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Research article

Efficacy and safety of anlotinib plus penpulimab as second-line treatment for small cell lung cancer: A multicenter, open-label, single-arm phase II trial☆

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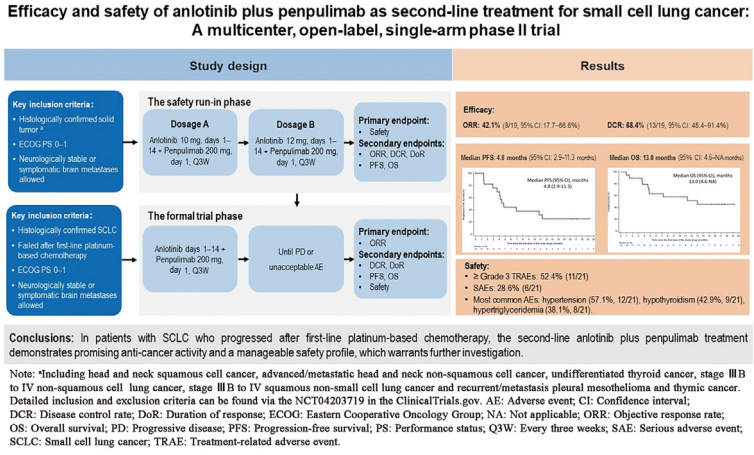
HIGHLIGHTS

- Anlotinib plus penpulimab shows promising anti-cancer activity and acceptable safety profile in the 2nd-line treatment of small cell lung cancer (SCLC).
- Patients who underwent the anlotinib plus penpulimab regimen had an objective response rate (ORR) of up to 42.1% (95% confidence interval [CI]: 17.7–66.6%), a median progression-free survival (PFS) of 4.8 months (95% CI: 2.9–11.3 months), and a median overall survival (OS) of 13.0 months (95% CI: 4.6–not applicable [NA] months).
- The anlotinib plus penpulimab regimen warrants further investigation for the treatment of patients with stage SCLC who progressed after first-line platinum-based chemotherapy.

GRAPHICAL ABSTRACT



☆ Given his role as Editor in Chief, Prof. Yuankai Shi had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Dr. Peng Lyu.

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ABSTRACT

Background: Currently, the need for new therapeutic strategies involving programmed cell death protein-1 (PD-1) monoclonal antibodies in the second-line setting of small cell lung cancer (SCLC) is urgent. This study aimed to evaluate the efficacy and safety of anlotinib plus penpulimab as a second-line treatment for patients with SCLC who progressed after first-line platinum-based chemotherapy.

Methods: This study included the patients from Cohort 4 of a single-arm, open-label, multicenter, phase II clinical trial. A safety run-in phase was performed under anlotinib (10/12 mg *quaque die* [QD], days 1–14) plus penpulimab (200 mg intravenously [IV], day 1) in a 21-day cycle, followed by the formal trial in which the patients received anlotinib (12 mg QD, days 1–14) plus penpulimab (200 mg IV, day 1) in a 21-day cycle. The primary endpoint of the safety run-in phase was safety. The primary endpoint of the formal trial phase was the objective response rate (ORR).

Results: From April 28, 2020, to November 24, 2020, 21 patients were enrolled from 11 hospitals, including 2 in the safety run-in phase and 19 in the formal trial phase. In the formal trial phase, the ORR was 42.1% (8/19; 95% confidence interval [CI]: 17.7–66.6%). The median progression-free survival was 4.8 months (95% CI: 2.9–11.3 months), and the median overall survival was 13.0 months (95% CI: 4.6–not applicable [NA] months). The incidence of ≥grade 3 treatment-related adverse events (TRAEs) was 52.4% (11/21), and the incidence of treatment-related serious adverse events (AEs) was 28.6% (6/21). Two AE-related deaths occurred. The most common AEs were hypertension (57.1%, 12/21), hypothyroidism (42.9%, 9/21), and hypertriglyceridemia (38.1%, 8/21).

Conclusions: In patients with SCLC who progressed after first-line platinum-based chemotherapy, the second-line anlotinib plus penpulimab treatment demonstrates promising anti-cancer activity and a manageable safety profile, which warrants further investigation.

Trial registration: No. NCT04203719, https://clinicaltrials.gov/.

