Adebrelimab plus chemotherapy and sequential thoracic radiotherapy as first-line therapy for extensive-stage small–cell lung cancer (ES-SCLC): a phase II trial

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Summary

Background This phase II prospective trial aimed to investigate the efficacy and safety of adebrelimab (PD-L1 antibody) plus first-line chemotherapy followed by sequential thoracic radiotherapy (TRT) combined with adebrelimab in extensive-stage small–cell lung cancer (ES-SCLC). Biomarkers associated with potential therapeutic effects were also explored.

Methods Patients with previously untreated ES-SCLC were enrolled at Shandong Cancer Hospital and Institute (Jinan, China). Patients received 4–6 cycles of adebrelimab (20 mg/kg, D1, Q3W) combined with EP/EC (etoposide, 100 mg/m^2, D1-3, Q3W and cisplatin, 75 mg/m^2, D1, Q3W or carboplatin, AUC = 5, D1, Q3W). Then patients with response sequentially underwent consolidative TRT (≥30 Gy in 10 fractions or ≥50 Gy in 25 fractions, involved-field irradiation), and maintenance adebrelimab until disease progression or intolerable adverse events (AEs). The primary endpoint was overall survival (OS). Genomic and circulating tumour DNA (ctDNA) profiling were also analyzed with tumour tissues and peripheral blood. This trial was registered with ClinicalTrials.gov, NCT04562337.

Findings From October 2020 to April 2023, 67 patients diagnosed with ES-SCLC were enrolled and received at least one dose of study treatment. All patients were included in the efficacy and safety analyses. 45 patients received sequential TRT as planned. The median OS and progression-free survival (PFS) was 21.4 months (95% CI: 17.2–not reached months) and 10.1 months (95% CI: 6.9–15.5 months), respectively. The confirmed objective response rate was 71.6% (48/67, 95% CI: 59.3–82.0%) and disease control rate was 89.6% (60/67, 95% CI: 79.7–95.7%). There were no treatment-related deaths. The most common grade 3 or higher treatment-related adverse events (TRAEs) were hematological toxicities. The incidence of any grade and G3+ pneumonitis was 25% (17/67) and 6% (4/67), respectively. No unexpected adverse events were observed. Patients without co-mutations of TP53/RB1 in both tissue and peripheral blood displayed longer PFS (tissue, P = 0.071; ctDNA, P = 0.060) and OS (tissue, P = 0.032; ctDNA, P = 0.031).

Interpretation Adebrelimab plus chemotherapy and sequential TRT as first-line therapy for ES-SCLC showed promising efficacy and acceptable safety.

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Keywords: Adebrelimab; Radiotherapy; Immunotherapy; Predictive biomarker; ES-SCLC

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Research in context

Evidence before this study

We searched PubMed for clinical trials published from database inception until April 17, 2024, using search terms of "extensive stage small cell lung cancer" and "thoracic radiotherapy". The Dutch CREST trial, a phase 3 randomized trial in patients with extensive-stage small cell lung cancer (ES-SCLC), reported that the addition of consolidative thoracic radiotherapy (TRT) did not improve the primary endpoint of 1-year overall survival, but a secondary analysis found improvement in 2-year overall survival compared with patients who did not receive consolidative TRT. The NCCN SCLC Panel recommends that sequential TRT be considered in select ES-SCLC patients with low-bulk extrathoracic metastatic who have a complete or near complete response after initial systemic therapy. In the era of immunotherapy, the role of TRT is not well defined, mainly because TRT was not allowed in most immunotherapy trials, secondly due to the concerns regarding the increased risk of pneumonitis.

Added value of this study

To our knowledge, this is the first prospective, phase 2 study to evaluate the combination of immunotherapy plus chemotherapy and sequential TRT in patients with ES-SCLC. The results indicated that adebrelimab plus chemotherapy and sequential TRT could improve the survival benefits of patients with ES-SCLC. The safety profile was manageable and no new safety signals were observed compared to previous reports. Biomarkers like TP53/RB1 mutations, tissue TMB and ctDNA status may suggest potential responders to this therapeutic regimen.

Implications of all the available evidence

Our results supported the further evaluation of adebrelimab in combination with chemotherapy and sequential TRT in patients with ES-SCLC. Adebrelimab plus chemotherapy and sequential TRT may be a valuable potential new treatment option for ES-SCLC.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide.[1,2] Small cell lung cancer (SCLC), which accounts for approximately 15% of all newly diagnosed lung cancers, is highly aggressive. Approximately two-thirds of SCLC are classified as advanced stage disease, known as extensive-stage SCLC (ES-SCLC), at the time of diagnosis.[3–5] In recent years, the emergence of PD-1/L1 inhibitors has improved the survival of ES-SCLC. Based on the CASPIAN, IMpower133, CAPSTONE-1 and ASTRUM-005 trials, PD-1/L1 inhibitors combined with chemotherapy, have been approved as the first-line treatment of ES-SCLC.[6–9] However, the median overall survival (OS) is about 12–13 months, only 2–3 months higher than that of the control group, highlighting the unmet clinical needs.[10]

Adebrelimab (SHR-1316) is a high-affinity, novel humanized IgG4 monoclonal antibody against PD-L1. In a phase 3 trial (CAPSTONE-1), compared to the placebo group, adebrelimab plus chemotherapy (carboplatin and etoposide) significantly improved OS (15.3 *vs.* 12.8 months, hazard ratio 0.72, P = 0.0017) in patients with ES-SCLC.[7] The most common grade 3 or 4 treatment-related adverse events (TRAEs) were decreased neutrophil count (76% in the adebrelimab group *vs.* 75% in the placebo group), decreased white blood cell count (46% *vs.* 38%), decreased platelet count (38% *vs.* 34%), and anaemia (28% *vs.* 28%). Based on the results, adebrelimab in combination with chemotherapy has been approved as first-line treatment in China.

Prior to the advent of immunotherapy into the therapeutic armamentarium in ES-SCLC, sequential thoracic radiotherapy (TRT) was associated with improved thoracic control and survival outcomes.[11–15] A randomized trial by Jeremic et al. assessed sequential TRT in patients experiencing a complete response at distant metastatic sites after 3 cycles of etoposide/cisplatin.[15] Patients were randomized to receive either 1) further etoposide/cisplatin; or 2) accelerated hyperfractionated RT (54 Gy in 36 fractions over 18 treatment days) in combination with carboplatin plus etoposide. The addition of RT resulted in improved median overall survival (17 *vs.* 11 months). The Dutch CREST trial, a phase 3 randomized trial in patients with ES-SCLC, reported that the addition of consolidative TRT (30 Gy in 10 fractions) did not improve the primary endpoint of 1-year overall survival (33% *vs.* 28%, P = 0.066), but a secondary analysis found improvement in 2-year overall survival (13% *vs.* 3%, P = 0.004) compared with patients who did not receive consolidative TRT.[12] A trial involving 32 patients who received consolidative TRT (40 Gy in 15 fractions) reported that only 16% (5/32) of patients had symptomatic chest recurrences.[11] The NCCN SCLC Panel recommends that sequential TRT be considered in select ES-SCLC patients with low-bulk extrathoracic metastatic who have a complete or near complete response after initial systemic therapy.[16] In the era of immune checkpoint inhibitors (ICIs), the role of TRT is not well defined, mainly because TRT was not allowed in most immunotherapy trials, secondly due to the concerns regarding the increased risk of pneumonitis.[17–19] Sequential TRT can be considered for selected patients, during or before maintenance immunotherapy; however, there are no data on optimal radiotherapy dose and sequencing.[16] The benefit of TRT in the context of chemoimmunotherapy remains to be defined.

