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Efficacy and safety analysis of anlotinib in combination with immune checkpoint inhibitors for second-line and subsequent extensive-stage small-cell lung cancer

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Currently, there is a lack of effective second-line and subsequent treatments for patients with extensive-stage small-cell lung cancer (ES-SCLC), and the establishment of a standardized treatment protocol is still underway. Considering the potential synergistic therapeutic effects of anti-angiogenic drugs and immune checkpoint inhibitors (ICIs), combination therapy could be a viable option for treating lung cancer. This research concentrates on assessing the efficacy and safety of anlotinib in combination with ICIs for the treatment of ES-SCLC. We undertook a retrospective analysis of patients with extensive-stage SCLC who received anlotinib in combination with ICIs as second-line and subsequent treatment at Zhejiang Cancer Hospital between April 2020 and April 2023. Survival rates were analyzed using the Kaplan-Meier method. Among the 43 patients who received combination therapy, there were no cases of complete response (CR), 16 patients who achieved partial response (PR), 21 patients who had stable disease (SD), and 6 patients who experienced disease progression (PD). This resulted in an overall response rate (ORR) of 37.2% (16/43) and a disease control rate (DCR) of 86.0% (34/43). The median progression-free survival (PFS) was 4.0 months (95% CI: 2.74–5.26), and the median overall survival (OS) time was 10 months (95% CI: 4.8–15.2). Cox multifactorial regression analysis disclosed that the performance score (PS) and the number of metastatic organs were independent factors influencing PFS in ES-SCLC ($p<0.001$). The combination therapy demonstrated acceptable toxicity, with a total grade 3/4 toxicity rate of 30.2%. The combination therapy showed a notable association with several adverse events, including hand-foot syndrome, hypertension, and fatigue, which were the most significant. Combining anlotinib with immune checkpoint inhibitors has demonstrated favorable efficacy and safety in the treatment of second-line and subsequent extensive-stage small-cell lung cancer.

Key words: anlotinib; immune checkpoint inhibitors (ICIs); extensive-stage small-cell lung cancer (ES-SCLC)

Small-cell lung cancer (SCLC) belongs to the group of neuroendocrine tumors characterized by rapid growth and high malignancy, accounting for 15% of all lung cancers [1, 2]. The proportion of new cases of SCLC with extensive stage is about 65% [3]. Patients with SCLC have a poor prognosis, with a 5-year survival rate of less than 5% and an average overall survival (OS) of only 2 to 4 months for those who do not receive systemic therapy [4]. Although SCLC is initially sensitive to treatment, most patients experience recurrence and develop metastases to other organs [5]. The standard first-line treatment for ES-SCLC involves the combination of immune checkpoint inhibitors (ICIs) with etoposide plus platinum-based chemotherapy. The median progression-free survival (PFS) and median OS durations were reported as 5.2–5.7 months and 12.3–15.4 months, respectively [6–9]. Second-line and subsequent therapies are limited, with topotecan being the standard second-line option. However, the OS of patients treated with topotecan was only 26 weeks, which represents a 12-week prolongation compared to patients treated with the best supportive care [10]. In recent years, ICI monotherapies, such as nivolumab and pembrolizumab, have been aggressively tested in the subsequent treatment of ES-SCLC. Some encouraging results have been observed; however, these treatments have not demon-

strated a significant survival benefit [11–14]. Anlotinib is a novel multi-target tyrosine kinase receptor inhibitor (TKI) that effectively inhibits VEGFR, PDGFR, FGFR, and c-Kit kinases, thereby suppressing tumor angiogenesis and inhibiting tumor growth [15, 16]. The phase II study (ALTER1202) evaluated the efficacy of anlotinib compared to placebo as a third-line or beyond treatment for SCLC. The study demonstrated that anlotinib extended PFS in SCLC patients by 3.4 months (4.1 months vs. 0.7 months) [17]. Furthermore, anlotinib promotes the infiltration of innate immune cells, and when combined with PD1 or PD-L1 inhibitors, it enhances the therapeutic effect on lung cancer [18]. Various clinical trials have explored the combination of immune-combination antivascular therapy for lung cancer, providing a solid rationale and demonstrating significant synergistic effects of this combination therapy [19–21]. Therefore, the objective of this study is to evaluate the efficacy and safety of anlotinib in combination with ICIs and to provide recommendations for the treatment of advanced metastatic SCLC.

