The Italian Mauris Phase IIIb Trial of Atezolizumab Plus Carboplatin and Etoposide for Patients With Newly Diagnosed Extensive-Stage Small Cell Lung Cancer: 3-Year End-of-Study Results

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Abstract

Atezolizumab combined to carboplatin and etoposide prolonged survival in the IMpower133 trial of untreated extensive-stage small-cell lung cancer (ES-SCLC). This end-of-study analysis from the MAURIS phase IIIb trial reported a median overall survival (OS) of 10.6 months, with OS rates of 45.5% at 1 year and 14.5% at 3 years, thus confirming long-term survival of a subgroup of ES-SCLC patients.

Background: Atezolizumab combined to carboplatin and etoposide prolonged survival in the IMpower133 trial of untreated extensive-stage small-cell lung cancer (ES-SCLC). Aim of this analysis is to provide end-of-study results from the phase IIIb MAURIS study on the efficacy and safety of atezolizumab plus chemotherapy in the same disease setting, in a patient population with broader inclusion criteria. **Materials and Methods:** MAURIS is a multicentric, open-label, single-arm study conducted between 2019 and 2023 in 25 Italian study centres. A total of 155 patients with untreated ES-SCLC were enrolled. Treatment was based on atezolizumab 1200 mg + carboplatin + etoposide every 21 days, for 4 to 6 cycles, during the induction phase, and atezolizumab every 3 weeks during the maintenance phase. Safety, overall survival (OS) and progression-free survival (PFS) were among study endpoints. **Results:** The median OS at end of study was 10.6 months, with OS rates of 45.5% at 1 year, 31.0% at 1.5 years, 17.1% at 2 years and 14.5% at 3 years. The median PFS was 5.5 months. Serious adverse events (AEs) occurred in 38.3% of patients, treatment-related

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Submitted: Jan 27, 2025; Revised: Jun 5, 2025; Accepted: Jul 4, 2025; Epub: 9 July 2025

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https://doi.org/10.1016/j.cllc.2025.07.003

serious AEs in 21.4%, and immuno-mediated treatment-emergent AEs in 26.6% of patients. Immune-mediated grade 3 to 4 AEs were inversely related with mortality (hazard ratio, HR = 0.36; 95% confidence interval, CI: 0.13-0.97) in a multivariate analysis. **Conclusion:** This study showed consistent findings with the IMpower133 trial on the safety and efficacy of atezolizumab plus chemotherapy in first-line treatment of ES-SCLC. Long-term survival of a subgroup of patients was also confirmed.

Clinical Lung Cancer, Vol. 26, No. 7, 541–551 © 2025 The Author(s). Published by Elsevier Inc.

Keywords: Immunotherapy, Survival, Overall survival, Extended stage, Safety

Introduction

Lung cancer is the most common and lethal neoplasm worldwide,[1] with 13% to 15% of cases being represented by small cell lung cancer (SCLC).[2] SCLC is an aggressive and rapidly growing tumour, often diagnosed at an advanced stage, with a critical 5-year survival rate below 10%.[3,4] Survival is even worse, i.e., < 2% at 5 years, in extensive-stage SCLC (ES-SCLC) patients.[5]

During the last 10 to 15 years, a greater understanding of disease biology led to the development and approval of new systemic treatments aimed to increase the survival of patients with ES-SCLC. Selected immunotherapies showed encouraging results in randomized clinical trials (RCT).[6,7] Among those, atezolizumab—a humanized IgG1 monoclonal antibody, immune checkpoint inhibitor of the interaction between PD-L1 and its PD-1 and B7-1 receptors—in addition to carboplatin and etoposide reported a benefit in overall survival (OS) and progression-free survival (PFS) in the phase III IMpower133 trial of newly diagnosed ES-SCLC patients (median OS 12.3 vs. 10.3 months in the placebo group; median PFS 5.2 vs. 4.3 months).[6]

Subsequent analyses from IMpower133 confirmed the safety and efficacy of atezolizumab in the long term, as well as its favourable effect on patients quality of life,[8-10] while a number of other studies from the Real-World setting provided information on the use of atezolizumab and other immunotherapies in the clinical practice of newly diagnosed ES-SCLC.[11-15] However, available data are still limited, and several questions on the role of atezolizumab in ES-SCLC (for example, whether long term benefits are associated to selected patient characteristics) remain unsettled.

In an interim data analysis from the MAURIS study,[16] a phase IIIb trial carried out in Italy, we previously showed that RCT findings of the IMpower133 study may be replicated in a broader ES-SCLC patient population, closer to everyday clinical practice, and after continuing treatment from 4 to up to 6 cycles according to physicians' choice. Aim of this study is to provide information on the final efficacy and safety results of atezolizumab plus chemotherapy at the end of study, i.e., 3 years after last enrolment, and to consider other selected open issues in the frontline immunotherapy of ES-SCLC by examining data from MAURIS.

Materials and Methods

MAURIS is a multicentric, open-label, single-arm study conducted between August 2019 and July 2023 in 25 study centres located throughout Italy. Patient enrolment lasted 12 months (August 2019-July 2020) and was based on the following main eligibility criteria: (1) histologically or cytologically confirmed ES-SCLC (according to the Veterans Administration Lung Study Group staging system); (2) measurable disease (as defined by RECIST v1.1); (3) Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale between 0 and 2; (4) no prior systemic treatment for ES-SCLC; (5) adequate hematologic and end organ functions. A total of 181 patients were screened, and 155 of them satisfied all the eligibility criteria and were enrolled. The study ended 36 months after the enrolment of the last study patient. Detailed information on the full inclusion/exclusion criteria and study methods was provided in an earlier analysis focused on interim data at 1 year, and is also given in the Supplemental Materials.[16]

The study was approved by the reference Ethics Committee at each study centre before the beginning of the investigation and was performed in accordance with the Declaration of Helsinki. All participants gave their written informed consent before the start of any study-related procedure.

The primary objective of the study was to evaluate the safety of treatment, measured according to 2 primary endpoints, i.e., incidence of serious adverse events (SAEs); and incidence of serious and nonserious immune-mediated adverse events (AEs). The latter were defined as those consistent with an immune-mediated mechanism of action requiring treatment with systemic corticosteroids or hormone replacement therapy and included, among others, the occurrence of hepatitis, colitis, myocarditis, skin rash and Guillain-Barré syndrome (the full list is reported in the Supplemental Materials, together with the definition of SAEs). Secondary endpoints were related to both safety and efficacy of treatment, and included: (1) incidence of AEs of special interest (AESI); (2) incidence of AEs associated with drug-induced liver injury (DILI); (3) overall survival (OS); (4) progression-free survival (PFS); (5) overall response rate (ORR), defined according to RECIST v1.1, and duration of response (DOR).

