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Investigation of poor predictive factors in extensive stage small cell lung cancer under etoposide-platinum-atezolizumab treatment

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Abstract

Background: The phase III trial IMpower133 showed that platinum and etoposide plus atezolizumab was associated with improved overall survival (OS) and progression free-survival (PFS) when compared to the placebo group in treatment-naïve extensive stage (ES) small cell lung cancer (SCLC). Due to superiority in clinical outcomes, combination immunotherapy plus chemotherapy have become mainstay treatment modalities as first-line treatment in ES-SCLC. Nevertheless, real-world data are still lacking and the search for potential biomarkers is essential. This study aimed to evaluate potential predictive biomarkers applicable in ES-SCLC under combination therapy.

Methods: Patients with ES-SCLC under etoposide-platinum-atezolizumab enrolled from seven university hospitals affiliated to the Catholic University of Korea were evaluated. Pretreatment clinical parameters were evaluated for association with OS and PFS. Adverse events (AEs) during induction and maintenance phases were also evaluated. *p*-values below 0.05 were considered statistically significant.

Results: A total of 41 patients were evaluated. Six-month survival was 68.6%. As best response to treatment, 26 (63.4%) showed partial response, nine (22.0%) showed stable disease, and four (9.8%) showed progressive disease. During the induction phase, grade I–II AEs occurred in 22 (53.7%) patients, and grade III–IV AEs occurred in 26 (63.4%) patients. During the maintenance phase, nine out of 25 (36.0%) patients experienced any grade AEs. In multivariate analysis for OS, lactate dehydrogenase

(LDH), c-reactive protein (CRP), and forced vital capacity (%) were significant factors. In multivariate analysis for PFS, sex, and LDH were significant.
Conclusion: In ES-SCLC under etoposide-platinum-atezolizumab, pretreatment CRP, LDH and FVC (%) were independent predictive factors.

KEYWORDS
atezolizumab, immunotherapy, prognosis, small cell lung cancer

INTRODUCTION

Small cell lung cancer (SCLC) is a fast proliferating and invasive pathological type comprising 13%–15% of all newly diagnosed lung cancer cases.[1–3] Among newly diagnosed patients with SCLC, about 70% of patients have extensive stage SCLC (ES-SCLC).[4] ES-SCLC patients have a median survival of 8–13 months with a poor prognosis. For past decades, etoposide in combination with a platinum regimen has been the standard first-line modality for ES-SCLC.[5,6] Despite response rates of 60%–65%, the median overall survival (OS) is only 10 months.[7,8]

However, following the results of the IMpower133 and CASPIAN studies, the landscape of ES-SCLC management has changed.[9,10] First-line combination treatment including immune checkpoint inhibitors (ICIs) plus chemotherapy have shown superior clinical outcomes when compared to a chemotherapy alone regimen for ES-SCLC.[11] The phase III trial IMpower133 including 403 treatment-naive ES-SCLC patients receiving platinum and etoposide plus atezolizumab or placebo showed that median OS was 12.3 and 10.3 months in the atezolizumab and placebo groups, respectively. Median PFS was 5.2 and 4.3 months, respectively.[10] Due to the improvement in clinical outcomes, combination immunotherapy plus chemotherapy has become the mainstay first-line treatment modality in ES-SCLC.[11,12]

Nevertheless, real-life data are still lacking and the search for potential biomarkers is necessary. From IMpower 133, in which clinical efficacy of the combination regimen was proven, no clinically applicable biomarker was shown, despite some potential predictive value of tumor mutation burden.[10] Furthermore, regional differences regarding treatment efficacy and the need for safety data are also important issues.

This study evaluated the multicenter data of treatment efficacy and safety profile of etoposide, carboplatin plus atezolizumab in ES-SCLC, and also searched for potential biomarkers predictive of clinical outcomes.

METHODS

Patient selection

Fourty-one consecutively treated ES-SCLC patients in seven university diagnosed with ES-SCLC between January 2019 and August 2020 were selected for the present study. Enrolling hospitals were Yeouido St. Mary's Hospital, Seoul St. Mary's Hospital, Bucheon St. Mary's Hospital, Incheon St. Mary's Hospital, Eunpyeong St. Mary's Hospital, St. Vincent Hospital, and Uijeongbu St. Mary's Hospital. All patients included in the study had been treated with etoposide-platinum plus atezolizumab, had complete pretreatment blood count (CBC) differential counts and blood chemistry both at the time of treatment initiation and time of progression, and all necessary clinical data available from their electronic medical records. The patient selection process is shown in Figure 1.

