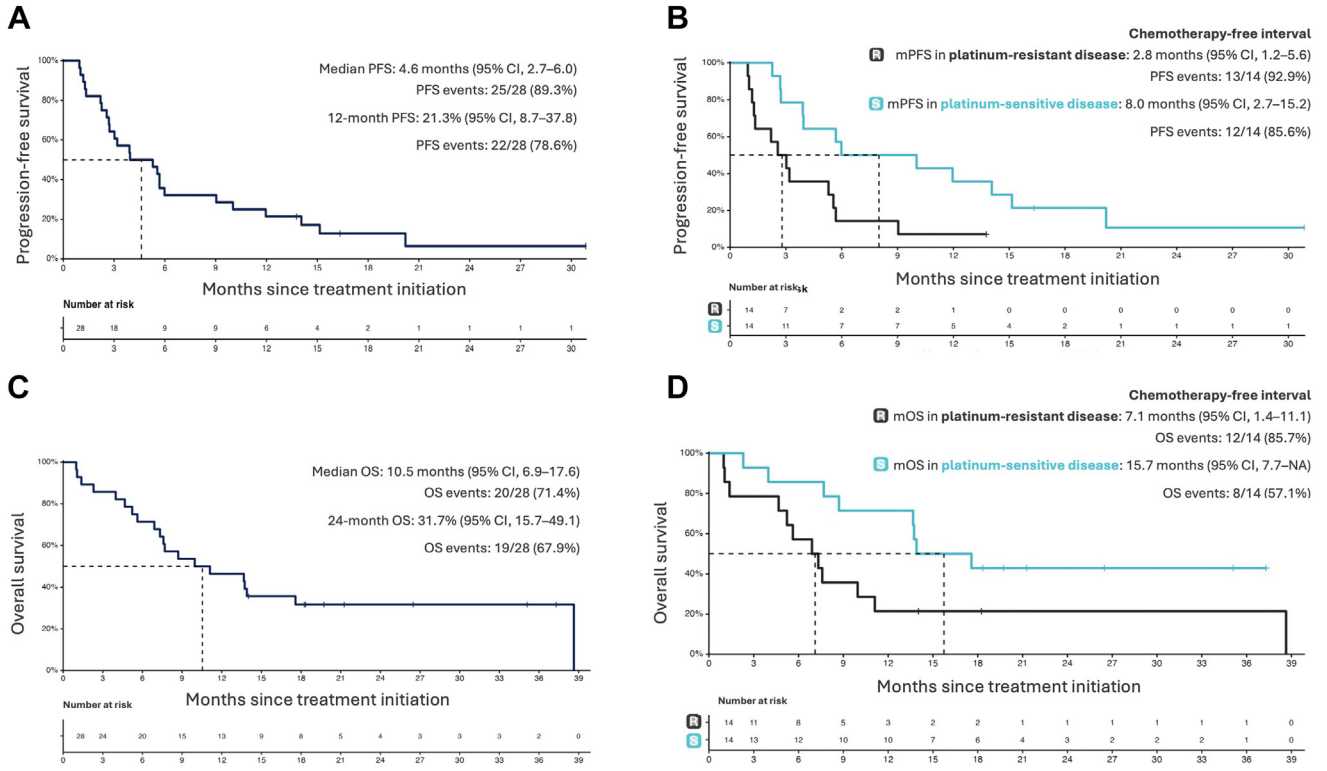

Figure 3. Median progression-free survival and median overall survival in phase II. *(A)* Overall PFS. *(B)* PFS by platinum sensitivity: resistant disease (CTFI $<$ 90 d), sensitive disease (CTFI $\geq$ 90 d). *(C)* Overall OS. *(D)* OS by platinum sensitivity: resistant disease (CTFI $<$90 days), sensitive disease (CTFI $\geq$ 90 d). CI, confidence interval; CTFI, chemotherapy-free interval; mOS, median overall survival; mPFS, median progression-free survival; NA, not applicable; OS, overall survival; PFS, progression-free survival.

understanding our findings, they should be interpreted with caution owing to the limited sample size of the present study.

Although grade 3 and 4 toxicities were reported, their incidence was consistent with the documented safety profiles of lurbinectedin and pembrolizumab.[9,12,22,39] The incidence of G3 and higher related TEAEs was 71.4%, with 17.9% of patients discontinuing treatment because of TEAEs and one treatment-related death reported. Hematologic toxicity affected 82.1% of patients, with 25% G4. Most toxicity was laboratory abnormalities, transient, and considered not clinically significant, with only one case of febrile neutropenia (3.6% G3) documented. High neutropenia rates were attributed to lurbinectedin (64.3%; 35.7% G $\geq$ 3), but no new toxicities were identified. irTEAEs included one G2 pneumonitis and only two instances of G3 or higher adverse events (14.3% increased ALT and 7.1% increased AST), all of which recovered with tapered steroids.

