Sintilimab plus anlotinib as second or further-line therapy for extensive disease small cell lung cancer: a phase 2 investigator-initiated non-randomized controlled trial

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Summary

Background Treatment options remain rather limited for extensive disease small cell lung cancer (ED-SCLC) patients in second or further-line setting.

Methods The phase 2 investigator-initiated non-randomized study enrolled patients who had disease progression on at least one line of platinum-based chemotherapy. Participants received intravenous sintilimab 200 mg on day one and oral daily anlotinib 12 mg on days 1–14 once every three weeks per cycle. The primary endpoint was progression-free survival (PFS). The secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR) and safety. This study is registered with ClinicalTrials.gov (NCT04055792).

Findings Forty-two patients were enrolled between August 29, 2019 and December 26, 2021 at Henan Cancer Hospital in China. 37 patients were evaluable for efficacy. The median follow-up was 24.8 months (IQR: 16.9–28.2). The median PFS was 6.1 months (95% CI: 5.0–7.3). The OS was 12.7 months (95% CI: 7.1–18.2). The ORR was 56.8% (21/37, 95% CI: 40.0–73.5) and the DCR was 89.2% (33/37, 95% CI: 78.7–99.7). Forty patients (40/42, 95%) had at least one treatment-related adverse event (TRAE). Immune-related adverse events (irAEs) were reported in 39 patients (39/42, 93%), while grade 3 or higher irAEs occurred in 11 patients (11/42, 26%). The most frequent irAEs were hypothyroidism (16/42, 38%), elevated gamma-glutamyl transpeptidase (15/42, 36%) and elevated creatine kinase MB (15/42, 36%). The most frequent grade 3 or higher irAEs were elevated gamma-glutamyl transpeptidase (5/42, 12%) and increased aspartate aminotransferase (3/42, 7%).

Interpretation Sintilimab plus anlotinib demonstrated promising antitumor activities as second or further-line therapy for ED-SCLC and had manageable toxicities. The findings support further randomized controlled trials of this combination regimen for ED-SCLC.

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Keywords: Extensive-disease small cell lung cancer; PD-1 inhibitor; Anti-angiogenesis; Transcription factors

Introduction

Small cell lung cancer (SCLC) is an aggressive neuroendocrine carcinoma with a dismal prognosis. Two thirds of SCLC patients present with extensive-disease SCLC (ED-SCLC) at the time of diagnosis, and the 5-year overall survival (OS) rate is only 3%–5%.[1,2] First-line treatment for ED-SCLC with cisplatin/carboplatin plus etoposide could achieve an objective response rate

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Research in context

Evidence before this study

Currently, treatment options remain rather limited for extensive disease small cell lung cancer (ED-SCLC) patients who have progressed after first-line therapy. To explore, we searched PubMed for articles published from inception until October 31, 2023, on second or further-line therapy in patients with ED-SCLC, using the terms "small cell lung cancer", "second or further line". Many anticancer drugs, including chemotherapeutic drugs, anti-angiogenic drugs, tyrosine kinase inhibitors, and immunotherapy have shown limited efficacy in ED-SCLC. The only approved second-line therapy for ED-SCLC until very recently was topotecan, with an objective response rate (ORR) of 22%–24% and a progression-free survival (PFS) of 2–3 months.

Added value of this study

To the best of our knowledge, this is the largest phase 2 study to evaluate the efficacy and safety of a PD-1 inhibitor in combination with an anti-angiogenic agent as second or further-line therapy for ED-SCLC. Sintilimab plus anlotinib exhibited favourable PFS and good tolerability in ED-SCLC.

Implications of all the available evidence

This study demonstrated promising anti-tumor activities and manageable toxicities of sintilimab plus anlotinib as second or further-line therapy for ED-SCLC. The findings support further randomized controlled trials of this combination regimen for ED-SCLC.

(ORR) of 40%–70% and an OS of ten months, but relapse is inevitable.[3] The addition of anti–programmed death ligand-1 (PD-L1) antibody atezolizumab (Impower 133) or durvalumab to chemotherapy (CASPIAN) as first-line treatment increases the 2-year OS rate from 11% to 22%, but again, the vast majority of patients relapse rapidly, and treatment options for relapsed patients are limited.[4,5] Besides, due to economic and other factors, a considerable number of patients cannot receive first-line anti–PD-L1 antibody, and the addition of immunotherapy is alternative for relapsed patients.

