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RESEARCH

Efficacy and safety analysis of atezolizumab continuation beyond progression in extensive-stage small cell lung cancer

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Abstract

The advent of immune checkpoint inhibitors (ICIs) has revolutionized the treatment landscape for extensive-stage small cell lung cancer (ES-SCLC) patients. However, many patients eventually develop resistance to immunotherapy. While continued ICI therapy beyond disease progression has shown survival benefits in various cancers, research specific to ES-SCLC remains limited. Our study aimed to further evaluate the efficacy and safety of atezolizumab continuation therapy to optimize the ICI continuation strategies for ES-SCLC. In this multicenter study, all enrolled patients received continued atezolizumab in combination therapy as second-line (2L) treatment after progression of first-line (1L) chemo-immunotherapy. The efficacy was measured by median overall survival (mOS) and median progression-free survival (mPFS). Safety was evaluated based on incidence of adverse events (AEs). Among the 28 eligible patients in this study, mPFS was 4.07 months [95% CI: 1.15 to 6.98], and mOS was 18.87 months [95% CI: 15.28 to 22.45]. In the safety analysis, respiratory-related AEs were the most common, including cough (35.7%), dyspnea (35.7%), pneumonitis (35.7%). Additionally, thyroiditis (17.9%) was the most generally reported immune-related adverse events (irAEs). In subgroup analysis, the LTR group (1L-PFS $\geq$ 6 months) showed longer mOS compared with the STR group (1L-PFS < 6 months) [19.98 vs. 8.68 months, $p = 0.021$]. Patients with greater DpR ($\geq$ 29% than < 29%) had longer mOS: 21.84 vs. 14.63, $p < 0.01$]. Atezolizumab continuation therapy demonstrated promising efficacy and manageable safety in ES-SCLC patients progressing after 1L chemo-immunotherapy, particularly in those with favorable 1L treatment responses.

Keywords Extensive-stage small cell lung cancer (ES-SCLC) · Immunotherapy · Atezolizumab · Survival · Safety

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Introduction

Small cell lung cancer (SCLC) is an aggressive disease characterized by rapid tumor cell growth and poor prognosis. Approximately two-thirds of SCLC patients present with advanced-stage disease [1]. The advent of immune checkpoint inhibitors (ICIs), particularly anti-programmed death-ligand 1 (PD-L1) antibodies like atezolizumab, has revolutionized the treatment landscape for extensive-stage small cell lung cancer (ES-SCLC) [2]. Trials such as IMpower133, CASPIAN, and ASTRUM005 have demonstrated that chemo-immunotherapy as first-line (1L) treatment can increase overall survival by three months compared to traditional chemotherapy [2–4]. However, despite these advancements, a significant proportion of ES-SCLC patients still develop resistance and experience early recurrence after initial treatment. Recommended second-line (2L) treatment options for patients who relapse within 6 months of 1L systemic treatment include topotecan, although its effectiveness is limited, with response rates of 25% in platinum-responsive and less than 10% in platinum-insensitive patients [5]. For those who relapse after 6 months, it is recommended to repeat the initial chemotherapy regimen [6]. Further chemotherapy has only led to a limited median overall survival of 10 months [7, 8]. The treatment options remain limited for ES-SCLC patients who have progressed after receiving chemo-immunotherapy. Notably, in the ASTRUM005 trail, a quarter of patients received continuation of ICI as part of subsequent therapy, leading to improved survival outcomes compared to IMpower133 and CASPIAN studies. Continuing ICI as part of treatment strategy may confer long-term survival benefits for ES-SCLC patients progressing after initial treatment. While the efficacy of continuing ICI beyond disease progression has been demonstrated in 2L treatments for metastatic melanoma and advanced non-small cell lung cancer, research in ES-SCLC remains limited [9, 10].