Introduction

Small cell lung cancer (SCLC) accounts for approximately 13–15% of all new lung cancer cases and has a high propensity to metastasize.[1] Indeed, approximately 70% of patients with SCLC are metastatic at diagnosis.[2] Extensive-stage SCLC occurs at American Joint Committee on Cancer (8th ed.) stage IV (any T, any N, and M1a/b) or T3–T4 exclusion from the limited-stage disease.[3] Most patients are prone to estensive--stage SCLC relapse within a relatively short time in spite of the high response rate to chemotherapy.[4–6] Based on the positive results from the IMpower133[7] and CASPIAN[8] trials, programmed cell death-ligand 1 (PD-L1) inhibitor combined with chemotherapy has become the standard first-line treatment of estensive-stage SCLC. Additionally, China's innovative PD-L1 monoclonal antibody adebrelimab and programmed cell death protein-1 (PD-1) monoclonal antibody serplulimab also achieved favorable efficacy in the first-line treatment of estensive-stage SCLC when combined with platinum-based chemotherapy.[9,10] Although SCLC exhibits significant responsiveness to initial treatment, most patients invariably relapse, often with more resistant disease manifestations.[11] For patients navigating these challenges, treatment decisions are frequently guided by the chemotherapy-free interval (CTFI). Those with CTFI >6 months can consider clinical trial participation, platinum-based doublets, or agents such as lurbinectedin and topotecan. For CTFI ≤6 months, patients might explore treatments such as lurbinectedin, topotecan, irinotecan, or even immune checkpoint inhibitors (ICIs) if not previously administered.[12] However, despite the initial promise of nivolumab and pembrolizumab as second-line treatments, their phase 3 confirmation clincial trial did not meet the primary endpoint.[13,14] Therefore, there is need for new therapeutic strategies involving PD-1 monoclonal antibodies in the second-line setting of estensive-stage SCLC.

Anlotinib is a novel oral multi-targeted tyrosine kinase inhibitor known for suppressing tumor angiogenesis by inhibiting a plethora of factors, including stem cell factor receptors, platelet-derived growth factor receptors α and β, vascular endothelial growth factor receptors 1–3, and fibroblast growth factor receptors 1–4.[15–17] Its efficacy as third-line SCLC therapy was demonstrated in the ALTER 1202 trial,[18] leading to its approval by the China National Medical Products Administration (NMPA). On the other hand, penpulimab, a humanized anti-PD-1 monoclonal antibody, originally gained recognition for its effects against Hodgkin's lymphoma. Its therapeutic potential has expanded, demonstrating promising anti tumor activity against non-small cell lung cancer (NSCLC) and various other solid tumors.[19] Anlotinib has been showed to exert effect to optimize the tumor microenvironment and bolster innate immunity[20] synergizes with the efficacy of ICIs such as penpulimab. This synergy was evident in NSCLC, where the combined regimen showcased promising clinical results.[21] Furthermore, the effectiveness of the anlotinib and penpulimab combination was reported in a patient with relapsed SCLC.[22] This growing body of evidence points toward the burgeoning potential of this combination, suggesting it might pave the way for improved management strategies for SCLC.

The phase II trial of anlotinib in combination with penpulimab as second-line therapy in treating advanced head and neck and chest cancer included seven cohorts (ClinicalTrials.gov NCT04203719). Cohort 4 of this trial was a pre-set cohort designated to evaluate the efficacy and safety of anlotinib plus penpulimab for the second-line treatment of patients with SCLC who progressed after first-line platinum-based chemotherapy. At the time when this study was being conceived, the use of PD-1/PD-L1 inhibitors combined with chemotherapy for first-line treatment of estensive-stage SCLC had not been approved by China NMPA. Chemotherapy, being the predominant and widely accepted therapeutic approach during that timeframe, was seen as the standard.[23] Against this backdrop, this study aimed to explore the therapeutic avenues addressing the challenges faced in instances of first-line standard chemotherapy failures in patients with SCLC.

Methods

Study design

This was a single-arm, open-label, multicenter, phase II trial, which was divided into two phases. The first phase was the safety run-in phase for participants with various cancers, whose purpose was to assess the safety of the combination of anlotinib and penpulimab and decide on anlotinib dosage. The second phase was the formal SCLC cohort (Cohort 4) single-arm trial, which aimed to evaluate the efficacy and safety of anlotinib plus penpulimab for the second-line treatment of SCLC.

Patients

The inclusion criteria included (1) histologically confirmed SCLC; (2) progression after first-line platinum-based chemotherapy; (3) adequate

organ function, including hemoglobin ≥ 90 g/L, absolute neutrophil count ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, alanine aminotransferase (ALT) ≤ 3 × the upper limit of normal (ULN), aspartate aminotransferase (AST) ≤ 3 × ULN, total bilirubin ≤ 1.5 × ULN, serum creatinine ≤ 1.5 × ULN; (4) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1.

The exclusion criteria included (1) received bevacizumab, ramucirumab, anlotinib, apatinib, lenvatinib, sorafenib, sunitinib, recombinant human endostatin, or other anti-angiogenesis drugs, or ICIs such as anti-PD-1/PD-L1 monoclonal antibody; (2) received chemotherapy, radiotherapy, or other anti-cancer therapy within 4 weeks before the first dose of study drugs or within five elimination half-lives of the drug (whichever occurred first); (3) symptomatic brain metastases or symptom control <4 weeks; (4) previous SCLC within 5 years or with other malignant tumors simultaneously; (5) computed tomography or magnetic resonance imaging showed that the tumor invaded large blood vessels or unclear boundaries of the blood vessels were observed; (6) severe or poorly controlled comorbidities such as uncontrolled hypertension; abnormal coagulation function; abnormal cardiac function, including prolonged corrected Q-T interval (QTc), severe cardiovascular disease, clinically significant bleeding symptoms, or clear bleeding tendency; or (7) active immune diseases (such as pure red cell aplasia, systemic lupus erythematosus, psoriasis, etc.) requiring systemic treatment within 2 years before the first dose of study drugs, or received immunosuppressant and continued treatment 2 weeks before the first dose of study drugs.