The only approved second-line therapy for ED-SCLC until very recently was topotecan, with an ORR of 22%–24% and a progression-free survival (PFS) of 2–3 months.[6–11] Amrubicin is an approved second-line chemotherapy option in some parts of the World for patients with ED-SCLC. It achieved numerically higher ORR but similar PFS and OS compared with topotecan.[7,8] Lurbinectedin was approved in February, 2020 for use in SCLC patients who have progressed after previous platinum-based therapy, but the subsequent phase III trial compared lurbinectedin/doxorubicin vs topotecan or cyclophosphamide/doxorubicin/vincristine failed to prolong OS for ED-SCLC in second-line setting (ATLANTIS).[12,13] Nivolumab plus ipilimumab or pembrolizumab (KEYNOTE 158 and 028) were approved by the USA Food and Drug Administration (FDA) in 2018 and 2019, respectively, but were withdrawn later based on the negative results of subsequent phase III trials.[14,15] Other immune checkpoint inhibitors (ICIs), including nivolumab (CheckMate 331) and atezolizumab (IFCT-1603), failed to show survival benefit as second-line monotherapy for ED-SCLC.[16,17]

Vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) are essential for sustained proliferation of cancer cells. Anti-angiogenesis agents, either as monotherapy or in combination with chemotherapy or ICIs, have demonstrated promising results for a variety of cancers. Anlotinib, a broad spectrum tyrosine kinase inhibitor of VEGFR-1/2/3, fibroblast growth factor receptor (FGFR)-1-4, PDGFR-α/β and c-Kit, has proven efficacious for a variety of solid tumors.[18,19] In 2019, anlotinib was approved in China as third or further-line therapy for ED-SCLC.[20] Synergistic action between immunotherapy and antiangiogenic therapy has been demonstrated. Sintilimab is a potent programmed cell death 1 (PD-1) inhibitor and has demonstrated promising efficacy for several types of solid tumors.[21–24] In a phase Ib trial in non-small cell lung cancer (NSCLC) patients, the combination of sintilimab and anlotinib exhibited synergistic activity and manageable safety profile.[25]

Despite molecular and clinical heterogeneity, SCLC is treated as a single entity.[26] In recent years, epigenetic and transcriptional analysis of both human SCLC tumors and murine models of disease have identified biologically distinct subtypes of SCLC based on differential expression of lineage-defining transcription factors including ASCL1, NEUROD1, and POU2F3. A fourth subtype with low or absent expression of these three transcription factors has been variously associated with expression of a fourth transcriptional regulator, YAP1, and/or with an immunologically inflamed pattern of gene expression. An initial consensus among SCLC investigators proposed a nomenclature of SCLC-A, SCLC-N, SCLC-P and SCLC-Y for these subtypes, respectively.[27–29] The SCLC-A and SCLC-N subtypes are neuroendocrine (NE) subtypes, and the SCLC-P and SCLC-I subtypes are non-neuroendocrine (non-NE) subtypes. Currently, no clinical studies have explored the subtypes using FFPE samples from needle biopsy and IHC methods to predict the efficacy or prognosis of SCLC patients.

The current phase 2 investigator-initiated non-randomized controlled trial investigated the efficacy safety, and biomarkers (SCLC-A/N/P/I subtypes) of sintilimab

plus anlotinib as second or further-line therapy in patients with ED-SCLC.

Methods

Study design, procedures, and outcomes

This phase 2 investigator-initiated non-randomized controlled trial was conducted at a tertiary teaching hospital (Henan Cancer Hospital, Zhengzhou, China). Eligible patients received intravenous sintilimab 200 mg on day one and oral daily anlotinib 12 mg on days 1–14 once every three weeks. Treatment was continued until disease progression, unacceptable toxicities, or withdrawal of consent. Dose delay (maximally four weeks) and reduction (to 10 or 8 mg) were allowed for anlotinib. For sintilimab, dose delay (eight weeks maximum) but no reduction was allowed. The primary efficacy endpoint was PFS. Secondary endpoints included OS, ORR, disease control rate (DCR) and safety.

