BMC Cancer

RESEARCH

Open Access

Anlotinib plus oral fluoropyrimidine S-1 in refractory or relapsed small-cell lung cancer (SALTER TRIAL): a multicenter, single-arm, phase II trial

Wei Wang[1,2†], Guixian Wu[3†], Wujun Luo[4†], Ling Lin[3], Chao Zhou[1], Guifei Yao[5], Meifang Chen[5], Xiaomai Wu[3], Ziran Chen [1], Junhui Ye[4,6*], Haihua Yang[1,2*] and Dongqing Lv[3*]

Abstract

Background Patients with small-cell lung cancer (SCLC) have few treatment options and dismal overall survival (OS) after failed platinum-based chemotherapy.

Methods The eligibility criteria of this phase II clinical trial included patients with measurable disease, age of 18 to 75 years, a confirmed diagnosis of disease progression or recurrence after prior platinum-based chemotherapy with a pathologically proven diagnosis of SCLC. Patients were treated with anlotinib at a dosage of 12 mg once daily (QD) and S-1 at 60 mg twice daily (BID) for 2 weeks, followed by a 1-week treatment-free interval. After six cycles of the above treatment, patients continued the maintenance therapy using S-1 monotherapy at 60 mg/ BID for 2 weeks, followed by a 1-week treatment-free interval until disease progression.

Results From March 2019 to June 2020, a total of 71 patients were initially assessed for eligibility in this study. Out of these, 52 patients who met the inclusion criteria were enrolled, and 48 patients received at least two doses of the study drug. The median follow-up time was 25.1 months. The ORR was seen in 21 patients (43.8%). The median PFS was 4.5 months (95% CI, 3.5–5.5 months), and the median OS was 5.9 months (95% CI, 4.6–7.3 months). The most common grade 3–4 treatment-related adverse events were thrombocytopenia (16.7%), anemia (14.6%), neutropenia (14.6%), and hypertension (10.4%). No treatment-related death occurred.

Conclusions The combination of anlotinib with oral fluoropyrimidine S-1 demonstrated notable activity in relapsed or refractory SCLC, showing a favorable ORR and an acceptable, manageable safety profile.

Trial registration This trial was registered with ClinicalTrial.gov (NCT03823118) on 3 January 2019.

Keywords Small-cell lung cancer, Antiangiogenic TKIs, Oral fluoropyrimidine S-1, Relapse, Treatment outcome

†Wei Wang, Guixian Wu and Wujun Luo contributed equally to this study as the first authors.

*Correspondence:
Junhui Ye
smyejh@163.com
Haihua Yang
yhh93181@hotmail.com
Dongqing Lv
lvdq@enzemed.com
Full list of author information is available at the end of the article

Introduction

Small cell lung cancer (SCLC) is a highly metastatic and recalcitrant carcinoma, which accounts for approximately 10–13% of all lung cancers [1–3]. Platinum-based chemotherapy has been the backbone of SCLC treatment over the past decades. While in addition of extensive-stage SCLC, the programmed death-ligand 1 (PD-L1) inhibitors has demonstrated a sustained overall survival (OS) benefit and currently is considered as the standard first-line treatment [4, 5]. Unfortunately, most patients inevitably develop resistance to these therapies. There is an absence of effective therapies for recurrent and progressive diseases.

Angiogenesis plays an important role in tumor initiation and progression in SCLC, and the therapeutic activity of single-agent vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI) by targeting VEGFRs has been shown a disheartening outcomes from previous phase 2 studies in second or later line treatment for SCLC [6–8]. Anlotinib, a potent novel oral multi-target anti-angiogenesis receptor tyrosine kinase (RTK) inhibitor, inhibits tumor angiogenesis by inhibiting VEGFRs and PDGFR. It also suppresses tumor cell proliferation by blocking c-Kit, PDGFR, Ret, c-FMS, Aurora-B, and discoidin domain receptor 1 (DDR1) [9]. Several clinical trials demonstrated that anlotinib had robust antitumor efficacy in many types tumor, therefore, it has been approved by the Chinese FDA to treat several types of cancer as a second or later-line option, such as non-small cell lung cancer [10]. advanced or metastatic medullary thyroid carcinoma [11], and refractory metastatic soft-tissue sarcom [12]. In a multinational, randomized phase II study (ALTER 1202), anlotinib monotherapy significantly improved overall response rate (ORR) (4.9% vs. 2.6%) compared with placebo in patients with progression SCLC who has been given at least two lines of chemotherapy, and median progression-free survival (PFS) was 4.1 and 0.7 months, respectively [13]. However, whether the combination of anlotinib and chemotherapy can improve outcome in second-line or later setting is unknown.

S-1, a new oral fluoropyrimidine cytotoxic anticancer drug, is a combination of three pharmacological compounds tegafur (prodrug of 5-fluorouracil), gimeracil, and oteracil potassium in a molar ratio of 1:0.4:1. S-1 was approved in Europe for the treatment of patients with non-small cell lung cancer (NSCLC) and gastrointestinal tumors. In a Japanese phase II trial enrolled 26 patients with relapsed SCLC who were treated with S-1 monotherapy, only one patient (3.8%) had an overall response, with a median PFS of 1.1 months [14].

Our previous basic research found that the treatment of combination of antitumor angiogenesis agent anlotinib with chemotherapy drug 5-FU may have synergistic cytotoxicity to SCLC in vitro and in vivo. This treatment modality reduced cell proliferation and migration via Src/AKT pathway [15]. We conducted this open-label, single arm, multicenter, Phase II Trial (SALTER TRIAL, NCT03823118) to assess the efficacy and safety of anlotinib in combination with oral fluoropyrimidine S-1 in patients with refractory or relapsed SCLC.