Overall and progression-free survival

Patients were treated with four cycles of etoposide (administered each cycle for 3 days), carboplatin (administered on day 1 of each cycle), and atezolizumab (1200 mg, administered on day 1 of each cycle). Patients in which there was no disease progression and had completed the induction phase underwent atezolizumab maintenance every 3 weeks. Treatment was continued if no disease progression, death, or unacceptable toxicity was present.

In order to assess treatment response, radiological assessment using computed tomography scan of target organs was

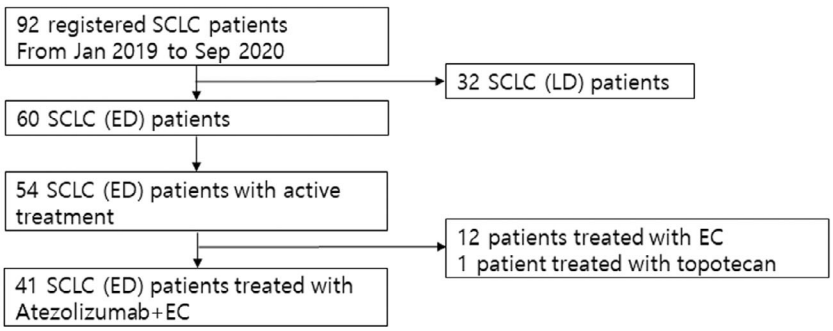

FIGURE 1 Study patient selection process

performed after completion of every two consecutive cycles. Response Evaluation Criteria in Solid Tumors version 1.1 was used to assess treatment response.[13] Independent radiologists and treating physicians assessed the responses. OS was defined as the time from treatment to death. PFS was defined as time duration from treatment initiation to radiologically confirmed disease progression. Patients were considered censored, if patients died or lost contact during the follow-up period,[14]

Safety/toxicity was assessed based on the Common Terminology Criteria for Adverse Events version 4.0. The adverse events, whether related to each drug, and presence of immune-related adverse events (irAEs), were based on the medical records entered by treating physicians.

PLR, NLR, derived NLR

From pretreatment complete blood counts measured at the time of lung cancer diagnosis, platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) were calculated. PLR and NLR were calculated as the ratio of platelet to lymphocyte count, and that of neutrophil to lymphocyte count, respectively. Derived NLR was calculated using the following formula: white blood cell count - absolute neutrophil count/total white blood cell count.

Statistical analysis

For statistical analyses, the Statistical Package for Social Sciences software version 20.0 (SPSS Inc.) was used. Data of continuous variables are illustrated as medians with ranges. Two-sided *t*-tests or the Mann–Whitney U test, depending on the distribution status was used to compare continuous variables. We used the Chi-squared test to compare categorical parameters.

Univariate analysis using the Cox regression model was performed to find variables significantly associated with OS and PFS. Risk factors with a p-value <0.1 in univariate analysis were entered into a multivariate analysis using the Cox proportional hazards regression model. $p < 0.05$ was considered statistically significant.

Ethics statement

The present study was approved by the Ethics Committees of Seoul St. Mary's Hospital, Incheon St. Mary's Hospital, Yeouido St. Mary's Hospital, Bucheon St. Mary's Hospital, Eunpyeong St. Mary's Hospital, St. Vincent Hospital, and Uijeongbu St. Mary's Hospital (XC21RIDI0137). The need for informed consent was waived by the Institutional Review Boards of the above hospitals affiliated to the Catholic Medical Center. This study was conducted in compliance with the Declaration of Helsinki.