Tumor responses were evaluated by investigators every two cycles (six weeks) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). After the end of treatment, patients were followed up once every three months until death or the data cut-off. Adverse events (AEs) were defined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

Participants

Adult patients (≥18 years of age) with histologically or cytologically confirmed ED-SCLC who had progressed after at least one line of platinum-based chemotherapy were eligible. ED-SCLC was diagnosed according to the staging system of the Veterans Administration Lung Study Group (VALG) and also staged by the TNM classification (version 8.0) jointly by the Union Internationale Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Chemotherapy-sensitive disease was defined as relapse ≥90 days after first-line platinum-based chemotherapy; chemotherapy-resistant disease was defined as relapse <90 days after or during first-line platinum-based chemotherapy. Additional inclusion criteria were: 1) an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–2; 2) at least one measurable lesion according to RECIST 1.1; 3) an estimated life expectancy of at least 12 weeks; 4) adequate hematologic, hepatic, renal, and coagulative function. Patients with asymptomatic brain metastasis were allowed. Key exclusion criteria were: 1) prior treatment with PD-1 inhibitor, PD-L1 inhibitor, or CTLA4 inhibitor, or anti-angiogenic treatment; 2) clinically active brain metastasis or meningeal metastasis; 3) active autoimmune diseases; 4) hemorrhagic tendency. We used the term "sex" based on the biological factors of each participant. We determined the sex of each participant through information of their identification cards, which are confirmed by the public security bureau of the People's Republic of China to verify participants' birth details.

Enrolled patients were consented to provide formalin-fixed paraffin embedded (FFPE) tissue for immunohistochemistry (IHC). Consecutive 4-μm-thick tissue sections were cut from FFPE tissues. The primary antibodies used were listed as follows: ASCL1, Clone 19840, ab211327, Abcam; NEUROD1, Clone EPR20766, ab213725, Abcam; and POU2F3, E5N2D, 36135S, CST. Positive tumor cells were confirmed by two independent pathologists.

Ethics

This study was approved by the Ethics Committee of Henan Cancer Hospital (reference number, 2019269), and was conducted in compliance with the Declaration of Helsinki and Guidelines for Good Clinical Practice. All enrolled patients provided written informed consent.

Statistics

This trial was designed as a prospective, single-arm, phase 2 study. Sample size estimation was based on the following assumptions: 1) a PFS of 2.8 months in historical control with topotecan treatment, and 4.6 months in patients receiving sintilimab plus anlotinib; 2) 2-side alpha at 0.05 and power at 80%; 3) 10% dropout rate. The calculation yielded a total of 42 subjects.

Efficacy was analyzed in all subjects who had received at least two doses of the study treatment and had at least one efficacy assessment (the full analysis set, FAS). Safety analysis was conducted in all subjects who received at least one dose of the study treatment (the intent-to-treat population, ITT). PFS and OS were analysed using the Kaplan–Meier method. Cox regression analysis was conducted to examine factors associated with poor prognosis; the risk was presented as hazard ratio (HR) with 95% CI. Probability was calculated using a log-rank test. The follow-up duration was defined as the intervals from trial enrollment to the earlier of loss to follow-up or the data cut-off date. The median follow-up duration was analyzed using the Reverse Kaplan–Meier method. All statistical analyses were conducted with SPSS version 24.0. This study is registered with ClinicalTrials.gov (NCT04055792).

Role of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Patient characteristics

A total of 54 patients were screened for eligibility between August 29, 2019 and December 26, 2021, 42 were enrolled and received treatment (ITT set). Two