Study design and methods

Study design and eligibility criteria

SALTER TRIAL was an open-label, multicenter, single arm phase II study designed to evaluate the efficacy and safety of anlotinib in combination with oral fluoropyrimidine S-1 in patients with relapsed or refractory SCLC (ClinicalTrial.gov number, NCT03823118).

Patients eligible for enrollment were required to meet the following criteria: histologically or cytologically confirmed diagnosis of SCLC; patients with platinum-resistant (relapse < 90 days after or during chemotherapy) or platinum-sensitive (relapse ≥ 90 days after chemotherapy) whose disease progression after at least one previous platinum-based chemotherapy regimen, for platinum-sensitive population whose disease progression after at least two chemotherapy regimens. another line chemotherapy is required; aged 18 to75 years; an estimated life expectancy of at least three months; adequate organ function per protocol; at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [16]; the Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2. Patients with limited-stage SCLC in our study conventionally received prophylactic brain irradiation.

Key exclusion criteria included tumour histology that was predominantly NSCLC, mixed small cell, or a combination of both histologies; previous treatment with anti-angiogenesis (VEGF/VEGFR) inhibitor; active symptomatic brain or meningeal metastases (a brain magnetic resonance imaging scan was mandatory); history of malignancy within the last 5 years except for in basal cell carcinoma or situ cervical carcinoma.

This study was approved by the Institutional Review Boards at each participating institution, and was carried out in accordance with Good Clinical Practices and the Declaration of Helsinki [17], and local ethical and legal requirements. All patients provided written informed consent before their participation in the study.

Treatment

Patients were treated with oral anlotinib (12 mg, QD) plus oral fluoropyrimidine S-1 (60 mg, BID). Each cycle was defined as consecutive 2 weeks on-treatment follow by 1 week off-treatment [8]. After six cycles of combined

treatment, S-1 single-agent maintenance treatment was continually followed (3-week as a cycle, 2 week on-treatment follow by 1 week off-treatment) unless the occurrence of disease progression, unacceptable toxicity, withdrawal of consent, or study completion.

Endpoints and assessments

The primary endpoint of this study was investigator-assessed ORR. Key secondary endpoints were PFS, OS and treatment-related adverse events (TRAEs). Treatment response was evaluated using a combination of conventional CT scans and MRI, selected to provide a comprehensive assessment, particularly for the detection of brain and liver metastases. Tumor response was assessed by at least two study investigators according to RECIST criteria v1.1 [16].

Investigator-assessed ORR was defined as the proportion of patients achieving a complete response (CR) or partial response (PR). PFS was defined at the time from initiation of therapy to the date of first documented tumor progression according to RECIST criteria v1.1 [16], or death due to any cause. OS was defined as the time between initiation of therapy and the date of death or censoring on the day of the last follow-up visit. Disease control rate (DCR) was defined as the proportion of patients who achieved a best ORRs of CR, PR, or stable disease (SD). TRAEs were assessed and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0 [18, 19].

Sample size and statistical analysis

We planned to enroll 37 patients to accept the hypothesis that the true ORR was 50% of with 80% power and to reject the hypothesis that the ORR was < 20%, with a two-sided alpha level of 5%. Considering a 20% drop-off rate, the total number of patients was estimated to be 45.

Descriptive statistics were used for baseline characteristics of included patients, tumor-response data analysis, and summary statistics for TRAEs. PFS and OS were calculated using the Kaplan–Meier method. Statistical analyses were performed using GraphPad Prism software (Version 9, GraphPad Software) and R software (version 4.1.3, R Foundation for Statistical Computing). Two-sided values of $p \leq 0.05$ were considered statistically significant.

Results

Patients and baseline characteristics

Between March 2019 to June 2020, a total of 71 patients with relapsed or refractory SCLC were reviewed for eligibility. Among those eligible, 19 patients were excluded (12 patients did not meet the eligibility criteria, 5 patients declined to participate and 2 patients with others), and 4 patients were excluded from the final analysis because of inadequate data (two patients received only one course combination treatment, two patients were not received response assessment). Therefore, a total of 48 patients were included for final analysis in the study, including 44 men (91.70%) and 4 women (8.30%) (Fig. 1). Their median age was 65 (range 37–75) years. Among those 48 patients, 47 (95.8%) were extensive-stage SCLC, and 27 (56.30%) were platinum-resistant (progression during or 90 days after platinum). A total of 29 patients (60.4%) in our study received 4–6 cycles of chemotherapy as part of their first-line treatment. including 21 platinum-sensitive and 8 platinum-resistant patients. The baseline characteristics are shown in Table 1.

Treatment and efficacy

Two-hundred one S-1 and anlotinib combination treatment courses in total were administered, with a median of three courses per patient, and 12 patients received S-1 single-agent maintenance treatment.