Variability in initial responses to ICI is evident in both efficacy and incidence of adverse events (AEs). Some patients exhibit resistance to initial ICI, necessitating discontinuation or switch in medication, ultimately leading to disease progression. Additionally, immune-related adverse events (irAEs) may occur following ICI initiation, manageable with appropriate treatment, yet some patients prematurely discontinue immunotherapy due to concerns. Previous studies attributed ICI resistance to factors such as brief treatment duration, inadequate drug exposure, and inconsistent receptor occupancy, thus limiting the full potential of immunotherapy [11]. Consequently, ICIs continuation has been proposed as a potential strategy to fully maximize therapeutic benefit, a concept supported by studies in renal cell carcinoma and non-small cell lung cancer [11, 12]. Understanding impact of initial response and duration of 1L ICI treatment on long-term survival benefits, as well as strategies for enhancing immune rechallenge treatment, are currently key areas of discussion. Furthermore, some patients may need to pause ICI treatment due to AEs. Therefore, in addition to evaluating the survival benefits of continuing ICI, further investigation into the safety profile is warranted.

This study retrospectively analyzed the treatment outcomes of ES-SCLC patients receiving atezolizumab continuation beyond disease progression, evaluating efficacy, safety, and identifying patient characteristics likely to benefit. Subgroup analysis aims to optimize rechallenge strategies, providing guidance for subsequent treatments in ES-SCLC patients experiencing disease progression following 1L chemo-immunotherapy.

Methods

Patients

We retrospectively reviewed the clinical data for ES-SCLC patients from 6 centrals between January 2020 and April 2024. The inclusion criteria were: (i) histological or cytological confirmation of SCLC; (ii) confirmation of extensive-stage characterized by the presence of distant metastasis or thoracic extension beyond a single radiation port; (iii) patients exhibiting progressive disease (PD) following 1L treatment with platinum-based chemotherapy combined with atezolizumab, who continued on atezolizumab as 2L therapy. Disease progression was assessed through periodic radiological surveillance. Patients with a previous history of severe systemic disease, autoimmune diseases, or incomplete information were excluded from this study.

Study design

This multi-center retrospective cohort study aimed to evaluate the survival outcomes and tolerability of atezolizumab continuation therapy in ES-SCLC patients who progressed following 1L chemo-immunotherapy. Follow-up duration was defined from the initiation of immunotherapy until death, occurrence of unacceptable AEs, or loss to follow-up. Demographic characteristics and treatment-related data were extracted from the Electronic Medical Records System using a standardized data collection form. Demographic characteristics included gender, age, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), and body mass index (BMI). Treatment-related data encompassed the prior radiotherapy history and administration of

anti-angiogenesis therapy or radiotherapy during atezolizumab continuation treatment.

The primary objective was to evaluate the efficacy of atezolizumab continuation therapy and explore associations between clinical variables and treatment efficacy. Efficacy endpoints included median overall survival (mOS) and median progression-free survival (mPFS) (mOS: the time between initiation of the post-PD treatment and death from any cause; mPFS: the time from the initiation of the post-PD treatment to disease progression or death from any cause, whichever came first). Depth of response (DpR), representing the percentage of maximal tumor shrinkage during 1L chemo-immunotherapy, was also assessed and we selected the median DpR value of the enrolled patients for subsequent subgroup analysis. Secondary endpoints comprised safety analysis, with the severity of AEs was classified according to the Common Terminology Criteria for Adverse Events v.5.0. Follow-up data were retrospectively collected from electronic medical records and telephone follow-up.

Statistical analysis

Data were analyzed using descriptive statistics, presenting median values with interquartile ranges for continuous variables, and frequencies with percentages for categorical variables. Statistical comparisons employed Student's t-test and chi-square test (or Fisher's exact test when appropriate). Kaplan–Meier methods estimated mPFS and mOS, with survival curves generated for each treatment group and compared using the log-rank test. Univariate Cox regression initially included all independent clinical variables, with those demonstrating $p < 0.05$ subjected to multivariate Cox regression. Statistical analyses were performed using GraphPad Prism (version 8.01, GraphPad Software, San Diego, CA, USA) and SPSS statistical software (version 20.0, IBM Corporation, Armonk, NY, USA), with significance set at $p < 0.05$ (two-sided) for all tests.

