Immunotherapy retreatment with serplulimab vs. chemotherapy in extensive-stage advanced small cell lung cancer

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Abstract. The present study compared the effectiveness and safety of immunotherapy retreatment with serplulimab vs. chemotherapy in extensive-stage small cell lung cancer (ES-SCLC). This real-world retrospective cohort study included patients with ES-SCLC who experienced failed first-line immunotherapy and received second-line immunotherapy retreatment (serplulimab) or chemotherapy. There were 67 and 93 patients in the serplulimab and chemotherapy groups, respectively. Progression-free survival (PFS) time was prolonged with the administration of serplulimab compared with chemotherapy [median, 7.65 vs. 5.25 months; hazard ratio (HR), 0.601; 95% confidence interval (CI), 0.426-0.848; P=0.003]; the results were similar after confounder adjustment in the multivariable Cox regression analysis (HR, 0.572; 95% CI, 0.395-0.828; P=0.003). The median overall survival (OS) time was 15.56 vs. 13.48 months (HR, 0.680; 95% CI, 0.478-0.966; P=0.031). Multivariable Cox regression analysis showed that serplulimab was also an independent protective factor for OS compared with chemotherapy (HR, 0.158; 95% CI, 0.096-0.261; P<0.001). The incidence of grade ≥3 adverse events was 29.9 and 34.4% with serplulimab and chemotherapy, respectively (P=0.760). In conclusion, immunotherapy retreatment with serplulimab is associated with prolonged PFS and OS times compared with chemotherapy in ES-SCLC, with a similar safety profile.

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Introduction

Lung cancer is the leading cause of death due to cancer in China, accounting for 828,000 new cases and 657,000 deaths annually. Small cell lung cancer (SCLC) is highly malignant and accounts for 15-20% of all lung cancer cases (1-3). Overall, 60-70% of patients with SCLC are in the advanced stages at diagnosis and have already lost the opportunity for radical surgery (4). The standard first-line doublet chemotherapy (etoposide plus cisplatin) results in a relatively dismal overall survival (OS) time of only 6.5-10.3 months in advanced extensive-stage SCLC (ES-SCLC), with a high rate of grade >3 adverse events (AEs) (1,4-9). As first-line treatment, immune checkpoint inhibitors (ICIs) plus chemotherapy have increased the OS time to 12-13 months. However, progressive disease may occur in the short term after first-line immunotherapy, with a progression-free survival (PFS) time of 4-5 months (4,10,11). When first-line treatment for patients with ES-SCLC fails, second-line chemotherapy is generally used, but the efficacy is often limited (4,12). Although topotecan and lurbinectedin provide treatment options, the OS time of patients with ES-SCLC receiving second-line treatment remains poor at only 6-9 months (4,13,14). Therefore, more effective second-line treatment options are needed to improve the prognosis of patients with ES-SCLC who failed first-line standard treatment.

Notably, ICI retreatment is an emerging concept for patients who have received first-line immunotherapy (15). In the context of the present study, 'immunotherapy retreatment' specifically refers to the administration of a second-line ICI with a distinct mechanism of action [such as switching from a programmed cell death 1 ligand 1 (PD-L1) inhibitor to a programmed cell death protein 1 (PD-1) inhibitor] after progression on first-line ICI therapy. Preclinical studies have suggested that the resistance to PD-L1 inhibitors could be related to the loss of JAK1/2 function or the downregulation of interferon-γ, and that retreatment with a second-line PD-1 inhibitor might circumvent the acquired resistance (16,17). To elaborate, ICIs exert their antitumor effects by blocking

inhibitory pathways that suppress T-cell activity (18,19). PD-1 is an inhibitory receptor expressed on activated T cells, while its primary ligand, PD-L1, is often expressed on tumor cells or other cells within the tumor microenvironment (20,21). PD-1 inhibitors (such as serplulimab) directly target the PD-1 receptor on T cells, preventing its interaction with both PD-L1 and PD-L2 (22). By contrast, PD-L1 inhibitors (such as atezolizumab or durvalumab) specifically block PD-L1 on tumor cells, preventing its binding to PD-1 (23). Although both strategies aim to disinhibit T-cell function, their distinct binding targets offer a mechanistic rationale for sequential therapy (16,17). A case report suggested that PD-1 inhibitors had good therapeutic effects in a patient with hepatocellular carcinoma who progressed after PD-L1 inhibitors (24). A retrospective study showed that patients with SCLC progressing after first-line immunotherapy could benefit from second-line immunotherapy (>6 weeks) and achieve median PFS and OS times of 4.8 and 17.4 months, respectively (25). Hence, ICI retreatment with PD-1 inhibitors might be a promising treatment strategy for patients with ES-SCLC who have experienced failed standard first-line immunotherapy with PD-L1 inhibitors (such as atezolizumab or durvalumab).

Serplulimab is a humanized anti-PD-1 IgG4 monoclonal antibody that can enhance the functional activity of human T cells (26). The ASTRUM-005 study demonstrated that additional serplulimab significantly prolonged the PFS and OS times of patients with ES-SCLC when compared with chemotherapy alone (27). A network meta-analysis also suggested the advantage of first-line serplulimab treatment for ES-SCLC over other regimens (28). Nevertheless, the effectiveness of second-line serplulimab treatment for ES-SCLC, especially after the failure of first-line immunotherapy, remains unknown.

Therefore, the objective of the present real-world retrospective cohort study was to examine the effectiveness of immunotherapy retreatment with serplulimab vs. chemotherapy in patients with ES-SCLC who were previously treated with first-line immunotherapy. The study responds to the urgent need for an effective second-line treatment for ES-SCLC, considering the potential of ICI retreatment.

Patients and methods

Study design and patients. In the present real-world retrospective cohort study, data was collected from patients with ES-SCLC who did not respond to first-line immunotherapy and were treated at Shandong Cancer Hospital and Institute (Jinan, China) between January 31, 2019, and May 1, 2023.