In the induction phase, patients were treated with atezolizumab 1200 mg + carboplatin (AUC 5 mg/ml/minute) + etoposide (100 mg/m^2 BSA on days 1-3 of each cycle) every 21 days, for 4 to 6 cycles according to investigator choice. In the maintenance phase, patients received atezolizumab every 3 weeks until progression of disease (PD), unacceptable toxicity or clinical deterioration. After PD (evaluated according to RECIST v1.1), investigators could choose to continue treatment if selected requirements were met (e.g., evidence of clinical benefit, absence of PD-related ECOG PS deterioration and of tumour progression at critical anatomical sites).

Other anticancer therapies, live attenuated vaccines, systemic immunostimulant, or immunosuppressive therapy were not allowed during the study. On the other hand, permitted drugs included: (1) prophylactic or therapeutic anticoagulation therapy; (2) corticosteroids used for chronic obstructive pulmonary disease or asthma; (3) low-dose corticosteroids used for orthostatic hypotension or adrenocortical insufficiency; (4) palliative radiotherapy not interfering with the assessment of tumour target lesions; and (5) local therapy such as surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation. The use of antihistamines, antipyretics, and/or analgesics as premedication was permitted starting from the second infusion of atezolizumab.

Tumour assessments were performed: (1) at screening; (2) after treatment cycle 1, every 6 weeks for the first 48 weeks; (3) then, every 9 weeks, until the occurrence of PD. In case of treatment continuation after PD, tumour assessments were performed every 6 weeks, until discontinuation of treatment.

The National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, was used to evaluate treatment-emergent AEs (TEAEs). AE terms were assigned to a preferred term and were classified by the primary system organ class according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus, version 23.0. The full lists of events included in AESI and DILI are reported in detail in the Supplemental Materials. OS was defined as the time from start of treatment to death from any cause, and PFS as the time from start of treatment to the first occurrence of PD or death from any cause, whichever occurred first. DOR was defined as the time from initial response to disease progression or death among patients who experienced a complete response or partial response during the study.

Statistical methods. Descriptive statistics were generated. Continuous variables were presented through median and/or mean values ± standard deviation (SD), and categorical variables as numbers and percentages. For categorical data, comparisons between groups (e.g., between patients with vs. without long-term benefit [LTB], defined as those with OS ≥ 24 months) were performed by using the contingency table analysis with the χ^2 test. Adverse events occurring during the study follow-up in the safety set (i.e., in all patients with at least 1 administration of the study treatment) were tabulated together with the corresponding percentages, overall and separately for the induction and maintenance phases. Median follow-up was computed using the observation time method. The intention-to-treat (ITT) set of all enrolled patients was used in the efficacy analyses. OS, PFS and DOR were analysed using Kaplan-Meier product-limit survival curve estimates and log-rank tests for comparison between groups.[17] Hazard ratios (HR) of all-cause mortality according to selected baseline and follow-up factors, as well as the corresponding 95% confidence intervals (CIs), were estimated using Cox proportional hazards models adjusting for age (in continuous) and sex.[18] The analyses involving thoracic RT included only patients eligible to the treatment, i.e., those who received at least 4 induction cycles. All statistical tests were 2-sided and a *P*-value of less than .05 was considered significant. Data analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) statistical software.

Results

A total of 155 patients were enrolled in the study (ITT set), with 154 of them (99.4%) starting treatment and thus being involved in the safety set analyses. The median duration of follow-up at end of study was 10.5 months, with a range of 0.2 to 44.9 and a mean ± SD of 15 ± 12 months.

Table 1 describes the characteristics at baseline of patients enrolled in the MAURIS study, overall and according to the number of induction cycles received. The mean age ± SD of cases was 65.1 ± 9.0 years. Out of 155 ES-SCLC patients, 68 (44.2%) had ECOG status = 0, 80 (51.9%) had ECOG =1 and 6 (3.9%) had ECOG = 2. Eighty-six cases (55.5%) had liver metastases and 16 cases (10.3%) had brain metastases at baseline. Eight autoimmune diseases were reported in 7 out of 155 patients (4.5%; 1 patient had 2 conditions) at the baseline visit: 4 with psoriasis, 2 with Hashimoto thyroiditis and 2 with chronic gastritis. A high tumour burden (i.e., at least 1 of the following criteria: SLD ≥ 60 mm, ≥ 2 metastatic sites, LDH > ULN) was present in most patients (94.8%). Twenty-three patients (14.8%) received less than 4 cycles, 43 (27.7%) had 4 cycles, 11 (7.1%) had 5 cycles and 78 (50.6%) had 6 treatment cycles of induction. Including both induction and maintenance phases, patients received a median of 8 cycles of atezolizumab (mean ± SD: 12.6 ± 14.8). A total of 14 patients (9.0%) received thoracic radiotherapy (RT) and 18 (11.6%) had prophylactic cranial irradiation (PCI) during follow-up.

The main results on the efficacy of treatment in terms of OS and PFS are presented in Table 2, overall and according to number of treatment cycles. OS and PFS curves are also shown graphically in Figures 1 and 2, respectively. A total of 120 deaths (77.4%) and 138 disease progression events (89.0%) occurred. The median OS at end of study was 10.6 months (95% CI: 9.8-13.7), with OS rates of 45.5% at 1 year, 31.0% at 1.5 years, 17.1% at 2 years and 14.5% at 3 years. Median OS stratified according to the number of cycles of induction was 2.7 months for < 4 cycles, 10.4 months for 4 cycles, and 13.7 months for 5 to 6 induction cycles (*P*-value < .001). The median PFS in the overall analysis was 5.5 months (95% CI: 5.3-5.7), while in stratified analysis it was 1.8 months for < 4 cycles, 4.5 months for 4 cycles, and 5.8 months for 5 to 6 induction cycles (*P*-value < .001). Survival curves were further stratified according to thoracic RT treatment (Supplemental Figure 1), occurrence of grade 3 or 4 immuno-mediated TEAEs (Supplemental Figure 2), and presence of untreated brain metastasis at baseline (Supplemental Figure 3). In 14 patients treated with thoracic RT, the median OS was 19.3 months (95% CI: 13.7-not reached). In 10 patients reporting at least 1 grade 3 or 4 immuno-mediated TEAEs, the median OS was 13.1 months (95% CI: 0.9-27.1). The ORR in the study was 72.3% (n = 112 out of 155 patients), with 6 patients (3.9%) achieving complete response and 106 (68.4%) partial response. Twenty-five patients (16.1%) had stable disease, 8 (5.2%) had progressive disease, and 9 (5.8%) could not be assessed. Duration of response (DOR) is shown in Supplemental Figure 4. The median DOR was 4.2 months (95% CI: 4.1-4.5). Human leukocyte antigen (HLA) data were available in a minority of patients (n = 11, 7.1%) and thus results of HLA analyses are not reported.

