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Efficacy and safety of TQB2450 combined with anlotinib as maintenance therapy for LS-SCLC after definitive concurrent or sequential chemoradiotherapy: a prospective phase Ib study

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Abstract

Purpose There is a significant unmet need in treating patients with limited-stage small-cell lung cancer (LS-SCLC). The ETER701 study showed that Benmelstobart (TQB2450, an anti-PD-L1 antibody) combined with Anlotinib and chemotherapy achieved the longest progression-free survival (PFS) and overall survival (OS) as a first-line therapy in patients with extensive-stage small cell lung cancer (ES-SCLC). This suggests that TQB2450 and Anlotinib represent a promising treatment combination for LS-SCLC. This prospective study aimed to evaluate the efficacy and safety of TQB2450 combined with Anlotinib as maintenance therapy for LS-SCLC following concurrent or sequential chemoradiotherapy (CCRT or SCRT).

Methods Patients who did not show disease progression after chemoradiotherapy were enrolled. They received TQB2450 and Anlotinib every 3 weeks for up to 24 months. TQB2450 was intravenously administered at a dose of 1200 mg every 3 weeks. Anlotinib was initiated at a dose of 8 mg daily for days 1–14; if well tolerated, the dose was increased to 10 mg. Adverse events (AEs) were recorded using electronic data capture system. The trial was registered at the ClinicalTrials.gov (NCT05942508, 06/07/2023).

Results Fifteen patients were enrolled in the study between May 31, 2023 and October 13, 2023. As of October 31, 2024, the median follow-up time was 15.13 months. The 12-month PFS rate was 86.7% (95% CI, 71.1–100.0), and the OS rate at 12 months was 100%. The disease control rate was 100%. AEs were reported in 13 patients (86.67%), with fatigue being the most common treatment related AE (40.00%). And two SAEs were observed (elevation in cardiac troponin T and cerebral infarction), which were determined to be unlikely unrelated to the trial drugs. Radiation

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pneumonitis (RP) occurred in three patients, all classified as grade 2, and one patient developed grade 1 immune-related pneumonitis. No grade 5 AEs occurred, and no patients withdrew from the study due to AEs.

Conclusions TQB2450 combined with Anlotinib showed promising efficacy and well tolerance in patients with LS-SCLC following first-line treatment. A randomized, double-blind, placebo-controlled Phase III clinical study (ClinicalTrials.gov Identifier: NCT06469879) is being conducted to further explore the efficacy and safety of TQB2450 combined with Anlotinib as maintenance therapy after definitive CCRT or SCRT for LS-SCLC.

Trial registration ClinicalTrials.gov Identifier: NCT05942508. Date of registration: 7 June 2023.

Keywords Limited-stage small cell lung cancer, Combined drug therapy, Anlotinib, TQB2450, Efficacy, Safety

Introduction

Small-cell lung cancer (SCLC) comprises approximately 13-15% of lung cancer cases [1] and is typically characterized by a large intrathoracic mass at diagnosis, poor cellular differentiation, and a high propensity for metastasis [2], resulting in a 5-year survival rate of only 8% [3]. According to the staging system of the Veterans Administration Lung Study Group (VALG), limited-stage SCLC (LS-SCLC) is a localized disease affecting only one hemithorax that can be treated with a single radiation field [4]. Currently, except for rare patients who are eligible for surgical resection, the first-line treatment for LS-SCLC is thoracic radiotherapy (RT) combined with concurrent platinum-etoposide chemotherapy [5]. Although SCLC initially responds to both chemotherapy and radiotherapy, these responses are transient due to the rapid development of drug resistance. Consequently, outcomes for patients with LS-SCLC remain unsatisfactory, with a median overall survival (OS) of only 16–24 months [6]. This underscores the urgent need to develop enhanced therapeutic strategies to effectively address the treatment gap during the maintenance phase following first-line therapy in LS-SCLC.

At the 2024 ASCO conference, the phase III ADRIATIC study demonstrated that durvalumab, an anti-programmed cell death-ligand 1 (PD-L1) checkpoint blockade, used as consolidation therapy after concurrent chemoradiotherapy (CCRT), resulted in statistically and clinically significant improvements in progression-free survival (PFS) and OS compared with placebo (median PFS (mPFS): 16.6 vs. 9.2 weeks; median OS: 55.9 vs. 33.4 months) [7]. These findings support durvalumab as a potential new standard of care for patients with LS-SCLC who do not experience disease progression after CCRT. However, not all immunotherapies yield positive results. In the STIMULI trial, no significant improvement in PFS or OS was observed in the experimental arm using a combination of nivolumab and ipilimumab versus chemoradiotherapy (CRT) [8].