TRT may synergize with immunotherapy. Several preclinical studies reported radiotherapy could affect the

immune environment in tumour.[20,21] Radiation can shrink tumour mass, lead to increased tumour antigen presentation, promote T cell infiltration, and affect the immune milieu in tumour.[22] This can enhance response, at local and distant sites (abscopal effect), and lead to better treatment outcomes.[23–25] Combining radiotherapy with ICIs showed more pronounced tumour regression in several solid tumour types, including in the nonirradiated tumours, than provided by either of these treatments alone.[26] It is possible that the relatively modest improvement in survival by addition of ICIs to chemotherapy in ES-SCLC could be further improved by the incorporation of sequential TRT.

Biomarkers play an increasingly important role in cancer treatment. Concurrent inactivation of *TP53* and *RB1* were identified to drive the transition and development of SCLC and putatively abrogated the antitumour immunity in tumour microenvironment.[27,28] Besides, a variety of biomarkers, including PD-L1, molecular subtype, tissue, and blood TMB (bTMB), cytokines, and peripheral blood mononuclear cell (PBMC) subpopulations have been investigated in the context of immunotherapy in SCLC.[29,30] However, no concordant conclusion has been reached to robustly predict therapeutic efficacy of immunotherapy.

In this phase 2 trial, we aimed to evaluate the efficacy and safety of adebrelimab plus chemotherapy and sequential TRT as first-line therapy for ES-SCLC, and to explore predictive biomarkers to indicate patients who could benefit from this combinational regimen.

Methods

Ethics statement

The study protocol (Supplement) was approved by the Ethics Committee of Shandong Cancer Hospital and Institute (approval ID: SDZLEC2020-071-02), and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent forms were completed by all patients before enrolment.

Study design and participants

The study was a single-arm, phase 2 trial conducted at Shandong Cancer Hospital and Institute (Jinan, China). Key inclusion criteria included: 18–75 years old with histologically or cytologically confirmed ES-SCLC per Veterans Administration Lung Study Group staging system; had no previous systemic treatment for ES-SCLC; had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; had measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1); had a life expectancy of at least 3 months; and had adequate organ function. Patients with brain metastases were eligible if they were asymptomatic (allowing patients with brain metastases who have previously received local treatment to be included in the study). Patients were ineligible if they had known, active central nervous system (CNS) metastases and/or carcinomatous meningitis; active autoimmune or interstitial lung disease; active serious infections; corticosteroid use within 14 days before the first study dose, and previous treatment with ICIs.

Procedures

The treatment was administered intravenously in 21-day cycles. Patients received 4–6 cycles of adebrelimab (20 mg/kg, D1, Q3W) combined with EP/EC (etoposide, 100 mg/m^2, D1-3, Q3W and cisplatin, 75 mg/m^2, D1, Q3W or carboplatin, AUC = 5, D1, Q3W). Patients with response sequentially received adebrelimab combined with TRT (≥30 Gy in 10 fractions or ≥50 Gy in 25 fractions, involved-field irradiation) based on investigator decision. TRT preferably had to start within 6 weeks, but not later than 7 weeks after chemotherapy. TRT was administered with 3D conformal radiotherapy (3D-CRT) or intensity-modulated radiation therapy (IMRT). The gross tumour volume (GTV) encompassed the primary tumour and the positive lymph nodes. The clinical target volume (CTV) was defined as the GTV with a 5 mm margin, and the planning target volume (PTV) was expanded from the CTV with a 5–8 mm margin. If the tumour lesion was too large to carry out a tolerable radiotherapy plan, a 5–10 mm margin was directly expanded on the basis of the GTV to form the planning gross target volume (PGTV). For 3D planning, the volume of normal lung tissue, minus planning target volume receiving more than 20 Gy, should be less than 35% and correction for tissue heterogeneity was mandatory. Considering different radiation fractionations, we employed the biological effective dose (BED) formula: $BED = d*n\ [1 + d/(\alpha/\beta)]$,[31] where n is the number of fractions, d represents the dose per fraction, $\alpha/\beta = 10$. All patients then entered the maintenance treatment stage with adebrelimab alone until disease progression, intolerable side effects, patients withdraw, investigator decision, or up to two years of treatment with adebrelimab. Dose modification of adebrelimab was not allowed and dose interruptions were permitted for up to 12 weeks. As per standard practice, prophylactic cranial irradiation (PCI) can be performed during the maintenance phase.

Endpoints and assessments

The primary endpoint was OS (time from first dose of study treatment to death from any cause). Secondary endpoints included PFS (time from first dose of study treatment to RECIST-defined disease progression or death, whichever occurred first), objective response rate (ORR, proportion of patients with confirmed CR or PR), disease control rate (DCR, proportion of patients with CR, PR or stable disease lasting for at least 4 weeks), duration of response (DoR, time from first documented objective response to disease progression or death from

any cause) and safety. Investigator-assessed tumour response were performed every 6 weeks until week 48, and then every 9 weeks until disease progression according to RECIST (version 1.1). Response was assessed by the investigators. Complete response (CR) and partial response (PR) had to be confirmed at least 4 weeks after the initial documentation. OS was assessed every 30 days during follow-up. Adverse events (AEs) were collected and graded by the investigators according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). AEs and serious AEs were monitored from the time of informed consent to 90 days after the last administration of adebrelimab.

DNA extraction and sequencing

DNA extraction from formalin-fixed paraffin-embedded (FFPE) samples were performed using MagPure FFPE DNA LQ Kit (Magen, Shanghai, China). DNA from whole blood samples were extracted with a DNeasy Blood and tissue kit (Qiagen, Duesseldorf, Germany). DNA concentration was quantified using by Quantus fluorometer and Quantus dsDNA HS Assay Kit (Promega, Madison, WI, USA). DNA integrity was determined using Agilent DNA HS Kit and an Agilent 2100 Bioanalyzer system (Agilent Technologies, Santa Clara, CA, USA). For DNA library preparation, the M220 sonicator (Covaris, Woburn, MA, USA) was used to fragment the DNA (200–250 bp). Then, indexed NGS libraries were prepared by end-repairing, A-tailing, adaptor ligation and amplification procedures using NEBNext® Ultra™ II DNA Prep Kit (NEB, Beverly, MA, USA). Quality of libraries was performed using an Agilent Bioanalyzer DNA 1000 kit (Agilent Technologies, Santa Clara, CA, USA) and a Qubit DNA HS fluorescence kit (Thermo Fisher Scientific, Waltham, MA, USA). DNA libraries from FFPE or blood samples were captured by AmoyDx® Master Panel, which targets a genomic region spanning 1.8 megabases and contains 571 genes (Supplementary Table S1) for DNA mutation (supporting single-nucleotide variation [SNV], insertion/deletion [Indel], fusion, copy number variation, microsatellite instability and TMB) detection. To rule out inherited mutations, we meticulously compared the circulating cell-free DNA profiles derived from liquid biopsy with corresponding germline DNA samples. Captured products were amplified and quantified by a Quantus fluorometer. Library size was assessed using Agilent 2100 Bioanalyzer system. After pooling, libraries were sequenced on Illumina NovaSeq 6000 (Illumina Inc., CA, USA) with 2 × 150 bp paired end reads. Then, sequencing data were analyzed and annotated through an in-house developed pipeline.