Table 1 Baseline Characteristics of 155 ES-SCLC Patients Enrolled in the MAURIS Study

	All Patients (n = 155)	< 4 Cycles (n = 23)	4 Cycles (n = 43)	5-6 Cycles (n = 89)
Age (years), n (%)				
< 65	72 (46.4%)	8 (36.4%)	20 (46.5%)	44 (49.4%)
≥ 65	83 (53.6%)	14 (63.6%)	23 (53.5%)	45 (50.6%)
Age (years), mean (SD)	65.1 (9.05)	67.2 (7.48)	67.2 (9.90)	63.6 (8.77)
Gender, n (%)				
Females	60 (38.7%)	5 (21.7%)	15 (34.9%)	40 (44.9%)
Males	95 (61.3%)	18 (78.3%)	28 (65.1%)	49 (55.1%)
ECOG performance status, n (%)[a]				
0	68 (44.2%)	5 (21.7%)	19 (44.2%)	44 (50.0%)
1	80 (51.9%)	16 (69.6%)	23 (53.5%)	41 (46.6%)
2	6 (3.9%)	2 (8.7%)	1 (2.3%)	3 (3.4%)
Smoking status, n (%)				
Never smoked	8 (5.2%)	1 (4.3%)	2 (4.7%)	5 (5.6%)
Current smoker	59 (38.1%)	9 (39.1%)	17 (39.5%)	33 (37.1%)
Former smoker	88 (56.8%)	13 (56.5%)	24 (55.8%)	51 (57.3%)
Previous diagnosis of limited stage SCLC, n (%)	14 (9.0%)	2 (8.7%)	8 (18.6%)	4 (4.5%)
Brain metastases at baseline, n (%)	16 (10.3%)	5 (21.7%)	2 (4.7%)	9 (10.1%)
Untreated brain metastases at baseline, n (%)	9 (5.8%)	2 (8.7%)	1 (2.3%)	6 (6.7%)
Liver metastases at baseline, n (%)	86 (55.5%)	14 (60.9%)	29 (67.4%)	43 (48.3%)
Presence of comorbidities, n (%)[b]	94 (60.7%)	16 (72.7%)	27 (62.8%)	50 (56.2%)
Presence of autoimmune diseases, n (%)	7 (4.5%)	0	5 (11.6%)	2 (2.2%)
Concomitant steroid treatment at baseline, n (%)	141 (91.0%)	20 (90.9%)	41 (95.3%)	80 (89.9%)
LDH > ULN at baseline, n (%)	92 (59.3%)	17 (77.3%)	25 (58.1%)	49 (55.1%)
High tumour burden, n (%)[c]	147 (94.8%)	22 (100%)	39 (90.7%)	85 (95.5%)

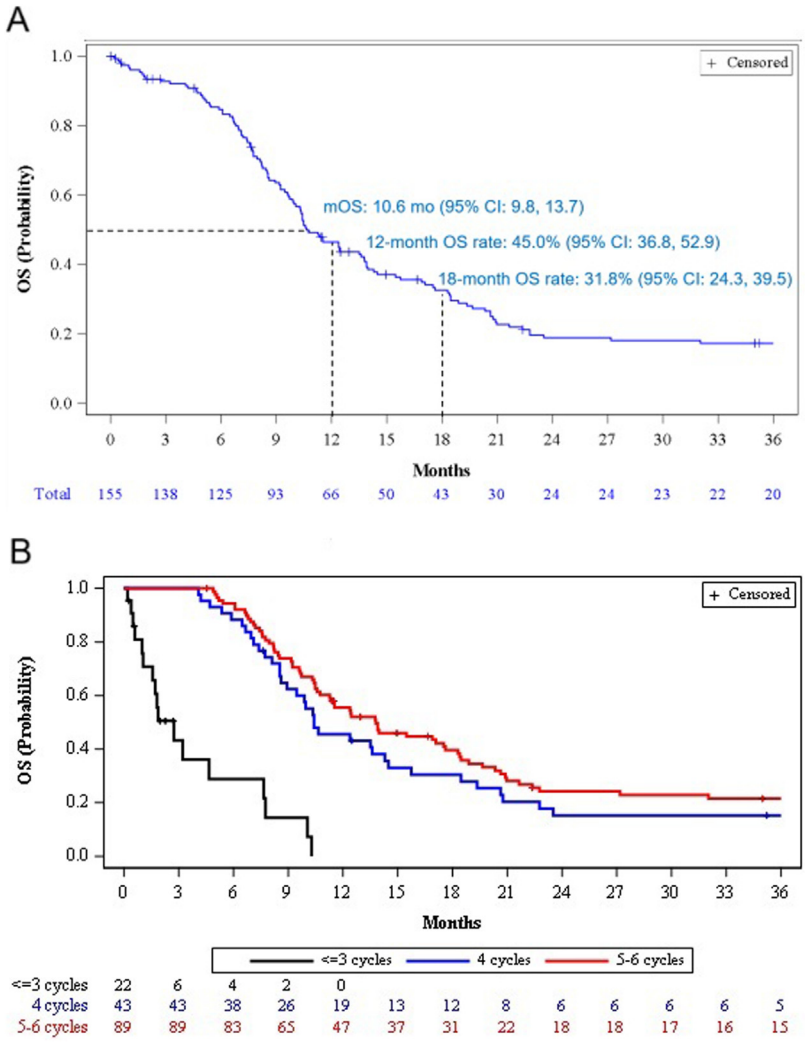
Abbreviations: ECOG = Eastern Cooperative Oncology Group; ES = extensive stage; LDH = lactate dehydrogenase; SCLC = small-cell lung cancer; SD = standard deviation; ULN = upper limit of normal.
[a] The sums may not add up to the total because of a few missing data.
[b] At least 1 comorbidity among the following: cardiovascular diseases, respiratory conditions, dyslipidaemia, diabetes.
[c] At least 1 criterium among the following: SLD ≥ 60 mm, ≥ 2 metastatic sites, LDH > ULN.