RESULTS

Clinical characteristics of patients

A total of 41 patients were enrolled of which 39 (95.1%) were male. Their median age was 69 years. Regarding

TABLE 1 Clinical characteristics of patients

	Overall patients ($n = 41$) (n, %)
Sex	
Male	39 (95.1)
Female	2 (4.9)
Age (year), median, range	69 (55–89)
6-month survival	24/35 (68.6%)
Smoking	
Never smoker	1 (2.5)
Ever smoker	40 (97.5)
Pack years	48 (0–122)
ECOG	
0–1	38 (92.7)
2–3	3 (7.3)
Primary mass size (cm)	5.5 (1.5–10)
Number of distant metastatic sites	
0	3 (7.3)
1	19 (46.3)
2 and more	19 (46.3)
Best response	
PR	26 (63.4)
SD	9 (22.0)
PD	4 (9.8)
Not evaluated	2 (4.9)
First-line	39 (95.1)
Second-line	2 (4.9)
Brain metastasis	7 (17.1)
Liver metastasis	7 (17.1)
Laboratory findings at EC-A initiation	
NLR	2.87 (0.86–12.38)
PLR	163.5 (73.3–591.4)
Derived NLR	1.89 (0.81–10.90)
CRP (mg/dl)	7.14 (0.30–182.6)
Lactate dehydrogenase (units/l)	351.0 (143–3271)
FVC (L)	2.98 (1.90–4.10)
FVC (%)	85.0 (46–103)
FEV1 (L)	1.98 (0.97–3.18)
FEV1 (%)	80.0 (32–121)
DLCO (%)	73.0 (45–110)

Abbreviations: cm, centimeter; CRP, c-reactive protein; DLCO, diffusing capacity of the lungs for carbon monoxide; EC-A, etoposide, carboplatin-atezolizumab; ECOG, Eastern Cooperative Oncology Group; FVC; forced vital capacity, FEV1; forced expiratory volume in the first second; NLR, neutrophil-lymphocyte ratio; PD, progressive disease; PLR, platelet-lymphocyte ratio; PR, partial response; SD, stable disease.

TABLE 2 Comparison of clinical characteristics between responders and nonresponders

	Nonresponders (SD, PD as best response) ($n = 13$)	Responders (PR as best response) ($n = 26$)	*p*-value
Sex			0.152
Male	12 (92.3)	26 (100)	
Female	1 (7.7)	0 (0)	
Age (year), median, range	68 (55–89)	70 (56–84)	0.800
6-month survival	7 (63.6)	17 (77.3)	0.407
Smoking			0.152
Never smoker	1 (7.7)	0 (0.0)	
Ever smoker	12 (92.3)	26 (100)	
Pack years	51 (0–90)	47.5 (12.2–122)	0.743
ECOG			0.305
0–1	13 (100)	24 (92.3)	
2–3	0 (0)	2 (7.7)	
Primary mass size	6 (1.5–9.0)	5 (1.8–10.0)	0.962
Number of distant metastatic sites			0.081
0	0 (0.0)	2 (7.7)	
1	7 (53.8)	12 (46.2)	
2 and more	6 (46.2)	12 (46.2)	
First-line	12 (92.3)	25 (96.2)	0.608
Second-line	1 (7.7)	1 (3.8)	
Brain metastasis	1 (7.7)	6 (23.1)	0.238
Liver metastasis	3 (23.1)	4 (15.4)	0.555
Laboratory findings at EC-A initiation			
NLR	2.65 (1.13–8.32)	2.89 (0.86–12.38)	0.766
PLR	141.2 (75.4–591.4)	183.3 (73.3–440.1)	0.882
Derived NLR	1.64 (0.84–4.26)	1.92 (0.81–10.90)	0.634
CRP (mg/dl)	29.87 (0.45–182.6)	5.25 (0.30–138.71)	0.065
Lactate dehydrogenase	510.0 (186.0–1631.0)	350.5 (143–3271)	0.439
FVC (L)	2.53 (2.09–4.10)	3.25 (1.90–3.97)	0.184
FVC (%)	85 (49–99)	86.5 (46–97)	0.664
FEV1 (L)	2.05 (1.64–2.77)	1.98 (0.97–3.18)	0.500
FEV1 (%)	81 (52–121)	77 (32–109)	0.210
DLCO (%)	72.5 (45–108)	74.5 (53–110)	0.597

Abbreviations: CRP, c-reactive protein; DLCO, diffusing capacity of the lungs for carbon monoxide; EC-A, etoposide; carboplatin-atezolizumab; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; NLR, neutrophil-lymphocyte ratio; PD, progressive disease; PLR, platelet-lymphocyte ratio; PR, partial response; SD, stable disease.