During the course of the LUPER trial, the combination of chemotherapy and immunotherapy in the first line reported improvement in PFS and OS, establishing atezolizumab and durvalumab as new standards of care alongside platinum-etoposide.[10,11] Conversely, a similar trial evaluating first-line pembrolizumab did not meet the prespecified efficacy endpoint, despite showing numerical improvement in PFS and OS.[12] Moreover, single-agent nivolumab[13] and atezolizumab[15] in relapsed SCLC reported inferior PFS compared with chemotherapy, probably due to the aggressive nature of the disease and insufficient time for immunotherapy to elicit a response. Thus, combining immunotherapy with cytotoxic chemotherapy may be critical to ensure its effectiveness and prevent early tumor progression in relapsed SCLC.

Our study presents compelling efficacy results for the potential of combining lurbinectedin with immunotherapy in relapsed SCLC. Similarly, the phase I 2SMALL trial reported remarkable preliminary antitumor activity when combining lurbinectedin and atezolizumab in relapsed extensive-stage SCLC.[40] Nevertheless, other studies investigating similar combinations were prematurely terminated owing to unacceptable toxicities or recruitment challenges.[41,42]

It is important to note that the combination of chemotherapy and immunotherapy in the first-line setting became the standard of care during the

Table 3. Treatment-Emergent Adverse Events (in ≥10% of Patients or of Grade 5) in Phase II

Adverse Event, n (%)	Grade 3-5[a]	Any Grade
TEAEs	23 (82.1)	28 (100.0)
Hematologic	17 (60.7)	23 (82.1)
Blood and lymphatic system disorders	17 (60.7)	23 (82.1)
Neutropenia	13 (46.4)	19 (67.9)
Anemia	4 (14.3)	15 (53.6)
Thrombocytopenia	3 (10.7)	8 (28.6)
Lymphopenia	2 (7.1)	6 (21.4)
Non-hematologic	17 (60.7)	28 (100.0)
General disorders and administration site conditions	3 (10.7)	22 (78.6)
Fatigue	2 (7.1)	21 (75.0)
Pyrexia	0 (0.0)	8 (28.6)
Chest pain	0 (0.0)	3 (10.7)
Gastrointestinal disorders	1 (3.6)	20 (71.4)
Nausea	0 (0.0)	13 (46.4)
Diarrhea	0 (0.0)	8 (28.6)
Vomiting	0 (0.0)	8 (28.6)
Constipation	0 (0.0)	7 (25.0)
Abdominal pain	0 (0.0)	3 (10.7)
Infections and infestations	9 (32.1)	18 (64.3)
Pneumonia	3 (10.7)	5 (17.9)
COVID-19	1 (3.6)	3 (10.7)
Febrile infection	1 (3.6)	1 (3.6)
Pseudomonal sepsis	1 (3.6)	1 (3.6)
Metabolism and nutrition disorders	1 (3.6)	17 (60.7)
Decreased appetite	0 (0.0)	11 (39.3)
Hyperglycemia	0 (0.0)	4 (14.3)
Musculoskeletal and connective tissue disorders	0 (0.0)	15 (53.6)
Arthralgia	0 (0.0)	6 (21.4)
Myalgia	0 (0.0)	5 (17.9)
Neck pain	0 (0.0)	3 (10.7)
Pain in extremity	0 (0.0)	3 (10.7)
Investigations	4 (14.3)	14 (50.0)
ALT increased	4 (14.3)	11 (39.3)
AST increased	2 (7.1)	10 (35.7)
Blood triglycerides increased	0 (0.0)	4 (14.3)
Weight decreased	0 (0.0)	3 (10.7)
Respiratory, thoracic, and mediastinal disorders	2 (7.1)	13 (46.4)
Dyspnea	0 (0.0)	7 (25.0)
Cough	0 (0.0)	6 (21.4)
Respiratory failure	1 (3.6)	1 (3.6)
Nervous system disorders	1 (3.6)	9 (32.1)
Dysgeusia	0 (0.0)	4 (14.3)
Dizziness	1 (3.6)	3 (10.7)
Skin and subcutaneous tissue disorders	1 (3.6)	6 (21.4)
Pruritus	1 (3.6)	3 (10.7)
Endocrine disorders	0 (0.0)	4 (14.3)
Hypothyroidism	0 (0.0)	4 (14.3)
Psychiatric disorders	0 (0.0)	3 (10.7)
Insomnia	0 (0.0)	3 (10.7)

n (%): number of participants (percentage on the basis of N).
[a]There were four grade 5 events reported in 3 patients: COVID-19 infection, febrile infection with respiratory failure, and sepsis due to *Pseudomonas aeruginosa*.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease-19; N, number of patients; TEAE, treatment-emergent adverse events.