Table 2 Summary of OS and PFS Outcomes, Overall and According to Number of Treatment Cycles

	All Patients (n = 155)	<4 Cycles (n = 22)[a]	4 Cycles (n = 43)	5-6 Cycles (n = 89)
Overall survival				
At 1-y, n (%)	66 (45.5)	0	19 (45.2)	47 (54.7)
At 1.5-y, n (%)	44 (31.0)	0	12 (29.3)	31 (37.3)
At 2-y, n (%)	24 (17.1)	0	6 (14.6)	18 (22.0)
At 3-y, n (%)	20 (14.5)	0	5 (12.5)	15 (18.5)
OS percentiles, months				
25° percentile (95% CI)	7.5 (6.6-8.2)	1.0 (0.1-1.8)	7.7 (5.8-8.9)	8.4 (7.4-10.3)
Median OS (95% CI)	10.6 (9.8-13.7)	2.7 (1.0-7.6)	10.4 (8.6-14.2)	13.7 (10.7-17.6)
75° percentile (95% CI)	20.6 (18.2-27.1)	7.6 (2.7-10.2)	20.6 (13.6-NR)	22.7 (18.8-NR)
Death events, n (%)	120 (77.4%)	17 (77.3)	35 (81.4)	68 (76.4)
Progression-free survival				
PFS percentiles, months				
25° percentile (95% CI)	4.0 (3.0-4.2)	1.0 (0.1-1.7)	3.9 (3.0-4.2)	5.3 (4.1-5.5)
Median PFS (95% CI)	5.5 (5.3-5.7)	1.8 (1.0-3.9)	4.5 (4.1-5.5)	5.8 (5.5-6.4)
75° percentile (95% CI)	7.1 (6.5-8.8)	3.9 (1.8-NR)	6.9 (5.5-18.4)	8.5 (6.9-11.9)
Progression events, n (%)	138 (89.0%)	17 (77.3)[b]	39 (90.7)	82 (92.1)

Abbreviations: CI = confidence interval; NR = not reached; OS = overall survival; PFS = progression-free survival
[a] One patient in the intention-to-treat set (n = 155) received no treatment cycles and was thus not included in the analyses stratified by number of cycles (n = 154).
[b] All patients died.

Figure 1 Overall survival in the whole patient population (Panel A) and according to number of treatment cycles (Panel B).[a]



CI = confidence interval; OS = overall survival. OS according to number of treatment cycles, log-rank test, *P*-value < .001. [a]One patient in the intention-to-treat set (n = 155) received no treatment cycles and was thus not included in the analyses stratified by number of cycles (n = 154).

Supplemental Table 1 describes the main characteristics of a restricted subgroup of patients (n = 53) treated after PD. Supplemental Figure 5 reports the corresponding OS curve (median OS = 13.7 months; 95% CI: 10.3-18.3).

Figure 3 shows the percentage distribution of selected characteristics at baseline and during follow-up according to the achievement of LTB of atezolizumab treatment. Patients achieving LTB had more frequently (vs. those not achieving LTB) a baseline LDH within upper limit of normal (ULN, 65% vs. 34%, respectively, *P*-value < .01), an associated auto-immune disorder (17% vs. 3%, *P*-value < .01) and treatment with thoracic RT during follow-up (21% vs. 7%, *P*-value < .01). On the contrary, patients with LTB had less frequently than non-LTB cases a liver metastasis at baseline (21% vs. 49%, *P*-value = .011).

Uni- and multivariate analysis of the association between selected factors and mortality from ES-SCLC is presented in Table 3. Presence of liver metastases at baseline (HR = 1.68; 95% CI: 1.17-2.41) and low number of cycles of induction (HR = 8.08; 95% CI: 4.28-15.23, for < 4 vs. 4 cycles) were associated with an increased mortality, whereas the occurrence of immune-mediated serious AEs during the follow-up period was inversely related with risk of death (HR = 0.36; 95% CI: 0.13-0.97) in the multivariate model.

The main results of the safety evaluation in the MAURIS study are given in Table 4. At least 1 TEAE occurred in most patients during the induction phase (90.3% of cases), maintenance phase (66.7%), and overall study period (96.8%). In 6 cases (3.9%) during the induction phase, TEAEs led to patient death, with one case being treatment-related (death due to pneumonia). SAEs

Table 3 Association Between Selected Factors and Mortality in Patients With ES-SCLC

	Univariate HR (95% CI)	Multivariate HR (95% CI)[a]
Age (years)		
< 65	Reference	Reference
≥ 65	1.36 (0.95-1.94)	1.35 (0.94-1.94)
Gender		
Females	Reference	Reference
Males	1.43 (0.98-2.07)	1.37 (0.94-2.00)
ECOG performance status		
0-1	Reference	Reference
2	2.12 (0.86-5.22)	2.28 (0.91-5.71)
Brain metastases at baseline		
No	Reference	Reference
Yes	1.49 (0.84-2.65)	1.55 (0.87-2.77)
Liver metastases at baseline		
No	Reference	Reference
Yes	**1.64 (1.15-2.36)****	**1.68 (1.17-2.41)***
High tumour burden[b]		
No	Reference	Reference
Yes	1.98 (0.87-4.52)	2.11 (0.92-4.84)
No. of treatment cycles		
< 4	**8.00 (4.26-15.04)*****	**8.08 (4.28-15.23)*****
4	Reference	Reference
5-6	0.79 (0.53-1.19)	0.87 (0.57-1.32)
Occurrence of immuno-mediated, grade 3-4, AEs		
No	Reference	Reference
Yes	0.38 (0.14-1.02)	**0.36 (0.13-0.97)******
Thoracic radiotherapy [c]		
No	Reference	Reference
Yes	0.54 (0.27-1.07)	0.54 (0.27-1.07)