Patients and methods

Patient eligibility. This research involved a retrospective analysis of 121 patients diagnosed with ES-SCLC between March 2018 and March 2023 at the Zhejiang Provincial Cancer Hospital and Taizhou City Cancer Hospital. The inclusion criteria were as follows: I) age 18 years or older; II) all patients were pathologically diagnosed with SCLC according to the criteria established by the World Health Organization Classification of Lung Tumors in 2021. Diagnoses were confirmed through immunohistochemical (IHC) analysis; III) diagnosed with stage IV SCLC according to the Tumor, Lymph Node, and Metastasis Staging System (version 8); IV) having a confirmed Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–2; V) experiencing progression after prior first-line standard therapy; and VI) patients with ES-SCLC who received anlotinib in combination with ICIs as second-line and subsequent therapy. The control group consisted of patients with advanced SCLC who received either irinotecan alone, irinotecan in combination with platinum-based chemotherapy, or anlotinib monotherapy as second-line treatment. This study adhered to the ethical principles outlined in the Declaration of Helsinki (revised 2013) and was approved by the Ethics Committee of Taizhou Cancer Hospital (No. SL2024060). Written informed consent was not required as this was a retrospective study.

Treatment and responses assessments. The assessment of treatment and responses in this study involved obtaining relevant clinical information from medical records. The regimen and dosage of anlotinib, in combination with ICIs, for all patients adhered to the National Comprehensive Cancer Network (NCCN) guidelines or clinical trials until disease progression or unacceptable toxicity was confirmed. Anlotinib is administered orally once daily, with dosages of 12 mg, 10 mg, or 8 mg, in 21-day cycles. It was taken during days 1–14 of the 21-day cycle. The initial dose of anlotinib depends on the patient's condition and was determined by the clinician. A single dose reduction (from 12 mg to 10 mg or 8 mg, or 10 mg to 8 mg) or discontinuation due to drug-related toxicity was permissible. The patients received various ICIs, including sintilimab (200 mg), tislelizumab (200 mg), pembrolizumab (2 mg/kg), toripalimab (2 mg/kg), durvalumab monotherapy (1,500 mg), nivolumab (3 mg/kg), atezolizumab therapy (1,200 mg), camrelizumab (200 mg), and srulizumab (3 mg/kg) immunotherapy, every 2 or 3 weeks, until disease progression or unacceptable toxicity was confirmed. Irinotecan was administered intravenously (IV) either alone on Day 1 and Day 8 at a dosage of 65 mg/m^2 of body surface area or in combination with cisplatin IV on the same days at a dosage of 30 mg/m^2 of body surface area, following a 21-day cycle. Additionally, before analysis, two oncologists conducted abdominal ultrasound, cranial magnetic resonance imaging (MRI), and bone emission computed tomography (ECT) scans, following the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), every two cycles or as needed soon after emergence, until disease progression, treatment termination, or the last follow-up, whichever came first. Key indicators of treatment effectiveness were evaluated based on tumor response, which encompassed partial response (PR), complete response (CR), stable disease (SD), and disease progression (PD). Overall response rate (ORR) was defined as the sum of complete response (CR) and partial response (PR). Disease control rate (DCR) was assessed as the sum of CR, PR, and SD.

Evaluation of adverse reactions. Drug toxicity was monitored based on the National Cancer Institute's Common Terminology Criteria for the Evaluation of Adverse Events (CTCAE), version 5.0. Immune-related adverse events (irAEs) are adverse events that have an immunological basis and require more frequent monitoring and intervention, including immunosuppressive and/or endocrine replacement therapy. The diagnosis and severity of irAEs are determined based on clinical examination, along with biological and imaging data. irAEs can occur during or after immunotherapy. The severity of the adverse reaction depends on whether a reduction in the ICI dose or discontinuation of the ICI is necessary. The severity of irAEs was assessed by two or more independent healthcare professionals using a grading system ranging from 1 to 5.