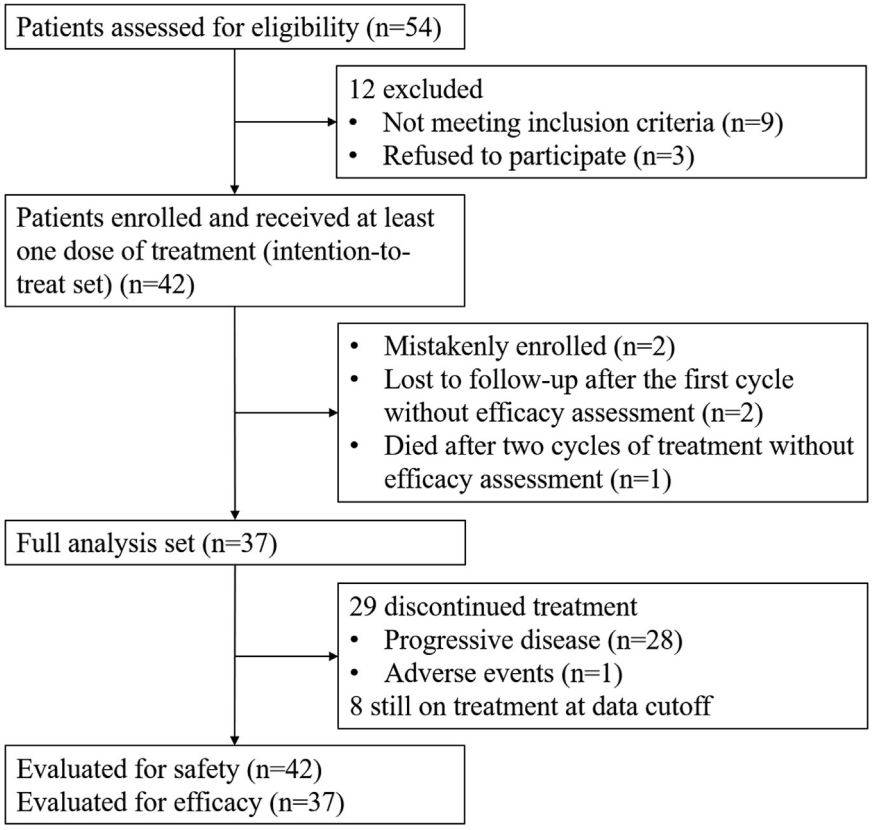

Fig. 1: Screening and disposition of patients.

patients were mistakenly enrolled, who used PD-L1 inhibitor in first-line treatment. One patient died after two cycles of treatment without efficacy assessment, and two patients were lost to follow up after one cycle. The remaining 37 patients were included in the analysis of efficacy (FAS set) (Fig. 1). At the data cut-off date (May 1, 2023), the median follow-up duration was 24.8 months (IQR: 16.9–28.2). Eight patients were still receiving the study treatment, and 28 patients had progressive disease (PD).

Baseline characteristics are presented in Table 1. In the FAS set, the median age was 58.4 years (IQR, 52.6–68.1; range, 41.7–77.4), and 76% patients (28/37) were men. Twenty-nine patients (29/37, 78%) were current or ever smokers. Most patients had an ECOG PS score of 1 (31/37, 84%) or 2 (5/37, 14%). Twenty-four patients (24/37, 65%) had ED-SCLC upon initial presentation, whereas 13 (13/37, 35%) relapsed after prior concurrent chemoradiotherapy (CCRT). Most patients had one (18/37, 49%) or two (18/37, 49%) prior lines of therapy and 23 patients (23/37, 62%) were sensitive to first-line platinum-based chemotherapy. Nineteen patients (19/37, 51%) had brain metastasis and 11 patients (11/37, 30%) had liver metastasis.

Efficacy

At the data cut-off date, 28 PFS events (28/37, 76%) had occurred. The median follow-up duration was 24.8 months (IQR: 16.9–28.2). The median PFS was 6.1 months (95% CI: 5.0–7.3), indicating an improvement over the 2.8 months median PFS specified in our sample size calculation (Fig. 2A). The PFS rate at 6 and 12 months was 54.1% and 31.7%, respectively. Twenty-three patients (23/37, 62%) died before the data cut-off date. The median OS was 12.7 months (95% CI: 7.1–18.2), and the OS rate at 12 and 18 month was 55.4% and 39.4%, respectively (Fig. 2B) (Appendix Table S1).

Subgroup analysis revealed that absence vs. presence of liver metastasis and ECOG performance status were significant predictors of both PFS and OS. Patients without liver metastases had a notably longer median PFS (9.4 vs. 2.8 months, HR 0.09, 95% CI: 0.03–0.26, $P < 0.0001$) and OS (19.7 vs. 7.7 months, HR 0.23, 95% CI: 0.10–0.54, $P < 0.0001$) than those with liver metastases. Patients with an ECOG PS score of 0 or 1 had longer median PFS (6.6 vs. 1.8 months, HR 0.35, 95% CI: 0.13–0.93, $P = 0.027$) and OS (16.1 vs. 4.5 months, HR 0.28, 95% CI: 0.09–0.86, $P = 0.017$) than those with