At data cut-off April 17, 2021, median follow-up time was 25.1 months. According to the investigator assessment of all treated patients, the ORR was 43.8% (Fig. 2), all responses were PR. The DCR was 89.3%, including the

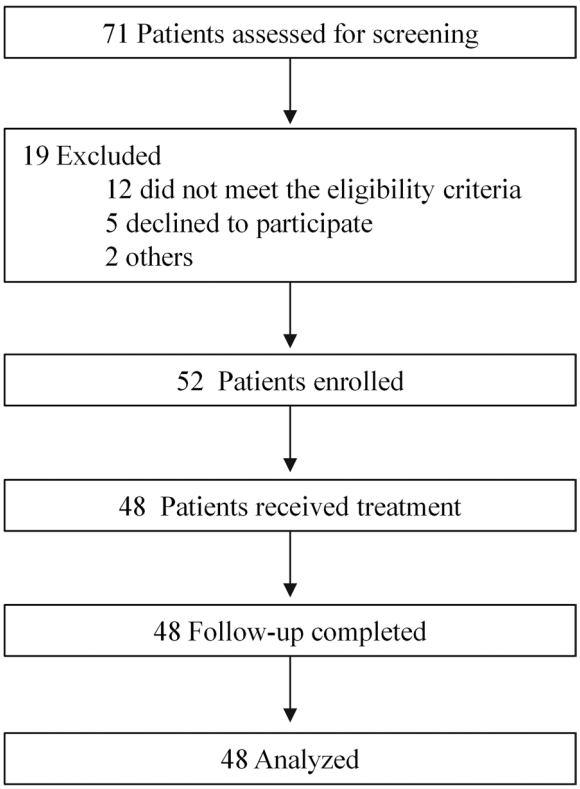

Fig. 1 CONSORT flow diagram of study enrollment

Table 1 Patient demographics and baseline characteristics

	Number (%)
Age, median (range), years	65 (37–75)
Sex	
male	44 (91.7%)
female	4 (8.3%)
ECOG performance status	
0	5 (10.4%)
1	28 (58.3%)
2	15 (31.1%)
Smoking status	
Current/former smoker	37 (77.1%)
Never smoked	11 (22.9%)
Disease classification at initial diagnosis	
Limited disease	1 (4.2%)
Extensive disease	47 (95.8%)
Response to first-line therapy	
Platinum sensitive	21 (43.7%)
Platinum resistant	27 (56.3%)
Central nervous system metastases	
Yes	13 (27.1%)
No	35 (72.9%)
Liver metastases	
Yes	18 (37.5%)
No	30 (62.5%)

21 (43.8%) patients had PR, and 22 (45.5%) patients had SD. Antitumor activity by investigator assessment are summarized in Table 2.

The Kaplan–Meier estimates for PFS and OS are shown in Fig. 3. Investigator-assessed median PFS was 4.5 months (95% CI, 3.5–5.5 months), median OS was 6.3 months (95% CI, 4.6–7.3 months).

We performed a subgroup analysis to assess the impact of response to first-line therapy, brain metastasis, liver metastasis, and smoking status on treatment outcomes, focusing on key clinical endpoints including ORR, median PFS, and median OS, as summarized in Tables 3 and 4. Notably, in the liver metastasis subgroup, patients without liver metastases demonstrated a significantly higher ORR compared to those with liver metastases (56.7% vs. 22.2%, $p=0.037$). However, despite this difference in ORR, no significant differences in PFS and OS were observed between these two groups. Furthermore, subgroup analyses based on response to first-line therapy, brain metastasis status, and smoking status did not reveal any significant differences in ORR, PFS, or OS.

Additionally, we conducted an analysis to examine whether there is a correlation between dose reduction and treatment response. Our results showed that in the dose-adjustment group, 3 out of 6 patients (50.0%) achieved PR, while 18 out of 42 patients (42.9%) in the full-dose group achieved PR. This analysis indicated that there was no significant difference in response rates between the dose-reduction group and the full-dose group.

Safety

Three patients had a dose reduction of 10 mg per day, one patient had a dose reduction to 8 mg in anlotinib treatment, and one patient had S-1 dose reduction to 40 mg per day due to anemia. Both anlotinib and S-1 dose administration was reduced in 1 (2.0%) patient because of TRAEs.

A safety summary of TRAEs was presented in Table 3 (grade 1–2 TRAEs that reported ≥ 10% of patients and all grade 3–4 TRAEs). At least one TRAE was reported in all 48 patients (100%), the most frequently reported TRAEs of any grade were hematological AEs (62.5%), hypertension (47.9%), skin hyperpigmentation (37.5%), fatigue (35.4%), appetite decrease (35.4%), weight loss (31.2%) and hyperbilirubinaemia (20.8%).

Grade 3 or 4 TRAES were observed in 19 (39.6%) patients, the most common grade 3 or 4 TRAEs were hematologcial (18.8%), hypertension (10.4%), fatigue (8.3%), hand-foot syndrome (4.2%), anorexia (6.3) and blurred vision (4.2%). All TRAEs during trial were controlled after dose modification or symptomatic treatment and no patients had discontinued treatment because of TRAEs. No treatment-related deaths occurred.

Discussion

The SALTER Trial meets its primary endpoint of improved ORR versus histological report standard treatment as second-line or later treatment in patients with SCLC whose disease progression after at least one platinum-based chemotherapy [18, 19]. Our findings showed that the combination of S-1 and anlotinib exhibited robust antitumor activity in ≥ 2L SCLC patients.

This study confirmed that the combination therapy of anlotinib and S-1 demonstrated greater clinical efficacy than either anlotinib or S-1 monotherapy in relapsed or refractory SCLC. Previous clinical trials reported objective response rates of only 3.8% with S-1 monotherapy and 4.9% with anlotinib monotherapy, whereas our study observed a notably higher ORR of 43.8% with combination therapy. This enhanced antitumor activity may be attributed to the synergistic effects of anlotinib and S-1, as combination therapies often produce better outcomes by targeting multiple pathways involved in tumor growth and progression. Our previous research supports this, showing that the combination of anlotinib and 5-FU (the active component of S-1) increases cytotoxicity against SCLC both in vitro and in vivo [15].