Therefore, immunotherapeutic regimens need to be explored to improve the prognosis of LS-SCLC. Further research is required to confirm whether combining immunotherapy with anti-vascular therapy can provide greater benefits for patients with LS-SCLC. Notably, at WCLC 2023, the ETER701 trial showed that Benmelstobart (TQB2450, an anti-PD-L1 antibody) combined with Anlotinib plus chemotherapy achieved the longest reported PFS (6.9 months) and OS (19.3 months) as first-line therapy in patients with extensive stage small cell lung cancer (ES-SCLC) [9]. Theoretically, this regimen may also hold promise for LS-SCLC.

Given the severe toxicity of CCRT [10] and the high proportion of older patients (aged ≥ 70 years) with LS-SCLC [11], it is safer to administer TQB2450 and Anlotinib after the completion of CRT. Therefore, this trial was designed to evaluate the efficacy and safety of TQB2450 in combination with Anlotinib as maintenance therapy for LS-SCLC following CCRT or sequential CRT (SCRT).

Methods

Study design and patients

This was an open-label, single-arm, phase Ib clinical trial evaluating the combination of TQB2450 and Anlotinib in patients with LS-SCLC (ClinicalTrials.gov Identifier: NCT05942508, 06/07/2023). The trial was conducted at Shandong Cancer Hospital, affiliated with Shandong First Medical University (Jinan, China). The study was performed the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Shandong Cancer Hospital, affiliated with Shandong First Medical University. Written informed consent was obtained from all the patients.

The key inclusion criteria were as follows: (1) age 18 to 75 years; (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;(3) pathologically confirmed LS-SCLC; (4) h life expectancy of at least 6 months; (5) receiving 4–6 cycles of platinum-based CCRT or SCRT, completed within 1 to 42 days before the first administration of the study drug; (6) radiotherapy initiated no later than the end of cycle 2 of chemotherapy, consisting of either 60–66 Gy within 6 weeks (standard once-daily schedule) or 45 Gy within 3 weeks (hyperfractionated twice-daily schedule), with dose calculation based on the planned target volume (PTV); (7) achievement of complete response (CR), partial response (PR),

or stable disease (SD) after receiving definitive CCRT or SCRT. Key exclusion criteria were: (1) history of or current malignancies within 3 years; (2) pathologically confirmed ES-SCLC, mixed SCLC, and NSCLC; (3) prior treatment with antiangiogenic therapy or immunotherapy; (4) history of grade ≥ 2 radiation pneumonitis (RP) after CRT. The full inclusion and exclusion criteria are provided in the Appendix.

Treatment

TQB2450 was administered intravenously at a dose of 1200 mg on day 1 every 3 weeks for 60 ± 10 min. The administration of TQB2450 was continued for up to 24 months, and the dose could not be adjusted during treatment. To reduce the toxicity of the combination treatment regimen, Anlotinib was started at a dose of 8 mg once daily from day 1 to day 14. The Anlotinib dose could be increased to 10 mg after two cycles, provided the patients tolerated the treatment well. A maximum of two dose reductions for Anlotinib therapy was allowed in the event of treatment-related adverse events (TRAEs). The Anlotinib dose could be reduced from 10 mg to 8 mg once daily and further reduced to 6 mg once daily at the investigator's discretion. If patients could not tolerate the 6 mg dose, Anlotinib was paused or discontinued. All patients received TQB2450 intravenously (1200 mg every 3 weeks) and Anlotinib orally (once daily, 2 weeks on / 1 week off) until disease progression, unacceptable toxicity, or withdrawal of consent.

Assessments

The primary endpoints of this study were the incidence and degree of adverse events (AEs), serious adverse events (SAEs), and abnormal laboratory test results. AEs were collected using an electronic data capture (EDC) system throughout the treatment period and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 5.0).

Secondary endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DOR), PFS, OS, 12-month and 24-month PFS rates, and 24-month OS rates. Tumor assessments were performed by investigators according to RECIST 1.1 every 6 weeks. ORR was defined as the proportion of patients who achieved CR and PR. DCR was defined as the overall proportion of patients who achieved CR, PR, or SD during the trial. PFS was defined as the time from the first date of TQB2450 and Anlotinib administration to disease progression (according to RECIST 1.1) or death from any cause, whichever occurred first. OS was measured from the date of drug administration to the date of death from any cause.