Results

Baseline characteristics

We conducted a study to analyze the efficacy and safety of atezolizumab continuation for 28 patients with ES-SCLC. Data collection was completed by April 11, 2024, with a median follow-up duration of 22.8 months (range, 21.1–24.4 months). The median age of the patients was 65 years (range, 55.3–69.0), and the majority were male (85.7%) and smokers (78.6%). Most patients (92.8%) had an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1, while two patients had a score of 2. At baseline, 15 patients (53.6%) presented with brain metastases and 11 patients (39.3%) had liver metastases. Among the participants, 12 patients (42.9%) received consolidative thoracic radiotherapy during 1L treatment, 11 patients (39.3%) underwent anti-angiogenesis therapy, and 12 patients (42.9%) received radiotherapy during 2L treatment (Table 1).

In the efficacy evaluation of 1L treatment for enrolled patients, 16 patients were categorized as the short-term response (STR) group (1L-PFS < 6 months), while 12 patients were classified as the long-term response (LTR)

Table 1 Baseline clinical characteristics

Characteristic	N (%)
Age, median (IQR)(years)	65 (55.3–69.0)
> 60	18 (64.3)
≤ 60	10 (35.7)
Sex	
Male	24 (85.7)
Female	4 (14.3)
Smoking	
No	6 (21.4)
Yes	22 (78.6)
BMI	
< 18.5	3 (10.7)
18.5–23.9	16 (57.1)
≥ 24	9 (32.1)
Performance status	
0	8 (28.6)
1	18 (64.3)
2	2 (7.1)
Previous consolidative thoracic radiotherapy	
Yes	12 (42.9)
No	16 (57.1)
Baseline brain metastasis	
Yes	15 (53.6)
No	13 (46.4)
Baseline liver metastasis	
Yes	9 (32.1)
No	19 (67.9)
Second-line combination therapy	
Radiotherapy [a]	6 (21.4)
Anti-angiogenesis therapy	11 (39.3)
First-line outcome	
Short-term response (1L PFS < 6 months)	16 (57.1)
Long-term response (1L PFS ≥ 6 months)	12 (42.9)
DpR [b] ≥ 29%	12 (42.9)
DpR < 29%	16 (57.1)

[a]Local radiotherapy therapies were administered concurrently with ICI continuation, which included primary thoracic tumor and lymph node

[b]The percentage of maximal tumor shrinkage during 1L chemo-immunotherapy

group (1L-PFS ≥ 6 months). The percentage of maximal tumor shrinkage from baseline during 1L chemo-immunotherapy according to RECIST version 1.1 are shown in Supplementary Fig. S1. Following the analysis of maximal tumor shrinkage in enrolled patients receiving 1L chemo-immunotherapy, the median value of DpR was found to be 29%. Among the patients, 12 exhibited maximal tumor shrinkage of less than 29% (DpR < 29%), while 16 patients demonstrated tumor reduction greater than or equal to 29% (DpR ≥ 29%).

Outcomes

At the final follow-up on April 11, 2024, 16 out of 28 patients (57.1%) receiving 2L treatment experienced progressive disease (PD). Among the patients, 15 (53.6%) had died, with a mOS of 18.87 months [95% CI: 15.28 to 22.45] (Fig. 1A). The mPFS for 2L treatment with atezolizumab continuation was 4.07 months [95% CI: 1.15 to 6.98] (Fig. 1B). Univariate COX regression analysis (Table 2) considering patients' baseline characteristics and treatment-related information showed that primary liver metastasis (HR = 0.12, $p < 0.01$) and 1L treatment response (HR = 3.16, $p = 0.03$; HR = 22.39, $p < 0.01$) significantly influenced prognosis. Subsequently, we included the factors with significant statistical significance in Univariate COX regression analysis into the Multivariable COX regression analysis. Multivariable COX regression analysis indicated that baseline liver metastasis (HR = 0.13, $p = 0.02$) and progression-free interval (HR = 12.51, $p < 0.01$) and depth of response (HR = 53.13, $p < 0.01$) during 1L chemo-immunotherapy independently affected OS.