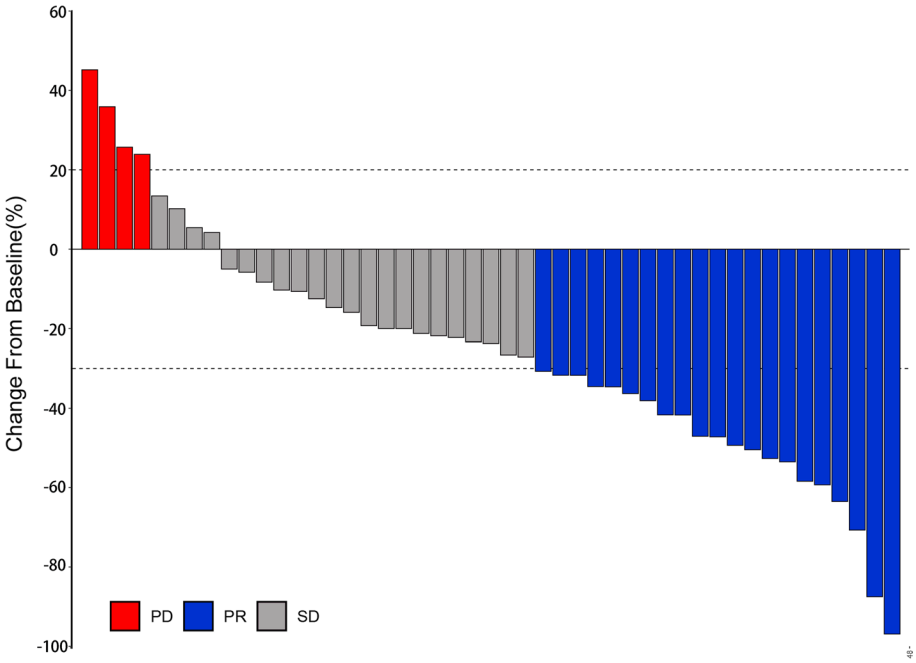

Fig. 2 Waterfall plot showing the best change in tumor burden from baseline ($n=47$). A waterfall plot depicting the best response to the study treatment in patients with refractory or relapsed small-cell lung cancer is presented. The Y-axis represents the percentage of maximum tumor reduction, assessed according to RECIST version 1.1. Out of the 48 study participants, 47 were eligible for inclusion in this analysis, as one patient (ID14) experienced rapid progression during the first-course combination treatment and did not undergo response assessment. The upper and lower dotted lines on the plot represent 20% tumor growth and 30% tumor reduction, respectively, which define progressive disease and partial response. Objective partial responses are denoted in blue ($n=21$), stable disease is shown in gray ($n=22$), and progression disease is shown in red ($n=4$)

Table 2 Summary of tumor response

Response	No. (%)
Objective response	
Patients with response, n % of patients	21(43.8%)
Disease control rate, n % of patients	43 (89.3%)
Best overall response, n (%)	
Complete response	0 (%)
Partial response	21 (43.8%)
Stable disease	22 (45.5%)
Progressive disease	4 (4.2%)
Could not be determined	1 (2.0%)

Additionally, differences in patient populations between studies may have contributed to the varying outcomes. Factors such as differences in patient characteristics, treatment history, and disease burden could all influence treatment response. The small sample size in our study might also amplify these differences, leading to the promising results observed. In addition, the ORR in our study was notably higher than immune-based treatment strategies and traditional cytotoxic chemotherapy for relapsed SCLC [20–22]. For Instance, FDA-approved topotecan, commonly used as second-line therapy, typically yields ORRs below 25% [18, 23, 24], while immune-based treatment strategies, such as nivolumab in the Checkmate 331 trial, showed response rates of just 13.6% [19]. Similarly, lurbinectedin monotherapy reported an ORR of 45% [25] and its combination with irinotecan reached an ORR of 62% [26], single agent amrubicin showed 31% ORRs [23]. PARP inhibitors, such as Olaparib combined with temozolomide, achieved a 41.7% ORR [27], while temozolomide with another PARP inhibitor veliparib showed a 39% ORR [28]. Meanwhile, in a phase 2 trial, PD-1inhibitor camrelizumab combined with apatinib demonstrated an ORR of 34.0% [29]. The most recent phase 2 DeLLphi-301 trial (NCT05060016), Ahn et al. evaluated the antitumor activity and safety of tarlatamab, a bispecific T-cell engager targeting delta-like ligand 3 (DLL3) and CD3, in patients with advanced SCLC who had previously received two or more lines of therapy. The study reported ORR,of 40% in the 10-mg cohort and 32% in the 100-mg cohort [30]. Furthermore, the ORR of the present trial was also higher than reported for other anti-VEGFR-TIKs monotherapy such as sorafenib [6], pazopanib [7], apatinib [8] in relapsed or refractory SCLC. Table 5