Statistical analysis

In this phase Ib trial, the sample size was not determined based on efficacy benefits or type I error considerations. A total of 15–20 patients were enrolled, with the sample size selected for clinical rather than statistical reasons.

Descriptive statistics were used to summarize the demographic data and safety outcomes of the clinical trials. The Kaplan-Meier method was used to calculate survival metrics, including mPFS, median OS, 12-month and 24-month PFS rates, and 24-month OS rates. The duration of follow-up was calculated using the reverse Kaplan–Meier estimate of OS. ORR and DCR are expressed as percentages, with 95% confidence intervals (CIs) calculated using the Clopper–Pearson method. Statistical analyses were performed using SPSS (version 26.0; IBM Corp., Armonk, NY, USA) and PRISM version 8.0.2 (GraphPad Software, La Jolla, CA, USA).

Results

Patient characteristics

From May 31, 2023 to October 13, 2023, 19 patients were screened for inclusion in the study, of whom 15 were enrolled and received the study treatment (Fig. 1). The baseline characteristics of the patients are presented in Table 1. The median patient age was 56 years (range: 47–73). The majority of patients were male (11 patients, 73.33%), and all presented with an ECOG performance status of 1. Five patients (33.33%) had a normal BMI, while three (20.00%) were obese. 60% of the patients were current or former smokers. Two-thirds of the patients received etoposide combined with carboplatin, while the remaining patients were treated with an etoposide and cisplatin protocol. Of the 15 patients, 10 (66.67%) received hyperfractionated radiotherapy, with a dose of 45 Gy administered twice daily, whereas the remaining five patients (33.33%) received conventional fractionated radiotherapy, with a total dose of 60 Gy delivered once daily. All 15 patients underwent CCRT, and only four (26.67%) did not receive prophylactic cranial irradiation (PCI). Among subjects who completed CRT prior to enrollment, 12 patients (80.00%) achieved PR, two (13.33%) achieved CR, and one patient (6.67%) achieved SD.

Clinical efficacy

As of the data cut-off date, October 31, 2024, the median follow-up time for PFS was 15.13 months (range, 2.83–17.07), and the mPFS has not yet been reached (95% CI, 13.9-not reached). The estimated PFS rate at 12 months was 86.7% (95% CI, 71.1–100.0; Fig. 2A). The median OS was not reached, and the 12-month OS rate was 100% (Fig. 2B).

As summarized in Table 2, during maintenance therapy with TQB2450 plus Anlotinib in this study, one patient