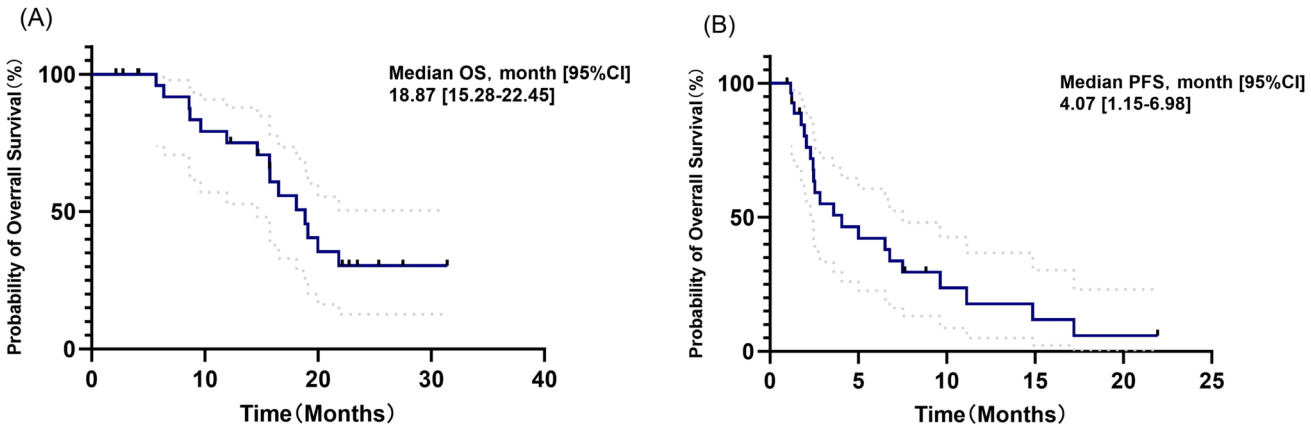

Fig. 1 Kaplan–Meier curves for overall survival **A** and progression-free survival **B**. CI, confidence interval; PFS, progression-free survival; OS, overall survival

Table 2 Univariate and multivariate analysis of factors associated with overall survival

Characteristic	Univariate analysis		Multivariate analysis	
	HR [95%CI]	Log–rank *p*	HR [95%CI]	Log–rank *p*
Age (> 60 vs. ≤ 60)	1.07 [0.37–3.15]	0.90	–	–
Sex (Male vs. female)	0.84 [0.23–3.00]	0.78	–	–
Smoking (Yes vs. no)	0.96 [0.30–3.02]	0.94	–	–
BMI (≥ 24 vs. < 24)	1.90 [0.53–6.76]	0.32	–	–
ECOG PS (2 vs. 0–1)	0.62 [0.13–2.84]	0.54	–	–
Disease–related data				
Baseline brain metastasis (Yes vs. no)	2.41 [0.82–7.10]	0.11	–	–
Baseline liver metastasis (Yes vs. no)	0.12 [0.03–0.53]	< 0.01	0.13 [0.03–0.72]	0.02
Treatment–related data				
Previous consolidative thoracic radiotherapy (Yes vs. no)	0.89 [0.32–2.48]	0.83	–	–
Second–line Radiotherapy (Yes vs. no)	1.02 [0.29–3.62]	0.98	–	–
Second–line Anti–angiogenesis therapy (Yes vs. no)	0.86 [0.31–2.38]	0.77	–	–
First–line outcome (Long–term response vs. Short–term response)	3.16 [1.13–8.83]	0.03	12.51 [2.86–54.69]	< 0.01
DpR (≥ 29% vs. < 29%)	22.39 [2.57–194.81]	< 0.01	53.13 [4.02–701.67]	< 0.01

Given the significant correlation between the initial response to 1L immunotherapy and efficacy of ICI continuation, we conducted a subgroup analysis based on this relationship. Subgroup analysis categorized patients into STR group (1L-PFS < 6 months) and the LTR group (1L-PFS ≥ 6 months), as well as into DpR < 29% and DpR ≥ 29% groups based on their DpR to 1L immunotherapy. The subgroup analysis (Fig. 2) demonstrated that patients in the STR group had a mOS of 8.67 months, whereas those in the LTR group showed a mOS of 19.98 months, with a statistically significant difference ($p = 0.021$). The study further explored the OS of patients with different DpR in 1L immunotherapy, revealing that patients with DpR ≥ 29% had mOS of 21.84 months compared to 14.63 months for those with DpR < 29%, with a p-value of less than 0.01 (Fig. 3).