Statistical analysis

To calculate the sample size, the OS of 14.0 months was anticipated in the new group when the median OS of the historic control group is 9.0 months. With a one-sided, one-sample log-rank test at a 0.025 significance and 80% power, 67 subjects were ultimately required (including a 10% dropout rate). Efficacy and safety were analyzed in the full analysis set, which included all enrolled patients who received at least one dose of study medication. OS, PFS and duration of response (DoR) were calculated with the Kaplan–Meier method, and any differences in survival were evaluated with a stratified log-rank test, with the 95% CIs estimated with the Brookmeyer and Crowley method. The ORR and DCR and the corresponding 95% CIs were calculated using the Clopper Pearson method. Univariate analyses with the Cox proportional-hazards model were used to estimate the effects of individual factors on survival. Significance tests were not applied to comparisons between those received TRT or no TRT treatment groups, as the Null hypothesis of no effect on OS or PFS was untenable. Comparisons of different TRT doses and fractions were not tested because of low numbers in individual groups, leading to low statistical power, except for the comparison of those with BED dose ≥60 Gy and <60 Gy groups. Fisher's exact probability tests were used to compare rates or percentages for significance. All bioinformatics data analyses were conducted using R Project (version 4.1.2; https://www.r-project.org/). P-values of <0.05 were considered statistically significant.

Role of the funding source

CHZ and JJY are employees of Jiangsu Hengrui Pharmaceuticals. CBZ and QL are employees of Amoy Diagnostics. The funder of the study had no role in the study design, patient recruitment, data collection, data analysis, data interpretation, manuscript writing or the decision to submit the study for publication. The corresponding author (LLW) had full access to the dataset of the study and had final responsibility for the decision to submit for publication.

Results

Patient characteristics and disposition

From Oct 14, 2020 to April 24, 2023, a total of 67 patients with ES-SCLC were enrolled. All patients received at least one dose of study treatment and were included in the efficacy and safety analyses (Fig. 1). At data cutoff (December 22, 2023), the median follow-up duration was 17.7 months (IQR, 12.7–23.4). Among all 67 patients, 8 (12%) patients were still receiving study treatment. The reasons for study treatment discontinuation were disease progression (34/67, 51%), patient decision (12/67, 18%), AEs (10/67, 15%), death (2/67, 3%), and end of treatment per study design (1/67, 1%). Demographics and baseline characteristics of patients are shown in Table 1. The median age was 63 years (IQR, 57–66) and 37% (25/67) of patients were ≥65 years old. Most patients were male (56/67, 84%), current or

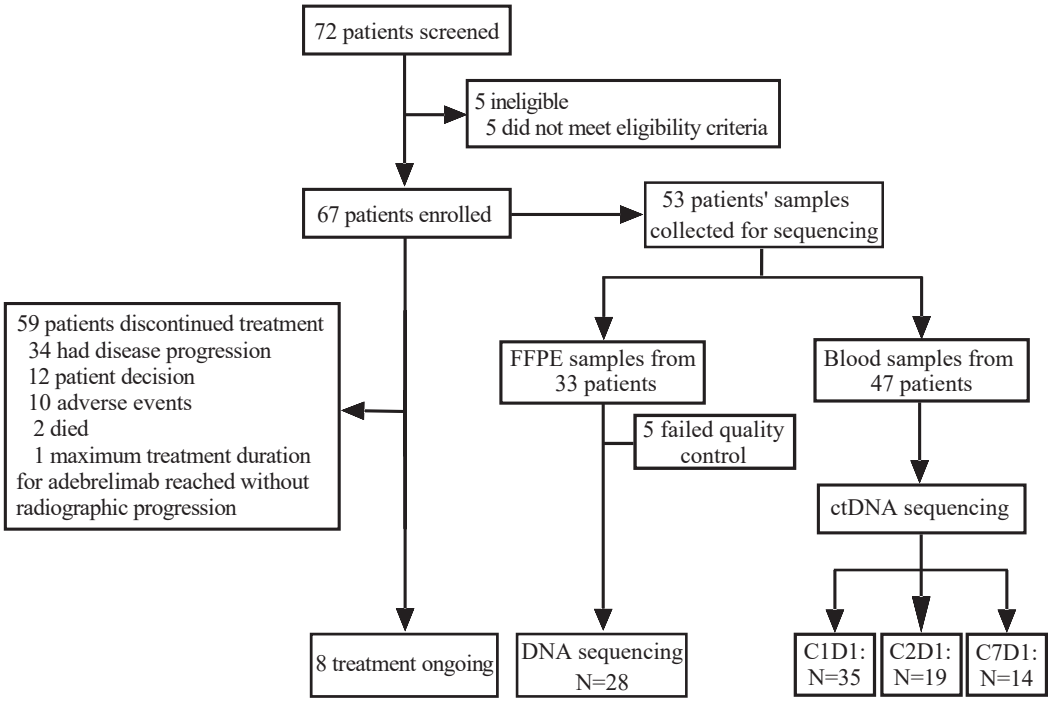

Fig. 1: Flow diagram of the trial. FFPE, formalin-fixed paraffin-embedded; C, cycle; D, day; ctDNA, circulating tumour DNA.

Characteristics	All patients (n = 67)	Patients with tissue DNA sequencing (n = 28)	Patients with ctDNA sequencing (n = 47)
Age, years, median (IQR)	63 (57, 66)	64 (58, 66)	62 (57, 65)
<65 years, n (%)	42 (63)	17 (61)	29 (62)
≥65 years, n (%)	25 (37)	11 (39)	18 (38)
Sex, n (%)			
Male	56 (84)	23 (82)	41 (87)
Female	11 (16)	5 (18)	6 (13)
ECOG performance status, n (%)			
0	3 (4)	2 (7)	3 (6)
1	64 (96)	26 (93)	44 (94)
Disease stage, n (%)			
III	3 (4)	1 (4)	3 (6)
IV	64 (96)	27 (96)	44 (94)
Smoking status, n (%)			
Current or former smoker	44 (66)	21 (75)	32 (68)
Never smoked	23 (34)	7 (25)	15 (32)
Brain metastases, n (%)			
Yes	22 (33)	7 (25)	11 (23)
No	45 (67)	21 (75)	36 (77)
Liver metastases, n (%)			
Yes	21 (31)	7 (25)	14 (30)
No	46 (69)	21 (75)	33 (70)
Lactate dehydrogenase at enrolment, n (%)			
≤ ULN	27 (40)	12 (42)	20 (43)
> ULN	40 (60)	16 (57)	27 (57)

ECOG, Easlegetern Cooperative Oncology Group; ctDNA, circulating tumor DNA; ULN, upper normal limit.