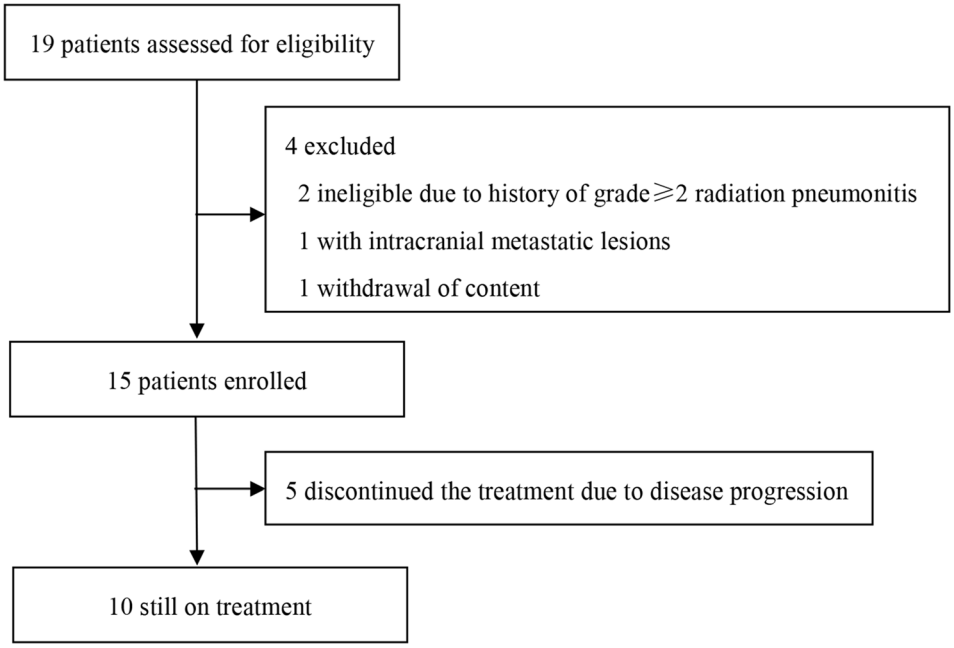

Fig. 1 Enrollment and trial flow diagram

(6.67%) achieved CR, resulting in an overall response rate of 6.67% (95% CI, 0.16–31.95). The DCR was 100% (Table 2). At the time of data cut-off, 10 patients (66.67%) remained on treatment, while five discontinued the treatment due to disease progres (Fig. 1). Two patients developed new extrathoracic lesions without target lesion progression. Progression of the target lesions was observed in two additional patients, and one patient developed new intrapulmonary lesions. The maximal percentage change from baseline in the sum of the target lesion diameters is shown in Fig. 3A, highlighting variability in tumor response among patients. Additionally, Fig. 3B-C present the spider and swimming plots, respectively, which illustrate the dynamic changes in tumor size over time from baseline. The swimmer plot details the duration of treatment for each individual patient, offering insight into individual treatment trajectories and disease responses.

Safety

TRAEs of any grade occurred in 13 patients (86.67%) (Table 3). The most common TRAEs were fatigue ($n=6$, 40.00%), decreased white blood cell count ($n=5$, 33.33%), hypothyroidism ($n=5$, 33.33%), and decreased platelet count ($n=5$, 33.33%). Three grade 3 AEs were observed in three patients: 1 with hyperkalemia, 1 with abdominal distension, and 1 with a decreased lymphocyte count. Hyperkalemia (6.77mmol/L) and abdominal distension may have been caused by Anlotinib. One patient experienced grade 4 hyponatremia, presumed to be associated with the underlying disease rather than the treatment. No grade 5 AEs occurred, and no patients withdrew from the study due to AEs.

Two SAEs were observed: elevation in cardiac troponin T and cerebral infarctions. These events led to a temporary one-cycle treatment interruption, after which the medication was resumed. Radiation pneumonitis (RP) was observed in three patients, all classified as grade 2, with improvement following active steroid-based symptomatic treatment. TQB2450 treatment was temporarily suspended for five cycles in one of these patients. One patient developed grade 1 immune-related pneumonitis and did not receive any specific treatment. Additionally, one patient required a dose reduction of Anlotinib due to fatigue, and one patient discontinued Anlotinib due to grade 3 abdominal distension. In summary, five patients required dose modification or treatment interruption due to AEs.

Randomized controlled phase III clinical trial

In this trial, the combination of TQB2450 and Anlotinib demonstrated favorable tolerability and a survival benefit for patients, suggesting its potential as a front-line therapy. Accordingly, a randomized, double-blind, placebo-controlled phase III clinical study is underway to further evaluate the efficacy and safety of TQB2450 plus Anlotinib as maintenance therapy for patients with LS-SCLC (ClinicalTrials.gov Identifier: NCT06469879). In this phase III trial, a total of 358 patients with LS-SCLC who had not progressed after CRT were enrolled and randomly assigned (1:1) to either the treatment or control group. The treatment group received TQB2450

Table 1 Baseline characteristics

Characteristics	*n* (%) Total *n* = 15
Age, median (range, years)	56 (47–73)
Sex	
Male	11 (73.33)
Female	4 (26.67)
ECOG performance status	
0	0
1	15 (100.00)
BMI	
18.5–23.9	5 (33.33)
24.0-27.9	7 (46.67)
≥ 28.0	3 (20.00)
Smoking status	
Never smoked	6 (40.00)
Former or current smoker	9 (60.00)
Tumor–node–metastasis stage at diagnosis	
II	3 (20.00)
III	12 (80.00)
Previous chemotherapy	
Etoposide + cisplatin	5 (33.33)
Etoposide + carboplatin	10 (66.67)
Radiotherapy fractionation schedule	
Once daily	5 (33.33)
Twice daily	10 (66.67)
PCI	
Yes	11 (73.33)
No	4 (26.67)
Best response to first-line treatment	
CR	2 (13.33)
PR	12 (80.00)
SD	1 (6.67)

Abbreviation: ECOG, Eastern Cooperative Oncology Group; BMI, Body Mass Index; CRT, chemoradiation therapy; PCI, prophylactic cranial irradiation; CR, complete response; PR, partial response; SD, stable disease

injections (1200 mg every three weeks) and Anlotinib (8 mg once daily for 2 weeks, followed by a 1-week break every 21-day cycle). The control group received placebos for both TQB2450 and Anlotinib at the same frequency and dosage. The primary endpoint is PFS, as evaluated by the Independent Review Committee (IRC). Secondary endpoints include PFS as assessed by the researchers, OS, ORR, DCR, DOR, and 12- and 24-month PFS rates.