Safety

Treatment-related AEs of any grades were observed in all patients included in our study, as shown in Table 3. The majority of these Aes were manageable and resolved spontaneously. The most frequently reported Aes were cough,

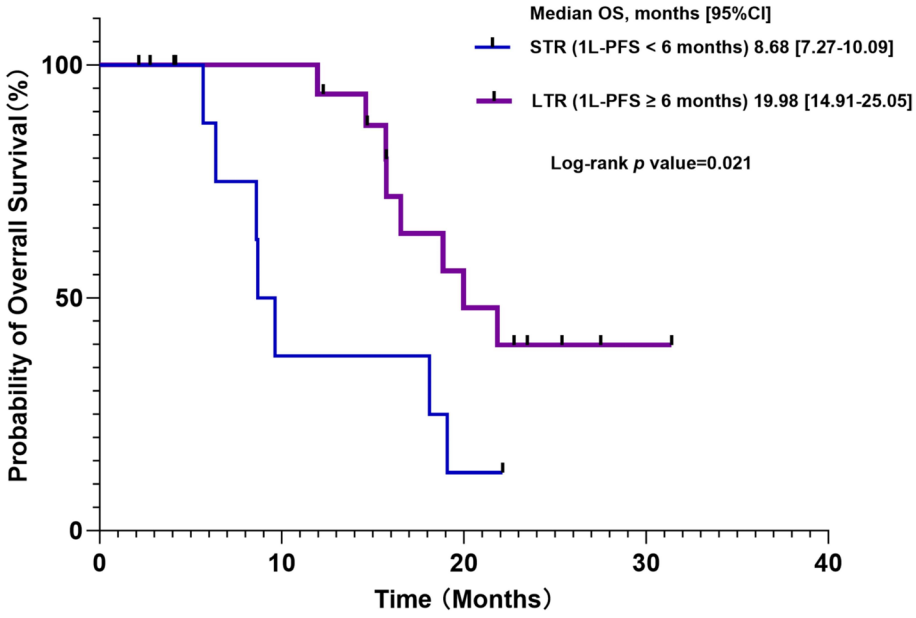

Fig. 2 Kaplan–Meier curves of OS for Long-term response (LTR) group and Short-term response (STR) group

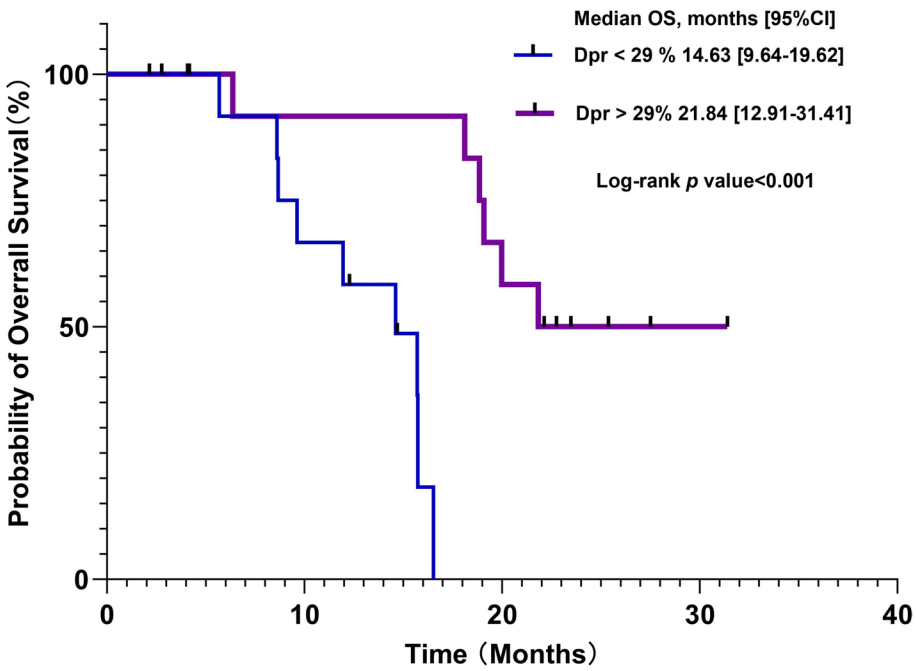

Fig. 3 Kaplan–Meier curves of OS for DpR ≥ 29% group and DpR < 29% group. CI, confidence interval; OS, overall survival