Follow-up and statistical analysis. All patients were required to be evaluated for PFS and OS during treatment. final follow-up was on August 1, 2023. PFS encompasses the period from the initiation of combination therapy until documented progression or death from any cause or until the last follow-up date for patients who remained alive without progression. OS is defined as the period from the start of combination therapy to either death or the last follow-up. Propensity score matching (PSM) was conducted to mitigate potential selection bias. Logistic regression models were

constructed to compute the propensity score using covariates including age, gender, ECOG PS, smoking history, BMI, and number of metastatic organs. The group receiving anlotinib combined with ICIs was matched to the group receiving irinotecan or anlotinib in a 1:1 ratio using a Greedy algorithm with a caliper of 0.05. Categorical variables were evaluated using the chi-square test. Patient survival was assessed using Kaplan-Meier survival analyses, and survival across prognostic factors was compared using time-series tests. Cox regression models were utilized to conduct separate univariate and multivariate analyses of PFS and OS. Statistics were analyzed statistically using SPSS version 27.0 (Chicago, IL, USA), set at $p<0.05$ for all tests on both sides.

Results

Patients' characteristics. The study encompassed 121 patients, with 43 allocated to the anlotinib combined with ICIs treatment group and 78 to the irinotecan anlotinib treatment group. PSM was conducted to mitigate confounding covariates between the groups, resulting in the selection of 43 patients for each treatment arm (including 8 who received anlotinib monotherapy). Tables 1 and 2 display the baseline characteristics of all patients. The anlotinib combined with the ICIs treatment cohort comprised 38 males (88.4%) and 5 females (11.6%), with a median age at diagnosis of 61 years (range: 48–75 years). The majority of patients (70.1%, 34/43) were smokers. All patients had stage IV disease. Thirteen patients (30.2%) had an ECOG PS of 2, and the remaining patients were classified as 0 to 1 (69.8%). Fifteen patients (34.9%) received second-line therapy, while twenty-eight patients (65.1%) received follow-up. The frequently utilized immunotherapeutic agents included sintilimab (37.2%; 16/43), durvalumab (16.3%; 7/43), treprostinil (14%; 6/43), and other PD-1 inhibitors (32.5%).

Clinical efficacy. During the study period in the anlotinib combined with ICIs treatment group, no patients achieved CR, 16 patients (37.2%) attained PR, 21 patients (48.8%) had SD, and 6 patients (14.0%) exhibited PD. The ORR of anlotinib combined with ICI therapy was 37.2% and the DCR was 86%. The median PFS (mPFS) and mOS were 4 months (95% CI: 2.743–5.257, Figure 1) and 10 months (95% CI: 4.8–15.2, Figure 1), respectively. Notably, 13 patients with advanced SCLC who continued the combination therapy of anlotinib and a PD-1/PD-L1 inhibitor experienced long-lasting benefits, with three of them achieving a PFS of over 33 months (Figure 1).

Subgroup analysis. The analysis revealed that 69.8% of patients (n=30) had PS 0–1, while 30.2% (n=13) had PS 2. Patients with PS 0–1 had a mPFS of 7 months (95% CI: 1.909–12.091, Figure 2A), whereas patients with PS 2 had a mPFS of 1 month (95% CI: 0.295–1.705, Figure 2A); the difference was statistically significant ($p<0.001$). Median OS (mOS) for PS 0–1 and PS 2 was 18 months (95% CI: 10.9–19.1, Figure 2B) and 12 months (95% CI: 1.484–6.516, Figure 2B), respectively, with a statistically significant difference ($p<0.001$). Notably, both the mPFS and mOS demonstrated statistically significant differences between PS 0-1 and PS 2.

In the combination therapy group, 29 patients had no more than 3 organ metastases, while 14 patients had more than 3 organ metastases. The mPFS was 15 months (95% CI: 11.94–18.06, Figure 2C) for patients with no more than 3 organ metastases, and 3 months (95% CI: 1.17–4.83, Figure 2C) for

Table 1. Patient characteristics before and after PSM.

Characteristics	Before PSM			After PSM		
	Anlotinib combine ICIs therapy (n = 43)	Irinotecan chemotherapy group (n = 78)	p-value	Anlotinib combine ICIs therapy (n = 43)	Irinotecan chemotherapy or anlotinib group (n = 43)	p-value
Gender			0.346			0.710
Female	5	4		5	3	
Male	38	74		38	40	
Age (years)	Mean 61	Mean 55	0.269	Mean 61	Mean 68	0.500
<65	26	39		26	29	
≥65	17	39		17	14	
Smoking status			0.822			0.397
No	9	15		9	6	
Yes	34	63		34	37	
PS			0.120			0.069
0–1	30	64		30	37	
2	13	14		13	6	
Number of metastatic organs			0.120			0.812
≤3	30	14		30	31	
>3	13	64		13	12	
Body mass index (kg/m^2)			0.784			0.276
<24	27	47		27	22	
≥24	16	31		16	21	