Table 2 Best objective response

Efficacy	All patients (*n* = 15)
CR, n (%)	1(6.67%)
PR, n (%)	0
SD, n (%)	14(93.33%)
PD, n (%)	0
ORR (%, 95% CI)	1(6.67%, 0.16-31.95%)
DCR (%, 95% CI)	15(100%)

Abbreviation: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate

Discussion

A total of 15 patients were enrolled in this study. Previous literature reported that over 95% of SCLC were current/former smokers [1], while 40% of patients were never smokers in the trial. However, the prevalence of SCLC among never-smokers exceeds global epidemiological patterns in the East Asian population [12]. And in a multicenter retrospective study led by our institution, 42.2% (451/1068) were never smokers [13]. Thus, this suggests that the smoking profile of the cohort, albeit small ($n = 15$), may reflect regional demographic characteristics.

This study highlights the efficacy of combining TQB2450 with Anlotinib as a maintenance regimen for patients with LS-SCLC, achieving a DCR of 100%. The 12-month PFS rates were 86.7%, and the 12-month OS rate was 100%. The clinical trial results also demonstrate an acceptable safety profile for this therapy, with a relatively low incidence of grade 3 or higher AEs and no grade 5 AEs.

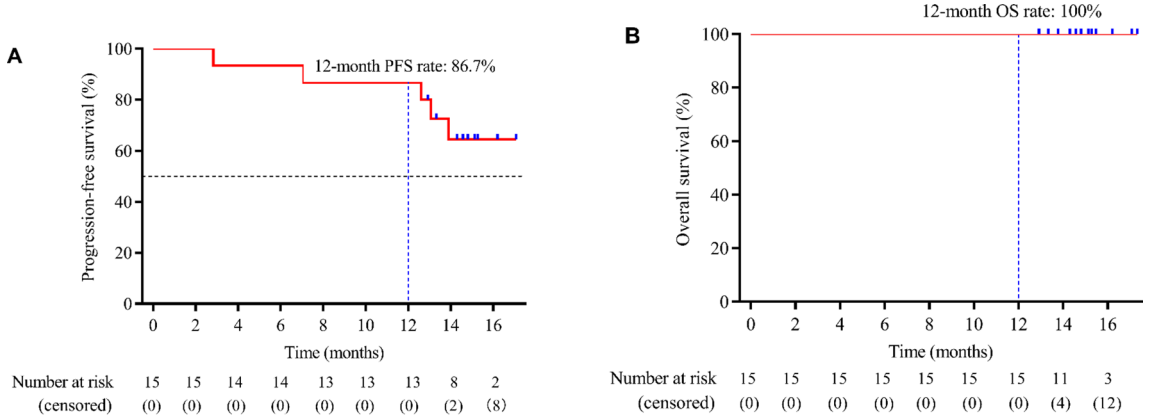

Fig. 2 Kaplan–Meier estimates for PFS (**A**) and OS (**B**) in all patients

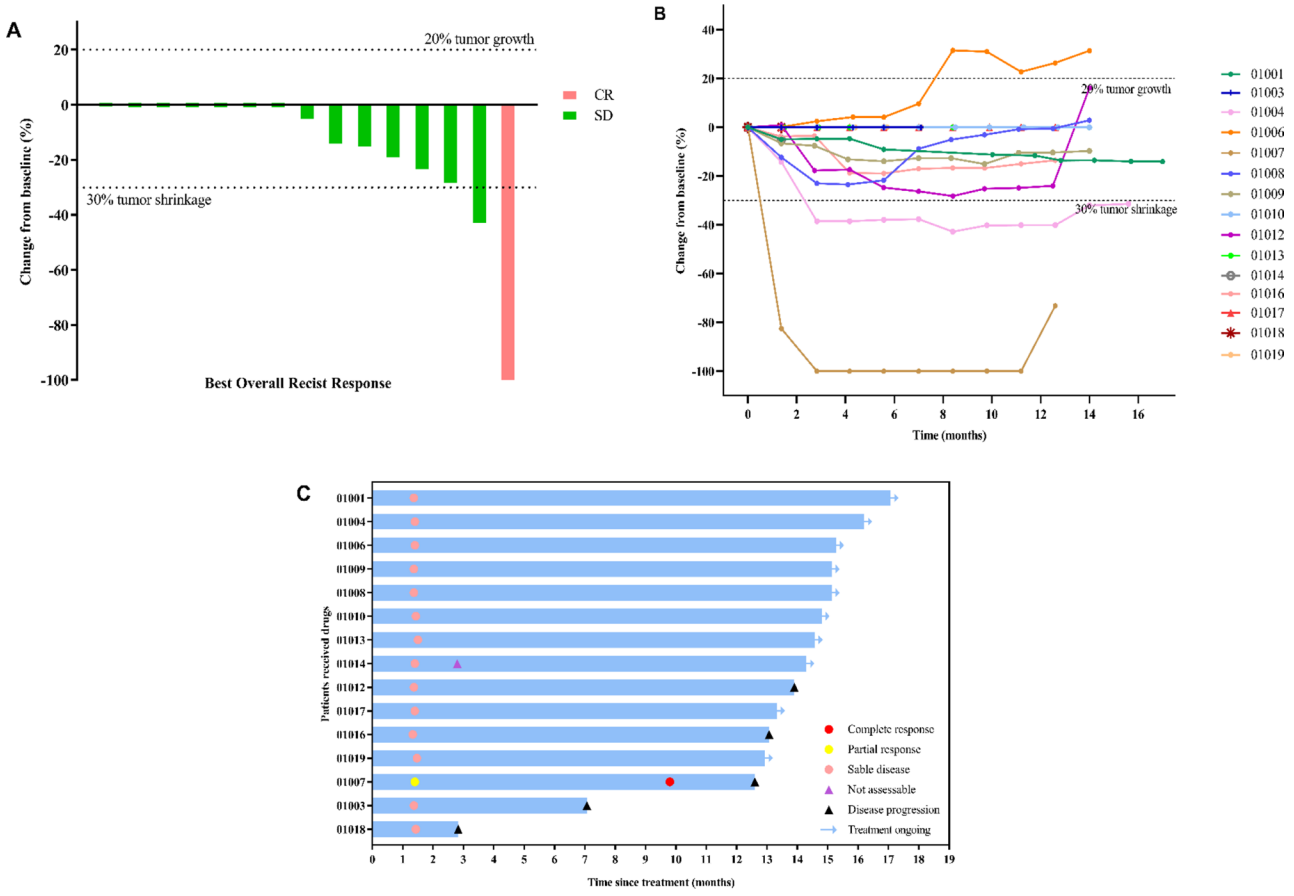

Fig. 3 Tumor response in individual patients. **A**, The best percentage change for the diameter of target lesions from baseline. **B**, Spider plot showing change in target lesions over time for each patient. **C**, Swimming plot. The length of each bar represents the duration treatment for each patient Time zero corresponds to the first administration of maintenance therapy

