TQB2450 with or without anlotinib as maintenance treatment in subjects with locally advanced/unresectable non-small cell lung cancer that have not progressed after prior concurrent/sequential chemoradiotherapy (R-ALPS): study protocol for a randomized, double-blind, placebo-controlled, multicenter phase III trial

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of non-small cell lung cancer (NSCLC). TQB2450 (benmelstobart) is a novel humanized immunoglobulin G1 monoclonal antibody against programmed death-ligand 1 (PD-L1). Anlotinib, an oral multitargeted anti-angiogenic agent with potential synergy with ICIs, has shown efficacy in relapsed and advanced NSCLC. Accumulating preclinical data suggest a synergism between immunological and anti-angiogenic therapies through the improvement of the immune microenvironment of the tumor. In this study, we hypothesized that the combination of TQB2450 and anlotinib as maintenance treatment would enable further improvements in the outcomes of patients with locally advanced/unresectable NSCLC without driver mutations that have not progressed after definitive chemoradiotherapy.

Methods: The Radiotherapy and Anlotinib Let PD-L1 Superb (R-ALPS) study is a randomized, double-blind, placebo-controlled, multicenter phase III study (Clinicaltrials.gov identifier, NCT04325763). A total of 534 eligible participants will be randomized to receive TQB2450 (1,200 mg) plus anlotinib (8 mg), or TQB2450 (1,200 mg) plus placebo, or placebo as maintenance therapy. Progression-free survival (PFS), assessed by the independent review committee is the primary endpoint. The secondary endpoints include additional measures of efficacy, safety, and biomarkers. An interim analysis of the effectiveness will be

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conducted when 70% (286 cases) of the total PFS events have been reached.

Discussion: The development of the R-ALPS study will contribute to a deeper insight into the interplay between immunotherapy and anti-angiogenic therapy and thus might expand the treatment options available to patients with locally advanced or unresectable NSCLC.

Trial Registration: Clinicaltrials.gov identifier: NCT04325763. Date of registration: May 27, 2020. Protocol version: Version 4.0, Sep 16, 2022 (https://classic.clinicaltrials.gov/ct2/show/NCT04325763).

Keywords: TQB2450; anlotinib; maintenance therapy; non-small cell lung cancer (NSCLC); survival

Introduction

Approximately one-third of patients with non-small cell lung cancer (NSCLC) have locally advanced stage III disease at diagnosis (1), which is complex to manage and the management strategy is a subject of debate. Prior to the advent of immune checkpoint inhibitors (ICIs), the standard treatment for unresectable stage III NSCLC with a good performance status was platinum-based definitive chemoradiotherapy (dCRT) (2). However, the prognosis of these patients is poor, with a 5-year survival of only 15% (1,3).

ICIs targeting programmed cell death protein 1 (PD-1) and its ligand programmed death-ligand 1 (PD-L1) have revolutionized the treatment of stage III NSCLC and new treatment combinations are constantly being evaluated (4,5). A growing body of evidence suggests that anti-angiogenic therapy can transform the immune-inhibitory tumor microenvironment into a more immune-active state (6,7). Anti-angiogenic therapy can rapidly normalize the blood vessels, which in turn stabilizes endothelial cells, reduces vascular permeability, increases drug and oxygen delivery, and promotes the infiltration of effector T cells into tumors (8,9). The combination of atezolizumab and bevacizumab has shown synergistic antitumor activity in advanced non-squamous NSCLC, regardless of PD-L1 expression (10). Similarly, the IMpower150 trial reported enhanced efficacy of anti-angiogenic and immunological therapy in combination with chemotherapy in patients with metastatic NSCLC (11).

Anlotinib, an oral multitarget tyrosine kinase inhibitor (TKI), has shown efficacy in relapsed and advanced NSCLC by suppressing the activation of proangiogenic signals such as vascular endothelial growth factor receptor 1–3 (VEGFR1–3), platelet-derived growth factor receptor-beta (PDGFR-β), fibroblast growth factor receptor 1 (FGFR1), and stem cell factor receptor (c-Kit) (12-17), which led to its approval by National Medical Products Administration (NMPA) of China (18,19). Based on preclinical data, first-line sintilimab combined with anlotinib in patients with advanced NSCLC attained a disease control rate (DCR) of 100% and an objective response rate (ORR) of 73%, with a median progression-free survival (PFS) of 15 months (20).