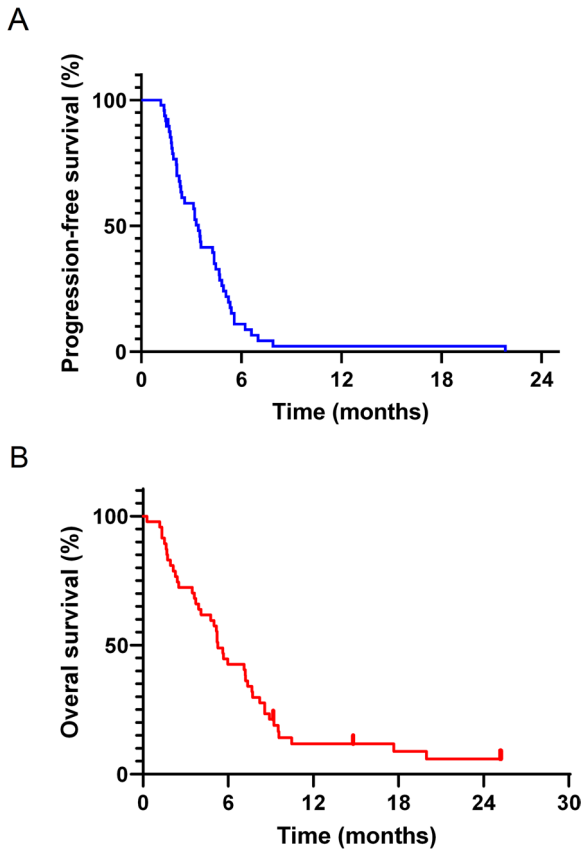

Fig. 3 Efficacy of S-1 in combination with anlotinib. **A** Kaplan–Meier estimates progression-free survival. **B** Kaplan–Meier estimates overall survival

summarized the outcomes of anlotinib for relapsed SCLC from selected studies.

However, while the combination of S-1 and anlotinib significantly improved ORR, this did not translate into significant PFS or OS benefits in the overall population. Previous studies have shown that OS outcomes in relapsed SCLC are strongly influenced by the time from initial therapy to relapse and the availability of subsequent treatment options [40]. Several factors may explain the lack of significant survival benefits in this study. First, approximately 56.3% of patients had a treatment-free interval of fewer than 90 days at study entry. Second, most patients (95.8%) were diagnosed with extensive-stage disease at baseline. Third, 56.7% of patients had already received third-line therapy. Lastly, there was a high incidence of brain metastasis (27.1%) and liver metastasis (37.5%), both of which are associated with poorer prognoses in SCLC.

Despite the absence of survival benefits in the overall population, S-1 maintenance therapy appeared promising in a subgroup of patients. Among the 12 patients who received maintenance treatment, 3 achieved long-term disease control, with 2 remaining alive for more than 24 months. The median OS in the maintenance therapy group was nearly double that of the non-maintenance group (10.1 months vs. 5.1 months, HR = 0.390, p = 0.003). These results suggest that S-1 maintenance therapy may provide durable benefits for a subset of patients, highlighting the need for further investigation in future studies.

In the subgroup analysis, ORR was similar between platinum-sensitive and platinum-resistant groups (47.6% vs. 40.7%), which contrasts with previous studies reporting inferior ORR in platinum-resistant patients. A systematic analysis included 21 clinical studies reported ORRs

Table 3 Clinical outcomes by subgroup analysis

	ORR		Median PFS		Median OS	
	(%, 95CI)	*p*	(HR, 95%CI)	p	(HR, 95%CI)	p
Response to first-line therapy						
Platinum resistant	47.6 (23.3–67.6)	0.576	0.89 (0.50–1.60)	0.456	0.55 (0.30–1.00)	0.093
Platinum resistant	40.7 (23.6–57.6)		1.12 (0.63–2.00)		1.82 (0.99–3.31)	
Brain metastases						
Yes	38.5 (17.7–64.5)	0.750	1.29 (0.65–2.56)	0.422	1.40 (0.68–2.88)	0.317
No	45.7 (30.5–61.8)		0.77 (0.39–1.50)		0.72 (0.35–1.47)	
Liver metastases						
Yes	22.2 (9.0- 45.2)	0.034	1.00(0.55–1.82)	0.995	1.37 (0.72–2.60)	0.308
No	56.7 (39.2–72.6)		1.00 (0.55–1.82)		0.73 (0.38–1.40)	
Smoking status						
Current/former smoker	36.4 (31.0–61.6)	0.670	1.64 (0.88–3.00)	0.137	1.57 (0.81–3.01)	0.160
Never smoked	45.9 (15.2–64.6)		0.61 (0.33–1.13)		0.64 (0.33–1.23)	

Table 4 Treatment-related adverse events occurring in ≥ 10% of patients

	Any grade	Grade 3 or 4
	48 (100.0%)	19 (39.6%)
Hematologic		
Leukopenia	22 (45.8%)	4 (8.3%)
Neutropenia	14 (29.2%)	7 (14.6%)
Lymphopenia	17 (35.4%)	3 (6.3%)
Thrombocytopenia	25 (52.1%)	8 (16.7%)
Anemia	37 (77.1%)	7 (14.6%)
Non-hematologic		
Fatigue	17 (35.4%)	4 (8.3%)
Appetite decreases (anorexia)	17 (35.4%)	3 (6.3%)
Nausea	4 (8.3%)	0
Vomiting	5 (10.4%)	0
Constipation	5 (10.4%)	0
Weight loss	15 (31.2%)	1 (2.8%)
Hand-food skin reaction	13 (27.1%)	2 (4.2%)
Hypertension	23 (47.9%)	5 (10.4%)
proteinuria	7 (14.5%)	1
Skin hyperpigmentation	18 (37.5%	1
blurred vision	6 (12.5%)	1
Hemoptysis	5 (10.4%)	1
Hyperbilirubinaemia	10 (20.8%)	none