Characteristics	ITT (n = 42)		FAS[a] (n = 37)	
	No.	%	No.	%
Age, median (IQR, range), years	58.0 (51.6–68.1, 41.7–77.4)		58.4 (52.6–68.1, 41.7–77.4)	
Sex				
Male	33	79	28	76
Female	9	21	9	24
Smoking status				
Never	8	19	8	22
Current/Former	34	81	29	78
ECOG performance status				
0	1	2	1	2
1	34	81	31	84
2	7	17	5	14
Disease classification at initial diagnosis				
Extensive disease	28	67	24	65
Limited disease	14	33	13	35
T stage at screening (AJCC TNM 8.0)				
T1	4	10	4	11
T2	11	26	11	30
T3	3	7	3	8
T4	23	55	19	51
Tx	1	2	–	–
N stage at screening (AJCC TNM 8.0)				
N1	4	10	3	8
N2	15	35	15	41
N3	23	55	19	51
M stage at screening (AJCC TNM 8.0)				
M1a	10	24	10	27
M1b	7	17	7	19
M1c	25	59	20	54
TNM stage at screening (AJCC TNM 8.0)				
IVa	17	40	17	46
IVb	25	60	20	54
Previous systemic therapies				
First-line	20	48	18	49
Second-line	21	50	18	49
Third-line	1	2	1	2
First-line platinum-treated patients				
Chemotherapy-sensitive[b]	24	57	23	62
Chemotherapy-resistant[c]	18	43	14	38
Radiation history				
Thoracic radiation	21	50	18	49
Cerebral radiation	24	57	21	57
Metastatic organs at screening				
Cerebral	22	52	19	51
Bone	8	19	6	16
Liver	14	33	11	30

ITT, intention-to-treat population; FAS, full analysis set; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer. [a]Two patients were mistakenly enrolled, who used PD-L1 inhibitor in first-line treatment. One patient died after two cycles of treatment without efficacy assessment, and two patients were lost to follow up after one cycle. The remaining 37 patients were included in the analysis of efficacy (FAS). [b]Chemotherapy-sensitive: defined as relapse ≥90 days after first-line platinum-based chemotherapy. [c]Chemotherapy-resistant: defined as relapse <90 days after or during first-line platinum-based chemotherapy.

Table 1: **Baseline characteristics of patients.**

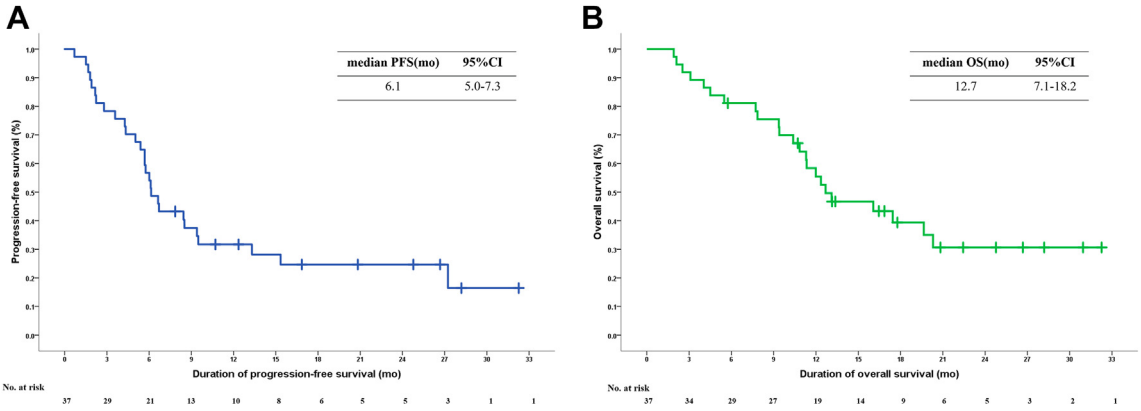

Fig. 2: Survival outcomes. (A) The Kaplan–Meier curves of PFS and (B) OS assessed in the full analysis set. No. at risk, number of subjects that were still accounted for in the study that had not yet experienced the event of interest. PFS, progression-free survival; OS, overall survival; CI, confidence interval.

an ECOG PS score of 2. Besides, patients with chemotherapy-sensitive disease had non-statistically longer median PFS (8.4 vs. 5.7 months, HR 0.65, 95% CI: 0.30–1.42, $P = 0.28$) and OS (16.1 vs. 11.3 months, HR 0.63, 95% CI: 0.27–1.48, $P = 0.29$) than those with chemotherapy-resistant disease (Fig. 3, Appendix Fig. S1).