Abbreviations: PSM-propensity score matching; ICIs-immune checkpoint inhibitors; PS-performance status

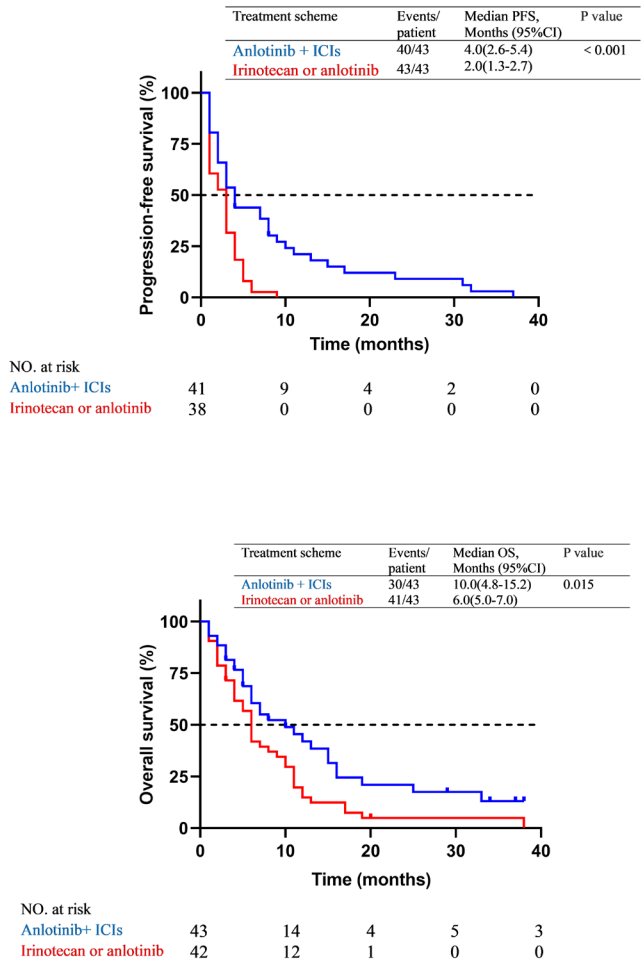

Figure 1. Kaplan-Meier curves estimate the PFS and OS of patients treated with anlotinib in combination with ICIs versus irinotecan or anlotinib.

patients with more than 3 organ metastases; the difference was statistically significant (p<0.001). Similarly, the mOS was 8 months (95% CI: 3.00–13.00, Figure 2D) for patients with no more than 3 organ metastases, and 1 month (95% CI: 0.842–1.520, Figure 2D) for patients with more than 3 organ metastases; the difference was statistically significant (p<0.001). There was a significant difference in the mPFS and mOS between patients with ≤ 3 and > 3 metastases.

Patients who received the combination of anlotinib and a PD-1/PD-L1 inhibitor as a second-line treatment had an mPFS of 3 months (95% CI: 2.07–3.93, Figure 2E) and a mOS of 10 months (95% CI: 1.12–18.88, Figure 2F). Patients undergoing combination therapy as a third-line or subsequent treatment option had a mPFS of 4 months (95% CI: 2.99–5.01, Figure 2E) and a mOS of 8 months (95% CI: 2.394–13.606, Figure 2F). The difference in mOS between patients receiving combination therapy as a second-line or subsequent treatment option was not statistically significant (p=0.722).

Table 2. The clinicopathologic features of anlotinib and ICIs combination therapy.

Characteristics	Number	Percentage (%)
Treatment lines		
Second line	15	34.9
Further line	28	65.1
Hypertension		
No	31	72.1
Yes	12	27.9
Previous immunotherapy		
No	22	51.2
Yes	21	48.8
Brain metastasis		
No	30	69.8
Yes	13	30.2
Multiple metastases	12	92.3
Single metastasis	1	7.7
Liver metastasis		
No	23	53.5
Yes	20	46.5
Multiple metastases	18	0.9
Single metastasis	2	0.1
Bone metastasis		
No	24	55.8
Yes	19	44.2
Multiple metastases	18	0.95
Single metastasis	1	0.05

Abbreviations: ES-SCLC-extensive-stage small-cell lung cancer; ICIs-immune checkpoint inhibitors

Patients who had not received an ICI before the initiation of combination therapy had an mPFS of 3 months (95% CI: 0.000–7.497, Figure 2G) and a mOS of 15 months (95% CI: 8.99–12.01, Figure 2H). Patients undergoing combination therapy as a third-line or subsequent treatment option had a mPFS of 4 months (95% CI: 2.589–5.411, Figure 2G) and a mOS of 7 months (95% CI: 5.04–8.96, Figure 2H). There was no significant difference in the mOS between patients who received prior immunotherapy and those who did not (p=0.539).