of 27.7% in the platinum-sensitive group and 14.8% in the platinum-resistant group [40]. Treatment with the multi-kinase inhibitor sorafenib resulted in an ORR of 11% in the platinum-sensitive and 2% in the platinum-refractory stratum [6]. In our study, the median PFS (4.7 m vs. 4.3 m, HR = 1.09, $p > 0.05$) and OS (6.6 m vs. 5.9 m, HR = 0.50. $p > 0.05$) were comparable between the platinum-sensitive and platinum-resistant groups in the current study. The sensitive disease derived more clinical benefit from subsequent system treatment than resistant/refractory disease both in terms of PFS and OS. A system analysis showed the median OS was 7.73 months for sensitive SCLC and 5.45 months for refractory disease [40]. Specifically, in the present study, the median number of treatment lines was 2 for platinum-resistant patients and 3 for platinum-sensitive patients. Furthermore, our study revealed a significantly higher ORR in patients without liver metastases compared to those without liver metastases (56.7% vs. 22.2%, p = 0.037). This finding is consistent with previously, where the presence of liver metastases has been associated with poorer outcomes in SCLC. Liver metastases are often considered a marker of more aggressive disease and are linked to a higher tumor burden, which may contribute to the reduced efficacy of systemic therapies.

The toxicity profile was consistent with previously reported findings for monotherapies or combination therapies involving the component agents [7, 14, 41]. In our study, any grade TRAEs were observed in 100% of

Table 5 Outcomes of anlotinib for relapsed SCLC from selected studies

	Study design	Treatment scheme	Number of Patients	Treatment Line	ORR	DCR	Median PFS (months)	Median OS (months)
Present study (NCT03823118)	Phase 2, pro	Anlo + S-1	48	≥ 2L	43.8%	89.3%	4.5	5.9
Chen et al. [13] (NCT03059797)	Phase 2, RCT	Anlo placebo	81 36	≥ 3L	4.9% 2.6%	71.6% 13.2%	4.1 0.7	7.3 4.9
Wu et al. [31] (NCT03732846)	Phase 2	Anlo	45	≥ 3L	11.0%	67.0%	4.1	6.1
Gao et al. [32]	Retrospective	Anlo	40	≥ 3L	10.0%	45.0%	3.0	7.8
Xia et al. [33, 34] (NCT04757779)	Phase 2	Anlo + irinotecan/docetaxel	24	2L(relapsed ≤ 6mon)	47.6%	90.5%	4.0	7.5
Ma et al. [35] (NCT04055792)	Phase 2	Anlo + sintilimab	26	≥ 2L	45.5%	86.4%	5.7	11.4
Zhang et al. [36] (NCT04203719)	Phase 2	Anlo + Penpulimab	20	2L	50.0%	75.0%	4.7	/
Wang et al. [37]	Retrospective	Anlo Chemo	28 27	≥ 3L	/	/	3.6 2.7	5.3 6..6
Hao et al. [38]	Retrospective	Anlo + PD(L)1i	36	≥ 2L	27.8%	80.6%	4.6	9.3
Chen et al. [39]	Retrospective	Anlo Anlo + ICI	58 62	3L	6.9% 19.4%	72.4% 87.1%	4.6 4.5	/

RCT Randomized controlled trial, *anlo* anlotinib, *chemo* chemotherapy, *ICI* immune checkpoint inhibitor

patients, with grade 3 or 4 TRAEs occurring in 39.6%. These rates appear slightly higher than those previously reported for either S-1 or anlotinib monotherapy. A Japanese phase II study of S-1 monotherapy for relapsed SCLC reported grade 3 or 4 AEs in 7.7% of patients [14], while another trial of anlotinib monotherapy reported grade 3 or 4 TRAEs in 35.8% of patients [7]. Furthermore, in our study, the combination of anlotinib and S-1 resulted in higher frequency of grade 3 or 4 TRAEs compared to prior reports in EGFR-mutant NSCLC populations treated with this combination [42]. Nonetheless, the toxicity profile observed in this combination treatment was manageable and acceptable within the context of the therapeutic benefit, supporting the overall safety of the treatment regimen for further clinical investigation.

There are several limitations to our study. First, the single-arm design lacked a control group for comparison, and the enrolled patient population was heterogeneous, which may have impacted the consistency of the findings. Additionally, the open-label nature of the trial introduces potential bias in both outcome reporting and assessment, as both investigators and patients were aware of the treatment being administered. Moreover, fresh tumor specimens were not collected before treatment, preventing biomarker analyses that could have offered deeper insights into the mechanisms underlying treatment response and resistance. Future studies should aim to incorporate a randomized control group and conduct biomarker analyses to better define the therapeutic potential of this regimen.

Conclusions

The combination of anlotinib and oral fluoropyrimidine S-1 showed robust antitumor activity in terms of ORR, with a manageable and acceptable safety profile as a second- or later-line treatment for relapsed or refractory SCLC. These results suggest that this regimen could be a viable therapeutic option for this patient population in second-line or beyond treatments.

Acknowledgements
We thank the patients, their families, and the participating trial teams for making this trial possible.

Disclosure
Part of this work was presented at the European Society for Medical Oncology (ESMO) Virtual Annual Meeting, September 16-21, 2021.

Authors' contributions
Wei Wang, Guixian Wu and Wujun Luo: Data analysis; Accessed and verified the underlying data; Manuscript writing & final approval of manuscript. Ziran Chen, Ling Lin, Chao Zhou, Guifei Yao, Meifang Chen: Provision of study materials or patient; Collection and assembly of data, writing & final approval of manuscript. Xiaomai Wu: Collection and assembly of data, writing & final approval of manuscript Junhui Ye, Haihua Yang, Dongqing Lv: Conception and design; Administrative support; Collection and assembly of data; Accessed and verified the underlying data writing & final approval of manuscript.

Funding
Medicine and Health Science and Technology Project of Zhejiang Province (2024KY1829).