smoking history, 40 (97.5%) patients were ever smokers. Among the 35 patients with survival data, 24 patients survived more than 6 months (68.6%). Twenty-six (63.4%) patients showed partial response (PR) as best response, while nine (22.0%) patients showed stable disease (SD) as best response, and four (9.8%) patients showed progressive disease only. Thirty-nine (95.1%) patients underwent combination treatment as first-line treatment, while two (4.9%) patients underwent second-line treatment. Regarding median laboratory values at etoposide-carboplatin plus atezolizumab (EC-A) initiation, NLR showed 2.87, PLR was 163.5, derived NLR was 1.89, c-reactive protein (CRP) was 7.14 mg/dl, and lactate dehydrogenase (LDH) was 351.0 units/l (Table 1).

Comparison of clinical characteristics between responders and nonresponders

Among 39 patients with treatment response data, 13 patients were categorized as nonresponders and 26 patients were categorized as responders. There was no statistically significant difference regarding sex and age. Six-month survival was 63.6% in the nonresponder group and 77.3% in the

TABLE 3 Treatment-related AEs

	Induction phase		Maintenance phase	
Any AE	35/40 (87.5)		9/25 (36.0)	
Gr I–II	22 (53.7)		6 (24.0)	
Gr III–IV	26 (63.4)		4 (16.0)	
	Grade I–II	Grade III–IV	Grade I–II	Grade III–IV
Neutropenia	7 (17.5)	18 (45.0)		
Neutropenic fever	0 (0.0)	5 (12.5)		
Anemia	7 (17.5)	4 (10.0)		
Thrombocytopenia	9 (22.5)	1 (2.5)		
Acute kidney injury	4 (10.0)	1 (2.5)		
Nausea	0 (0.0)	3 (7.5)		
Diarrhea	2 (5.0)	0 (0.0)		
Liver function abnormality	2 (5.0)	1 (2.5)		
Hiccup	1 (2.5)	0 (0.0)		
Anaphylaxis	0 (0.0)	1 (2.5)		
Pneumonia	1 (2.5)	1 (2.5)		
Hypotension	1 (2.5)	0 (0.0)		
Oral thrush	1 (2.5)	0 (0.0)		
Polyneuropathy	0 (0.0)	1 (2.5)		
Immune-related AEs				
Hyperthyroidism			1 (4.0)	0 (0.0)
Hypothyroidism			1 (4.0)	0 (0.0)
Pancreatitis			0 (0.0)	1 (4.0)
Hepatitis			0 (0.0)	1 (4.0)
Pneumonitis			0 (0.0)	1 (4.0)
Colitis			1 (4.0)	0 (0.0)
Adrenal insufficiency			1 (4.0)	0 (0.0)
AKI			1 (4.0)	1 (4.0)
Thrombocytopenia			1 (4.0)	0 (0.0)

Abbreviations: AE, adverse events; AKI, acute kidney injury; Gr, grade.

responder group, with no statistically significant difference. There was one (7.7%) patient with brain metastasis in the nonresponder group, while six (23.1%) patients in the responder group had brain metastasis at the time of treatment initiation. CRP and LDH were tended to be higher in the nonresponder group (29.87 vs. 5.25 and 510 vs. 350.5, respectively), but there were no statistically significant differences. Also, there were no significant differences in pulmonary function tests parameters (Table 2).

Treatment-related AEs

Treatment-related AEs were evaluated separately for induction (combination) and maintenance (atezolizumab) phases. Total of 40 patients were evaluated for AEs during the induction phase. For patients who completed the induction phases, 25 patients were evaluated for AEs during the maintenance phase. Among the 40 patients, 35 (87.5%) patients showed any grade AEs: 22 of 40 (53.7%) patients showed grade I-II AEs, and 26/40 (63.4%) patients showed grade III-IV AEs. Regarding grade I–II AEs, thrombocytopenia ($n = 9$, 22.5%), neutropenia ($n = 7$, 17.5%), anemia ($n = 7$, 17.5%), and acute kidney injury ($n = 4$, 10.0%) were the most frequent AEs. Among grade III–IV AEs, neutropenia ($n = 18$, 45.0%), neutropenic fever ($n = 5$, 12.5%), anemia ($n = 4$, 10.0%), and nausea ($n = 3$, 7.5%) were the most frequent Aes.