Toxicity evaluation. All patients in the anlotinib combined with the ICIs treatment group were evaluated for toxicity, and grade 3 toxicity was observed in 30.2% (13/43) of the cases. Treatment had to be interrupted in 8 patients due to toxicity. One patient required a dose reduction due to hypertension (both 12 mg and 10 mg). Common grade 3 adverse reactions included hand-foot syndrome (1 patient), hypertension (2 patients), and fatigue (1 patient). Grade 1–2 adverse events (AEs) were effectively managed and reversible, as indicated in Table 3. Among the combination therapy-related AEs, the hand-foot syndrome was the most commonly observed (41.8%), followed by hypertension (37.2%), fatigue (39.5%), and liver dysfunction (27.9%). Notably, no grade 4 or 5 AEs were reported in this study (Table 3).

Discussion

This investigation assessed the effectiveness and safety of anlotinib in combination with an immunosuppressant as a

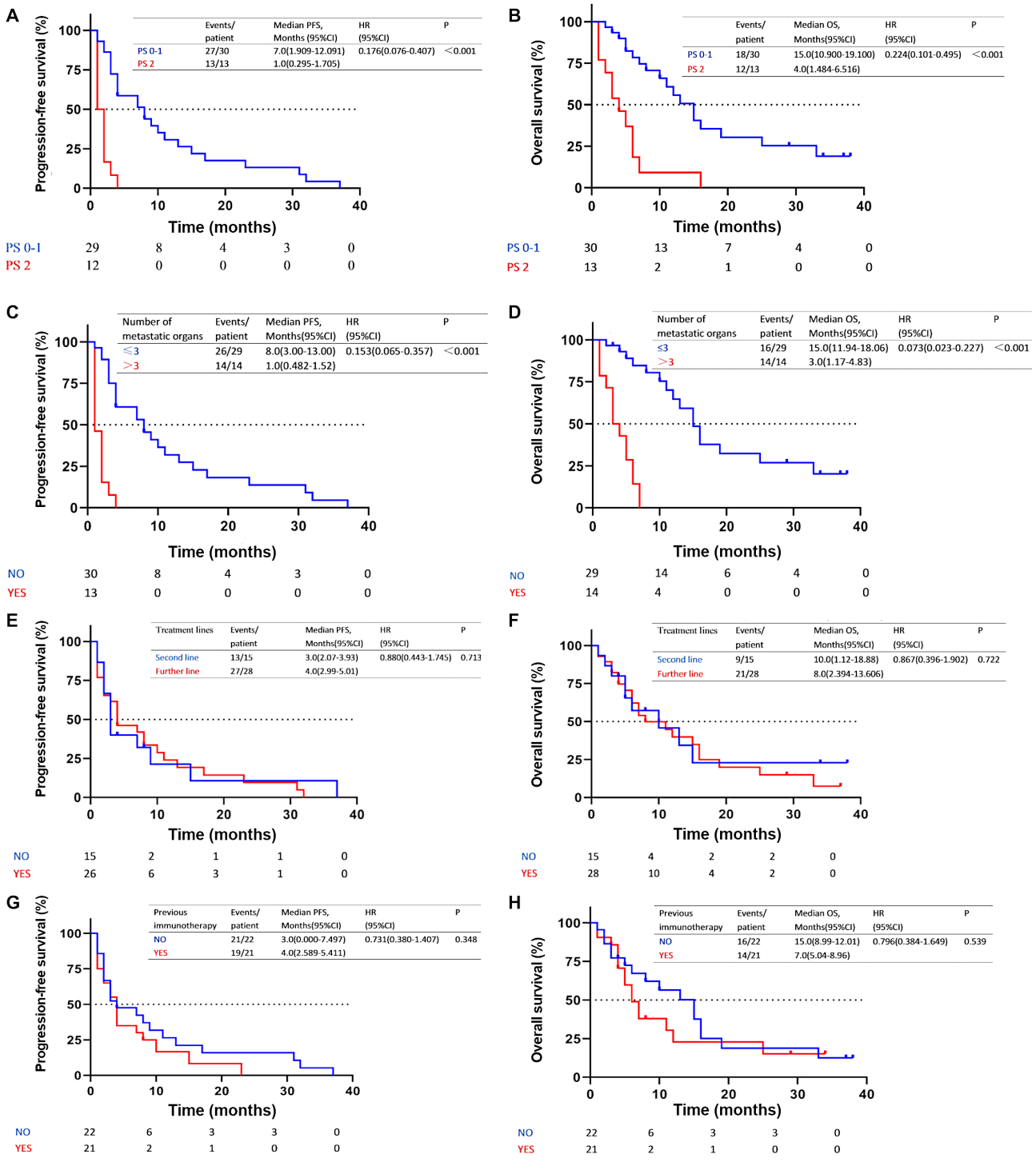

Figure 2. Kaplan-Meier estimates of A) PFS and B) OS according to the ECOG PS (PS0–1 vs. PS2). Kaplan-Meier estimates of C) PFS and D) OS according to the number of metastatic organs (≤3 vs. >3). Kaplan-Meier estimates of E) PFS and F) OS according to treatment lines (Second line vs. Further line). Kaplan-Meier estimates of G) PFS and H) OS according to previous immunotherapy (NO vs. YES).

second-line and subsequent treatment for stage IV SCLC patients. Patients subjected to this combined regimen exhibited enhanced clinical outcomes characterized by favorable therapeutic efficacy and manageable AEs when juxtaposed with conventional second-line cytotoxic agents or erlotinib used as a single agent.

Significant differences in response and survival were not observed among the available second-line and subsequent chemotherapy regimens. Topotecan was the most extensively studied drug, but it was also associated with higher toxicity. Additionally, some patients were unable to receive second-line therapy