Treatment

In the safety run-in phase of the multi-cohort trial, three patients with various cancers received anlotinib (10 mg *quaque die* [QD], days 1–14) plus penpulimab (200 mg intravenously [IV], day 1) in a 21-day cycle. If dose-limited toxicity (DLT) was not observed in the first cycle, those three patients would continue receiving the same dose until disease progression or unacceptable toxicity, whichever occurred first. The next three patients would receive anlotinib (12 mg QD, days 1–14) plus penpulimab (200 mg IV, day 1) in a 21-day cycle. If no DLT occurred, the subsequent patients would receive this dosage. In the formal trial phase, all patients received anlotinib (12 mg QD, days 1–14) plus penpulimab (200 mg IV, day 1) in a 21-day cycle. During the trial, the dose of anlotinib could be reduced if treatment-related adverse events (TRAEs) occurred, and dose reduction was performed sequentially from 12 to 10 to 8 mg. No cross-dose adjustment was permitted. Patients would be withdrawn from this trial if they could not tolerate the 8-mg dose of anlotinib.

Follow-up

During the safety run-in and formal trial phases, from the first day of the first cycle, efficacy was evaluated every two cycles, and imaging evaluation was performed every 6 weeks after baseline until disease progression. After the patients were discharged from the trial, they were followed up every 8 weeks until death or loss of follow-up.

Endpoints

The primary endpoint of the safety run-in phase was the safety of the first cycle. The primary endpoint of the formal trial phase was the investigator-assessed objective response rate (ORR). The secondary endpoints of the two phases included the ORR (only for the safety run-in phase), disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety (only for the formal trial phase) which were all assessed by the investigator. The ORR was calculated as complete response (CR) and partial response (PR). The DCR was calculated as CR, PR, and stable disease (SD). The DoR was the time from the confirmed response to the date of disease progression. PFS was defined as the date of the first dose of study drugs to the date of disease progression or death from any cause. OS was defined as the date of the first dose of study drugs to the date of death from any cause or loss of follow-up.

The safety indicators included vital signs, laboratory indicators, treatment-emergent adverse events (TEAEs), TRAEs, and serious adverse events (SAEs), which were assessed in the safety set (SS) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Immune RECIST (iRECIST) was also used to verify patient progression based on RECIST version 1.1. If clinically confirmed patients could still benefit, they could continue to receive the study drugs treatment.

The full analysis set (FAS) was used for efficacy analysis and included all patients enrolled in this trial who used the study drugs at least once. The SS included all patients who received the study drugs at least once and whose safety assessments were available after using the study drugs.

Statistical analysis

The sample size of the multi-cohort, single-arm phase II trial was regularly calculated. However, the sample size of Cohort 4 (SCLC cohort) was not formally calculated; it was considered that recruiting 10–20 patients was feasible.

Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC, USA). The analyses of the baseline data and all efficacy indicators were performed on the FAS. The SS was used for the safety analysis. Continuous data are presented as mean ± standard deviation or median (minimum, maximum) according to their distribution (Shapiro–Wilk test). Categorical data are presented as *n* (%). Confidence interval (CI) was calculated at 95% CI. The Kaplan–Meier method was used to determine PFS, OS, and DoR. The safety analysis was mainly descriptive.

Results

Patient baseline characteristics

Twenty-eight patients were screened from April 28, 2020, to November 24, 2020, from 11 hospitals in China. Three did not meet the inclusion criteria, and four were excluded according to the exclusion criteria. Finally, 21 patients were enrolled in this trial, as shown in Figure 1. The safety run-in phase included 12 patients, but only 2 patients had SCLC. No DLT was observed in any of the 12 patients. Therefore, anlotinib 12 mg was used in the formal trial phase, which enrolled 19 patients with SCLC. In the formal trial phase, two patients did not complete the radiographic assessment of efficacy after one cycle of anlotinib plus penpulimab treatment: one patient withdrew voluntarily due to disease progression, and the other withdrew due to TEAE of paraplegia in both lower extremities, which was possibly unrelated to treatment according to the investigators' evaluation.

At baseline, the median age of the patients was 62 years (range 37–75), and 66.7% (14/21) were male. In addition, 95.2% (20/21) of the patients had an ECOG PS of 1; 23.8% (5/21) had brain metastases; 33.3% (7/21) were sensitive to first-line chemotherapy (recurrence ≥3 months after the end of chemotherapy); and 66.7% (14/21) were refractory or resistant to first-line chemotherapy (recurrence <3 months after the end of chemotherapy) [Table 1].

At the cut-off date on March 9, 2022, the median follow-up time was 17.1 months (range, 0.9–19.3 months). The two patients in the safety run-in phase discontinued the study drugs due to progressive disease (PD) (n = 1) and TRAEs (n = 1). Among the 19 patients in the formal trial phase, four patients were still receiving treatment of the study drugs. Other 15 patients discontinued the study drugs and the reason included PD (n = 5), TRAEs (n = 2), TEAEs (n = 1), death (n = 4), and voluntary withdrawal (n = 3).