Most patients (33/37, 89.2%) experienced tumor size reduction relative to the baseline target lesions and 56.8% of the patients (21/37) had at least a 30% reduction in the target lesion size (Appendix Table S1) (Appendix Fig. S2). Four patients showed complete response (CR) and 17 patients showed partial response (PR). The ORR was 56.8% (21/37, 95% CI: 40.0–73.5). Twelve patients had stable disease (SD) and the DCR was 89.2% (33/37, 95% CI: 78.7–99.7).

Safety

Forty-two patients were included in the safety analysis. Forty patients (40/42, 95%) had at least one treatment-related AE (TRAE). Grade 3 or higher TRAEs occurred in 22 patients (22/42, 52%). Common (reported in ≥10% of patients) and grade 3 or 4 TRAEs appear in Table 2. The most frequent TRAEs were hypothyroidism (19/42, 45%), hypoproteinemia (17/42, 41%) and elevated gamma-glutamyl transpeptidase increased (16/42, 38%). The most frequently reported grade 3 or higher TRAEs included elevated gamma-glutamyl transpeptidase (11%), elevated bilirubin (7%), and elevated alanine aminotransferase (5%). Fourteen patients (33%) developed grade 1 or 2 hypertension, but no grade 3 or higher hypertension was reported (Table 2).

Sintilimab was discontinued in two patients due to TRAEs (hyperthyroidism and elevated myocardial zymogram each in one case). The dose of anlotinib was reduced in four patients (hyperthyroidism, grade 4 leucopenia, appetite and weight reduction, and fatigue each in one case), and was discontinued in one patient (brain infarction).

Immune-related adverse events (irAEs) were reported in 39 patients (93%), while grade 3 or higher irAEs occurred in 11 patients (26%). The most frequent irAEs were hypothyroidism (38%), elevated gamma-glutamyl transpeptidase (36%) and elevated creatine kinase MB (36%). The most frequent grade 3 or higher irAEs were elevated gamma-glutamyl transpeptidase

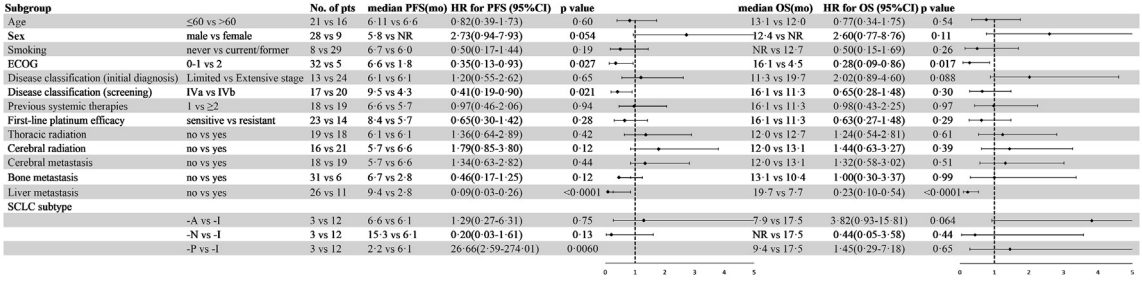

Fig. 3: Subgroup analysis of PFS and OS. ECOG, Eastern Cooperative Oncology Group; SCLC, small cell lung cancer; pts, patients; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; NR: not reached.

Adverse events	Any grade n (%)	Grade 3 or 4 n (%)
Any grade	40 (95)	22 (52)
Hypothyroidism	19 (45)	–
Hypoproteinemia	17 (41)	–
GGT increased	16 (38)	5 (12)
CK-MB increased	15 (36)	1 (2)
Hypertension	14 (33)	–
Cholesterol increased	13 (31)	–
ALP increased	12 (29)	–
Anemia	11 (26)	–
Urine occult blood	10 (24)	–
Appetite loss	10 (24)	–
Bilirubin increased	9 (21)	3 (7)
AST increased	9 (21)	2 (5)
Hyperglycemia	9 (21)	1 (2)
ALT increased	8 (19)	3 (7)
Hyperthyroidism	8 (19)	1 (2)
Nausea	8 (19)	–
Thrombocytopenia	8 (19)	1 (2)
Hypertriglyceridemia	7 (17)	1 (2)
Hyperuricemia	7 (17)	–
Proteinuria	4 (10)	–
Leucopenia	4 (10)	1 (2)
Neutropenia	4 (10)	1 (2)

GGT, gamma-glutamyl transpeptidase; CK-MB, creatine kinase MB; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase. [a]Adverse events with an incidence ≥10% and grade 3 or 4.