Table 3 Adverse events

AEs, N (%)	Any grade	Grade 3–5
Any events	28(100.0)	5(14.3)
Cough	10(35.7)	0(0.0)
Dyspnea	10(35.7)	1(3.6)
Pneumonitis [c]	10(35.7)	0(0.0)
Pyrexia	3(10.7)	0(0.0)
Fatigue	5(17.9)	0(0.0)
Rash	4(14.3)	1(3.6)
Alopecia	4(14.3)	0(0.0)
Pruritus	4(14.3)	0(0.0)
Insomnia	1(3.6)	0(0.0)
Nausea	9(32.1)	0(0.0)
Decreased appetite	10(35.7)	2(7.1)
Vomiting	7(25.0)	0(0.0)
Constipation	3(10.7)	0(0.0)
Diarrhea	2(7.1)	0(0.0)
Anemia	4(14.3)	0(0.0)
Neutropenia	3(10.7)	0(0.0)
Thrombocytopenia	2(7.1)	0(0.0)
IrAEs	6(21.5)	1(3.6)
Thyroiditis [d]	5(17.9)	0(0.0)
Severe skin reactions	1(3.6)	1(3.6)

[c]Pneumonitis is a grouped term that includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, and pulmonary fibrosis.

[d]Thyroiditis included hypothyroidism and hyperthyroidism

dyspnea, pneumonitis, and decreased appetite, which all achieved an incidence rate of 35.7%. Four patients (14.3%) suffered from Grade 3 Aes, including one with dyspnea (3.6%), one with rash (3.6%), and two with decreased appetite (7.1%). No Grade 4 or 5 Aes were reported. IrAEs were observed in 6 patients (21.5%), with immune-related thyroiditis (17.9%) being the most common. A single patient (3.6%) developed a Grade 3 immune-mediated rash, while no Grade 4 or 5 immune-mediated Aes were recorded.

Discussion

The combination of platinum-containing two-drug chemotherapy with PD-L1 inhibitors has led to a change in the landscape of 1L treatment for ES-SCLC. However, the emergence of ICI resistance limits the lasting benefits for patients with ES-SCLC. Exploring effective therapies has become a pressing clinical issue. Atezolizumab, a humanized IgG1 monoclonal anti-PD-L1 antibody, has been approved as a 1L treatment for various cancers, including ES-SCLC. The IMpower 133 trial demonstrated that combining atezolizumab with chemotherapy significantly enhanced survival, establishing chemo-immunotherapy as the preferred initial treatment for ES-SCLC [2]. However, long-term benefits from atezolizumab are limited due to the development of resistance and disease progression. Therefore, an effective subsequent therapy for ES-SCLC patients progressing after 1L chemo-immunotherapy remains an unmet need. Our study revealed that continuing atezolizumab after 1L chemo-immunotherapy leads to enhanced antitumor activity, with a mOS of 18.87 months compared to approximately 10 months with traditional chemotherapy regimens [6]. Importantly, patients tolerated atezolizumab continuation well, underscoring survival benefit of atezolizumab continuation therapy for ES-SCLC patients who progressed after 1L chemo-immunotherapy.

Discontinuation of immunotherapy often occurs due to disease progression or intolerable irAEs, potentially denying patients the full benefits of ICIs. To achieve long-term benefits, the concept of immunotherapy rechallenge has been proposed. Several factors contribute to the underutilization of immunotherapy. Firstly, the initial assessment of disease progression by RECIST1.1 may not accurately reflect actual progression, resulting in what is known as pseudoprogression. Secondly, the immune system requires time to prime for an antitumor response, resulting in a delayed immune response [13, 14]. Thus, patients who experienced progression during 1L immunotherapy retain sufficient immune reserves to benefit from ICI continuation. Moreover, ICI continuation might reset immune memory and alleviate prior immunosuppression [15, 16]. Recent research supports continued ICI as a viable strategy across various cancers, demonstrating efficacy comparable to initial treatment with manageable side effects [17–23]. For instance, Chiarion et al. reported significant disease control and prolonged mOS in rechallenged melanoma patients treated with ipilimumab [22]. Similarly, studies in advanced or metastatic non-small cell lung cancer (NSCLC) have shown prolonged mPFS with ICI rechallenge [24]. Our study corroborates these findings, firstly demonstrating that atezolizumab continuation with other anti-tumour therapies improves survival benefits in ES-SCLC, with an mOS of 18.11 months compared to 15.4 months in Astrum005 and 12.3 months in IMpower133.