Table 1: **Baseline characteristics.**

former smokers (44/67, 66%) with an ECOG performance status 1 (64/67, 96%). 22 (22/67, 33%) patients were diagnosed with brain metastasis and 21 (21/67, 31%) patients had liver metastasis at baseline. 40 (40/67, 60%) patients had elevated lactate dehydrogenase (LDH) level.

Of the 67 patients enrolled, 48 (48/67, 72%) patients received more than 4 cycles of chemotherapy. 40 (40/67, 60%) patients received adebrelimab as consolidation therapy. The median cycle of adebrelimab consolidation was 4 (IQR, 2–10). 45 (67%) received sequential TRT. All TRT was administered with IMRT. 30 patients used the PGTV volume and 1 patient received PCI. The major reasons for not receiving TRT were patient decision (11/67, 16%), disease progression (7/67, 10%), AEs (3/67, 4%) and death (1/67, 1%). 27 patients received conventional fractionated radiotherapy. 18 patients received hypofractionated radiotherapy. The median TRT dose for patients received radiotherapy was 50 Gy (IQR, 45–50), with most patients receiving 45 Gy/15f (11/45, 24%) and 50 Gy/25f (16/45, 36%). The median BED dose was 60 Gy. 24 patients received TRT at BED dose ≥60 Gy (BED-high) while 21 received TRT at BED dose <60 Gy (BED-low). Tumour tissues and blood samples were collected from 53 patients after getting their permissions. DNA sequencing was performed in 28 tumour tissue samples. ctDNA was analyzed in blood samples collected from 47 patients at 3 time points.

Efficacy

At data cutoff, all 67 patients were included in the efficacy analysis set. 28 (41.8%) patients had died. The median OS was 21.4 months [95% CI: 17.2–not reached (NR) months] (Fig. 2A). 1-year and 2-year OS rate were 74.1% (95% CI: 63.6–86.4%) and 39.7% (95% CI: 25.5–61.9%). For those received TRT (TRT) or no TRT treatment (No-TRT), the median OS was 22.9 months (95% CI: 20.1- NR months) and 13.4 months (95% CI: 13.3-NR months) respectively (Fig. 2B). According to the assessment of PFS by the investigators, 36 (53.7%) patients in the study had disease progression or died. The median PFS was 10.1 months (95% CI: 6.9–15.5 months) in all patients (Fig. 2C). 6-month and 1-year PFS rate was 72.9% (95% CI: 62.0–85.7%) and 39.0% (95% CI: 26.3–57.8%). For those with TRT or No-TRT, the median PFS was 11.3 months (95% CI: 8.3-NR months) and 4.1 months (95% CI: 3.5-NR months) respectively (Fig. 2D).

As shown in Tables 2 and 3 (3/67, 4%) patients achieved CR, 45 (45/67, 67%) patients achieved PR and 12 (12/67, 18%) achieved SD. The confirmed ORR was 71.6% (48/67, 95% CI: 59.3–82.0%) and DCR was 89.6% (60/67, 95% CI: 79.7–95.7%). The median DoR was 8.2 months (95% CI: 5.8–NR months). For those with TRT or No-TRT, the confirmed ORR was 93.3% (42/45, 95% CI: 81.7–98.6%) and 27.3% (6/22, 95% CI: 10.7–50.2%), DCR was 100% (45/45, 95% CI: 92.1–100%) and 68.2% (15/22, 95% CI: 45.1–86.1%) respectively.

Efficacy by TRT dose and fraction

For patients received 45 Gy in 15 fractions (3 Gy × 15f, N = 11) or 30 Gy in 10 fractions (3 Gy × 10f, N = 5) TRT, the median PFS was 8.2 months (95% CI: 6.4-NR months) and 14.0 months (95% CI: 10.1-NR months; Supplementary Figure S1A), respectively. The median OS was 21.4 months (95% CI: 21.4-NR months) and 18.6 months (95% CI: 15.8-NR months; Supplementary Figure S1B). For patients received 50 Gy in 25 fractions (2 Gy × 25f, N = 16) or greater than that (2 Gy × 25f+, N = 6) TRT, the median PFS was 11.3 months (95% CI: 8.3-NR months) and 11.1 months (95% CI: 5.8-NR months; Supplementary Figure S1C). The median OS was 22.9 months (95% CI: 11.6-NR months) and NR (95% CI: 7.0-NR months; Supplementary Figure S1D). For those received BED-high (N = 24) and BED-low (N = 21), the median PFS was 11.3 months (95% CI: 6.9-NR months) and 13.1 months (95% CI: 8.2-NR months; P = 0.81; Supplementary Figure S1E). The median OS was NR months (95% CI: 11.7-NR months) and 21.4 months (17.2-NR months; P = 0.90) respectively (Supplementary Figure S1F).

Safety

All 67 patients were evaluable for safety analysis. The median cycle number of adebrelimab exposure was 7 (IQR, 5–10), and the median cycle number of chemotherapy exposure was 6 (IQR, 4–6). There were no treatment-related deaths. Treatment-related adverse events (TRAEs) occurred in 60 (60/67, 90%) patients. Grade 3 or higher TRAEs occurred in 39 (39/67, 58%) patients. As illustrated in Table 3, the most commonly reported TRAEs were neutrophil count decreased (48/67, 72%), anemia (46/67, 69%), white blood cell count decreased (43/67, 64%), lymphocyte count decreased (29/67, 43%) and nausea (23/67, 34%). The most common grade 3 or higher AEs were neutrophil count decreased (28/67, 42%), white blood cell count decreased (13/67, 19%) and lymphocyte count decreased (9/67, 13%). For those with TRT or No TRT, TRAEs occurred in 43 (43/45, 96%) and 17 (17/22, 77%) patients, respectively. The incidence of Grade 3 or higher TRAEs was higher in TRT compared to No-TRT [62% (28/45) *vs.* 50% (11/22)]. Serious adverse events occurred in 9 (9/67, 13%) patients, with pneumonitis (2/67, 3%) as the most common events. TRAEs leading to discontinuation occurred in 10 (10/67, 15%) patients, with hematological toxicities being the most common reason. No unexpected AEs were observed.