Table 2: **Common treatment-related adverse events[a] (n = 42).**

(12%) and increased aspartate aminotransferase (7%). Infusion-related reactions occurred in 4 patients (10%). Pneumonia was reported in 3 patients. Pneumonia with an immune-mediated mechanism was reported by 2 patients (5%). No grade 3 or higher treatment-related adverse event of pneumonia was reported (Appendix Table S2).

Exploration of biomarkers

Twenty-one patients had adequate FFPE tumor samples for biomarker exploration analysis. 3, 3, 3, and 12 patients were defined as the SCLC-A, -N, -P, and -I subtypes according to differential immunohistochemical expression of ASCL1, NEUROD1, and POU2F3. Of which, SCLC-N subtype showed longest PFS (–N 15.3 vs –A 6.6 vs –P 2.2 vs –I 6.1 months, $P < 0.0001$), while SCLC-I showed longest OS (–I 17.5 vs –A 7.9 vs –N unreached vs –P 9.4 months, $P = 0.15$). (Appendix Figs. S3–S6).

Discussion

In this trial, sintilimab plus anlotinib achieved a median PFS of 6.1 months (95% CI: 5.0–7.3), indicating an improvement over the 2.8 months median PFS specified in our sample size calculation. The 6- and 12-month PFS rate was 54.1% and 31.7%, respectively. The median OS was 12.7 months (95% CI: 7.1–18.2), with the 18-month OS rate standing at 39.4%. Overall, this treatment regimen was well tolerated. To the best of our knowledge, this is the largest phase 2 study to evaluate the efficacy and safety of a PD-1 inhibitor in combination with an anti-angiogenic agent as second or further-line therapy for ED-SCLC.

Treatment option in ED-SCLC patients with relapse after first-line chemotherapy is limited, and for many years, the only approved agent was the topoisomerase I inhibitor topotecan.[6–11] In a phase 3 study of topotecan vs cyclophosphamide, doxorubicin, and vincristine for SCLC patients who failed first-line therapy, topotecan did not significantly increase the ORR (24.3% vs. 18.3%, $P = 0.29$) or OS (25 vs. 24.8 weeks, $P = 0.7$) vs cyclophosphamide, doxorubicin, and vincristine.[9] In a phase II study, topotecan as second-line treatment for ED-SCLC achieved an ORR of 21.7%, with a median PFS of 2.8 months and a median OS of 5.4 months.[11] Notably, the hematologic toxicity of topotecan is considerable. Amrubicin is a topoisomerase II inhibitor. It is an approved second-line chemotherapy option in some parts of the World for patients with ED-SCLC.[7,8] In a randomized phase III study, the ORR of amrubicin was numerically higher than topotecan (31% vs 17%), however, the median PFS and OS were not significantly different. Importantly, amrubicin was associated with more grade ≥3 infections and a higher incidence of febrile neutropenia.[7] Though lurbinectedin, an oncogenic transcription inhibitor, achieved an ORR of 35.2%, with a median PFS and OS of 3.5 and 9.3 months, respectively, in a phase II basket trial in patients with ED-SCLC, the results failed to be upheld by a subsequent phase III trial.[12,13] Chemo-immunotherapy followed by maintenance immunotherapy is the new standard treatment for ED-SCLC in the frontline setting.[4,5] However, survival benefit occurs in only a small subset of patients. Besides, due to economic and other factors, a considerable number of patients cannot receive first-line anti–PD-L1 antibody, and the addition of immunotherapy is alternative for relapsed patients. However, the efficacy of ICI monotherapy as second or further-line treatment in ED-SCLC patients is modest, with an ORR of 10%–33%.[14,16,17] Many other anticancer drugs, including chemotherapeutic drugs, anti-angiogenic drugs, and tyrosine kinase inhibitors, have shown limited efficacy in ED-SCLC.[7,30–35]