Availability of data and materials
The de-identified datasets created and analyzed during the current study are available with investigator support, after approval of a proposal and with a signed data access agreement.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Ethics Review Boards at each participating institution, including the Institutional Medical Ethics Review Board at Taizhou Hospital of Zhejiang Province, the Institutional Medical Ethics Review Board at Enze Hospital, Taizhou Enze Medical Center (Group), and the Institutional Medical Ethics Review Board at Sanmen People's Hospital. The study was conducted in accordance with Good Clinical Practices, the Declaration of Helsinki, and local ethical and legal requirements. All patients provided written informed consent before they participated in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Radiation Oncology, Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University, Taizhou, Zhejiang 317000, China. [2]Department of Radiation Oncology, Key Laboratory of Radiation Oncology of Taizhou, Radiation Oncology Institute of Enze Medical Health Academy, Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University, Taizhou, Zhejiang 317000, China. [3]Department of Respiratory and Critical Care Medicine, Enze Hospital, Taizhou Enze Medical Center (Group), Taizhou, Zhejiang Province 318050, China. [4]Department of Respiratory and Critical Care Medicine, Sanmen People Hospital, Taizhou, Zhejiang Province 317100, China. [5]Department of Respiratory and Critical Care Medicine, Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University, Taizhou, Zhejiang Province 317000, China. [6]Department of Pulmonary Medicine, Sanmen People Hospital, Taizhou, Zhejiang Province 317100, China.

Received: 22 May 2024 Accepted: 13 September 2024
Published online: 27 September 2024

References

1. Alexopoulos G, Zhang J, Karampelas I, Patel M, Kemp J, Coppens J, et al. Long-term time series forecasting and updates on survival analysis of glioblastoma multiforme: A 1975–2018 population-based study. Neuroepidemiology. 2022;56:75–89.
2. Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, et al. Changing epidemiology of small-cell lung cancer in the united states over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol. 2006;24:4539–44.
3. Dingemans A-MC, Früh M, Ardizzoni A, Besse B, Faivre-Finn C, Hendriks LE, et al. Small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up☆. Ann Oncol. 2021;32:839–53.
4. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394:1929–39.
5. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379:2220–9.
6. Gitlitz BJ, Moon J, Glisson BS, Reimers HJ, Bury MJ, Floyd JD, et al. Sorafenib in platinum-treated patients with extensive stage small cell lung cancer: a Southwest Oncology Group (SWOG 0435) phase II trial. J Thorac Oncol. 2010;5:1835–40.