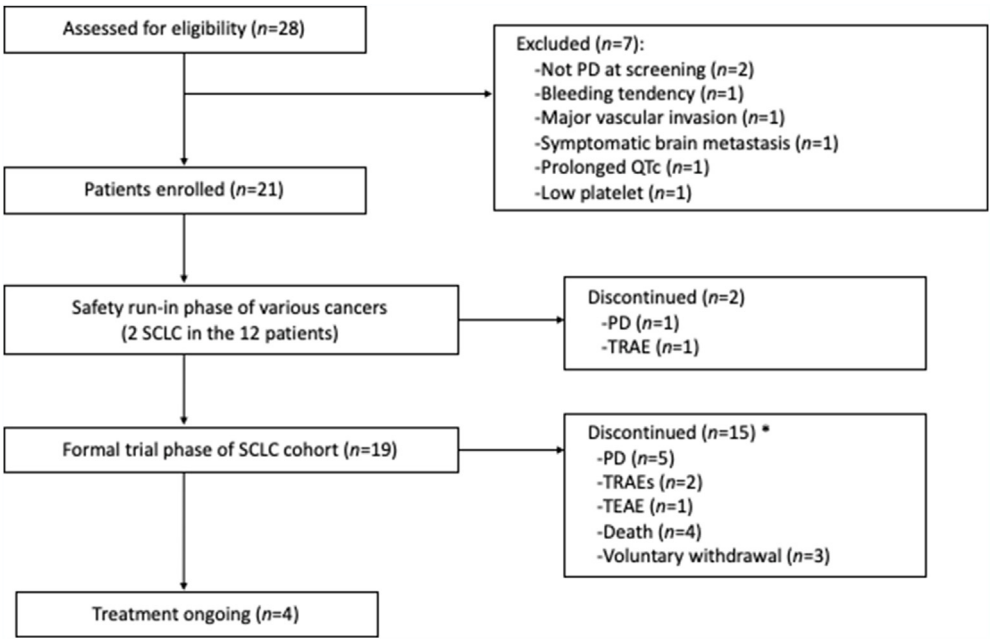

Figure 1. The flowchart of the study. PD: Progressive disease; QTc: Corrected Q-T interval; SCLC: Small cell lung cancer; TEAE: Treatment-emergent adverse event; TRAE: Treatment-related adverse event. * indicates that two patients did not complete the radiographic assessment of efficacy after one cycle of the study drugs treatment during the formal trial phase. One patients withdrew voluntarily due to disease progression, while the other withdrew due to TEAE.

Table 1
Patient baseline characteristics in the FAS.

Characteristic	Patients (n = 21)
Age (years), median (range)	62 (37–75)
Sex, *n* (%)	
Male	14 (66.7)
Female	7 (33.3)
ECOG PS, *n* (%)	
0	1 (4.8)
1	20 (95.2)
Smoking history, *n* (%)	
Never	9 (42.9)
Former	10 (47.6)
Current	2 (9.5)
First-line chemotherapy regime, *n* (%)	
Etoposide plus carboplatin or cisplatin or lobaplatin	20 (95.2)
Irinotecan plus cisplatin	1 (4.8)
Pattern of relapse after chemotherapy, *n* (%)[a]	
Sensitive	7 (33.3)
Refractory/resistant	14 (66.7)
Brain metastases, *n* (%)	
Yes	5 (23.8)
No	16 (76.2)
Anlotinib dosage, *n* (%)	
10 mg[b]	3 (14.3)
12 mg	18 (85.7)

[a]Chemotherapy sensitivity was defined as recurrence time ≥3 months after chemotherapy. Chemotherapy refractoriness/resistance was defined as recurrence time <3 months after chemotherapy.
[b]Two patients in the safety run-in phase received anlotinib (10 mg QD). One patient in the formal trial phase received anlotinib (10 mg QD) as the initial dose due to cardiac and chronic obstructive pulmonary diseases after negotiations between the investigator and sponsor.
ECOG: Eastern Cooperative Oncology Group; FAS: Full analysis set; PS: Performance status; QD: *Quaque die*.

Efficacy

In the formal trial phase, tumor shrinkage was observed in 73.7% (14/19) of the patients [Figure 2A]. The radiographic change in volume of the overall tumor burden from baseline, as assessed by the investigator, is shown in Figure 2B. The exposure and response duration of the study drugs are shown in Figure 2C. The median exposure time of anlotinib was 4.8 months (range: 0.5–19.6 months), while that of penpulimab was 4.5 months (range: 0.0–19.8 months). The ORR was 42.1% (8/19, 95% CI: 17.7–66.6%), and the DCR was 68.4% (13/19, 95% CI: 45.4–91.4%) according to the RECIST version 1.1. The median DoR was 9.4 months (95% CI: 6.8–12.0 months, the median PFS was 4.8 months (95% CI: 2.9–11.3 months), and the median OS was 13.0 months (95% CI: 4.6–not applicable [NA] months), as shown in Figure 3.

In the FAS, the ORR was 42.9% (9/21) (95% CI: 19.8–65.9%), and the DCR was 71.4% (15/21) (95% CI: 47.0–89.3%) according to the RECIST version 1.1. The median DoR was 9.4 months (95% CI: 6.8–12.0 months), the median PFS was 4.8 months (95% CI: 3.6–11.3 months), and the median OS was 14.9 months (95% CI: 4.8–NA months), as shown in Supplementary Figure 1.