Tissue and circulating biomarkers for predicting the efficacy of immunotherapy

Patients with different responses to immunotherapy were divided into durable clinical benefit (DCB, N = 18)

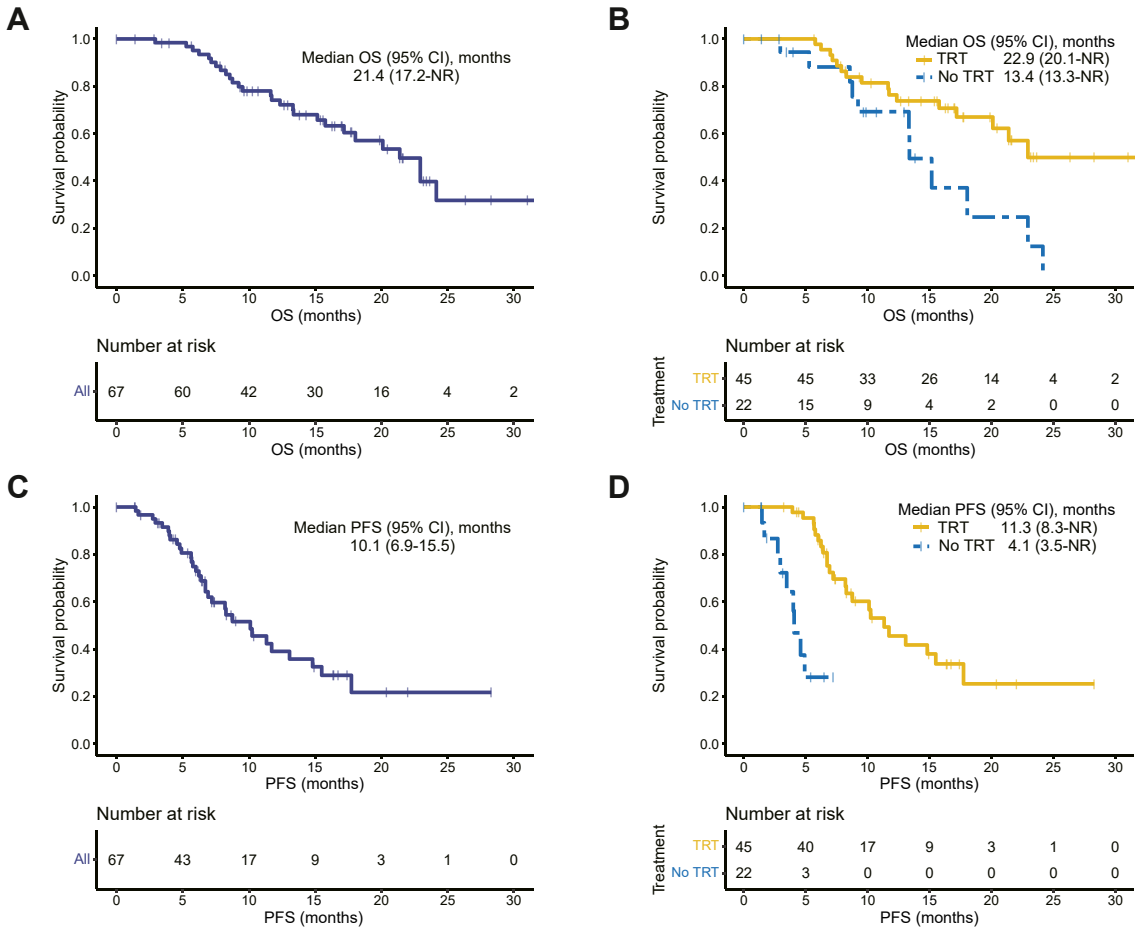

Fig. 2: Kaplan–Meier curves for PFS and OS. (A) OS in all patients. (B) OS in patients received TRT or no TRT. (C) PFS in all patients. (D) PFS in patients received TRT or no TRT. PFS, progression-free survival; OS, overall survival; CI, confidence interval; NR, not reached; TRT, thoracic radiotherapy.

and no durable clinical benefit (NDB, N = 7) groups according to whether they progressed within 6 months, and the differences in tissue gene mutations between the two groups were compared. Significantly different distribution of somatic mutations in genes such as TP53, MAP3K1 were identified between these two groups in biopsy tissues. The mutation rate of RB1 was also higher in the NDB group than in the DCB group, although the difference was not significant (Fig. 3A). Fig. 3B shows the univariate Cox regression analysis of

Variables	All patients (n = 67)	TRT (n = 45)	No TRT (n = 22)
Best overall response, n (%)			
Complete response (confirmed)	3 (4)	3 (7)	0
Partial response (confirmed)	45 (67)	39 (87)	6 (27)
Stable disease	12 (18)	3 (7)	9 (41)
Progressive disease	2 (3)	0	2 (9)
Not evaluable[a]	5 (7)	0	5 (23)
Confirmed ORR, n (%; 95% CI)	48 (71.6; 59.3–82.0)	42 (93.3; 81.7–98.6)	6 (27.3; 10.7–50.2)
DCR, n (%; 95% CI)	60 (89.6; 79.7–95.7)	45 (100; 92.1–100)	15 (68.2; 45.1–86.1)

ORR, objective response rate; DCR, disease control rate; CI, confidence interval. [a]5 patients were not evaluable due to study discontinuation (patient decision).

Table 2: **Investigator-assessed best overall response.**

Adverse events	TRT, n (%)		No TRT, n (%)		All patients, n (%)	
	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3
Any TRAE	43 (96)	28 (62)	17 (77)	11 (50)	60 (90)	39 (58)
Hematological toxicities						
Neutrophil count decreased	35 (78)	20 (44)	13 (59)	8 (36)	48 (72)	28 (42)
Anemia	35 (78)	3 (7)	11 (50)	0 (0)	46 (69)	3 (4)
White blood cell count decreased	31 (69)	9 (20)	12 (55)	4 (18)	43 (64)	13 (19)
Lymphocyte count decreased	27 (60)	8 (18)	2 (9)	1 (5)	29 (43)	9 (13)
Platelet count decreased	12 (27)	2 (4)	4 (18)	0 (0)	16 (24)	2 (3)
Non-hematological toxicities						
Nausea	18 (40)	1 (2)	5 (23)	0 (0)	23 (34)	1 (1)
Vomiting	12 (27)	0 (0)	7 (32)	2 (9)	19 (28)	2 (3)
Pneumonitis	16 (36)	3 (7)	1 (5)	1 (5)	17 (25)	4 (6)
Asthenia	8 (18)	0 (0)	0 (0)	0 (0)	8 (12)	0 (0)
Hypothyroidism	5 (11)	0 (0)	1 (5)	0 (0)	6 (9)	0 (0)
Hyperglycaemia	5 (11)	1 (2)	0 (0)	0 (0)	5 (7)	1 (1)
Abdominal distension	5 (11)	0 (0)	0 (0)	0 (0)	5 (7)	0 (0)
Constipation	3 (7)	0 (0)	1 (5)	0 (0)	4 (6)	0 (0)
Diarrhoea	4 (9)	0 (0)	0 (0)	0 (0)	4 (6)	0 (0)
Alanine aminotransferase increased	3 (7)	1 (2)	1 (5)	0 (0)	4 (6)	1 (1)
Aspartate aminotransferase increased	3 (7)	0 (0)	0 (0)	1 (5)	3 (4)	1 (1)
Blood urine present	1 (2)	0 (0)	2 (9)	0 (0)	3 (4)	0 (0)
Hypokalaemia	2 (4)	0 (0)	0 (0)	0 (0)	2 (3)	0 (0)
Hyponatraemia	2 (4)	1 (2)	0 (0)	0 (0)	2 (3)	1 (1)
Blood bilirubin increased	2 (4)	1 (2)	0 (0)	0 (0)	2 (3)	1 (1)
Abdominal pain	2 (4)	0 (0)	0 (0)	0 (0)	2 (3)	0 (0)
Rash	1 (2)	0 (0)	1 (5)	0 (0)	2 (3)	0 (0)

TRAE, treatment-related adverse events.