The inclusion criteria were as follows: i) ≥18 years of age; ii) histologically or cytologically confirmed stage IV ES-SCLC (4); iii) previously treated with standard first-line immunotherapy (such as atezolizumab or durvalumab) combined with chemotherapy; and iv) second-line treatment with serplulimab or chemotherapy. Consistent with the aforementioned definition, patients in the serplulimab group received immunotherapy retreatment by switching from a first-line PD-L1 inhibitor to the PD-1 inhibitor serplulimab. Patients with incomplete data on effectiveness or who died within 2 months from the start of second-line treatment were excluded. The cut-off of 2 months was selected as it represented the median time to response for immunotherapy and the first routine response evaluation, which was conducted 2 months after the initial dose of treatment (29).

Treatment. The patients were grouped into the serplulimab and chemotherapy groups according to the second-line treatment they received. The routine serplulimab treatment was an intravenous infusion of 4.5 mg/kg of serplulimab every 3 weeks. The chemotherapy regimens were chosen by the physicians based on the specific situation of the patients. Other treatment options, such as anti-angiogenesis drugs, radiotherapy and combining serplulimab with chemotherapy, were all at the discretion of the physicians.

Data collection. The baseline characteristics of the patients were collected from their medical records, including demographic characteristics at the diagnosis of advanced ES-SCLC, the first-line immunotherapy regimen, the PFS time for the first-line immunotherapy and the reasons for discontinuation of first-line immunotherapy. The reasons for discontinuing first-line immunotherapy were divided into AEs and primary and secondary resistance (30).

Outcome. The outcomes of the present study included the PFS time, objective response rate (ORR) and disease control rate (DCR) of the second-line treatment. PFS time was calculated from the start of second-line treatment to progressive disease or death from any cause, whichever occurred first. OS time was measured from the start of second-line treatment to death from any cause. ORR was the proportion of patients with a complete response (CR) or partial response (PR), and DCR was the proportion of patients with a CR, PR or stable disease. The response to treatment was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1 criteria (31). The metastatic sites of the patients who progressed after second-line treatment were recorded.

A combination of AEs, immune-related AEs (irAEs) and irAEs requiring systemic glucocorticoid treatment were collected. The severity of AEs was graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0 (32). The second-line treatment pattern was recorded, including a combination of other systemic therapy and radiotherapy.

Statistical analysis. The continuous data were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as the mean ± standard deviation and were analyzed using unpaired Student's t-test; otherwise, the data are presented as the median and interquartile ranges (IQR) and were analyzed using the Mann-Whitney U-test. The categorical data are represented as n (%), and the groups were compared using the χ^2 test when the expected frequency in each category was ≥5; otherwise, Fisher's exact test was used. The median PFS and OS, and the 95% confidence interval (CI), were evaluated using the Kaplan-Meier method. The comparison of PFS and OS between groups was performed using the log-rank test, and the hazard ratio (HR) was calculated using Cox regression. The multivariable Cox regression model was used to analyze the factors associated with the PFS and OS of the second-line

treatment. The variables with P<0.10 in the univariable analysis were included in the multivariable analysis. Two-sided P<0.05 was considered to indicate a statistically significant difference. The statistical analysis software was R 4.2.3 (The R Project for Statistical Computing; www.r-project.org).

Results

Characteristics of the participants. The present study included 160 patients with ES-SCLC who failed first-line immunotherapy, and included 67 treated with serplulimab and 93 treated with chemotherapy as second-line treatment. Most patients (n=148; 92.5%) discontinued first-line immunotherapy due to secondary resistance, while primary resistance and adverse events were the reasons in 5 (3.1%) and 7 (4.4%) patients, respectively.

Table I shows that age, sex distribution, Karnofsky performance status scores and Eastern Cooperative Oncology Group Performance Status scores were similar between the two groups (all P>0.05) (33,34). Compared with the chemotherapy group, the serplulimab showed a higher proportion of smokers (53.7 vs. 28.0%; P=0.001) and a lower frequency of radiotherapy in the first-line treatment (38.8 vs. 64.5%; P=0.001). Notably, the first-line immunotherapy regimen (P=0.391), reasons for discontinuation of first-line immunotherapy (P>0.999) and median PFS of the first-line treatment (8.40 vs. 8.82 months; P=0.531) were similar between the two groups.

Treatment patterns. In the serplulimab group, serplulimab was administered as monotherapy in 4 patients (6.0%), combined with chemotherapy in 35 patients (52.2%), combined with anti-angiogenesis drugs plus chemotherapy in 20 patients (29.9%) or combined with anti-angiogenesis drugs in 8 patients (11.9%). In the chemotherapy group, chemotherapy was administered as monotherapy in the majority of the patients (n=69; 74.2%) and combined with anti-angiogenesis drugs in 24 patients (25.8%) (Table SI).

In the serplulimab group, the combined chemotherapy regimens involved etoposide plus cisplatin (n=31; 46.3%), nab-paclitaxel (n=16; 23.9%) and etoposide plus carboplatin (n=8; 11.9%). Similarly, in the chemotherapy group, the most commonly used regimen was also etoposide plus cisplatin (n=55; 59.1%), followed by nab-paclitaxel (n=25; 26.9%), and etoposide plus carboplatin (n=13; 14.0%). The anti-angiogenesis drugs in this study were all anlotinib (Table SI).

Compared with the chemotherapy group, the serplulimab group showed significantly higher use of anti-angiogenesis drugs (41.8 vs. 25.8%; P=0.033) and radiotherapy (16.4 vs. 6.5%; P=0.044). There were no differences in the timing of radiotherapy between the two groups (synchronous: 27.3 vs. 33.3%; P>0.999). Specifically, 4 and 3 patients received prophylactic cranial irradiation as part of their treatment regimen in the two groups, respectively (Table SI).