Over the past two decades, numerous clinical trials have explored various drugs as maintenance treatments for patients with LS-SCLC following first-line CRT with the aim of extending survival [14–18]. However, these efforts have yielded disappointing results. Recently, immunotherapy has emerged as a promising strategy for treating SCLC, showing potential for improved survival rates [19–21]. Notably, the ADRIATIC trial is the first clinical study to report positive findings in this area. In this trial, Cheng et al. demonstrated that durvalumab, used as a maintenance treatment, significantly improved PFS and OS compared with placebo [22]. This represents a substantial advancement in the therapeutic landscape of LS-SCLC.

In the ETER701 trial, the combination of TQB2450 and Anlotinib with EC demonstrated the longest survival reported to date for patients with ES-SCLC [9]. Additionally, this combination has been investigated across multiple solid tumors, including ovarian cancer, triple-negative breast cancer, advanced acral melanoma, biliary tract cancer, and soft tissue sarcoma, demonstrating promising efficacy and a manageable safety profile [23–27]. In line with these findings, this prospective study aimed to evaluate whether the combination of TQB2450 and Anlotinib can offer enhanced efficacy while maintaining an acceptable toxicity profile in patients with LS-SCLC.

It is encouraging to note that in this trial, while the mPFS has not yet been reached (95% CI,13.9-not reached), it has already surpassed the 10.7 months reported in the STIMULI trial, which utilized dual immunotherapy as maintenance treatment following CRT [8]. In the ADRIATIC trial, the mPFS was reported to be 16.6 months, and the 18-month PFS rate in this study was 48.8%. Although the current median follow-up period for PFS in our study was only 15.13 months, this trial achieved a 12-month PFS rate of 86.7% and a 12-month OS rate of 100%. These findings suggest a potential survival advantage of our treatment regimen compared with that observed in the ADRIATIC trial. These preliminary data highlight the potential efficacy of this regimen, and continued follow-up will be conducted to monitor outcomes, with data updates provided as they become available.