Table 3: **Treatment-related adverse events.**

TP53/RB1 double mutations and TMB. Compared with other gene mutations, patients with TP53/RB1 double mutations had shorter OS (P = 0.023, Fig. 3C). Meanwhile, patients with higher TMB (≥10 Mut/Mb) had longer OS (P = 0.074, Fig. 3D).

ctDNA was measured at three time points during treatment: the first day of the first cycle of immunotherapy (C1D1), the first day of the second cycle of immunotherapy (C2D1), one day after the end of six cycles of immunotherapy, and before radiotherapy (C7D1). Univariate Cox regression analysis, TP53/RB1 double mutations detected in ctDNA of C1D1 were more associated with patient outcomes than TMB either in patients who received immunotherapy only, or immunotherapy sequential with radiotherapy (Fig. 4A). Patients with ctDNA TP53/RB1 double mutations in C1D1 had shorter PFS (P = 0.073, Fig. 4B) and OS (P = 0.042, Fig. 4C) compared to patients with other ctDNA mutations.

Patients with paired blood samples at different time points were also analyzed (C1D1 *vs.* C2D1, Supplementary Figure S2A; C1D1 *vs.* C7D1, Supplementary Figure S2B; C1D1 *vs.* C2D1 *vs.* C7D1, Supplementary Figure S2C), these results all showed that the number of ctDNA mutations in patients after immunotherapy was greatly reduced.

Especially, mutations detected in ctDNA of C7D1 were associated with PFS in patients who received immunotherapy sequential with radiotherapy (Fig. 4A). Mutation landscape, the treatment strategies, ORR, immune-related AEs (irAEs) and whether rapid progress of the 14 patients detected the ctDNA in C7D1 is illustrated in Fig. 4D. Survival of patients with ctDNA mutations in C7D1 was compared with those without ctDNA mutations, and PFS was significantly shorter (P = 0.0069, Fig. 4E). Through dynamic monitoring, continuous reduction of ctDNA may indicate a sustained progression-free status. However, if ctDNA residue was found, it may indicate disease progression (Supplementary Figure S2D–F).

Discussion

To our knowledge, this is the first prospective, phase 2 study to evaluate the combination of adebrelimab plus chemotherapy and sequential TRT in patients with ES-SCLC. The results indicated that adebrelimab plus chemotherapy and sequential TRT could improve the

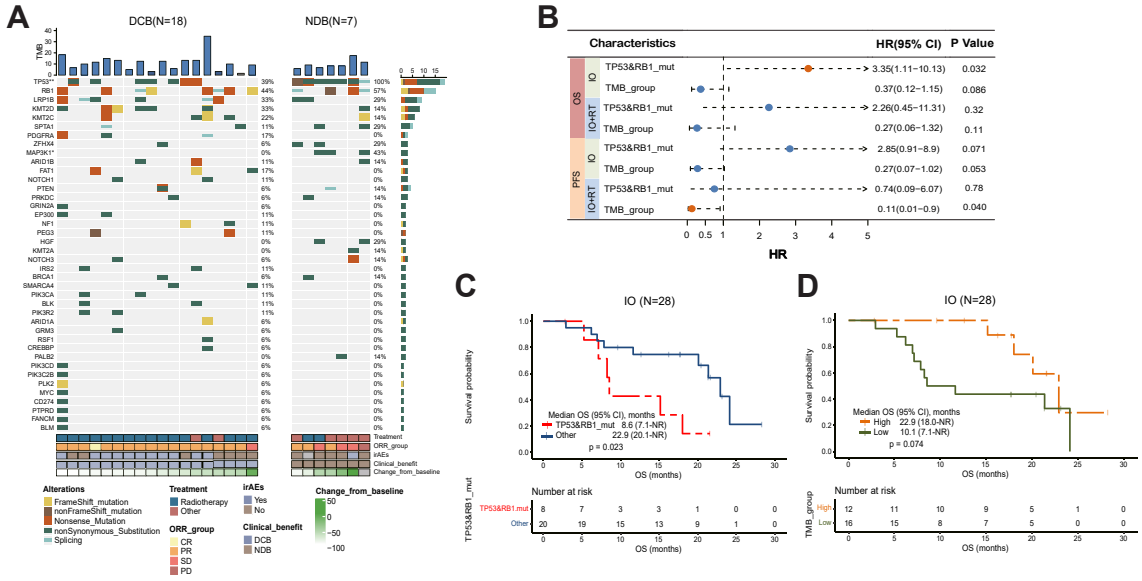

Fig. 3: DNA sequencing results from SCLC patients' FFPE samples. (A) Patients with immunotherapy were divided into DCB and NDB groups according to whether they progressed within 6 months, somatic mutational features, including TMB between the two group were compared. (B) A forest plot showed the association of different variables with OS or PFS in the patients receiving immunotherapy with or without radiotherapy (IO, N = 28), and in the patients receiving both immunotherapy and sequential radiotherapy (IO + RT, N = 20). "TMB_group" indicates the calculation of the HR and p-value for the TMB_high group (IO, N = 12; IO + RT, N = 8) compared to the TMB_low group (IO, N = 16; IO + RT, N = 12). "TP53&RB1_mut" indicates the calculation of the HR and p-value for patients with concurrent mutations in TP53 and RB1 genes (IO, N = 8; IO + RT, N = 3) compared to other patients (IO, N = 20; IO + RT, N = 17). (C) OS of SCLC patients harboring TP53/RB1 double mutations, compared with patients with other somatic mutations. (D) OS of SCLC patients with high TMB level (≥10 Mut/Mb), compared with patients with low TMB level (<10 Mut/Mb). FFPE, formalin-fixed paraffin-embedded; DCB, durable clinical benefit; NDB, no durable clinical benefit; TMB, tumour mutation burden; OS, overall survival; ctDNA, circulating tumour DNA.

survival benefits of patients with ES-SCLC. The median OS was 21.4 months. 1-year and 2-year OS rate were 74.1% and 39.7%. The median PFS was 10.1 months. The safety profile was manageable and no new safety signals were observed compared to previous reports.