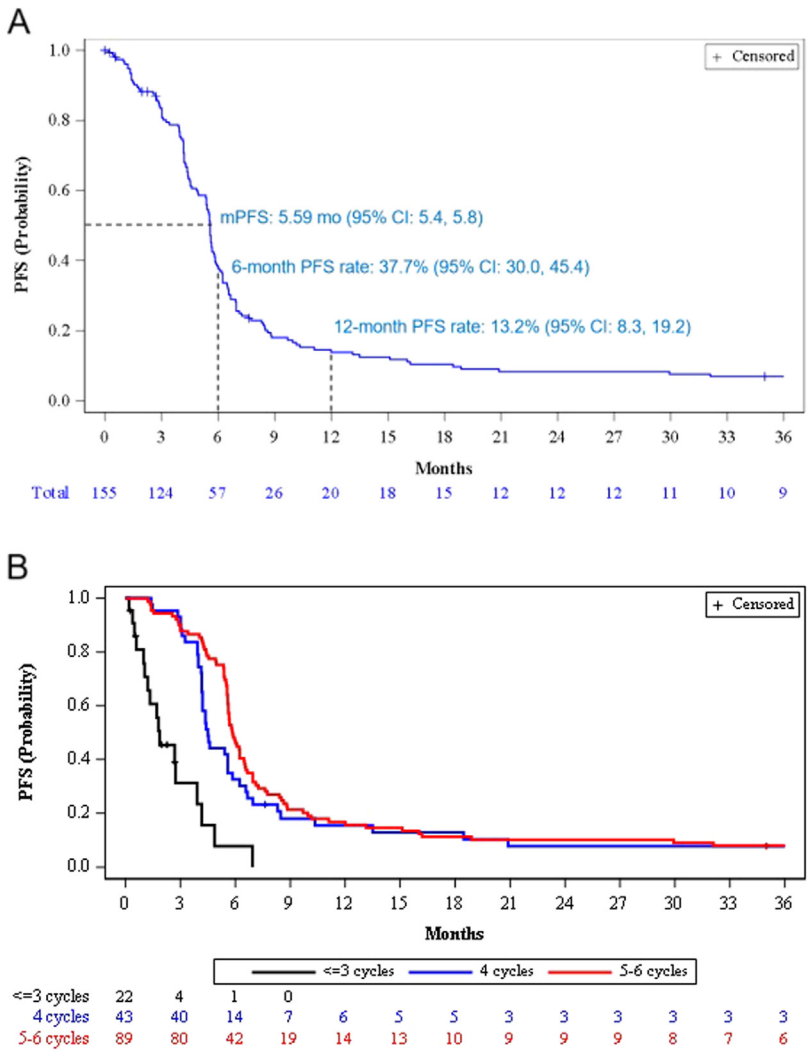
Abbreviations: AE = adverse event; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ES = extensive stage; HR: hazard ratio; SCLC = small-cell lung cancer.
Significance of bold values * $p = 0.005$, ** $p = 0.007$, *** $p < 0.0001$, **** $p = 0.046$.
[a] From multivariate Cox regression models including terms for sex, age (in continuous) and, in turn, the other covariates reported in the Table; statistically significant results are reported in bold.
[b] At least 1 criterium among the following: SLD ≥ 60 mm, ≥ 2 metastatic sites, LDH > ULN.
[c] Analysis conducted by including only patients eligible for thoracic radiotherapy, i.e., those who completed at least 4 treatment cycles.

Table 4 Adverse Events Occurring in 154 Patients (Safety Set) During the Study Period

	Induction Phase	Maintenance Phase	Induction + Maintenance Phases
TEAEs, n (%)	139 (90.3)	80 (66.7)	149 (96.8)
Treatment-related TEAEs, n (%)	118 (76.6)	43 (35.8)	128 (83.1)
Grade 3-4 treatment-related TEAEs, n (%)	74 (48.1)	11 (9.2)	83 (53.9)
SAEs, n (%)	46 (29.9)	16 (13.3)	59 (38.3)
Treatment-related SAEs, n (%)	28 (18.2)	5 (4.2)	33 (21.4)
TEAEs leading to death, n (%)	6 (3.9)	0 (0.0)	6 (3.9)
Treatment-related TEAEs leading to death, n (%)	1 (0.6)	0 (0.0)	1 (0.6)
Immune-mediated TEAEs, n (%)	23 (14.9)	25 (20.8)	44 (26.6)
Immune-mediated SAEs, n (%)	4 (2.6)	7 (5.8)	7 (4.5)
AESI, n (%)	18 (11.7)	16 (13.3)	34 (22.1)
DILI, n (%)	6 (3.9)	5 (4.2)	11 (7.1)

Abbreviations: AESI = adverse events of special interest; DILI = drug-induced liver injury; SAE = serious adverse events TEAEs = treatment-emergent adverse events.

Figure 2 Progression free survival in the whole patient population (Panel A) and according to number of treatment cycles (Panel B).[a]



CI = confidence interval; PFS = progression-free survival. PFS according to number of treatment cycles, log-rank test, *P*-value < .001. [a]One patient in the intention-to-treat set (n = 155) received no treatment cycles and was thus not included in the analyses stratified by number of cycles (n = 154).

were recorded in 38.3% of patients, and treatment-related SAEs in 21.4% of cases. There were 23 patients (14.9%) reporting at least 1 immuno-mediated TEAE during the induction phase, 25 (20.8%) during the maintenance phase, and 44 (26.6%) in the overall study period. The main immuno-mediated TEAEs were endocrine disorders (in 10 patients, 6 of whom reporting hypothyroidism), skin and subcutaneous tissue disorders such as pruritus, rash and psoriasis (in 10 patients) and respiratory disorders (in 7 patients, of whom 5 reporting pneumonitis). Seven patients (4.5%) had at least 1 immuno-mediated SAE during the study. Two immuno-mediated SAEs were due to acute kidney injury and one each to diarrhoea, decreased platelet count, ataxia, autoimmune encephalitis and pruritus. Additional information on other safety outcomes, including data on treatment discontinuations due to TEAEs, is given in Supplemental Table 2, while information on AEs occurring in the subgroup of 14 patients treated with thoracic RT is reported in Supplemental Table 3.

Discussion

The main findings of this prospective study are consistent with those of the IMpower133 trial, confirming the efficacy and safety of atezolizumab plus chemotherapy in the frontline treatment of ES-SCLC. These results were derived in a population of patients slightly older and with worse prognostic features than in the registrative RCT, and over a long period of observation. In particular, OS rate after 3 years was about 15%, thus confirming previous reports about the existence of a selected subgroup of patients obtaining LTB from atezolizumab immunotherapy. In our analysis, this subset was

Figure 3 Characteristics at baseline and during follow-up of patients in relation to LTB (i.e., OS ≥ 24 months) of atezolizumab treatment. Analyses based on 24 patients with LTB and 116 with no LTB.