7. Koinis F, Agelaki S, Karavassilis V, Kentepozidis N, Samantas E, Peroukidis S, et al. Second-line pazopanib in patients with relapsed and refractory small-cell lung cancer: a multicentre phase II study of the Hellenic Oncology Research Group. Br J Cancer. 2017;117:8–14.
8. Liu Q, Xu J-Y, Xu Y-H, Chen M, Deng L-C, Wu J-P, et al. Efficacy and safety of apatinib as second or later-line therapy in extensive-stage small cell lung cancer: a prospective, exploratory, single-arm, multi-center clinical trial. Transl Lung Cancer Res. 2022;11:832–44.
9. Sun Y, Niu W, Du F, Du C, Li S, Wang J, et al. Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. J Hematol OncolJ Hematol Oncol. 2016;9:105.
10. Han B, Li K, Wang Q, Zhang L, Shi J, Wang Z, et al. Effect of anlotinib as a third-line or further treatment on overall survival of patients with advanced non-small cell lung cancer: the ALTER 0303 phase 3 randomized clinical trial. JAMA Oncol. 2018;4:1569.
11. Li D, Chi Y, Chen X, Ge M, Zhang Y, Guo Z, et al. Anlotinib in locally advanced or metastatic medullary thyroid carcinoma: a randomized, double-blind phase IIB rial. Clin Cancer Res. 2021;27:3567–75.
12. Chi Y, Fang Z, Hong X, Yao Y, Sun P, Wang G, et al. Safety and efficacy of anlotinib, a multikinase angiogenesis inhibitor, in patients with refractory metastatic soft-tissue sarcoma. Clin Cancer Res. 2018;24:5233–8.
13. Cheng Y, Wang Q, Li K, Shi J, Liu Y, Wu L, et al. Anlotinib vs placebo as third- or further-line treatment for patients with small cell lung cancer: a randomised, double-blind, placebo-controlled Phase 2 study. Br J Cancer. 2021;125:366–71.
14. Kudo K, Ohyanagi F, Horiike A, Miyauchi E, Tahanaka H, Yanagitani N, et al. A phase II study of S-1 in relapsed small cell lung cancer. Mol Clin Oncol. 2013;1:263–6.
15. Xia X, Pi W, Lan Y, Wu X, Lv D, Meng Y, et al. Synergistic antitumor effects of anlotinib combined with oral 5-fluorouracil/S-1 via inhibiting Src/AKT signaling pathway in small-cell lung cancer. Anal Cell Pathol. 2022;2022:1–9.
16. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: evised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.
17. World Medical Association Declaration of Helsinki. JAMA. 2013;310:2191.
18. O'Brien MER, Ciuleanu T-E, Tsekov H, Shparyk Y, Čučeviá B, Juhasz G, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol. 2006;24:5441–7.
19. Eckardt JR, von Pawel J, Pujol J-L, Papai Z, Quoix E, Ardizzoni A, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. J Clin Oncol. 2007;25:2086–92.
20. Spigel DR, Vicente D, Ciuleanu TE, Gettinger S, Peters S, Horn L, et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331☆. Ann Oncol. 2021;32:631–41.
21. Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016;17:883–95.
22. Ready NE, Ott PA, Hellmann MD, Zugazagoitia J, Hann CL, de Braud F, et al. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: results from the CheckMate 032 randomized cohort. J Thorac Oncol. 2020;15:426–35.
23. von Pawel J, Jotte R, Spigel DR, O'Brien MER, Socinski MA, Mezger J, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. J Clin Oncol. 2014;32:4012–9.
24. Blackhall F, Jao K, Greillier L, Cho BC, Penkov K, Reguart N, et al. Efficacy and safety of rovalpituzumab tesirine compared with topotecan as second-line therapy in DLL3-High SCLC: results from the phase 3 TAHOE tudy. J Thorac Oncol. 2021;16:1547–58.
25. Trigo J, Subbiah V, Besse B, Moreno V, López R, Sala MA, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol. 2020;21:645–54.
26. Ponce-Aix S, Coté G, Falcón A, Jimenez-Aguilar E, Lin J, Sánchez Simón I, et al. OA11.04 lurbinectedin with irinotecan in relapsed small cell lung cancer. results from the expansion stage of a phase I-II Trial. J Thorac Oncol. 2021;16:S127.
27. Farago AF, Yeap BY, Stanzione M, Hung YP, Heist RS, Marcoux JP, et al. Combination olaparib and temozolomide in relapsed small-cell lung cancer. Cancer Discov. 2019;9:1372–87.
28. Pietanza MC, Waqar SN, Krug LM, Dowlati A, Hann CL, Chiappori A, et al. Randomized, double-blind, phase II study of temozolomide in combination with either veliparib or placebo in patients with relapsed-sensitive or refractory small-cell lung cancer. J Clin Oncol. 2018;36:2386–94.
29. Fan Y, Zhao J, Wang Q, Huang D, Li X, Chen J, et al. Camrelizumab plus apatinib in extensive-stage SCLC (PASSION): a multicenter, two-stage, phase 2 trial. J Thorac Oncol. 2021;16:299–309.
30. Ahn M-J, Cho BC, Felip E, Korantzis I, Ohashi K, Majem M, et al. Tarlatamab for patients with previously treated small-cell lung cancer. N Engl J Med. 2023;389:2063–75.
31. Wu D, Nie J, Hu W, Dai L, Zhang J, Chen X, et al. A phase II study of anlotinib in 45 patients with relapsed small cell lung cancer. Int J Cancer. 2020;147:3453–60.
32. Gao X, Peng L, Zhang L, Huang K, Yi C, Li B, et al. Real-world efficacy and safety of anlotinib as third- or further-line treatment in refractory small cell lung cancer. J Cancer Res Clin Oncol. 2022;148:2661–71.
33. Xia B, Chen X, Jiang H, Wang J, Ye J, Ma S, et al. 1657P Anlotinib plus irinotecan or docetaxel in small-cell lung cancer (SCLC) relapsed within six months: Updated results from a single-arm phase II study. Ann Oncol. 2021;32:S1167.
34. Zhang M, Chen X, Jiang H, Wang J, Ye J, Ma S, et al. The effect and safety of anlotinib combined with irinotecan or docetaxel in small-cell lung cancer (SCLC) relapsed within six months: a single-arm phase I study. J Clin Oncol. 2021;39:39 15_suppl:e20583-e20583.
35. Shuxiang M, Zhen H, Lili W, Yufeng W, Sen Y, Haiyang C, et al. 69P Combining sintilimab with anlotinib as second-line or later therapy in patients with extensive-disease small cell lung cancer: a prospective, single-arm, phase II trial. Ann Oncol. 2021;32:S1402.
36. Zhang C, Yang S, Chen J, Wu H, Wang J, Li Y, et al. Penpulimab plus anlotinib as second-line treatment for the small cell lung cancer after failure of platinum-based systemic chemotherapy. J Clin Oncol. 2021;39(15_suppl):8568–8568.
37. Wang Y, Ling X, Cao S, Li J, Zhou Y, Nie W, et al. P48.11 Anlotinib versus chemotherapy as a third-line or further treatment for advanced small cell lung cancer. J Thorac Oncol. 2021;16:S504.
38. Hao Y-Y, Qiao Y-P, Cheng J-D. Clinical activity and safety of anlotinib combined with PD-1 blockades for patients with previously treated small cell lung cancer. Int J Gen Med. 2021;14:10483–93.
39. Chen Q, Li Y, Zhang W, Wang C, Yang S, Guo Q. Safety and efficacy of ICI plus anlotinib vs. anlotinib alone as third-line treatment in extensive-stage small cell lung cancer: a retrospective study. J Cancer Res Clin Oncol. 2022;148:401–8.
40. Owonikoko TK, Behera M, Chen Z, Bhimani C, Curran WJ, Khuri FR, et al. A systematic analysis of efficacy of second-line chemotherapy in sensitive and refractory small-cell lung cancer. J Thorac Oncol. 2012;7:866–72.
41. Nokihara H, Lu S, Mok TSK, Nakagawa K, Yamamoto N, Shi YK, et al. Randomized controlled trial of S-1 versus docetaxel in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy (East Asia S-1 trial in lung cancer). Ann Oncol. 2017;28:2698–706.
42. Xie X-H, Wang F, Lin X-Q, Qin Y-Y, Xie Z-H, Zhang J-X, et al. Anlotinib plus S-1 for patients with EGFR mutation-negative advanced squamous cell lung cancer with PS scores of 2–3 after progression of second-line or later-line treatment. Cancer Manag Res. 2020;12:12709–14.

Publisher's Note