Combination treatment with an anti-angiogenic agent and an ICIs has attracted increasing interest recently. In a phase Ib trial in 22 patients with advanced NSCLC, sintilimab plus anlotinib as first-line therapy achieved an ORR of 72.7% and a DCR of 100%, with a PFS of 15 months. The rate of grade 3 or higher TRAEs (most commonly hypertension) was 54.5%.[25] A two-stage, phase II trial examined camrelizumab plus

apatinib in ED-SCLC patients (PASSION).[36] Among the 59 enrolled patients, 47 participated in the QD cohort (camrelizumab 200 mg every two weeks plus apatinib 375 mg once daily, five days on and two days off, or seven days on and two days off). The ORR and DCR were 34.0% and 68.1%, respectively, with a PFS of 3.6 months and an OS of 8.4 months. The rate of TRAEs is high: grade 3 or higher TRAEs were reported in 72.9% patients, and 8.5% patients discontinued the treatment due to TRAEs.

Consistent with previous studies, subgroup analysis in this trial demonstrated that absence of liver metastasis was a significant favourable predictor of both PFS and OS. Liver metastasis occurs in 20%–30% patients of ED-SCLC at initial diagnosis.[2] In the IMpower 133 trial,[4] the PFS in patients with liver metastasis was 9.3 months in the chemoimmunotherapy group and 7.8 months in the chemotherapy group. In contrast, brain metastasis was not a significant predictor of PFS or OS.

While ICIs leads to durable benefit in a minority of patients (e.g. increasing 3-year survival from 5.8% to 17.6% with durvalumab), most ED-SCLC patients derive minimal if any benefit (e.g. the median OS improves only from 10.5 to 12.9 months). So far, there are no effective biomarkers for predicting efficacy in ED-SCLC. PD-L1 expression level has been used as a predictive biomarker of ICIs for NSCLC. However, PD-L1 expression level was not associated with the efficacy of ICIs in the IMpower 133 and CASPIAN trial.[4,5] In the CheckMate 032 trial, objective response was also observed in patients irrespective of PD-L1 expression.[37] The use of tumor mutational burden (TMB) in SCLC also yielded inconclusive results. A correlation between TMB and tumor response was observed in the CheckMate 032 trial but not in the Impower 133 trial using a blood-based analysis.[4,37] Future studies are needed to define SCLC characteristics associated with immunotherapy response.

In recent years, researches on cells, animal models and tumor samples have promoted the identification of molecular subtypes of SCLC, discovered unique biological and clinical characteristics, and proposed potential specific therapeutic targets for different subtypes. The widely recognized subtypes are four subtypes (SCLC-A, SCLC-N, SCLC-P and SCLC-I) identified by Carl et al. based on the gene expression profiles of SCLC tumor samples and cell lines, which are mainly characterized by the expression of transcription factors ASCL1, NEUROD1 and POU2F3.[29] We found SCLC-N subtype showed longest PFS (–N 15.3 vs –A 6.6 vs –P 2.2 vs –I 6.1 months, $P < 0.0001$), while SCLC-I showed longest OS (–I 17.4 vs –A 7.9 vs –N unreached vs –P 9.4 months, $P = 0.15$). The results are consistent with the predicted efficacy of the treatment.

This study has several limitations. Most notably, this is a phase 2 investigator-initiated nonrandomized controlled trial with a small number of participants. Future studies with a parallel control group, especially in the first-line setting combined with chemotherapy are needed to improve outcomes of ED-SCLC patients. Besides, in the biomarker exploration analysis, only 21 patients provided sufficient FFPE samples, large-scale data are needed to verify the effect of different SCLC subtypes on the efficacy and prognosis prediction of ED-SCLC.

Contributors

Shuxiang Ma: Designed the study, analysed and interpreted these data, and wrote the manuscript.

Zhen He: Recruited patients, collected the clinical data, reviewed the manuscript and contributed to the study supervision.

Yang Liu: Collected the clinical data and contributed to original writing.

Lili Wang, Sen Yang, Yufeng Wu, Haiyang Chen, Yingxi Wu: Recruited patients and assisted with follow-up.

Qiming Wang: Conceived and designed the study, critically reviewed the manuscript and contributed to the study supervision.

Shuxiang Ma and Qingming Wang have directly accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication. All authors read and approved the final version of the manuscript.

Data sharing statement

Data are available from the corresponding author upon reasonable request and with the permission of The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital.

Declaration of interests

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102543.

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