[a] At least 1 comorbidity among the following: cardiovascular diseases, respiratory conditions, dyslipidaemia, diabetes. *P-value < .05 for comparison of patients with versus without LTB. **P-value < .01 for comparison of patients with versus without LTB. ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; LTB = long-term benefit; PD = progressive disease; PS = propensity score; RT = radiotherapy; ULN = upper limit of normal.

more frequently characterized by a LDH value at baseline within ULN and by the concomitant presence of autoimmune disorders, and survival was favourably impacted by the occurrence of immune-related grade 3 to 4 AEs.

Safety was the primary outcome of the MAURIS study. Overall, safety findings were acceptable and in line with those expected for this treatment combination on the basis of previous data from the IMpower133 and—although comparison is more difficult—of early Real-World studies.[6,12] The proportion of patients reporting 1 or more treatment-related SAE in all study phases (i.e., combined induction and maintenance) of MAURIS was close to that of the atezolizumab arm in the IMpower133 trial (21.4% vs. 22.7%, respectively). Likewise, the corresponding proportions of any SAE in the 2 studies were very similar, 38.1% vs. 37.4%. Immune-mediated AEs occurred in 26.6% of MAURIS patients, generally in line with phase III trials of chemoimmunotherapies for ES-SCLC,[19] as well as with the IMpower133 trial (20.2%),[20] when using the same definition of immune-related events as in the MAURIS study (where treatment with systemic corticosteroids or immunosuppressive drugs was required for characterization). The proportion of patients experiencing AEs was generally higher in the induction than in the maintenance phase, as was reported in IMpower133,[9] with the exception of immune-mediated AEs that, if any, tended to occur more frequently during maintenance. This may, at least in part, be explained by the association with chemotherapeutic agents with an immunosuppression mechanism during the induction phase.

However, on the other side, the continuous and extended treatment with atezolizumab during the maintenance phase may have led to the development of delayed cumulative immune-mediated AEs. The differential and evolving definition of immune-mediated AEs in the MAURIS trial as compared to earlier atezolizumab studies should in any case be aknowledged. A better understanding of long-term side effects of immune checkpoint inhibitors is increasingly important in order to establish an early recognition and treatment. The median OS (10.6 months) and PFS (5.5 months) reported at end of MAURIS study confirmed the early findings of the interim analysis[16] and were largely consistent with those of the IMpower133 trial and of a preliminary analysis of the companion Spanish IMfirst phase IIIb study.[6,21] If any, OS was slightly lower in MAURIS than in the registrative trial, this being possibly explained by the worse prognostic characteristics at baseline of the patient population included. Differently from IMpower133, the phase IIIb MAURIS study included also patients with ECOG status equal to 2 (n = 6, 3.9%) and those with untreated brain metastases at baseline (n = 9, 5.8%). Further, the proportion of patients with liver metastases at baseline was higher in the MAURIS (n = 86, 55.5%) than in the IMpower133 (37%) study. Thus, the population involved in this analysis was closer to Real-World clinical practice .[16] The ORR in MAURIS (72.3%) was higher than the one in IMpower133 (60.2%), and comparable to those of IMfirst (69.0%) and of most other prospective investigations.[13,21] Over a longer observation period as compared to the interim analysis at 1 year,[16] this report showed consistent efficacy results, at least in terms of median survival. However, the extended follow-up allowed us to provide meaningful data on long-term survival rates, with 17.1% of patients alive at 2 years and 14.5% at 3 years from treatment initiation. This finding confirms earlier observations from both RCT and Real-World studies indicating that a subgroup of 15-20% of ES-SCLC cases survives at least 3-years following atezolizumab plus chemotherapy treatment and related inhibition of the PD-1 axis,[8,22] with a recent report from the phase IV extension study of IMpower133 (i.e., IMbrella A study) showing a durable survival rate of 12% at 5-years.[10]

We tried, therefore, to identify the characteristics associated to a favourable prognosis after first-line immunotherapy. Presence of liver and bone metastases and/or elevated LDH at baseline emerged as detrimental factors on survival after ES-SCLC in this and other investigations focused specifically on atezolizumab[12] or on any chemoimmunotherapy.[13] On the other hand, we found no significant association with ECOG PS (likely due to small numbers and limited statistical power), that emerged as a key prognostic factor in several other studies.[13,22,23] No clear OS benefit was found in multivariate analysis for patients treated with 5 to 6 induction cycles as compared to 4 cycles. Similarly to a previous Korean Real-World study,[12] and in accordance with other data on immunotherapies in non-small cell lung cancer patients,[24,25] we reported a favourable impact of the occurrence of immune-related AEs (grade 3-4) on OS in multivariate analyses, also with a comparable, strong magnitude of the association with the Korean analysis (HR = 0.33, vs. HR = 0.36 in MAURIS). This observation, in combination with the favourable results of LTB reported in patients with autoimmune disorders, requires further investigation in future studies.

Limits of this investigation are those typical of phase IIIb studies, e.g., the lack of a comparison arm, the limited sample size for some subgroup analysis, and the inclusion of partially selected patients, that may not be fully representative of the real-life population. Still, enrolment criteria were larger than in the registrative trial and thus closer to the real practice. The cutoff to define patients with LTB (i.e., 24 months) may be somewhat arbitrary, although this was determined in line with the companion IMfirst study.[26] Among the strengths of the study are the long (3-years) period of follow-up, the wide national population coverage (the study involved centres in 14 out of 20 Regions of Italy), and the availability of information on factors associated to LTB of atezolizumab. Further, we were able to analyse selected patient subgroups for which data are still limited. In particular, we characterized patients treated after PD, reporting a median OS of 13.7 months in this group; and we could examine patients treated with combined immunotherapy and thoracic RT[4]: although based on a limited number of cases, our findings supported the applicability and a potential synergistic effect of combined thoracic RT and immunotherapy with atezolizumab.[2,27]

Conclusions

In conclusion, the results of this analysis at the end of the MAURIS study show that safety and efficacy of atezolizumab plus carboplatin and etoposide in the frontline treatment of ES-SCLC in a population more similar to real-life patients are consistent with findings from the IMpower133 phase III trial. In the context of a disease with traditionally sporadic cases remaining alive in the long-term, prolonged survival of a (albeit restricted) subset of patients treated with chemoimmunotherapy was also confirmed by our data.