The current standard first-line treatment for ES-SCLC is immunotherapy in combination with platinum-etoposide. In the IMpower133 trial, the addition of atezolizumab to chemotherapy resulted in significantly longer OS (12.3 *vs.* 10.3 months, HR 0.70, P = 0.007) and PFS (5.2 *vs.* 4.3 months, HR 0.77, P = 0.02) than control group.[9] In the CASPIAN trial, the addition of durvalumab to chemotherapy resulted in significantly longer OS (13.0 *vs.* 10.3 months, HR 0.73, P = 0.0047) and PFS (5.1 *vs.* 5.4 months, HR 0.78) than chemotherapy alone.[6] As both IMpower 133 and CASPIAN trials did not allow TRT, the combination of TRT and immunotherapy has not been well defined in ES-SCLC first-line treatment.

Many retrospective studies have reported the benefit of TRT after chemoimmunotherapy.[32–36] Xie Z et al. retrospectively enrolled 118 patients of ES-SCLC treated with first-line chemoimmunotherapy with (45 patients) or without TRT (73 patients) after that. The median PFS (8.0 *vs.* 5.9 months, P = 0.025) and OS (22.7 *vs.* 14.7 months, P = 0.015) were significantly longer in patients received TRT.[33] The incidence of pneumonitis (grade 3 and 4) was 4% (2/45) and 1% (1/73), respectively. Longo V et al. reported that consolidative TRT (30 Gy in 10 fractions, up to definitive dose in selected patients) was associated with a significantly longer PFS than systemic therapy alone (one-year PFS of 61% *vs.* 31%, P < 0.001), with a trend toward improved OS (1-year OS of 80% *vs.* 61%, P = 0.027).[34] Peng J et al. reported that the addition of TRT [median dose of TRT was 50 Gy (IQR, 45–60)] to durvalumab or atezolizumab plus chemotherapy significantly improves PFS (9.5 *vs.* 7.2 months, P = 0.009) and OS (24.1 *vs.* 18.5 months, P = 0.016) compared to No-TRT.[35] Treatment-related pneumonitis occurred in 20 (20/57, 35%) patients and 9 (9/57, 16%) patients in the TRT and non-TRT groups (P = 0.018). Another retrospective study conducted by Yao Y et al. included 99 consecutive patients with ES-SCLC who received TRT [hypofractionation (n = 29), hyperfractionation (n = 12) and conventional fraction (n = 58)] in combination with chemo-immunotherapy. The median OS was 21.6 months and the median PFS was 10.76 months. The incidence of pneumonitis was 16.2%.[37]

A phase I trial evaluated pembrolizumab and TRT (45 Gy in 15 fractions) after induction chemotherapy for

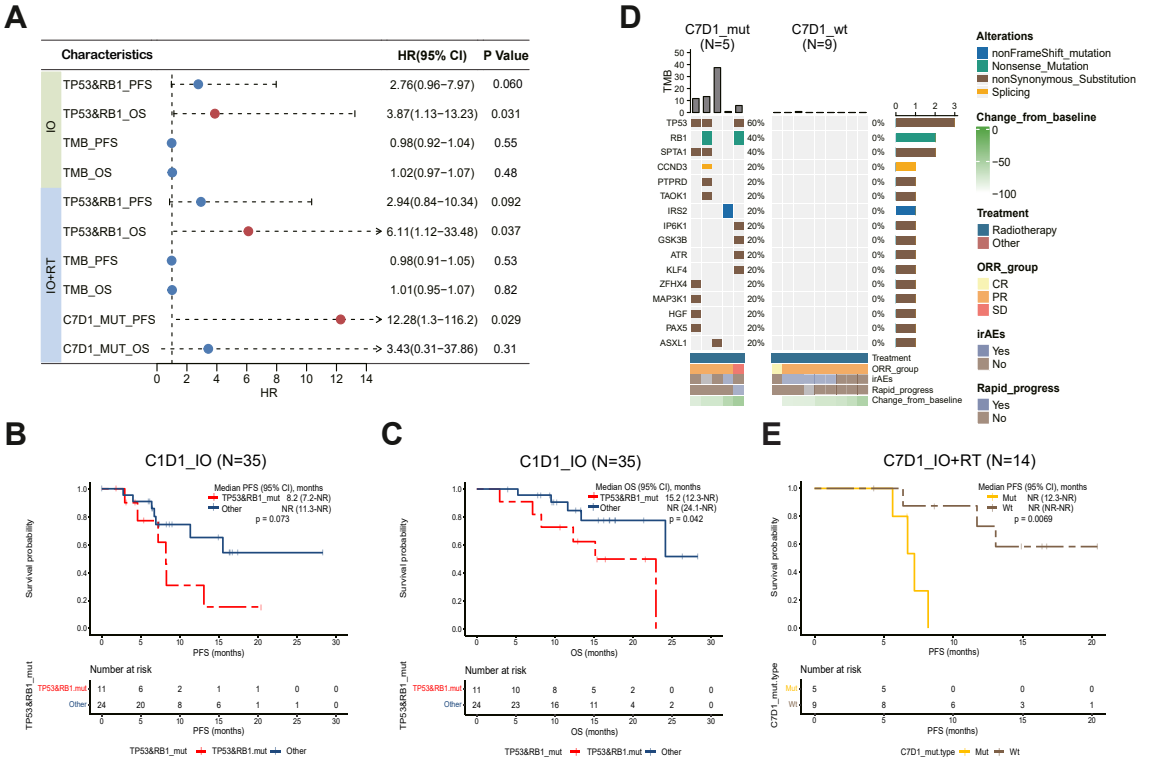

Fig. 4: Dynamic monitoring of ctDNA in SCLC patients. (A) A forest plot showed the association of different markers with survival (PFS or OS) in the patients receiving immunotherapy with or without radiotherapy (IO), and in the patients receiving both immunotherapy and sequential radiotherapy (IO + RT). "TP53&RB1" indicates the calculation of the HR and p-value for patients with concurrent mutations in TP53 and RB1 genes (IO, N = 11; IO + RT, N = 6) compared to other patients (IO, N = 24; IO + RT, N = 18) in ctDNA of C1D1. "TMB" indicates the calculation of the HR and p-value for the TMB_high group (IO, N = 14; IO + RT, N = 10) compared to the TMB_low group (IO, N = 21; IO + RT, N = 14) in ctDNA of C1D1. "C7D1_MUT" indicates the calculation of the HR and p-value for the C7D1_mut group (IO + RT, N = 5) compared to the C7D1_wt group (IO + RT, N = 9). PFS (B) and OS (C) of patients with ctDNA TP53/RB1 double mutations in C1D1, compared with patients with other ctDNA mutations. (D) ctDNA mutation landscape and clinical features of each patient at C7D1. (E) PFS of patients with ctDNA mutation in C7D1, compared with patients without ctDNA mutations in C7D1. ctDNA, circulating tumour DNA; PFS, progression-free survival; OS, overall survival; C, cycle; D, day.