due to their poor clinical status at relapse [22, 23]. While immunotherapy has shown high effectiveness in various solid tumors, single-agent immunotherapy has not yielded satisfactory results in ES-SCLC. In CheckMate-032 and CheckMate-331 trials, the mOS were 6 and 7.5 months, respectively, indicating the limited efficacy of single-agent immunotherapy in ES-SCLC [11, 13]. This could be attributed to the absence of corresponding T-cell activation in the tumor microenvironment (TME) [26].

Single anti-VEGF (bevacizumab, avastin) antivascular-targeted therapies have demonstrated little antitumor activity or survival benefit and do not significantly improve prognosis [27]. In contrast, the multi-targeted angiogenesis inhibitor anlotinib has shown some efficacy [17]. Mutual regulation between immune cells and the tumor vasculature system is critical to the anti-tumor efficacy of immunotherapy; an abnormal tumor vasculature system promotes immunosuppression within the TME, and normalizing the vasculature may restore immune cell function and promote its anti-tumor activity [28]. Various strategies have been proposed to normalize the tumor vasculature, including blocking pro-angiogenic factors such as Ang2 and VEGF signaling pathways [29, 30]. These strategies aim to facilitate antigen-presenting cells' ability to trigger lymphocytes, induce tumor-associated macrophages' (TAMs) polarization towards an M1-like phenotype, and promote the accumulation of activated IFNγ-expressing CD8+ T cells within the perivascular space [31]. However, it should be noted that simultaneous blockade of Ang2 and VEGF has been found to upregulate PD-L1 expression in tumor cells [29]. Anlotinib, as a multi-targeted angiogenesis inhibitor, exerts its effects by simultaneously inhibiting VEGFR, FGFR, PDGFR, and c-kit. Its activity extends beyond the tumor vasculature system, also influencing the TME and the tumor itself [32]. Notably, anlotinib has been shown to enhance the infiltration