Clinical Practice Points

- This phase IIIb trial confirmed over a long period of observation the efficacy and safety of atezolizumab plus chemotherapy in the frontline treatment of ES-SCLC.
- A restricted subset of about 15% of ES-SCLC patients treated with frontline chemoimmunotherapy showed prolonged survival.
- In multivariate analyses, survival was favourably impacted by the occurrence of immune-related grade 3 to 4 adverse events.

Consent for Publication

This manuscript does not contain any individual person's data in any form.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request. Requests for the data underlying this publication requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and company subject matter experts. For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: go.roche.com/data_sharing

Anonymised records for individual patients across more than 1 data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

Disclosure

Prof. Ardizzoni has received honoraria for lectures from BMS, Astra Zeneca, MSD and has been member of the Advisory Board of Roche, Astra Zeneca, BMS, Sanofi and Eli Lilly. Dr. Bearz has received consulting fees from Pfizer and honoraria for lectures from Pfizer, MSD, Roche and Astra Zeneca and has been a member of the Advisory Board of Lilly, Astra Zeneca, Pfizer and Roche. Prof. Berardi has received grants or contracts, consulting fees, payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AZ, Boeringher, MSD, Lilly, Roche, Amgen, GSK, Eisai and BMS; she has been member of Data Safety Monitoring Board or Advisory Board of AZ, Boeringher, MSD, Lilly, Roche, Amgen, GSK, Eisai, BMS and Expert member of AIFA Oncological Team Board, President of FONICAP, Member of AIOM National Council Board, President LOTO ODV Scientific Committee; she had a Leadership or fiduciary role in AZ, Boeringher, MSD, Lilly, Roche, Amgen, GSK, Eisai and BMS. Prof. Bria has received grants or contracts from Italian Association for Cancer Research, Università Cattolica del Sacro Cuore, Italian Ministry of Health, Astra-Zeneca, Roche and honoraria for lectures from Merck-Sharp and Dome, Astra-Zeneca, Pfizer, Eli-Lilly, Bristol-Myers Squibb, Novartis and Roche; he has been member of Data Safety Monitoring Board or Advisory Board of Merck-Sharp and Dome, Pfizer, Novartis, Bristol-Myers Squibb, Astra-Zeneca, and Roche.

Prof. Ciardiello has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Merck, MSD, Servier, Pierre Fabre and has been member of Data Safety Monitoring Board or Advisory Board of MSD, Pierre Fabre, Servier, Merck, Roche, Pfizer. Prof. De Marinis has received payment or honoraria for speakers' bureaus from Roche, Astrazeneca, BMS, Novartis, Merck and has been a member of the Advisory Board of Roche, AZ, BMS, Novartis, Merck. Dr. Del Signore has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Roche. Dr. Delmonte has received support for attending meetings and/or travel from MSD, Roche, Takeda and has been a member of Data Safety Monitoring Board or Advisory Board of Novartis, Pfizer, Immunocore. Prof. Garassino has received consulting fees from AstraZeneca, MSD International GmbH, Bayer, BMS, Boehringer Ingelheim Italia S.p.A, Celgene, Eli Lilly, Incyte, Novartis, Pfizer, Roche, Takeda, Seattle Genetics, Mirati, Daiichi Sankyo, Regeneron, Merck, Blueprint, Jansenn, Sanofi, AbbVie, BeiGenius and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AstraZeneca, MSD International GmbH, Merck, Celgene, Eli Lilly, Incyte, Roche. Dr. Gridelli has received consulting fees from Menarini, Roche and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Roche, Astra Zeneca, MSD, BMS, Amgen, Pfizer, GSK, Takeda, Kyriopharm, Sanofi, Boehringer, Eli Lilly; he has been member of Data Safety Monitoring Board or Advisory Board of Roche, Astra Zeneca, MSD, BMS, Amgen, Pfizer, GSK, Takeda, Kyriopharm, Sanofi, Boehringer, Eli Lilly. Dr. Iero is an employee of Roche Farma Spa. Dr. Migliorino has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Roche, Astra Zeneca, Pfizer, Sanofi, Novartis, Eli Lilly and support for attending meetings and/or travel from Novartis, Sanofi, Takeda. Dr. Morabito has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Roche, BMS, AstraZeneca, MSD, Novartis, Takeda, Lilly, Pfizer, Boehringer and he has been member of Data Safety Monitoring Board or Advisory Board of AstraZeneca, Takeda, Pfizer, MSD. Prof. Morgillo has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from MSD International GmbH, BMS, Boehringer, Ingelheim Italia S.p.A, Roche and support for attending meetings and/or travel from MSD.

Dr. Tonini has been a member of the Advisory Board of Molteni, Novartis, MSD, Pharmamar. Prof. Verderame has received grants or contracts from Roche, Astra Zeneca, GSK, MSD, Janssen, Servier, Takeda and support for attending meetings and/or travel from Janssen, Roche, MSD. Dr. Fadda, Dr. Gilli, Dr. Stefani, Dr. Sbrana, Dr. Taveggia declare no potential competing interests.

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Floriana Morgillo: Writing – original draft, Data curation, Writing – review & editing. **Ester Del Signore:** Writing – review & editing, Data curation, Writing – original draft. **Emilio Bria:** Supervision, Data curation, Conceptualization, Writing – review & editing, Formal analysis. **Filippo de Marinis:** Writing – review & editing, Conceptualization, Supervision, Formal analysis, Data curation. **Fortunato Ciardiello:** Formal analysis, Writing – review & editing, Data curation, Conceptualization, Supervision. **Marina Chiara Garassino:** Conceptualization, Supervision, Data curation, Writing – review & editing, Formal analysis. **Alessio Stefani:** Data curation, Writing – review & editing. **Francesco Verderame:** Writing – review & editing, Data curation. **Alessandro Morabito:** Data curation, Writing – review & editing. **Andrea Sbrana:** Data curation, Writing – review & editing. **Giuseppe Tonini:** Data curation, Writing – review & editing. **Marina Gilli:** Data curation, Writing – review & editing. **Rossana Berardi:** Writing – review & editing, Data curation. **Paola Adriana Taveggia:** Writing – review & editing, Data curation. **Alessandra Bearz:** Data curation, Writing – review & editing. **Angelo Delmonte:** Writing – review & editing, Data curation. **Maria Rita Migliorino:** Writing – review & editing, Data curation. **Cesare Gridelli:** Writing – review & editing, Data curation. **Giovanni Maria Fadda:** Data curation, Writing – review & editing. **Manuela Iero:** Writing – review & editing, Data curation. **Andrea Ardizzoni:** Supervision, Data curation, Writing – review & editing, Formal analysis, Conceptualization.