Effectiveness. Table II presents the responses to treatments. There were no statistical differences in ORR (53.7 vs. 40.9%; P=0.107) and DCR (100 vs. 100%; P=1.000) between the two groups. The median follow-up time was 21.28 months (range, 5.44-34.62 months) in the overall population, 22.7 months (range, 7.45-34.40 months) in the serplulimab group and 20.66 months (range, 5.44-34.62 months) in the chemotherapy group (data not shown). As shown in Fig. 1A, the median PFS time was significantly longer with serplulimab (7.65 months; 95% CI, 7.20-8.62) compared with chemotherapy (5.25 months; 95% CI, 4.92-5.74) (HR, 0.601; 95% CI, 0.426-0.848; P=0.003). As shown in Fig. 2A, the serplulimab group also had a longer median OS time of 15.56 months (95% CI, 14.13-17.12) than the chemotherapy group (13.48 months; 95% CI, 12.84-14.40) (HR, 0.680; 95% CI, 0.478-0.966; P=0.031).

After second-line treatment, the proportion of patients developing metastases was comparable in the serplulimab group to that in the chemotherapy group (67.1 vs. 73.2%; P=0.415). There were no significant differences in the development of the brain (41.8 vs. 45.2%; P=0.672), liver (38.8 vs. 36.6%; P=0.772), lung (13.4 vs. 17.2%; P=0.517), or adrenal gland (10.4 vs. 9.7%; P=0.873) metastases, but the serplulimab group showed a lower frequency of bone metastases (25.4 vs. 50.5%; P=0.001) (Fig. 3).

Subgroup analysis and risk factor of PFS and OS. Similar to the results in the total population, in the patients with secondary resistance to first-line immunotherapy, serplulimab achieved significantly longer median PFS (7.78 vs. 5.28 months; HR, 0.634; 95% CI, 0.445-0.904; P=0.012; Fig. 1B) and OS (15.58 vs. 13.53 months; HR, 0.691; 95% CI, 0.480-0.994; P=0.046; Fig. 2B) times compared with chemotherapy. In other subgroup analyses for PFS, (Fig. 1B), compared with the chemotherapy group, serplulimab provided significantly superior benefits in patients aged ≤65 years (P=0.027), males (P=0.018), females (P=0.015), non-smokers (P=0.017), those who received first-line atezolizumab (P<0.001), patients with secondary resistance (P=0.012), and those with a first-line PFS ≤8.62 months (P=0.006). Notably, serplulimab also demonstrated a significant PFS advantage over chemotherapy in patients with brain metastases (P=0.018) or liver metastases (P=0.001) during second-line treatment. For other subgroups, including patients aged >65 years, those with ECOG PS 0 or 1, and those with first-line radiotherapy, serplulimab showed an improved PFS, although these results did not reach statistical significance compared with the chemotherapy group (all P>0.05). For OS (Fig. 2B), serplulimab achieved significantly better outcomes than chemotherapy in male patients (P=0.014), smokers (P=0.020), patients with ECOG PS 0 (P=0.038) and those with secondary resistance (P=0.046). Similarly, compared with chemotherapy, serplulimab significantly prolonged OS in patients with a first-line PFS ≤8.62 months (P <0.001), as well as in those with brain metastases (P=0.023) or liver metastases (P=0.014) during second-line treatment. In the remaining subgroups, serplulimab showed a trend of OS benefit, but the differences compared with the chemotherapy group were not statistically significant (all P>0.05).

In addition, the different second-line treatment patterns among the serplulimab and chemotherapy groups separately did not impact the PFS (log-rank P=0.358 and 0.480, respectively; Fig. S1A and B) or the OS (log-rank P=0.222 and 0.793, respectively; Fig. S2A and B). In the subgroup analysis (Fig. S1C), serplulimab combined with anti-angiogenesis treatment showed a longer median PFS time (8.21 months; 95% CI, 6.80-9.72) compared with serplulimab alone or chemotherapy with/without anti-angiogenesis drugs

Table I. Baseline characteristics.

Patient characteristics	Total (n=160)	Serplulimab (n=67)	Chemotherapy (n=93)	P-value
Mean age ± SD, years	60.98±8.56	60.10±8.65	61.61±8.49	0.273
Sex, n (%)				0.195
Male	125 (78.1)	49 (73.1)	76 (81.7)	
Female	35 (21.9)	18 (26.9)	17 (18.3)	
KPS score, n (%)				0.058
70	7 (4.4)	0 (0.0)	7 (7.5)	
80	79 (49.4)	34 (50.7)	45 (48.4)	
90	73 (45.6)	32 (47.8)	41 (44.1)	
100	1 (0.6)	1 (1.5)	0 (0.0)	
ECOG PS, n (%)				0.248
0	109 (68.1)	49 (73.1)	60 (64.5)	
1	51 (31.9)	18 (26.9)	33 (35.5)	
Smoking history, n (%)				0.001[a]
Smoking	62 (38.8)	36 (53.7)	26 (28.0)	
No smoking	98 (61.3)	31 (46.3)	67 (72.0)	
First-line immunotherapy regimen, n (%)				0.391
Durvalumab	94 (58.8)	42 (62.7)	52 (55.9)	
Atezolizumab	66 (41.3)	25 (37.3)	41 (44.1)	
Combined chemotherapy regimen with first-line immunotherapy, n (%)				0.680
Etoposide plus cisplatin	115 (71.9)	47 (70.1)	68 (73.1)	
Etoposide plus carboplatin	45 (28.1)	20 (29.9)	25 (26.9)	
Received radiotherapy in first-line treatment, n (%)	86 (53.8)	26 (38.8)	60 (64.5)	0.001[a]
Timing of radiotherapy, n (%)[b]				
Before systemic treatment	16 (10.0)	10 (14.9)	6 (6.5)	0.078
After systemic treatment	20 (12.5)	8 (11.9)	12 (12.9)	0.856
Synchronous	50 (31.3)	8 (11.9)	42 (45.2)	<0.001[a]
PFS of first-line treatment[c]	8.62 (7.87-9.33)	8.40 (7.56-9.45)	8.82 (7.80-9.80)	0.531[d]
Reasons for discontinuation of first-line treatment, n (%)				>0.999
Secondary resistance	148 (92.5)	62 (92.5)	86 (92.5)	
Primary resistance	5 (3.1)	2 (3.0)	3 (3.2)	
AEs	7 (4.4)	3 (4.5)	4 (4.3)	
Second-line treatment pattern, n (%)				
Serplulimab group				
Monotherapy	-	4 (6.0)	-	
Combined with chemotherapy	-	35 (52.2)	-	
Combined with anlotinib and chemotherapy	-	20 (29.9)	-	
Combined with anlotinib	-	8 (11.9)	-	
Chemotherapy group, n (%)				
Monotherapy	-	-	69 (74.2)	
Combined with anlotinib	-	-	24 (25.8)	