Table 3 Treatment-related adverse events, occurring in ≥ 10%

Adverse event	All grades, *n* (%)	Grade 1–2, *n* (%)	≥Grade 3, *n* (%)
Fatigue	6 (40.00)	6 (40.00)	0
Decreased white blood cell count	5 (33.33)	5 (33.33)	0
Hypothyroidism	5 (33.33)	5 (33.33)	0
Decreased platelet count	5 (33.33)	5 (33.33)	0
Hyperglycemia	4 (26.67)	4 (26.67)	0
Hypertension	4 (26.67)	4 (26.67)	0
Skin xerosis	4 (26.67)	4 (26.67)	0
Decreased neutrophil count	4 (26.67)	4 (26.67)	0
Sinus bradycardia	3 (20.00)	3 (20.00)	0
Radiation Pneumonitis	3 (20.00)	3 (20.00)	0
Hyperthyroidism	3 (20.00)	3 (20.00)	0
Anemia	3 (20.00)	3 (20.00)	0
Hoarseness	3 (20.00)	3 (20.00)	0
Elevated aspartate aminotransferase	3 (20.00)	3 (20.00)	0
Anorexia	3 (20.00)	3 (20.00)	0
Elevated alanine aminotransferase	2 (13.33)	2 (13.33)	0
Nausea	2 (13.33)	2 (13.33)	0
Arthralgia	2 (13.33)	2 (13.33)	0
Hand-foot syndrome	2 (13.33)	2 (13.33)	0
Dizziness	2 (13.33)	2 (13.33)	0
Limb pain	2 (13.33)	2 (13.33)	0

The favorable survival outcomes observed in this study may be attributed to the combination of angiogenesis inhibitors and immune checkpoint inhibitors (ICIs). To the best of our knowledge, this is the first prospective trial to evaluate the safety and efficacy of this combination therapy in an LS-SCLC population. Effective antitumor immunity requires immune cell infiltration into the tumor microenvironment (TME). Elevated levels of vascular endothelial growth factor (VEGF) have been shown to promote immunosuppression during tumor progression through multiple mechanisms, thereby reducing the effectiveness of immunotherapeutic agents [28]. As a novel multitarget tyrosine kinase inhibitor (TKI), Anlotinib targets tumor angiogenesis and cell proliferation by inhibiting pro-angiogenic signaling pathways associated with VEGF receptors 2 and 3, fibroblast growth factor receptor 1, platelet-derived growth factor receptor β, and the stem cell factor receptor [29]. This inhibition facilitates immune cell infiltration and fosters an immune-supportive TME, thereby enhancing the efficacy of immunotherapy through a synergistic mechanism [28, 30, 31]. Previous studies have indicated that combining Anlotinib with an ICI offers superior efficacy in lung cancer treatment compared to monotherapy with either chemotherapy or ICIs alone [32, 33].

The safety profile of this combination in our trial was favorable. In the ETER701 trial, the combination of TQB2450 and Anlotinib with EC achieved the longest survival reported among patients with ES-SCLC. Nevertheless, the incidence of TRAEs of grade 3 or higher was 94.3%, and 4.5% of patients experienced TRAEs that resulted in death [9]. For patients with LS-SCLC, first-line treatment is effective, and separating the administration of CRT from TQB2450 plus Anlotinib significantly reduced the severity of AEs. In our trial, while TRAEs were observed in 13 of 15 patients (86.67%), the majority were classified as grade 1 or 2. The incidence of grade 3 or 4 AEs was slightly higher in our trial than that reported in the ADRIATIC trial (26.67% vs. 24.4%). Notably, no deaths due to AEs were reported in our study, whereas 2.7% of patients in the durvalumab group of the ADRIATIC trial died due to AEs. Two patients (13.33%) in our trial experienced SAEs, which is lower than the rate observed in the experimental group in the ADRIATIC trial (29.8%). Additionally, only one patient (6.67%) in our study discontinued TQB2450 due to grade 3 abdominal distension, a lower rate compared to the 16.4% discontinuation rate in the ADRIATIC trial due to adverse reactions. Five other patients temporarily interpreted treatment due to AEs but resumed therapy after symptom resolution.