Acknowledgments

This work was funded by Roche Farma S.p.A., Via G.B. Stucchi 110, 20900 Monza (MB), Italy. Authors thank Statinfo Srl for the editorial service in the preparation of this manuscript and editorial assistance with manuscript submission, and SPARC Consulting (Milan, Italy) for data analysis. Authors also thank all participating

sites and personnel involved in the study, all participating patients and their families for their contribution in the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2025.07.003.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74:229–263.
2. Megyesfalvi Z, Gay CM, Popper H, et al. Clinical insights into small cell lung cancer: tumor heterogeneity, diagnosis, therapy, and future directions. *CA Cancer J Clin*. 2023;73:620–652.
3. Thai AA, Solomon BJ, Sequist LV, Gainor JF, Heist RS. Lung cancer. *Lancet*. 2021;398:535–554.
4. Dingemans AC, Fruh M, Ardizzoni A, et al. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆). *Ann Oncol*. 2021;32:839–853.
5. Arriola E, Trigo JM, Sanchez-Gastaldo A, et al. Prognostic value of clinical staging according to TNM in patients with SCLC: a real-world surveillance epidemiology and end-results database analysis. *JTO Clin Res Rep*. 2022;3:100266.
6. Horn L, Mansfield AS, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379:2220–2229.
7. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394:1929–1939.
8. Liu SV, Reck M, Mansfield AS, et al. Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). *J Clin Oncol*. 2021;39:619–630.
9. Mansfield AS, Kazarnowicz A, Karaseva N, et al. Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small--cell lung cancer (IMpower133): a randomized phase I/III trial. *Ann Oncol*. 2020;31:310–317.
10. Reck M, Dziadziuszko R, Sugawara S, et al. Five-year survival in patients with extensive-stage small cell lung cancer treated with atezolizumab in the Phase III IMpower133 study and the Phase III IMbrella A extension study. *Lung Cancer*. 2024;196:107924.
11. Bonanno L, Calvetti L, Dal Maso A, et al. Real-world impact of the introduction of chemo-immunotherapy in extended small cell lung cancer: a multicentric analysis. *Front Immunol*. 2024;15:1353889.
12. Lee S, Shim HS, Ahn BC, et al. Efficacy and safety of atezolizumab, in combination with etoposide and carboplatin regimen, in the first-line treatment of extensive-stage small-cell lung cancer: a single-center experience. *Cancer Immunol Immunother*. 2022;71:1093–1101.
13. Porte M, Vaudron A, Crequit P, et al. A multicenter study assessing the real-world use and effectiveness of first-line chemotherapy plus immunotherapy in advanced small-cell lung cancer (SCLC) patients. *Clin Lung Cancer*. 2024;25:e101–e111.e102.
14. Qiu G, Wang F, Xie X, et al. A retrospective real-world experience of immunotherapy in patients with extensive stage small-cell lung cancer. *Cancer Med*. 2023;12:14881–14891.
15. Sugisaka J, Fujimoto D, Tamiya M, et al. Long-term outcome of chemoimmunotherapy for extensive-stage small-cell lung cancer according to key clinical trial eligibility: 3-year outcomes from a prospective cohort study. *Lung Cancer*. 2025;199:108056.
16. Bria E, Morgillo F, Garassino MC, et al. Atezolizumab plus carboplatin and etoposide in patients with untreated extensive-stage small-cell lung cancer: interim results of the MAURIS Phase IIIb trial. *Oncologist*. 2024;29:e690–e698.
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457–481.
18. Cox DR. Regression models and life-tables. *J Royal Stat Soc: Series B (Methodol)*. 1972;34:187–202.
19. Zugazagoitia J, Paz-Ares L. Extensive-stage small-cell lung cancer: first-line and second-line treatment options. *J Clin Oncol*. 2022;40:671–680.
20. Horn L, Liu SV, Mansfield AS, et al. *AACR Virtual Annual Meeting II*. IMpower133: updated overall survival and exploratory analyses of first-line atezolizumab plus carboplatin/etoposide in extensive-stage small cell lung cancer; 2020.
21. Garcia Campelo MR, Domine Gomez M, De Castro Carpeno J, et al. 1531P Primary results from IMfirst, a phase IIIb open label safety study of atezolizumab (ATZ)+ carboplatin (CB)/cisplatin (CP)+ etoposide (ET) in an interventional real-world (RW) clinical setting of extensive-stage small cell lung cancer (ES-SCLC) in Spain. *Ann Oncol*. 2022;33:S1246–S1247.
22. Falchero L, Guisier F, Darrason M, et al. Long-term effectiveness and treatment sequences in patients with extensive stage small cell lung cancer receiving atezolizumab plus chemotherapy: results of the IFCT-1905 CLINATEZO real–world study. *Lung Cancer*. 2023;185:107379.
23. Sagie S, Maixner N, Stemmer A, Lobachov A, Bar J, Urban D. Real-world evidence for immunotherapy in the first line setting in small cell lung cancer. *Lung Cancer*. 2022;172:136–141.
24. Haratani K, Hayashi H, Chiba Y, et al. Association of immune-related adverse events with Nivolumab efficacy in non-small-cell lung cancer. *JAMA Oncol*. 2018;4:374–378.
25. Paz-Ares LG, Ramalingam SS, Ciuleanu TE, et al. First-line Nivolumab plus Ipilimumab in advanced NSCLC: 4-year outcomes from the randomized, open-label, phase 3 CheckMate 227 part 1 trial. *J Thorac Oncol*. 2022;17:289–308.
26. García-Campelo M, Dómine M, de Castro Carpeño J, et al. 1995P Long-term benefit of atezolizumab plus chemotherapy in extensive stage small cell lung cancer (ES-SCLC): exploratory analysis from the IMfirst study. *Ann Oncol*. 2023;34:S1064–S1065.
27. Donlon NE, Power R, Hayes C, Reynolds JV, Lysaght J. Radiotherapy, immunotherapy, and the tumour microenvironment: turning an immunosuppressive milieu into a therapeutic opportunity. *Cancer Lett*. 2021;502:84–96.