[a]P<0.05. [b]n=86. [c]Data are presented as median (95% confidence interval). [d]Log-rank test. All other P-values were calculated using the χ^2 test or Fisher's exact test for categorical variables, and unpaired t-test or Mann-Whitney U test for continuous variables. -, not applicable; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group Performance Status; KPS, Karnofsky performance status; PFS, progression-free survival; AE, adverse event.

Table II. Tumor response.

Best response, n (%)	Total (n=160)	Serplulimab (n=67)	Chemotherapy (n=93)	P-value
CR	0 (0.0)	0 (0.0)	0 (0.0)	-
PR	74 (46.3)	36 (53.7)	38 (40.9)	-
SD	86 (53.8)	31 (46.3)	55 (59.1)	-
PD	0 (0.0)	0 (0.0)	0 (0.0)	-
ORR (CR + PR)	74 (46.3)	36 (53.7)	38 (40.9)	0.107
DCR (CR + PR + SD)	160 (100.0)	67 (100.0)	93 (100.0)	1.000

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

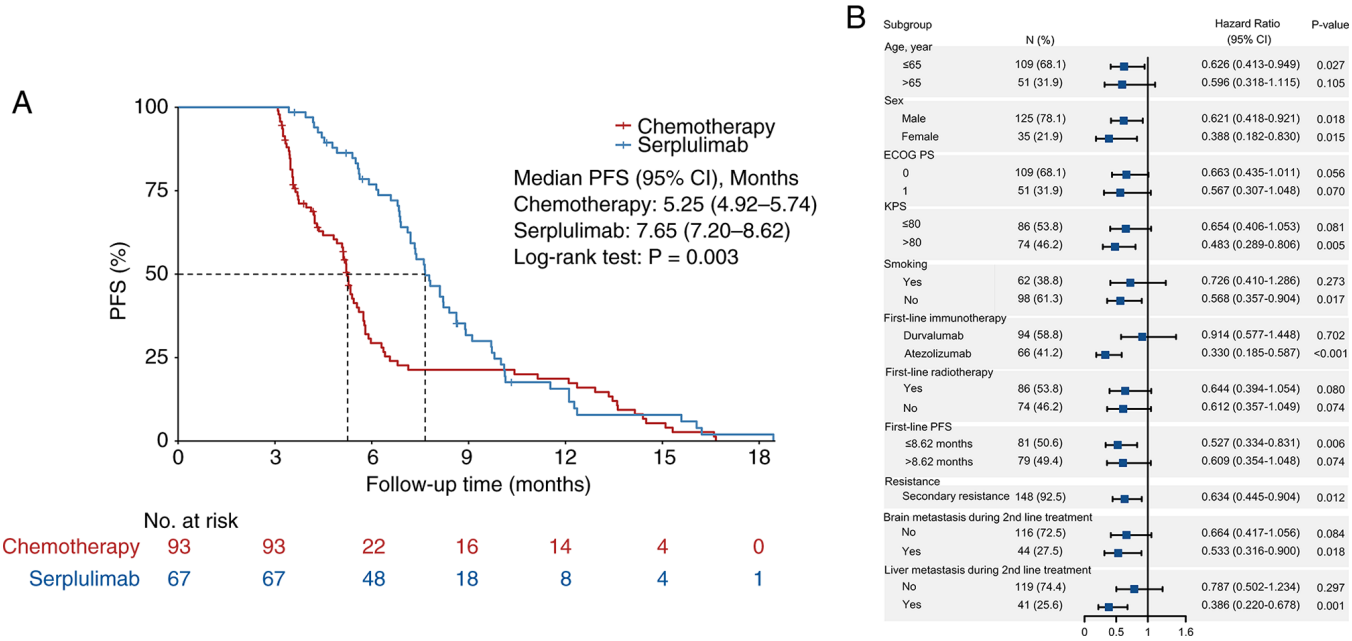

Figure 1. PFS analysis. (A) Total population. (B) Subgroup analyses. PFS, progression-free survival; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; KPS, Karnofsky performance status.

(P=0.021). Serplulimab combined with radiotherapy was also associated with a longer median PFS time (8.89 months; 95% CI, 7.2-NA) compared with serplulimab alone or chemotherapy with/without radiotherapy (P=0.004) (Fig. S1D). However, these subgroups showed no statistically significant difference in terms of OS (log-rank P=0.127 and 0.087, respectively; Fig. S2C and D).