Among the 25 patients evaluated for Aes occurred in the maintenance phase, nine (36.0%) patients showed any grade Aes: six (24.0%) patients showed grade I–II Aes and four (16.0%) patients showed grade III–IV Aes. Regarding grade I–II Aes, there was one case per each AE (hyperthyroidism, hypothyroidism, colitis, adrenal insufficiency, AKI and thrombocytopenia). There were four documented cases of grade III–IV Aes: pancreatitis, hepatitis, pneumonitis, and AKI (Table 3).

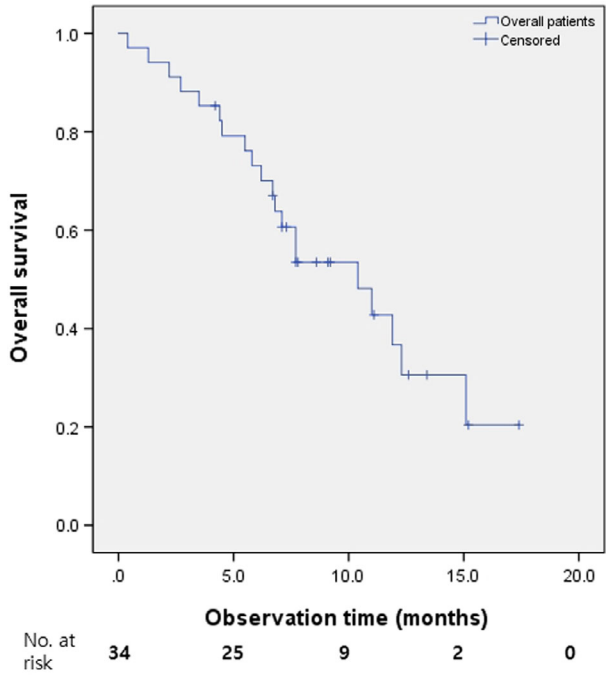

FIGURE 2 Kaplan–Meier graph showing overall survival of patients available for survival analyses

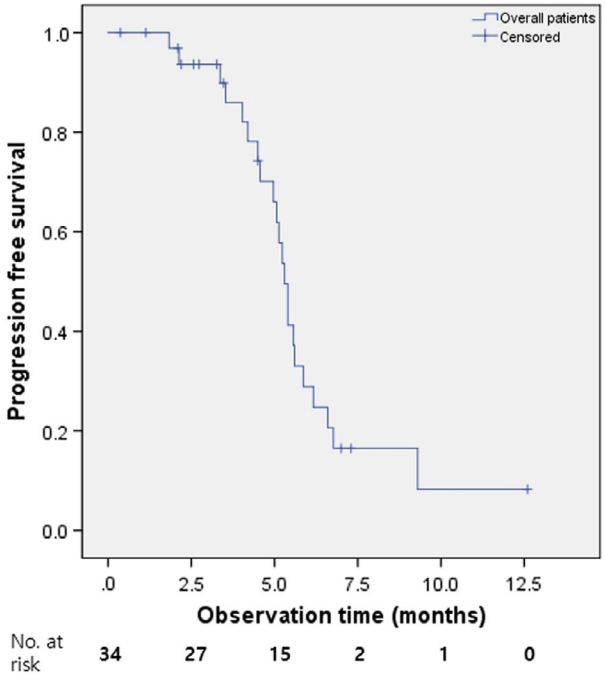

FIGURE 3 Kaplan–Meier graph showing progression-free survival of patients available for survival analyses

Analysis for association with OS and PFS

Figures 2 and 3, respectively show Kaplan–Meier survival curves of OS and PFS of the patients available for survival analyses. Among the patients who have valid survival data, Cox regression analysis for OS was performed. Age, sex, smoking history, Eastern Cooperative Oncology Group (ECOG) score, primary mass size, number of metastatic sites, NLR, PLR, dNLR, LDH, CRP, FEV1 (%), FVC (%) and diffusing capacity of the lungs for carbon monoxide (DLCO) (%) were entered for univariate analysis. In the multivariate analysis, age, sex, number of metastatic sites, LDH, CRP and FVC (%) were entered (Model 1). LDH (HR = 1.001, 95% CI: 1.000–1.003, $p = 0.036$), CRP (HR = 1.036, 95% CI: 1.014–1.059, $p = 0.001$), and FVC (%) (HR = 1.135, 95% CI: 1.012–1.273, $p = 0.031$) were statistically significant factors that showed association with OS. In another multivariate analysis model (Model 2) in which DLCO (%) was entered instead of FVC (%), age (HR = 1.170, 95% CI: 1.013–1.351, $p = 0.032$), and CRP (HR = 1.034, 95% CI: 1.011–1.057, $p = 0.004$) showed significant association with OS. DLCO (%) did not show significant association with OS, as the p-value was 0.077 (Table 4).