completion of our trial, limiting the generalizability of our results. However, some patients still do not receive immunotherapy in the first-line setting due to factors such as drug access, contraindications (e.g., active autoimmune disorders), or progression after definitive chemoradiation, making them candidates for second-line therapy with lurbinectedin plus an immune checkpoint inhibitor. Meanwhile, ongoing trials are evaluating lurbinectedin with PD-(L)1 inhibitors as maintenance therapy after first-line chemo-immunotherapy without progression.[43,44] The IMforte phase III trial, which assesses lurbinectedin and atezolizumab in extensive-stage SCLC after atezolizumab plus carboplatin and etoposide induction therapy, has reported positive results for both primary endpoints of PFS and OS.[45,46] Findings from these trials will finally position the combination of lurbinectedin plus immunotherapy in the treatment strategy of patients with SCLC.

The main strengths of this study are the outcomes improvement in the second-line treatment of SCLC, in which options are limited, using a novel combination regimen; a representative population comprising patients with platinum-resistant or platinum-sensitive disease, extensive or limited disease, and central nervous involvement; the long follow-up and mature data; and the use of iRECIST 1.1 for efficacy evaluation, with results comparable to those of RECIST v.1.1. The study is limited by its single-arm design with no control group and the relatively small cohort of patients. Moreover, the applicability of these results is limited to patients who have not previously received immunotherapy, which conflicts with the current recommendation of first-line therapy with chemotherapy and immunotherapy for these patients.[6,47] Despite these limitations, the reported feasibility and activity of this combination warrant further evaluation in switch maintenance in the metastatic setting or consolidation after definite chemoradiation for patients with limited-stage SCLC.

In conclusion, the combination of lurbinectedin and pembrolizumab reported significant activity in relapsed SCLC, representing a valuable advancement in treatment and warranting further studies in other SCLC treatment settings.

CRediT Authorship Contribution Statement

Antonio Calles: Conceptualization, Methodology, Writing - original draft, Supervision, Funding acquisition, Writing - review & editing, Data Interpretation, Data Validation, Resources, Final approval of manuscript.

Alejandro Navarro: Conceptualization, Methodology, Supervision, Writing - review & editing, Data

Interpretation, Data Validation, Resources, Final approval of manuscript.

Bernard Gaston Doger Speville Uribe: Data interpretation, Data validation, Resources, Writing - review & editing, Final approval of manuscript.

Enric Álvarez Colomé: Data interpretation, Data validation, Resources, Writing - review & editing, Final approval of manuscript.

María de Miguel: Data interpretation, Data validation, Resources, Writing - review & editing, Final approval of manuscript.

Rosa Álvarez: Data interpretation, Data validation, Resources, Writing - review & editing, Final approval of manuscript.

Marta Arregui: Data interpretation, Data validation, Resources, Writing - review & editing, Final approval of manuscript.

Víctor Moreno: Data interpretation, Data validation, Resources, Writing - review & editing, Final approval of manuscript.

Pedro Rocha: Data interpretation, Data validation, Resources, Writing - review & editing, Final approval of manuscript.

Emiliano Calvo: Data interpretation, Data validation, Resources, Writing - review & editing, Final approval of manuscript.

Jorge Ramon-Patino: Data interpretation, Data validation, Resources, Writing - review & editing, Final approval of manuscript.

Elena Corral de la Fuente: Data interpretation, Data validation, Resources, Writing - review & editing, Final approval of manuscript.

Daniel Alcalá-López: Formal analysis, Data curation, Visualization, Writing - review & editing, Final approval of manuscript.

Olga Boix: Administrative support, Writing - original draft, Writing - review & editing, Final approval of manuscript.

Melissa Fernández-Pinto: Administrative support, Writing - review & editing, Final approval of manuscript.

Jose Rodríguez-Morató: Administrative support, Writing - review & editing, Final approval of manuscript.

Ramón Palmero: Data interpretation, Data validation, Resources, Writing - review & editing, Final approval of manuscript.

Ernest Nadal: Data interpretation, Data validation, Resources, Writing - review & editing, Final approval of manuscript.

Maria Jove: Data interpretation, Data validation, Resources, Writing - review & editing, Final approval of manuscript.

Enriqueta Felip: Data interpretation, Data validation, Resources, Writing - review & editing, Final approval of manuscript.