Tables III and IV show the univariable and multivariable analysis of the factors associated with the PFS and OS, respectively. In the multivariable analysis, second-line serplulimab was independently associated with a higher PFS time after adjusting for other confounding factors (HR, 0.572; 95% CI, 0.395-0.828; P=0.003). Additionally, a longer PFS time after first-line treatment was identified as a significant independent predictor for better second-line PFS (HR, 0.921; 95% CI, 0.867-0.978; P=0.007). Similarly, second-line serplulimab was also independently associated with a higher OS time (HR, 0.158; 95% CI, 0.096-0.261; P<0.001). Furthermore, the reason for discontinuation of first-line treatment was significantly associated with OS; specifically, patients with primary resistance to first-line therapy exhibited a significantly higher risk of death compared to those without (HR, 4.338; 95% CI, 1.422-13.232; P=0.010).

Safety. The incidence of AEs of any grade and grade ≥3 in the serplulimab group was 74.6% (n=50) and 29.9% (n=20), respectively, which was 81.7% (n=76) and 34.4% (n=32) with chemotherapy. The occurrence of any irAEs was reported in 17.9% (n=12) of the patients with serplulimab, and 9 were treated with systemic glucocorticoid. The most common hematological toxicities with serplulimab were thrombocytopenia (35.8%), leukopenia (31.3%) and anemia (28.4%), while non-hematological toxicities were mostly drug-induced liver injury (23.9%), loss of appetite (19.4%) and immune-associated pneumonia (17.9%). In the chemotherapy group, the most common AEs were hematological toxicities, including leukopenia (41.9%), thrombocytopenia (36.6%), anemia (36.6%), and neutropenia (30.1%), as listed in Table V.

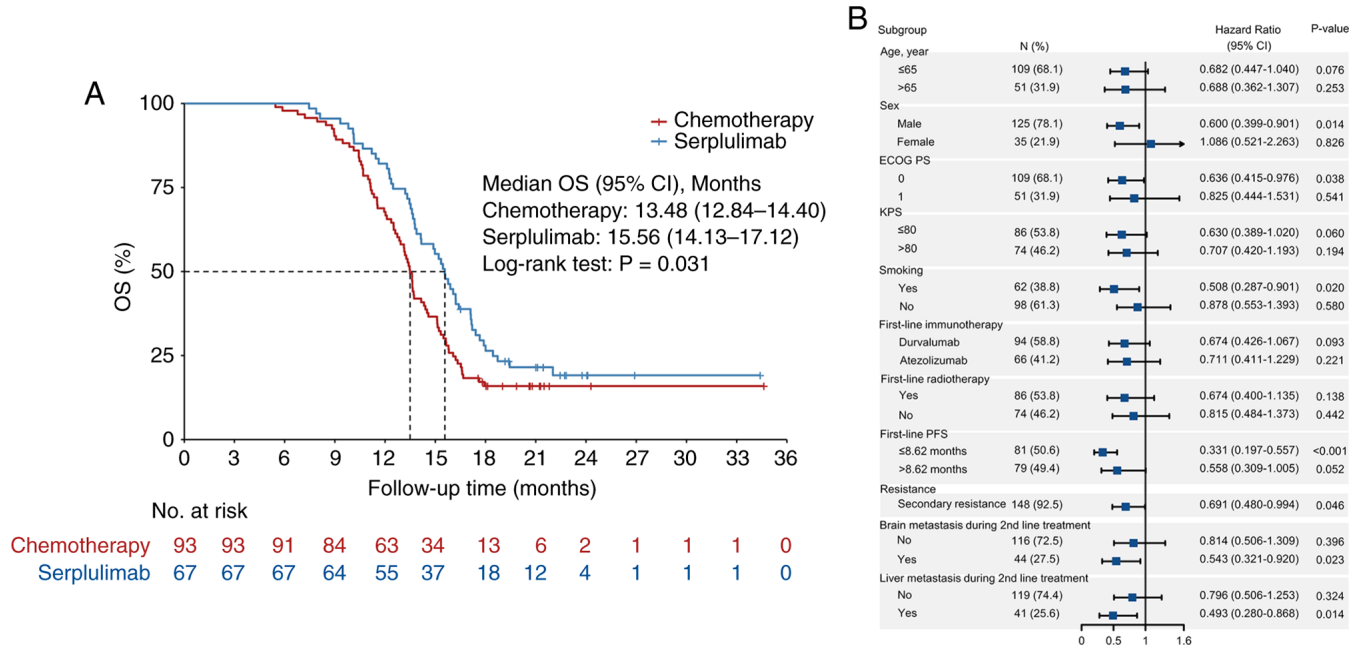

Figure 2. OS analysis. (A) Total population. (B) Subgroup analyses. OS, overall survival; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; KPS, Karnofsky performance status.