Cox regression analysis for PFS was performed. In the univariate analysis, sex, smoking history, number of metastatic sites, and LDH showed a p-value <0.1. In the multivariate analysis, sex (HR 16.892, 95% CI: 1.348–211.7, $p = 0.028$) and LDH (HR 1.001, 95% CI: 1.000–1.002, $p = 0.003$) were statistically significant factors associated with PFS (Table 5).

DISCUSSION

The present study showed that CRP, LDH and FVC (%) were significantly associated with OS and LDH was associated with PFS in patients with ES-SCLC under etoposide-carboplatin-atezolizumab.

IMpower133 study results showed that the combination regimen including atezolizumab showed a comparable safety profile to placebo plus carboplatin + etoposide.[15]

In our study, patients showed an objective response rate of 66.7% which was a little higher than that of Impower 133.[10] Due to the relatively recent introduction of the combination regimen in ES-SCLC, not many biomarkers were evaluated for use. Although use of immunotherapy is based on PD-1/PD-L1 axis, there is no concrete evidence for the use of PD-L1 expression for immunotherapy in SCLC.[16,17] The combination of high tumor mutational burden (TMB) and smoking history showed a predictive value for better response to immunotherapy.[18,19] However, TMB requires a validated cutoff to define high versus low, and platform for testing TMB should be more available for practical use as a biomarker. Inflammatory markers such as lung immune prognostic index (LIPI), NLR and PLR showed a significant association with clinical outcomes in patients with SCLC under conventional chemotherapy which include etoposide-based regimen.[20–22] In the present study, CRP and LDH showed a significant association with OS, and LDH was predictive of PFS. It is expected that LDH has potential predictive value for prognosis since it has been shown as a biomarker predictive of prognosis in SCLC. A meta-analysis suggested significant correlations between elevated serum

TABLE 4 Survival analysis of OS

	Univariate analysis			Multivariate analysis (model 1)[a]			Multivariate analysis (model 2)[a]		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Age	1.072	1.009–1.139	0.024	1.116	0.991–1.256	0.070	1.170	1.013–1.351	0.032
Sex (male/female)	2.128	0.276–16.399	0.469	1.068	0.101–11.253	0.956	2.302	0.213–24.872	0.492
ECOG (0–1/≥2)	0.647	0.082–5.128	0.680						
Smoking history (never vs. ever)	0.470	0.061–3.622	0.469						
Primary mass size	1.160	0.951–1.413	0.142						
Number of metastatic sites (≥2)	2.610	0.984–6.925	0.054	3.494	0.624–19.562	0.155	1.504	0.319–7.091	0.606
NLR	0.979	0.830–1.156	0.806						
PLR	0.998	0.994–1.002	0.259						
Derived NLR	0.946	0.764–1.171	0.609						
LDH	1.001	1.000–1.001	0.075	1.001	1.000–1.003	0.036	1.000	0.999–1.001	0.937
CRP	1.006	0.999–1.014	0.095	1.036	1.014–1.059	0.001	1.034	1.011–1.057	0.004
FEV1 (%)	1.018	0.990–1.046	0.210						
FVC (%)	1.055	1.004–1.110	0.036	1.135	1.012–1.273	0.031			
DLCO (%)	1.053	1.010–1.099	0.011				1.060	0.994–1.130	0.077

Abbreviations: CRP, c-reactive protein; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PD, progressive disease; PLR, platelet-lymphocyte ratio; PR, partial response; SD, stable disease.
[a]Model 1 included FVC (%), but not DLCO (%); Model 2 included DLCO (%), but not FVC (%).