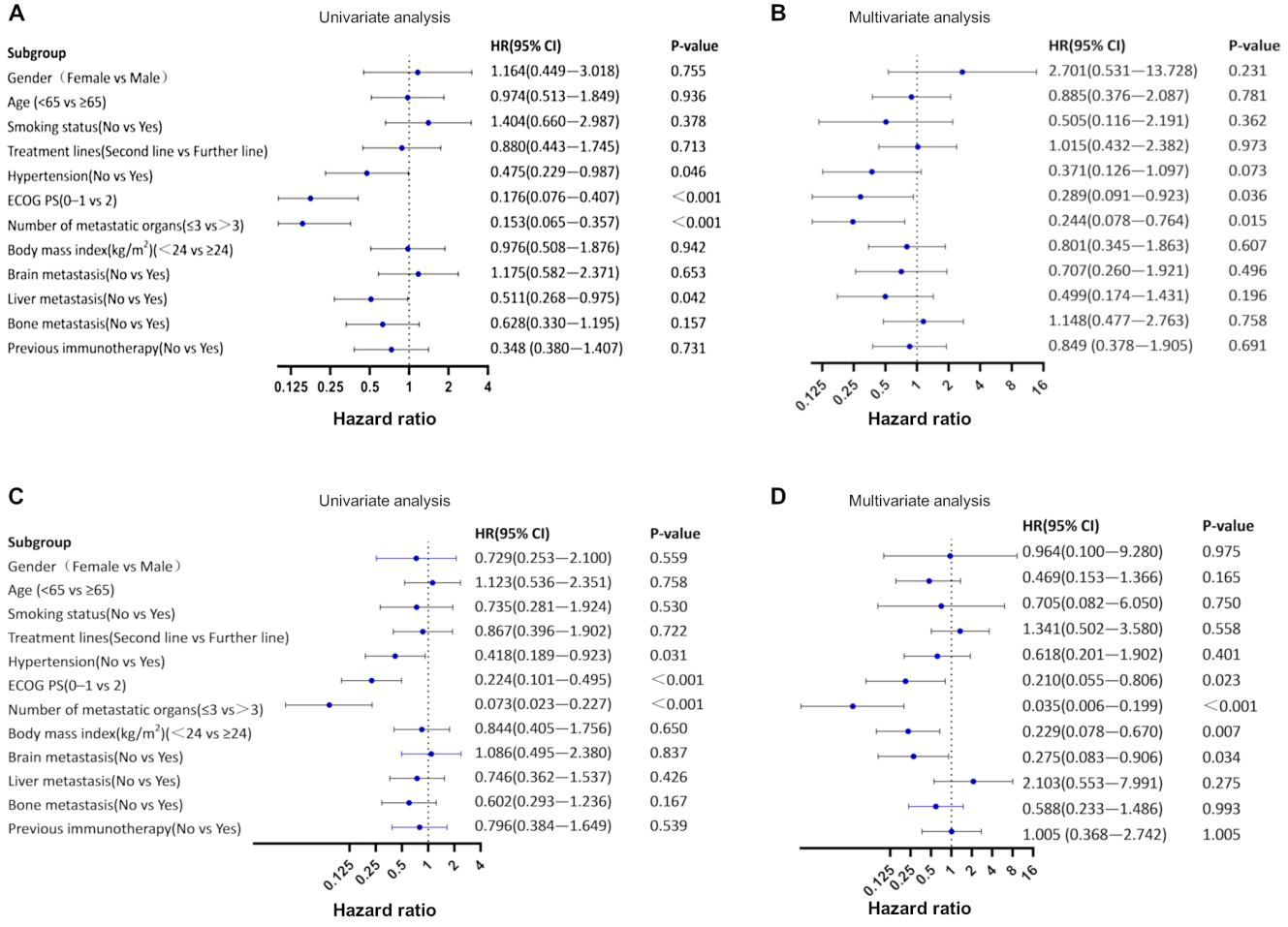

Figure 3. Univariate and multivariate analysis of factors PFS and OS. A) Univariate analysis of factors PFS; B) Multivariate analysis of factors PFS; C) Univariate analysis of factors OS; D) Multivariate analysis of factors OS.

of innate immune cells, including natural killer (NK) cells and antigen-presenting cells (APCs) such as M1-like TAMs and dendritic cells (DCs) while reducing the percentage of M2-like TAMs. Combining anlotinib with ICIs has shown a synergistic therapeutic effect [18]. Anlotinib, through its promotion of tumor vascular normalization via CD4+ T cells, can inhibit tumor growth and prevent systemic immunosuppression. Combining anlotinib with a PD-1 checkpoint inhibitor not only eliminates the immunosuppression caused by the up-regulation of PD-L1 induced by a single agent but also extends the duration of vascular normalization [33]. These findings are supported by several clinical trials that have demonstrated significant efficacy when using a combination of anti-vascular targeted drugs and ICIs for the treatment of solid tumors [20, 34, 35].