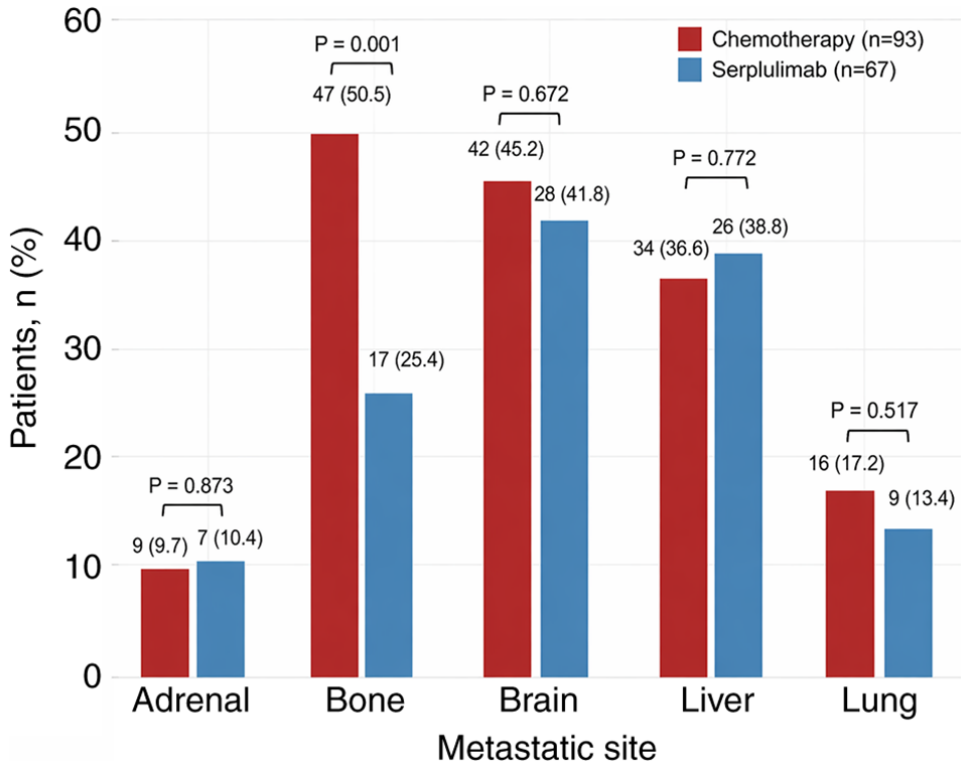

Figure 3. Progression pattern during second-line treatment.

Discussion

The present study compared the real-world effectiveness of immunotherapy retreatment with serplulimab vs. chemotherapy in patients with ES-SCLC after failure of first-line immunotherapy. The findings suggested that second-line serplulimab can significantly prolong the PFS time compared with chemotherapy in patients with ES-SCLC previously treated with first-line immunotherapy, regardless of the first-line immunotherapy regimen or the duration of PFS for first-line immunotherapy. This study may provide evidence for the feasibility of immunotherapy retreatment by switching to a PD-1 inhibitor after failure of a first-line PD-L1 inhibitor.

Table III. Risk factors of PFS.

	Univariable analysis		Multivariable analysis	
Patient characteristics	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.003 (0.983-1.023)	0.795		
Sex				
Male	Reference			
Female	1.173 (0.784-1.753)	0.438		
KPS score				
≤80	Reference			
>80	1.287 (0.919-1.801)	0.142		
ECOG PS				
0	Reference			
1	1.288 (0.903-1.837)	0.162		
Smoking history				
No smoking	Reference			
Smoking	0.827 (0.587-1.167)	0.280		
First-line immunotherapy regimen				
Durvalumab	Reference			
Atezolizumab	1.172 (0.834-1.646)	0.361		
Radiotherapy in first-line treatment				
No	Reference		Reference	
Yes	1.361 (0.973-1.903)	0.072	1.090 (0.762-1.560)	0.638
Reasons for discontinuation of first-line treatment				
Secondary resistance	Reference		Reference	
Primary resistance	3.210 (1.298-7.937)	0.012	2.387 (0.901-6.320)	0.080
AEs	1.424 (0.523-3.878)	0.489	2.128 (0.754-6.000)	0.153
Second-line treatment				
Chemotherapy	Reference		Reference	
Serplulimab	0.601 (0.426-0.848)	0.003	0.572 (0.395-0.828)	0.003
Second-line treatment with anti-angiogenesis drugs				
No	Reference			
Yes	0.921 (0.648-1.309)	0.646		
Second-line treatment with chemotherapy				
No	Reference			
Yes	1.101 (0.661-1.835)	0.711		
PFS of first-line treatment	0.922 (0.872-0.974)	0.004	0.921 (0.867-0.978)	0.007
PFS of first-line treatment, months				
≤8.62	Reference			
>8.62	0.746 (0.530-1.051)	0.094		
Brain metastasis during second-line treatment				
No	Reference		Reference	
Yes	1.399 (1.001-1.956)	0.050	1.350 (0.962-1.895)	0.083
Liver metastasis during second-line treatment				
No	Reference			
Yes	1.318 (0.937-1.854)	0.113		

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance status; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PFS, progression-free survival; AE, adverse event.

Table IV. Risk factors of overall survival.

	Univariable analysis		Multivariable analysis	
Patient characteristics	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.014 (0.994-1.034)	0.184		
Sex				
Male	Reference			
Female	0.944 (0.624-1.427)	0.784		
KPS score				
≤80	Reference			
>80	0.938 (0.664-1.324)	0.715		
ECOG PS				
0	Reference			
1	1.282 (0.891-1.845)	0.181		
Smoking history				
No smoking	Reference			
Smoking	0.824 (0.578-1.175)	0.285		
First-line immunotherapy regimen				
Durvalumab	Reference			
Atezolizumab	1.108 (0.783-1.569)	0.561		
Radiotherapy in first-line treatment				
No	Reference		Reference	
Yes	1.448 (1.025-2.047)	0.036	1.229 (0.813-1.857)	0.328
Reasons for discontinuation of first-line treatment				
Secondary resistance	Reference		Reference	
Primary resistance	24.237 (8.987-65.360)	<0.001	4.338 (1.422-13.232)	0.010
AEs	0.503 (0.185-1.366)	0.178	2.282 (0.806-6.462)	0.120
Second-line treatment				
Chemotherapy	Reference		Reference	
Serplulimab	0.680 (0.478-0.966)	0.031	0.158 (0.096-0.261)	<0.001
Second-line treatment with anti-angiogenesis drugs				
No	Reference			
Yes	0.851 (0.591-1.227)	0.388		
Second-line treatment with chemotherapy				
No	Reference			
Yes	1.195 (0.708-2.017)	0.505		
PFS of first-line treatment	0.619 (0.572-0.670)	<0.001	0.520 (0.472-0.574)	<0.001
PFS of first-line treatment, months				
≤8.62	Reference			
>8.62	0.184 (0.125-0.269)	<0.001		
Brain metastasis during second-line treatment				
No	Reference			
Yes	1.265 (0.897-1.784)	0.181		
Liver metastasis during second-line treatment				
No	Reference			
Yes	1.318 (0.928-1.872)	0.122		

HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance status; PFS, progression-free survival; AE, adverse event.