Atypical responses were observed in five patients whose target tumor lesion shrank, but new lesions appeared at other sites. According to the iRECIST, the efficacy evaluation of these five patients with new lesions was immune PR (iPR) (n = 4) and immune CR (iCR) (n = 1). The investigator concluded that the patients were stable and could continue treatment, and the five patients received 1–3 cycles of treatment. All five patients had a relatively long OS: two with an OS of 13.0 and 14.9 months, and the other three were still alive at the cut-off date on March 9, 2022 (the shortest follow-up time was 10 months). Among the three surviving patients, one patient was withdrawn due to an AE, which was followed by anti-cancer therapy with etoposide. The two other patients were withdrawn due to disease progression, one of them did not receive any anti-cancer therapy after that, and the other one received anlotinib plus etoposide orally. The detailed efficacy of anlotinib plus penpulimab is summarized in Table 2.

Safety

In the safety run-in phase, the two patients with SCLC received anlotinib (10 mg QD, days 1–14) plus penpulimab (200 mg IV, day 1) in a 21-day cycle. In the formal trial phase, 18 patients were administered anlotinib (12 mg QD, days 1–14) plus penpulimab (200 mg IV, day 1) in a 21-day cycle, while only one patient received anlotinib (10 mg QD, days 1–14) plus penpulimab (200 mg IV, day 1) in a 21-day cycle due to