TABLE 5 Survival analysis of PFS

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Age	1.017	0.960–1.077	0.568	1.042	0.975–1.113	0.230
Sex (male/female)	8.708	0.902–84.052	0.061	16.892	1.348–211.7	0.028
ECOG (0–1/≥2)	0.034	0.000–19.014	0.295			
Smoking history (never vs. ever)	0.115	0.012–1.109	0.061	N/A	N/A	N/A[a]
Primary mass size	1.149	0.951–1.386	0.149			
Number of metastatic sites (≥2)	2.248	0.952–5.305	0.065	2.312	0.929–5.754	0.072
NLR	0.955	0.815–1.119	0.568			
PLR	1.000	0.996–1.004	0.940			
Derived NLR	0.894	0.716–1.115	0.319			
LDH	1.001	1.000–1.001	0.009	1.001	1.000–1.002	0.003
CRP	1.005	0.998–1.012	0.177			
FEV1 (%)	1.004	0.974–1.035	0.801			
FVC (%)	0.994	0.959–1.029	0.723			

Abbreviations: CRP, c-reactive protein; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio; PD, progressive disease; PFS, progression-free survival; PLR, platelet-lymphocyte ratio; PR, partial response; SD, stable disease.
[a]Statistical significance regarding smoking history could not be calculated because all patients enrolled in the multivariate analysis were smokers.

LDH and overall survival in patients with SCLC.[23] A study by Lee et al., in which 68 patients with ES-SCLC under EC-A combination treatment were included, showed that baseline bone metastasis, IrAEs, and elevated LDH were associated with OS.[24] A question arises if the factors have predictability for platinum-based regimen or atezolizumab components. A larger study population is necessary to validate the predictive values of LDH and CRP, and to find other biomarkers for clinical outcomes.

In the analysis for association with OS, FVC (%) was also a significant factor. Decreased FVC has previously been associated with poor prognosis patients with underlying cardiovascular diseases.[25,26] In a study of Korean female lung cancer patients, decreased FVC (%) was an independent predictor for poor OS in non-small cell lung cancer.[27] In another multicenter retrospective study, decreased FVC was independently associated with poor OS in both all stage SCLC and ES-SCLC patients.[28] In patients with both lung cancer and pre-existing interstitial lung disease (ILD), lower FVC (%) was determined to be a risk factor for severe events of ILD acute exacerbation.[29] In our study, all but one patient were smokers, and showed high number of pack years. We assumed that many of the patients would have concurrent chronic lung disease, and it would be relevant to FVC (%) having a significant association with OS in the study populations. It would also require further validation process to confirm potential predictive value of lung function parameters such as FVC (%) in terms of impact of concurrent lung diseases.

In survival analyses for OS, DLCO (%) was significant in the univariate analysis for, but did not show, statistical significance in multivariate analysis. DLCO (%) reflects the severity of lung emphysema,[30] and is associated with poor exercise capacity and prognosis in lung cancer patients.[31,32] Considering that *p*-value of DLCO (%) was 0.077 in the multivariate analysis, and the number of study patients was small, it is necessary to re-evaluate the predictive value of DLCO in ES-SCLC patients under combination treatment in larger study populations.

Prevalence of adverse events during the induction phase was 87.5% in which hematological abnormalities were the most frequent. During the maintenance phase, any grade irAEs were prevalent in 36.0%. This result is similar to that of IMpower 133, and Lee et al., in which any grade treatment-related adverse events was 89.7% and 32.4% patients experienced irAEs.[10,24] In the present study, there was a variety of irAEs which included thyroid disorder, pancreatitis, hepatitis, acute kidney injury, etc. IrAEs show different manifestations when compared to AEs during the induction phase, and clinicians should be aware of the diverse clinical signs related to irAEs.

There are several limitations in this study. First, this was a retrospective study with a relatively small number of patients enrolled. Out of 41 patients, 34 patients were available for OS and PFS analysis. Despite the short time of enrolments, seven centers participated in the study. Second, we also included two patients who had previously been treated with other chemotherapy regimens, and this could have affected the results of our study.

In conclusion, we evaluated the efficacy and safety profile of EC-A in ES-SCLC in our study. The response rate was 66.7% and adverse events which occurred in the induction phase were 87.5%, and comparable to previous studies. In addition, LDH and CRP showed a significant association with OS, and LDH was further predictive of PFS in patients under an atezolizumab-etoposide-carboplatin combination regimen.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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