Table V. AEs.

AE	Total (n=160)	Serplulimab (n=67)	Chemotherapy (n=93)
Any AE	126 (78.8)	50 (74.6)	76 (81.7)
Any ≥grade 3 AE	52 (32.5)	20 (29.9)	32 (34.4)
Any irAE	28 (17.5)	12 (17.9)	16 (17.2)
irAE treated with systemic glucocorticoids	24 (15.0)	9 (13.4)	15 (16.1)
Specific AE			
Leukopenia	60 (37.5)	21 (31.3)	39 (41.9)
Thrombocytopenia	58 (36.2)	24 (35.8)	34 (36.6)
Anemia	53 (33.1)	19 (28.4)	34 (36.6)
Neutropenia	40 (25.0)	12 (17.9)	28 (30.1)
Nausea	33 (20.6)	11 (16.4)	22 (23.7)
Loss of appetite	33 (20.6)	13 (19.4)	20 (21.5)
Drug-induced liver injury	33 (20.6)	16 (23.9)	17 (18.3)
Rash	32 (20.0)	10 (14.9)	22 (23.7)
Immune associated pneumonia	28 (17.5)	12 (17.9)	16 (17.2)
Vomiting	27 (16.9)	10 (14.9)	17 (18.3)
Hypothyroidism	13 (8.1)	8 (11.9)	5 (5.4)
Specific grade ≥3 AE			
Thrombocytopenia	18 (11.2)	9 (13.4)	9 (9.7)
Anemia	17 (10.6)	6 (9.0)	11 (11.8)
Rash	11 (6.9)	3 (4.5)	8 (8.6)
Neutropenia	9 (5.6)	2 (3.0)	7 (7.5)
Leukopenia	9 (5.6)	3 (4.5)	6 (6.5)
Drug-induced liver injury	5 (3.1)	3 (4.5)	2 (2.2)
Nausea	4 (2.5)	3 (4.5)	1 (1.1)
Immune associated pneumonia	4 (2.5)	2 (3.0)	2 (2.2)
Loss of appetite	3 (1.9)	0 (0.0)	3 (3.2)
Vomit	1 (0.6)	0 (0.0)	1 (1.1)
Hypothyroidism	1 (0.6)	0 (0.0)	1 (1.1)

AE, adverse event; irAE, immune-related adverse event.

As a highly malignant disease, ES-SCLC treated with first-line systemic therapy will eventually relapse and require second-line therapy. Second-line chemotherapy is associated with relatively poor survival, with a median PFS time of 4.7 months for carboplatin/etoposide (35). Systematic reviews and meta-analyses revealed a PFS time of 4.5-8.1 months (12,36), similar to the PFS time with chemotherapy reported in the present study (5.25 months). Regarding second-line immunotherapy in general, the KEYNOTE-028 trial reported a median PFS time of 1.9 months with pembrolizumab (37), while the IFCT-1603 trial reported 1.4 months with atezolizumab (38). Furthermore, the exploration of doublet immunotherapy failed to demonstrate benefits in PFS, with a similar median PFS time of 1.4 vs. 1.5 months for nivolumab vs. nivolumab/ipilimumab in the CheckMate 032 trial (39). Indeed, in previous studies of second-line immunotherapy, the median PFS time was numerically short (36-39). Notably, in these studies of second-line chemotherapy or immunotherapy, a relatively small proportion of patients had received first-line immunotherapy. As for immunotherapy retreatment, a previous retrospective study reported that for patients with ES-SCLC with progression after first-line immunotherapy, the median PFS time of patients given second-line immunotherapy for <6 weeks was 2.8 months, while the median PFS time of those receiving >6 weeks of treatment could reach 4.8 months (25), highlighting the potential of immunotherapy retreatment. Nevertheless, the second-line immunotherapy in the aforementioned studies included both PD-1 and PD-L1 inhibitors, and none examined serplulimab in that context.

The ASTRUM-005 study demonstrated that first-line serplulimab improved the PFS and OS outcomes of patients with previously untreated ES-SCLC compared with chemotherapy alone (27). On the other hand, caution has been raised regarding the conclusions of the ASTRUM-005 trial (40), suggesting the need for real-world data. Indeed, in ASTRUM-005, the control intervention was not the standard therapy used nowadays; the trial enrolled exclusively Eastern European and Asian patients and 20% of the participants were non-smokers. Therefore, the results of the ASTRUM-005 trial might be taken with caution and need to be confirmed by additional studies. For instance, the high proportion of non-smokers might be a potential limitation to the conclusions in the ASTRUM-005 study (40), as

non-smokers with SCLC might have better efficacy outcomes. Although the proportion of non-smokers was smaller in the serplulimab group in the present study, the results suggest a better efficacy of serplulimab compared with chemotherapy alone. A Bayesian meta-analysis of 4,352 patients treated with nine regimens suggested that the combination of serplulimab with chemotherapy as first-line therapy should be recommended for patients with ES-SCLC since it achieved the highest probability for better PFS (94.5%) (28). Although such results highlight the clinical value of serplulimab, the present study examined the clinical value of challenging patients with ES-SCLC with a PD-1 inhibitor after failure of a PD-L1 inhibitor. In the present study, although there were no differences in ORR and DCR between immunotherapy retreatment with serplulimab and chemotherapy in second-line treatment, PFS and OS were significantly prolonged with serplulimab as supported by the results from the multivariable analysis. Nevertheless, as this study was retrospective, large-scale head-to-head studies are needed for validation.