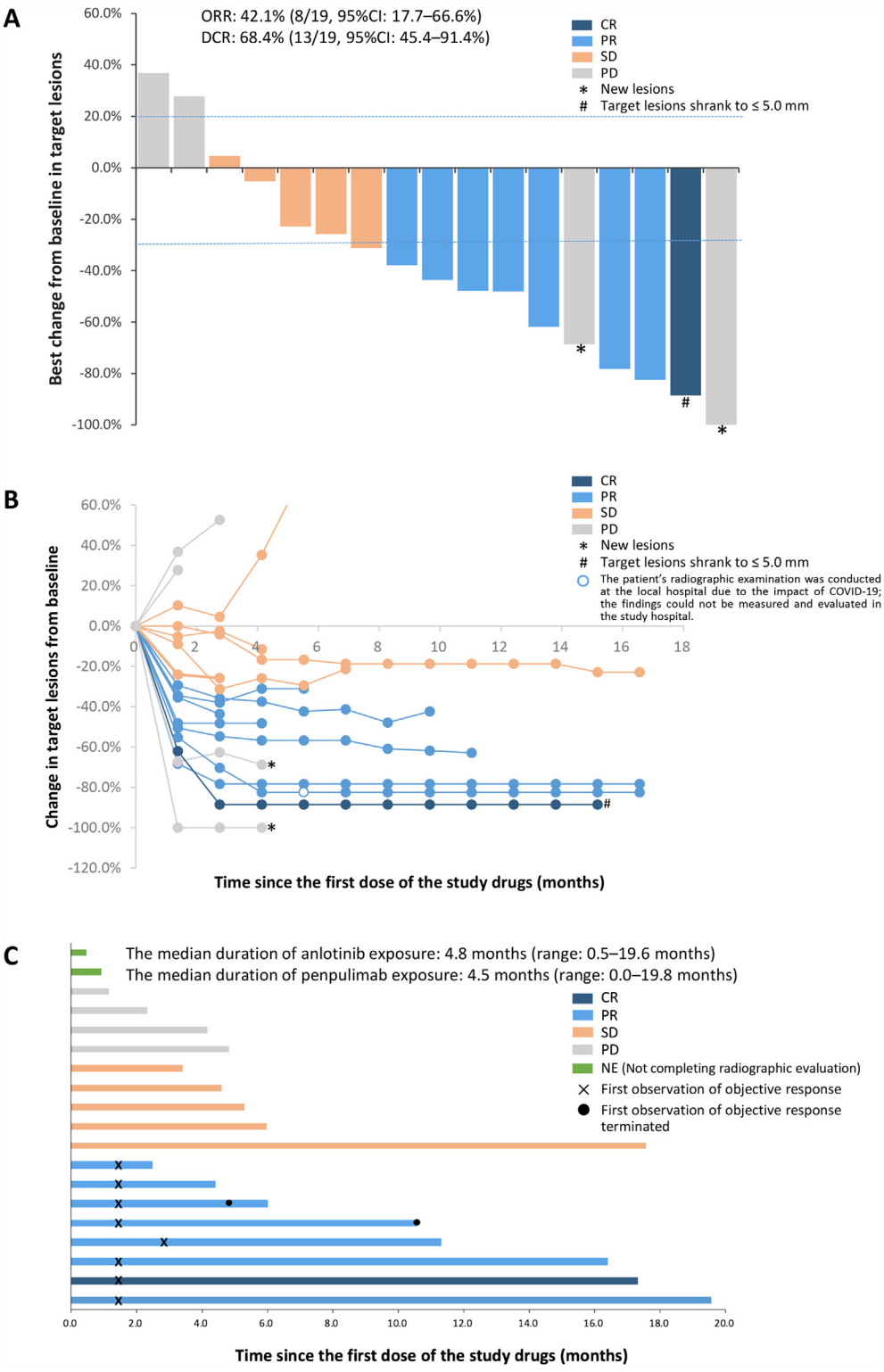

Figure 2. Anti-cancer response. (A) Waterfall plot of the best percentage change from the baseline. The *y*-axis represents the best percentage changes compared with the baseline in the sum of target lesion diameters in individual patients with the best objective response per the RECIST version 1.1 ($n = 17$), as indicated by the color codes. The dashed line at 20% represents the boundary for the determination of PD, and the dashed line at −30% represents the boundary for the determination of PR. An * indicates when the patients with target lesion shrinkage have new lesions appearing. An # indicates when the target lesion shrank to ≤ 5.0 mm. (B) The radiographic change in volume of the overall tumor burden from baseline as assessed by the investigator according to the RECIST version 1.1 ($n = 17$). An * indicates when the patients with target lesion shrinkage have new lesions appearing. An # indicates when the target lesion shrank to ≤ 5.0 mm. (C) Swimmer plot showing the exposure and response duration of the study drugs according to the RECIST version 1.1 ($n = 19$). The green column indicates not completing one radiographic assessment. The time when the objective response was first observed is indicated by a ×, and the time when the objective response was terminated is indicated by a circle. Note: In the formal trial phase, two patients did not complete the radiographic assessment of efficacy after one cycle of stduy drugs treatment. One patients withdrew voluntarily due to PD, while the other withdrew due to TEAE. Therefore, Figures 2A and Figure 2B included the anti-cancer response of 17 patients. The patient marked by # in the Figure 2A and the Figure 2B had the best tumor response assessed as CR by the investigator according to the RECIST version 1.1, as his target lesions shrank from 43.5 mm to ≤ 5.0 mm and maintained for more than one year. CI: Confidence interval; COVID-19: Coronavirus disease 2019; CR: Complete response; DCR: Disease control rate; NE: Not evaluable; ORR: Objective response rate; PD: Progressive disease; PR: Partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: Stable disease.

cardiac disease and chronic obstructive pulmonary disease. The investigators considered it safer for this patient to receive an initial dose of 10 mg of anlotinib.

All patients reported TRAEs. Eleven patients reported ≥ grade 3 TRAEs (52.4%), and three patients reported immunotherapy-related AEs (irAEs) (14.3%). Nine patients discontinued penpulimab treatment (42.9%), and eight patients discontinued anlotinib treatment (38.1%). Anlotinib was reduced in nine patients (42.9%). SAEs were reported in 11 patients (52.4%), with six patients being treatment-related SAEs (28.6%) [Supplementary Table 1]. Five patients died, and two deaths were considered treatment-related. Among these two patients, one had immune-related pneumonia complicated with chronic obstructive pulmonary and cardiac diseases, considered related to penpulimab. One patient had hemoptysis, which was considered possibly related to anlotinib. For the three remaining patients whose deaths were unrelated to the study drugs, one patient had cholangitis with obstruction of the

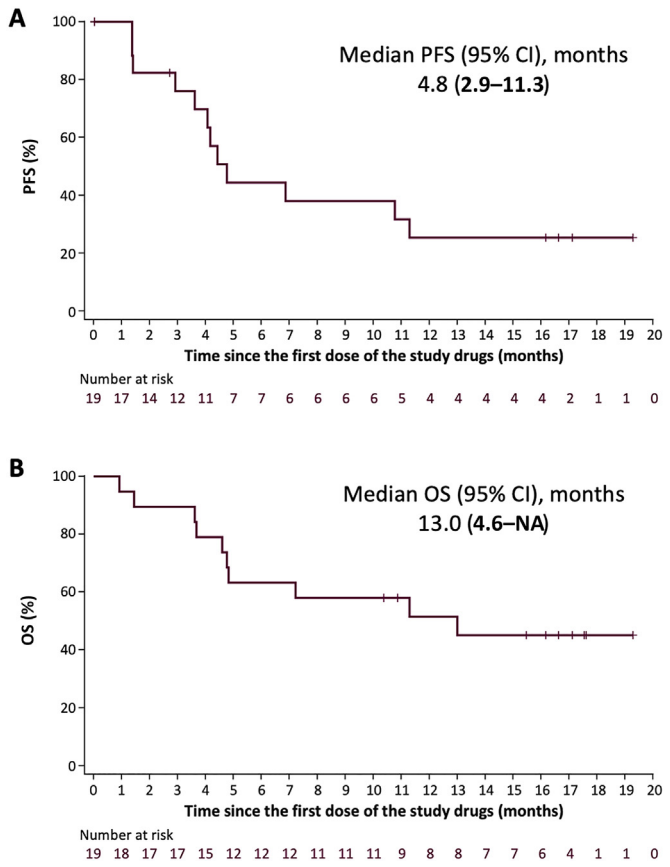

Figure 3. Kaplan–Meier curves of median progression-free survival (A) and median overall survival (B). CI: Confidence interval; NA: Not applicable; OS: Overall survival; PFS: Progression-free survival.

common bile duct, while the deaths of the other two patients were due to unknown causes.