ES-SCLC. Concurrent pembrolizumab-TRT was tolerated well with few high-grade adverse events in the short-term. The median PFS and OS were 6.1 months (95% CI: 4.1–8.1) and 8.4 months (95% CI: 6.7–10.1). However, those results are difficult to interpret due to heterogeneity in eligibility criteria as progressors on induction chemotherapy were allowed to enroll.[38] Perez BA et al. conducted a study to investigate the combination of ipilimumab and nivolumab with TRT (30 Gy in 10 fractions) after platinum chemotherapy in ES-SCLC.[39] 21 patients with stable disease or better after platinum doublet chemotherapy were enrolled. The 1-year OS was 48% (95% CI: 29%–64%) with a median OS of 11.7 months (95% CI: 4.7–16.0). The incidence of pneumonitis were reported in 5 (5/21, 24%, any grade) patients and 2 patients (2/21, 10%, Grade 3–5), respectively.

Our results were comparable to those reports, the median OS was 21.4 months for all patients and 22.9 months for those received TRT treatment. In addition, more patients with brain metastasis (22/67, 33%) were enrolled in our study compared to IMpower 133 (17/201, 8.5%) and CASPIAN (28/268, 10%).[6,9] The overall safety profile in the study was acceptable, with hematological toxicity as the major TRAEs. The hematological toxicity profile was similar to those reported in CASPIAN, IMpower 133 and CAPSTONE-1.[6,7,9] In the study, we paid close attention to pulmonary toxicity. In patients received TRT the incidence of pneumonitis was 36% (16/45, any grade) and 7% (3/45, grade 3 and 4). The incidence of pneumonitis in this study was consistent with previous reports.

A randomized trial by Jeremic et al. reported that accelerated hyperfractionated RT (54 Gy/36 fractions over 18 treatment days) in combination with carboplatin plus etoposide improved median overall survival (17 *vs.* 11 months).[15] The CREST trial demonstrated a 10% 2-year overall survival benefit and almost 50% reduction

in intrathoracic recurrences for consolidative TRT (30 Gy in10 fractions).[12] However, in the CREST trial, more than 40% of patients who received thoracic radiotherapy had an intrathoracic recurrence, which might suggest that even higher doses of radiation, as assessed in other studies, might be needed.[11,13–15] RTOG-0937 is a randomized phase-II trial evaluating 1-year OS with PCI or PCI plus consolidative TRT to intra-thoracic disease and extracranial metastases for ES-SCLC. RTOG-0937 used 45 Gy in 15 fractions TRT and the results indicated that OS exceeded predictions in both arms and consolidative RT delayed progression.[40] However, 1-year OS was not improved. In the era of immunotherapy, is the higher the dose of TRT, the more significant the benefit for patients? In this study, we found no difference in both PFS and OS for patients received hypofractionated or conventional radiotherapy at different dose. Also, there was no significant difference between the subgroup with BED ≥60 Gy and the subgroup with BED <60 Gy.

Given that SCLC is characterized by high TMB and ubiquitous concomitant inactivation of TP53 and RB1,[27,41] therefore, association of TMB and TP53/RB1 co-mutations with therapeutic efficacy of combinational immunotherapy were analyzed. TMB correlated with immunotherapy efficacy in various tumour types, including lung cancer,[42] but the use of TMB to predict immunotherapy efficacy in SCLC remains controversial and results from different studies are inconsistent.[43] This study showed high tissue TMB (≥10 Mut/Mb) level was correlated with better outcomes for patients received first-line immunotherapy and sequential with radiotherapy. For patients receiving first-line immunotherapy, there was still numerical benefit from combinational immunotherapy in patients with high tissue TMB. Additionally, co-occurrence of TP53/RB1 mutations correlated with unfavored overall survival. Previous studies suggested TP53/RB1 double mutations as major drivers of SCLC.[44] And co-mutations of TP53/RB1 putatively resulted an immune-suppressive microenvironment,[45] which may hamper the response of immune checkpoint inhibitors in SCLC.

It has been established that ctDNA has the potential to predict the efficacy and prognosis of tumour immunotherapy in many cancers such as non-small cell lung cancer, melanoma, and colorectal cancer.[46–48] However, there was insufficient evidence available for its use in SCLC patients. A recent report on SCLC has demonstrated that ctDNA analysis via TEC-seq, alongside the assessment of tumor-derived sequence alterations and plasma aneuploidy, offers a robust method for monitoring alterations in the total cell-free tumor load (cfTL). This methodology has been shown to be a precise approach for the assessment of early on-therapy molecular responses.[49] Results from the IFCT-1603 Trial-based analysis suggested that ctDNA mutation status after immunotherapy could be used as a predictive biomarker of efficacy in ES-SCLC patients receiving second-line immunotherapy.[50] In this study, we monitored the dynamic changes of ctDNA levels during treatment. Consistent with previous reports,[51,52] baseline bTMB could not predict the efficacy for both patients receiving first-line immunotherapy and patients receiving first-line immunotherapy sequential with radiotherapy. In line with the findings from genomic profiling in tissue, TP53/RB1 double mutations detected in baseline ctDNA were associated with poorer outcomes both in patients receiving first-line immunotherapy and in patients receiving first-line immunotherapy sequential with radiotherapy. Furthermore, ctDNA before immunotherapy with radiotherapy (C7D1), indicating cancer cell residue after chemo-immunotherapy, associated with the PFS in patients receiving first-line immunotherapy sequential with radiotherapy. These results suggested that patients with ctDNA clearance or absence of TP53/RB1 double mutations were more likely to benefit from first-line immunotherapy sequential with radiotherapy. While more clinical studies are needed to further validate these findings.

The current study had several limitations. First, the trial was a single-arm phase 2 study design, with no PD-1/PD-L1 plus chemotherapy as a control arm. A randomized controlled clinical trial is planned. Second, patient recruitment and follow-up were disturbed by the outbreak of coronavirus disease 2019 (COVID-19). Third, the subgroup analysis of different treatment was exploratory and should be interpreted with caution. With the advancement of radiotherapy technology, clinicians can choose appropriate radiation doses for patients based on tumour size, metastasis, and basic lung function. More studies are needed to further explore the optimal dose of TRT in ES-SCLC.

Contributors

DWC: Conceptualization, Methodology, Project Administration, Formal analysis, Writing—Original Draft, Writing–Review & Editing; BZ, BTL, AQG, WH, QS, XJM, PLZ, XYT, XDH, YZ, JG: Investigation, Data curation, Writing—Original Draft, Writing–Review & Editing; CHZ, JJY, QL, CBZ: Investigation, Formal analysis, Writing—Original Draft, Writing–Review & Editing; JMY: Conceptualization, Methodology, Project Administration, Formal analysis, Writing—Original Draft, Writing–Review & Editing; LLW: Conceptualization, Methodology, Project Administration, Formal analysis, Supervision, Writing—Original Draft, Writing–Review & Editing.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of interests

CHZ and JJY are employees of Jiangsu Hengrui Pharmaceuticals. CBZ and QL are employees of Amoy Diagnostics. All other authors declare that they have 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.2024.102795.

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