In this retrospective investigation, the mPFS was 4.0 months ($p<0.001$), and 2 months in the anlotinib combined with ICIs treatment group, compared to the irinotecan anlotinib treatment group. The mOS was 10.0 months ($p=0.015$) and 6 months, respectively. These findings align with Yu et al. research on the efficacy of anlotinib combined with ICIs in treating advanced SCLC, indicating similar efficacy. However, our study encompassed patients with more advanced diseases, all of whom were at stage IV [36]. The combination therapy was administered as a second-line and beyond terminal treatment to 43 patients. Among them, 28 patients (65.1%) achieved a mOS of 8 months. Furthermore, some patients experienced long-term benefits, with three of them having a PFS of over 33 months. There were no significant differences in survival between patients with or without metastases in the brain, liver, or bones in the subgroup analyses. However, patients with fewer than three metastatic organs experienced a survival benefit, highlighting the negative impact of high tumor load on anticancer immunity (Figures 3A–3D). These results are consistent with previous reports [37, 38]. Patients with an ECOG PS ≥2 were found to be strong independent predictors of poor efficacy response and OS ($p<0.001$, Figures 3A–3D). This finding aligns with the results of similar investigations conducted by Ma et al. on prognostic factors for SCLC [39]. When used as a third-line or beyond therapy, the combination of ICIs and anlotinib did not yield a significant difference in mOS compared to second-line therapy. However, it is worth noting that this combination may provide synergistic therapeutic benefits, even in late-stage treatment, for patients with ES-SCLC.

There was no significant difference in survival between patients with or without prior use of ICIs in this study. The 2020 Society for Immunotherapy of Cancer (SITC) working group defines tumor resistance to PD-1 pathway blockade. In this context, secondary resistance is characterized by disease progression following clinical benefit (objective remission or disease stabilization [CR/PR/SD] lasting 6 months or more) with ICI therapy [40]. All previous administrations of ICIs resulted in acquired resistance, and the addition of other ICIs may reactivate T cells, synergistically delaying T cell depletion [41]. Li et al.'s study on the reintroduction of immunotherapy after progression in patients with ES-SCLC demonstrated that the rechallenge group with ICIs after progression (RIBP) had a significantly longer overall survival of 6.2 months compared to the group that discontinued ICI therapy (DIBP) (mOS: 11.6 months vs. 5.4 months, HR 0.39, 95% CI 0.16–0.92) [42]. The majority of patients in this study did not undergo genetic testing, highlighting the need to identify appropriate biomarkers for treatment guidance.

Table 3. Main toxicities of anlotinib combine ICIs therapy.

Toxicity	Grades 1–2	Grade 3
Hand-foot syndrome	18 (41.8%)	1 (2.32%)
Hypertension	16 (37.2%)	2 (4.65%)
Fatigue	17 (39.5%)	0
Anorexia	10 (23.2%)	1 (2.32%)
Liver dysfunction	12 (27.9%)	0
Thrombocytopenia	7 (16.3%)	1 (2.32%)
Pruritus	5 (11.6%)	0
TSH elevation	4 (9.3%)	0
Oral mucositis	3 (6.98%)	1 (2.32%)
Proteinuria	2 (2.32%)	0
Skin rashes	2 (2.32%)	0
Cystitis	1 (2.32%)	0
Skin capillary hyperplasia	1 (2.32%)	0
Low hemoglobin	1 (2.32%)	1 (2.32%)
Hematochezia	1 (2.32%)	0
Diarrhea	1 (2.32%)	1 (2.32%)
Arthralgia	0	1 (2.32%)
Hypopituitarism	0	1 (2.32%)
Pneumonitis	0	1 (2.32%)
Hyperglycemia	0	1 (2.32%)
Hemoptysis	0	1 (2.32%)

Moreover, attention should be given to the management of AEs in ES-SCLC when using anlotinib in combination with ICIs. Eight patients experienced grade 3 AEs, including hand-foot syndrome and hypertension, which necessitated discontinuation of the drug. However, all of these AEs were successfully resolved after intervention. In the majority of patients, AEs were manageable, and all patients were able to recover with intervention. Additionally, some patients were able to maintain their condition even after reducing the dosage of the medication.

It is important to note that this investigation was retrospective, had a relatively small sample size, and was connected to selection bias, lacking a scientifically rigorous cohort design. Consequently, we advocate for prospective clinical trials with larger sample sizes to validate the feasibility of this therapy and identify predictive biomarkers for patient prognosis.

In conclusion, our findings indicate that the combination of anlotinib and ICIs is an effective regimen for the second- or subsequent-line treatment of advanced SCLC. Moreover, this combination therapy is well-tolerated by the study patients.

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