Disclosure

Dr. Calles reports having received personal honoraria for advisory board participation from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Roche, Sanofi, and Takeda; having received personal honoraria for speaker participation from Bayer, PhamaMar; having received institutional financial support for clinical trials from Merck Sharp & Dohme. Dr. Navarro reports having received personal honoraria for advisory board participation from Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, and Oryzon Genomics; having received personal honoraria for speaker participation from AstraZeneca, Pfizer, Roche, Takeda, and Tecnofarma; having received personal honoraria for expert testimony from Hengenix Biotech and MEDSIR. Dr. Doger reports non-financial interest as Principal Investigator for Abbvie, Ascendis, AstraZeneca, Bicycle therapeutics, BioInvent, BioNTech, Boehringer, Enliven, Immutep, Ipsen, Janssen, Merck, NEC Bio Therapeutics, Novartis, Revolution, Takeda, Totus Medicines, Zai Lab. Dr. Miguel reports having participated in a consulting/advisory board for Boxer and Fenix; having participated as an invited speaker for Janssen and Merck Sharp & Dohme. Dr. Álvarez reports having participated in a consulting/advisory board for Novartis; having consulting fees for AstraZeneca, Novartis, PharmaMar, and Roche; having received personal honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events for Boehringer and Deciphera; having personal support for attending meetings and travel from Merck Sharp & Dohme, PharmaMar, and Roche. Dr. Arregui reports having received personal honoraria for speaker participation from AstraZeneca and Roche; having personal support for travel from PharmaMar; and having received institutional financial support from Lilly. Dr. Rocha reports having received financial support for attending meetings and travel from AstraZeneca, Bristol Myers Squibb, Kyowa Kirin, Merck Sharp & Dohme, and Roche. Dr. Calvo reports having received personal honoraria for advisory board participation from Adcendo, Amunix, Anaveon, AstraZeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Chugai, Debio, Diaccurate, Elevation Oncology, Ellipses Pharmacy, Genmab, Grey Wolf, Incyte, iTeos, Janssen, Merus, MonTa, Merck Sharp & Dohme, Nanobiotix, Nouscom, Novarits, Servier, SyneosHealth, T-knife; having received personal honoraria for speaker participation from OncoDNA, PharmaMar, and Roche/Genentech; being a member of board of directors at PharmaMar. Dr. Alcalá-López is a full-time employee at MEDSIR. Dr. Boix is a full-time employee at MEDSIR. Ms. Fernández-Pinto is a full-time employee at MEDSIR. Dr. Rodríguez-

Morató is a full-time employee at MEDSIR. Dr. Palmero reports having received consulting fees from AstraZeneca; having payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events for Guardant Health and Pfizer; having received personal support for attending meetings and travel from Merck Sharp & Dohme; and having participated in a consulting/advisory board for AstraZeneca. Dr. Nadal reports having received personal honoraria for speaker participation from Amgem, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Illumina, Janssen, Lilly, Merck Sharp & Dohme, Pfizer, Qiagen, Roche, Sanofi, Takeda; having received personal honoraria for advisory board participation from Amgem, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Genmab, Janssen, Lilly, Merck Serono, Merck Sharp & Dohme, Pfizer, Qiagen, Regeneron, Roche, Sanofi, Takeda; having received institutional financial support for clinical trials from Bristol Myers Squibb and Merck Serono. Dr. Jove reports having received personal support for travel and accommodation from Merck Sharp & Dohme, Roche, Takeda, and VCN; and having received personal financial support for educational activity from AstraZeneca, Bristol Myers Squibb, and Roche. Dr. Felip reports having received personal honoraria for advisory board participation from Abbvie, Amgen, AstraZeneca, Bayer, Beigene, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, Genmab, Gilead, GSK, Janssen, Merck Serono, MSD, Novartis, Peptomyc, Pfizer, Regeneron, Sanofi, Takeda, Turning Point, Daiichi Sankyo; personal speaker honoraria from Amgen, AstraZeneca, BMS, Daiichi Sankyo, Eli Lilly, F. Hoffmann-La Roche, Genentech, Janssen, Medical Trends, Medscape, Merck Serono, MSD, Peervoice, Pfizer, Sanofi, Takeda, Touch Oncology; Board of Director role: Grifols; financial support for meeting attendance and travel from AstraZeneca, Janssen, Roche; having personal support for attending meetings and travel from AstraZeneca, Janssen, Roche; being a member of board of directors at Grifols; having receive institutional financial support for clinical trials from Astra Zeneca, Abbvie, Amgen, Bayer, Beigene, Boehringer Ingelheim, BMS, Daiichi Sankyo, Exelixis, F. Hoffmann-La Roche, Genentech, GSK, Janssen, MSD, Merck KGAA, Mirati, Novartis, Nuvalent, Pfizer, Takeda. The remaining authors declare no conflict of interest.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2025.02.005.

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