In the SS, the most common TEAEs (>15.0%) were hypertension (57.1%), hypothyroidism (42.9%), hypertriglyceridemia (38.1%), fatigue (33.3%), leukopenia (33.3%), elevated ALT or AST (33.3%), weight loss (33.3%), hand-foot syndrome (28.6%), hyponatremia (28.6%), proteinuria (28.6%), increased γ-glutaryl transferase (23.8%), hyperthyroidism (23.8%), and diarrhea (23.8%) [Table 3]. Hypertension (≥ grade 3) accounted for 19%, while other AEs of ≥ grades 3 did not exceed 10%. All-grade hypo- and hyperthyroidism occurred in nine (42.9%) and five patients (23.8%), respectively, among whom four patients developed hyperthyroidism first and then hypothyroidism, consistent with the pattern of thyroid abnormalities with immunotherapy.

Table 2
Summary of efficacy in the formal trial phase.

Efficacy	Patients (n = 19)
Best overall response, n (%)	
CR*	1 (5.2)
PR	7 (36.8)
SD	5 (26.3)
PD	4 (21.1)
No radiographic assessment results	2 (10.5)
ORR, % (95% CI)	42.1 (17.7–66.6)
DCR, % (95% CI)	68.4 (45.4–91.4)
DoR (months), median (95% CI)	9.4 (6.8–12.0)
PFS (months), median (95% CI)	4.8 (2.9–11.3)
OS (months), median (95% CI)	13.0 (4.6–NA)

*The patient had best tumor response assessed as CR by the investigator according to the RECIST version 1.1, as his target lesions shrank from 43.5 mm to ≤ 5.0 mm and maintained for more than one year. CI: Confidence interval; CR: Complete response; DCR: Disease control rate; DoR: Duration of response; NA: Not applicable; ORR: Objective response rate; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; SD: Stable disease; RECIST: Response Evaluation Criteria in Solid Tumors.

Table 3
TEAEs and TRAEs that occurred in at least ≥15% of the patients in the SS.

Parameters	TEAEs, n (%)		TRAEs, n (%)	
	All-grade	Grade 3–4	All-grade	Grade 3–4
Hypertension	12 (57.1)	4 (19.0)	12 (57.1)	4 (19.0)
Hypothyroidism	9 (42.9)	1 (4.8)	9 (42.9)	1 (4.8)
Hypertriglyceridemia	8 (38.1)	1 (4.8)	8 (38.1)	1 (4.8)
Fatigue	7 (33.3)	2 (9.5)	6 (28.6)	2 (9.5)
WBC count decreased	7 (33.3)	1 (4.8)	6 (28.6)	1 (4.8)
Elevated ALT or AST	7 (33.3)	0	7 (33.3)	0
Weight loss	7 (33.3)	0	5 (23.8)	0
Hand-foot syndrome	6 (28.6)	2 (9.5)	6 (28.6)	2 (9.5)
Hyponatremia	6 (28.6)	1 (4.8)	4 (19.0)	0
Proteinuria	6 (28.6)	0	6 (28.6)	0
GGT increased	5 (23.8)	1 (4.8)	5 (23.8)	1 (4.8)
Hyperthyroidism	5 (23.8)	0	5 (23.8)	0
Diarrhea	5 (23.8)	0	4 (19.0)	1 (4.8)
Loss of appetite	4 (19.0)	1 (4.8)	3 (14.3)	0
Hypercholesterolemia	4 (19.0)	0	4 (19.0)	0
Hyperlipidemia	4 (19.0)	0	4 (19.0)	0
Backache	4 (19.0)	0	1 (4.8)	0

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutaryl transferase; SS: Safety set; TEAE: Treatment-emergent adverse event; TRAE: Treatment-related adverse event; WBC: White blood cell.

Discussion

To our knowledge, this is the first study to evaluate the efficacy and safety of anlotinib plus penpulimab as a second-line treatment for SCLC. The results of this trial suggested that for patients with SCLC who progressed after first-line platinum-based chemotherapy, second-line anlotinib plus penpulimab treatment showed promising anti-cancer activity and a manageable safety profile.

Currently, chemotherapy remains the standard second-line treatment for SCLC, albeit with limited efficacy. For instance, second-line topotecan and lurbinectedin yield ORRs of 24% and 35.2%, respectively, and their associated median OS are approximately 5.8–9.3 months.[24,25] The ATLANTIS trial revealed no significant OS improvement when comparing lurbinectedin plus doxorubicin with cyclophosphamide/doxorubicin/vincristine (CAV) chemotherapy.[26] Notably, the immune-suppressive microenvironment of SCLC, characterized by a few tumor-infiltrating lymphocytes and low PD-L1 expression, results in diminished ICI response rates.[27–30] The rapid-onset drug resistance due to SCLC heterogeneity further complicates the therapeutic landscape.[31,32] The synergy between anlotinib and ICIs is promising.[20] The present study showed that anlotinib combined with penpulimab yielded an ORR of 42.9% and a median OS of 14.9 months. Anlotinib's potential to downregulate protein kinase B (Akt), reducing PD-L1 expression on vascular endothelial cells, allows for enhanced CD8+ T and FoxP3+ T cell tumor infiltration.[33] This effect bolsters the potential of ICIs, even in low PD-L1-expressing tumors. Combining anlotinib with an anti-PD-1 monoclonal antibody might further optimize immune responses.