Serplulimab, as an anti-PD-1 drug, targets the PD-1 receptor directly on T cells, whereas atezolizumab or durvalumab target the PD-L1 ligand (10,17). This difference in binding targets offers several potential explanations for the observed efficacy of PD-1 inhibitors after PD-L1 blockade failure. First is the circumvention of PD-L1-specific resistance mechanisms: Resistance to anti-PD-L1 agents can arise from various mechanisms, including downregulation or structural alterations of PD-L1 on tumor cells, which may reduce the binding affinity of PD-L1 inhibitors (16,41). In such scenarios, directly blocking the PD-1 receptor on T cells with a PD-1 inhibitor such as serplulimab can bypass these PD-L1-specific resistance mechanisms, as it can still effectively block the interaction of PD-1 with any remaining PD-L1 or other ligands such as PD-L2 (42). Second are the dynamic changes in the tumor microenvironment: The tumor microenvironment is highly dynamic (43,44), and the initial PD-L1 blockade may induce adaptive changes that, while leading to resistance to the initial agent, could render the tumor more susceptible to subsequent PD-1 blockade (45). For instance, the initial therapy may alter the immune cell composition or cytokine milieu, creating a more favorable environment for PD-1 inhibitor activity. Finally is the re-invigoration of exhausted T cells: Even if resistance to PD-L1 inhibitors develops, T cells may still exhibit PD-1-mediated exhaustion (46). Direct PD-1 blockade can re-invigorate these exhausted T cells, restoring their cytotoxic potential and antitumor activity (47). Therefore, targeting the receptor instead of solely the ligands represents a valid and mechanistically sound strategy to improve survival in patients who have progressed on PD-L1 inhibitors.

The subgroup analysis of the secondary resistance population in the present study indicated that serplulimab can still be an effective choice for second-line treatment when patients benefit from first-line immunotherapy. In addition, the PFS time with first-line therapy is also considered an important prognostic factor for the second-line PFS time (12,48). Most patients in the serplulimab group in the present study were simultaneously treated with anti-angiogenesis targeted drugs, chemotherapy or radiotherapy, and the combination of these treatment modalities may affect the tumor microenvironment of the patients (49), allowing immunotherapy to exert antitumor effects once again. Nevertheless, due to the sample size in this study, the number of subgroups of patients with different combination therapies was relatively small, and further research is needed to determine the optimal combination treatment strategies. In addition, only a small proportion of patients stopped first-line immunotherapy due to primary resistance or AEs. The effectiveness of serplulimab in patients' primary resistance or intolerance to first-line immunotherapy needs to be verified in future studies.

In the present study, the rates of any grade and grade ≥3 AEs in the serplulimab and chemotherapy groups were similar, which may be related to the combined chemotherapy for most patients in the serplulimab group. In this study, no new safety signals were found for serplulimab treatment. Of note was that it was a real-world study, and no formal active monitoring of AEs was performed, as in clinical trials. The present study collected AE data from the medical record, which can lead to underreporting.

Although a multivariable Cox regression analysis was performed to adjust for potential confounders, including smoking history, first-line radiotherapy and concomitant use of anti-angiogenic agents, the retrospective nature of this study precludes complete elimination of selection bias. Several baseline characteristics differed significantly between the serplulimab and chemotherapy groups. Notably, the serplulimab group had a higher proportion of smokers (53.7 vs. 28.0%; P=0.001) and a lower frequency of first-line radiotherapy (38.8 vs. 64.5%; P=0.001). Smoking status is a known prognostic factor in SCLC and may also influence the efficacy of immunotherapy, potentially biasing the observed PFS and OS benefit in favor of serplulimab (50). Conversely, the lower use of first-line radiotherapy in the serplulimab group may have placed these patients at a disadvantage, as radiotherapy can synergize with immunotherapy by modulating the tumor microenvironment (51). The direction and magnitude of these opposing biases are difficult to quantify. Additionally, the use of anti-angiogenic agents (anlotinib) was more frequent in the serplulimab group (41.8 vs. 25.8%; P=0.033), which may have contributed to the observed survival benefits independent of serplulimab. While the multivariable analysis adjusted for these factors, residual confounding from unmeasured variables (such as tumor mutational burden, PD-L1 expression levels and detailed smoking pack-years) cannot be excluded. Therefore, prospective studies with balanced treatment arms are warranted to confirm the superiority of serplulimab retreatment over chemotherapy.

There were limitations to the present study. Tumor assessments and follow-ups are not as strict and regular in real life as in randomized controlled trials. Therefore, the duration of the response could not be accurately evaluated. The treatment pattern in the serplulimab group was complex, including various chemotherapy combinations or given alone, and the PFS and OS benefits might not be attributed merely to serplulimab, despite the independent association revealed by the multivariable analysis. Future prospective studies are needed to address these issues.

Immunotherapy retreatment with serplulimab can significantly prolong PFS and OS times compared with chemotherapy for patients with ES-SCLC who have been

treated with first-line immunotherapy. As immunotherapy is the standard first-line treatment for ES-SCLC, a feasible treatment strategy may include switching to a PD-1 inhibitor as second-line immunotherapy after first-line PD-L1 inhibitor failure. Further research is needed to validate this hypothesis and identify the patients who would benefit the most from second-line immunotherapy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XG was responsible for conceptualization, methodology, data curation, formal analysis, investigation, writing the original draft and visualization. XW was responsible for conceptualization, methodology, supervision, visualization, writing, reviewing and editing. JG was responsible for conceptualization, methodology and visualization. YW was responsible for conceptualization, methodology, supervision, visualization, writing, reviewing and editing. CL was responsible for conceptualization, methodology, supervision, formal analysis, visualization, writing, reviewing, editing and funding acquisition. XG and CL confirm the authenticity of all the raw data. All authors have made substantial intellectual contributions to the conception, design, and execution of this study. Each author has actively participated in drafting the work and revising it critically for important intellectual content. All authors have read and approved the final version of the manuscript. Furthermore, all authors agree to be accountable for all aspects of the work, ensuring that questions related to any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of Shandong Cancer Hospital and Institute (Jinan, China; approval no. SDTHEC202410078) on October 12, 2024. The requirement for informed consent was waived due to the retrospective nature of this research.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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