The outcomes of ICI continuation are influenced by the response to 1L immunotherapy, as demonstrated in several studies [24–26]. Levra et al. found that patients who underwent initial ICI treatment for 6 months or longer, as well as those treated for 3–6 months, had a longer mOS compared to those treated for less than 3 months [24]. One hypothesis proposed is that longer initial immunotherapy may enhance immune memory. Similarly, we conducted a subgroup analysis based on the duration of their initial treatment and whether the 1L-PFS time exceeded 6 months. The final results showed that the LTR group had better survival benefits with mOS of 19.98 months than the STR group

with mOS of 8.68 months, which is consistent with previous research findings. Further analysis was performed to assess the impact of 1L immunotherapy using the DpR index. Stratified analysis based on the degree of tumor reduction revealed that patients with a DpR greater than 29% after 1L immunotherapy experienced improved long-term survival benefits. Overall, our study suggests that the initial response to 1L immunotherapy significantly impacts the long-term survival benefits of patients receiving ICIs continuation. Therefore, even in cases of AEs, if the criteria for discontinuing immunological drugs are not met—particularly for patients who have demonstrated positive initial outcomes from immunotherapy—it is advisable to extend the overall duration of ICIs.

The safety profile of atezolizumab for ES-SCLC patients aligned with previous studies [27–30], with manageable Grade 1 or 2 AEs predominating. Respiratory toxicities, including cough, dyspnea, and pneumonitis, were notable concern, although severe AEs were rare. Immune-related thyroiditis was the most common immune-mediated adverse event, observed in five patients. These all suggest that long-term use of ICI does not lead to an increase in the accidence of AEs.

Debate persists regarding whether to continue the initial regimen or switch to other ICIs during immunotherapy rechallenge. Some studies suggest significant benefits with the same regimen, yielding substantial disease control rates [31, 32], while others caution against switching due to potential adverse effects [33, 34]. Our study involved 28 patients who received atezolizumab continuation therapy beyond progression, and the results indicated that this approach led to survival benefits and good tolerability. This provides a clinical basis for considering new treatment strategies in the second -line against different types of cancer.

Our study has limitations, including its retrospective design and small sample size, potentially introducing selection bias and limiting subgroup analyses. Additionally, variability in toxicity profiles from different anti-tumor treatments poses challenges for safety assessments. Future research should address these limitations by expanding cohort sizes and conducting detailed subgroup analyses across various treatment modalities to better understand the impact on ICI efficacy and safety.

In our pooled analysis of patients with ES-SCLC who progressed after 1L immunotherapy, the continuation of atezolizumab showed promising antitumor activity with durable clinical benefit. Our pooled analysis supports atezolizumab continuation as a viable 2L treatment for ES-SCLC patients, contributing to the standardization of ICI continuation protocols.

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Author contributions Wenhao Shi: Conceptualization; data curation; formal analysis; writing– review and editing. Xiaohui Bao: Resources; software; writing – original draft. Jin Xiong: Resources; writing—review and editing. Yanqiao Wu、Jianguo Sun、Zhi Xu、Dairong Li、Yang Wei、Jun Ge、Biyong Ren、Yu Jiang and Kaijin Wang: Resources. Yusheng Huang: Validation; writing—review and editing. Zhenzhou Yang: Investigation; methodology; supervision; visualization. Yuan Peng: Conceptualization; funding acquisition; project administration; resources; supervision; writing—review and editing.

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Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest The authors declare no competing interests.

Ethics Approval and Consent to Participate This study was approved by the Ethics Committee of The Second Affiliated Hospital of Chongqing Medical University. Clinical trial number: No: 63, Date: 2024. This waiver was granted because it is an ethics committee-approved retrospective study, all patient information was deidentified and patient consent was not required.

Consent to Publish Not applicable.

Data availability Data generated and/or analyzed during the study are available from the authors upon request.

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