In the current study, five patients exhibited atypical responses where target lesions reduced in size, but new lesions emerged elsewhere. Such outcomes, not previously observed with anlotinib monotherapy, might be attributed to penpulimab or its combination treatment. This pattern, known as a dissociated response (DR), has been identified with ICIs in NSCLC and other tumors.[34] DR captures the scenario where some tumors regress while others advance. Typically, its incidence ranges from 7.5 to 10%, with potential causes being the emergence of resistant clones, varied ICI distribution in the body, or

differing immune cell infiltration across tissues.[34–36] In the current study, the DR incidence was 23.8%. Notably, patients with DR often benefit from continued treatment, even when new lesions indicate progression, and can experience extended survival.[34–36] Our findings suggest the potential inadequacy of the RECIST version 1.1 criteria for evaluating ICI treatments, highlighting the relevance of the iRECIST criteria to ensure optimal patient benefits.

Previous reports on anlotinib combined with ICIs showed safety profiles consistent with those of the present study, with no new AEs or safety signals identified.[22,37] The AEs of combination therapy were generally manageable. The most common ≥ grade 3 AEs, such as hypertension, diarrhea, and fatigue, are relatively not difficult to manage and control. 52.4% of the patients experienced ≥ grade 3 TRAEs and 28.6% of patients had treatment-related SAEs, numbers comparable to or better than certain other combination therapies.[7,8,38] Hypertension (19%) and hand-foot syndrome (9.5%) were the most prevalent ≥ grade 3 TRAEs; nevertheless, they were controllable through dose adjustments. Two patients unfortunately died due to immune pneumonia and hemoptysis. Notably, the study recorded a hypothyroidism incidence of 42.9%, considerably higher than the 7% in single ICI treatments for SCLC.[39] This elevated incidence might be attributable to drug pairing, given that it was 16.1% in ALTER 1202.[40] Additionally, four patients initially developed hyperthyroidism, which transitioned to hypothyroidism, a trend observed in ICI monotherapy but not with anlotinib alone.[41] This could offer insights into the specific drug responsible for thyroid dysfunctions, serving as a guide for managing AEs.

This study had some limitations. First, the sample size is a critical factor in ensuring the robustness and statistical power of a study, and the sample size (21 patients) in this study was relatively small. However, this study was designed as an early exploratory single-arm trial aimed at preliminary exploration of the treatment efficacy and safety. Unlike comparative studies with specific hypotheses, this study did not have a rigidly defined hypothesis comparing the intervention to other treatments. The primary objective was to gain initial insights into the effects and safety profile of the treatment. Thus, the sample size was determined based on the exploratory nature of the study rather than stringent statistical considerations. Second, ICIs combined with chemotherapy are now considered the standard of care as the first-line treatment for estensive-stage SCLC, but atezolizumab with chemotherapy was approved by China NMPA for estensive-stage SCLC until February 13, 2020, which was after the present study started patient recruiting. Given this timeline, a notable number of patients might have missed the opportunity to benefit from the first-line ICI combination treatments due to various reasons. Thus, the findings of this study offer a valuable therapeutic alternative for those who progressed following initial chemotherapy. Recognizing the evolving treatment landscape, further exploring and validating potential second-line options such as anlotinib plus penpulimab for these patients is essential. Another limitation of this study is the high rate of treatment discontinuation among patients. However, as reflected in survival curves, most patients underwent extensive follow-up, ensuring the reliability of the PFS and OS outcomes despite these discontinuations. Future studies should address this discontinuation rate for enhanced clarity.

In conclusion, for patients with SCLC who progressed after first-line platinum-based chemotherapy, second-line anlotinib plus penpulimab treatment demonstrated promising anti-cancer activity and a manageable safety profile. The combination of anlotinib plus penpulimab proves to be a beneficial therapeutic approach for clinical treatment in the second-line setting of SCLC, warranting further investigation.

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Authors contributions

Yuankai Shi: conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing – original draft, writing – review & editing, visualization, supervision, project administration, and funding acquisition; Changgong Zhang: investigation, resources, and data curation; Jianhua Chen: investigation, resources, and data curation; Huijuan Wu: investigation, resources, data curation, and project administration; Jun Wang, Liying Gao, Jun Zhao, Yan Sun, Zhongyao Jia, Xinlin Mu, Chunmei Bai, Rui Wang, Kailiang Wu, and Qiang Liu: investigation, resources, and data curation. All authors reviewed and approved the submission of the final version of the manuscript.

Ethics statement

This study was conducted in accordance with the International Council on Harmonization Guidelines on Good Clinical Practice (ICH-GCP) and the principles of the *Declaration of Helsinki* and was approved by the ethics committee of the main participating hospital (National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, approval no. 19/278-2062). All methods were carried out in accordance with relevant guidelines and regulations. Written informed consent was obtained from all patients before the enrollment.

Data availability statement

The datasets used in the current study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpt.2024.02.001.

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