Regarding the two SAEs (elevation in cardiac troponin T and cerebral infarction) observed in the study, investigators concluded that these events were likely unrelated to TQB2450 or Anlotinib. The former occurred during a treatment hiatus in a patient with the history of hypertension. Although the cardiac troponin T was over 3× the upper limit of normal (ULN), left ventricular ejection fraction (LVEF) remained preserved at 59%. Prioritizing the patient's safety, the combination therapy was temporarily suspended for one cycle, and the experimental medication was resumed following a comprehensive evaluation by investigators. Notably, troponin T normalized within 6 weeks of treatment resumption, with no recurrence of symptoms, which further supports the lack of causal association with study drugs, as resolved symptoms and biomarker normalization occurred despite continued therapy. The cerebral infarction occurred in a patient with baseline hypercholesterolemia. The combination therapy was temporarily suspended for one cycle, after which therapy was resumed, with one additional cycle administered safely and no recurrent cerebrovascular events. Subsequent discontinuation was due to tumor progression, not treatment toxicity. Although the SAEs occurred during the treatment period, the absence of mechanistic plausibility and the presence of other susceptibility factors strengthened the investigators in drawing the conclusion that these events were unrelated to the study regimen. Nonetheless, vigilant monitoring of metabolic and cardiovascular parameters is advisable in patients receiving the combination therapy, particularly those with risk factors.

The incidence of RP or immune-related pneumonitis was also within acceptable ranges. Specifically, three patients (20%) experienced grade 2 RP, with symptoms improving following active steroid-based treatment. Additionally, one patient developed grade 1 immune-related pneumonitis. Compared with the ADRIATIC trial, our study demonstrated a lower incidence of pneumonitis (26.7% vs. 38.2%) and reduced severity, as no cases reached grade 3 or higher (vs. 3.1% in the ADRIATIC trial). Additionally, the safety profile was generally consistent with those observed in previous trials involving other solid tumors [23–27], and no new AEs were identified.

This study has some limitations. The sample size was relatively small, and as a single-arm study without a comparator treatment arm, it was susceptible to selection bias. Additionally, due to the short follow-up period, the mPFS and mOS were not reached. However, patients are still being followed, and additional data will be collected in the future. Furthermore, based on the data indicating favorable survival benefits and an acceptable incidence of AEs, a randomized, double-blind, placebo-controlled phase III clinical study is underway to further evaluate the efficacy and safety of TQB2450 plus Anlotinib as maintenance therapy for patients with LS-SCLC (ClinicalTrials.gov Identifier: NCT06469879). This further research is expected to provide a more comprehensive and in-depth analysis of the advantages of this combination therapy and address the gap in treatment following first-line therapy for LS-SCLC.

Conclusion

The combination of TQB2450 and Anlotinib showed promising clinical efficacy and manageable AE profiles, addressing an unmet need in the post-CRT setting. This combination shows potential as a maintenance treatment for patients with LS-SCLC who have not experienced disease progression after first-line CRT. To validate these preliminary findings, a randomized, double-blind, placebo-controlled phase III clinical trial (ClinicalTrials.gov Identifier: NCT06469879) is currently underway, aiming to offer robust evidence for its integration into clinical practice.

Abbreviations

LS-SCLC	Limited-stage small-cell lung cancer
ES-SCLC	Extensive-stage small cell lung cancer
PD-L1	Programmed cell death-ligand 1
PFS	Progression free survival
OS	Overall survival
CCRT or SCRT	Concurrent or sequential chemoradiotherapy
AEs	Adverse events
TRAEs	Treatment-related adverse events
SAEs	Serious adverse events
EDC	Electronic data capture
RP	Radiation pneumonitis
RT	Thoracic radiotherapy
CRT	Chemoradiotherapy
ECOG	Eastern Cooperative Oncology Group
PTV	Planned target volume
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive disease
PCI	Prophylactic cranial irradiation
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective response rate
DCR	Disease control rate
DOR	Duration of response
RECIST	Response Evaluation Criteria in Solid Tumors
BMI	Body Mass Index
IRC	Independent Review Committee
ICIs	Immune checkpoint inhibitors
TME	Tumor microenvironment
VEGF	Vascular endothelial growth factor
TKI	Tyrosine kinase inhibitor

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Author contributions

X.L. performed formal analysis and wrote the original draft. X.Y., L.Z., J.W., Z.W., W.C., and M.Y. conducted investigation and curated data. K.Z., L.L., L.K., L.J., J.X., and H.Z. were responsible for enrollment, treatment, and follow-up. X.W. and D.X. acquired funding and provided resources. J.Y. and X.M. conceptualized and designed the clinical studies, supervised the project, and reviewed and edited the manuscript. Dr Meng had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and received approval from the Ethics Committee of Shandong Cancer Hospital, affiliated with Shandong First Medical University, and secured its registration at the Clinical Trials. All participants provided written informed consent before the study's commencement.

Competing interests

The authors declare no competing interests.

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