TQB2450 (benmelstobart) is a novel humanized immunoglobulin G1 (IgG1) monoclonal antibody against PD-L1 developed by Chia Tai Tianqing Pharmaceutical Group Co. Ltd. Ongoing early phase clinical studies, including NSCLC and other solid tumors, demonstrate that TQB2450 in combination with anlotinib has promising antitumor activity and acceptable safety (7,21-26). A phase Ib study randomized pretreated stage IIIB or IV NSCLC to receive TQB2450 with or without anlotinib, and the median PFS was 8.7 months for TQB2450 plus anlotinib compared with 2.8 months for TQB2450 plus placebo. Further subgroup analysis revealed that in patients with PD-L1 ≥1% the ORR was 50.0% in the TQB2450 plus anlotinib group, and 5.3% in the TQB2450 plus placebo group (21). ETER701 was a double-blind, randomized, placebo-controlled phase III trial that investigated the efficacy of TQB2450 with anlotinib and standard chemotherapy for treating extensive-stage small-cell lung cancer. It demonstrated that the median overall survival (OS) was prolonged with TQB2450 and anlotinib plus etoposide/carboplatin compared with chemotherapy alone (19.3 *vs.* 11.9 months; P<0.001) (26).

The Radiotherapy and Anlotinib Let PD-L1 Superb (R-ALPS) study will explore the efficacy and safety of this treatment combination in participants with locally advanced/unresectable (stage III) NSCLC. The objectives
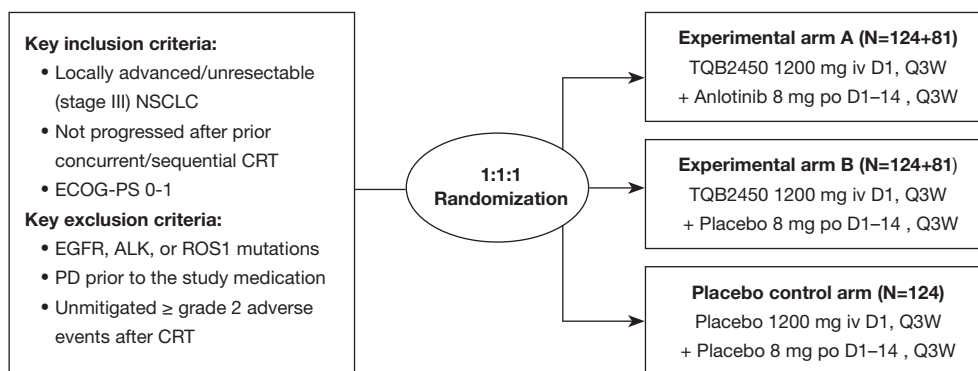
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Figure 1 The R-ALPS study design. NSCLC, non-small cell lung cancer; CRT, chemoradiotherapy; ECOG-PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1; PD, progressive disease; iv, intravenous injection; Q3W, every 3 weeks; po, oral administration; R-ALPS, Radiotherapy and Anlotinib Let programmed death-ligand 1 Superb.

of the R-ALPS study are to: (I) enhance the efficacy of treatment after dCRT in patients with NSCLC by adding TQB2450 with or without anlotinib; (II) evaluate the safety and tolerability of the combination of immunological and anti-angiogenic therapy after dCRT as the maintenance treatment for NSCLC; and (III) collect tumor tissue and blood samples for translational research. The protocol is presented in accordance with the SPIRIT reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-362/rc).

Methods

Study design and characteristics of participants

This randomized, double-blind, placebo-controlled, multicenter phase III trial will examine the treatment efficacy and tolerability of TQB2450, with or without anlotinib, in the maintenance treatment of patients with stage III NSCLC after dCRT. Because durvalumab had not yet been approved by the NMPA and was unavailable during the application of this trial to the Center for Drug Evaluation of China (September 2019), and observation after dCRT was still the standard treatment for locally advanced/unresectable NSCLC in China at the time, a placebo control arm was set up in this study. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013), and supervised by Chia Tai Tianqing Pharmaceutical Group Co., Ltd. [a contract research organization (CRO)].

Given that durvalumab has been approved by the

NMPA for maintenance treatment of patients with stage III NSCLC after concurrent chemoradiotherapy (December 2019), our study encourages patients to receive standard immunotherapy. Patients who decline maintenance therapy with durvalumab and are eligible for study inclusion will be approached and informed about the study when they arrive at the medical site. At the time of inclusion in the study, all participants must have been diagnosed with stage III NSCLC without progression after prior dCRT, independent of the study, as part of the standard treatment (*Figure 1*). Prior to study enrollment, all archives of documents and their imaging will be reviewed by a board-certified radiation oncologist and radiotherapist to estimate whether lung tumor formation after dCRT can safely be treated with immunological and anti-angiogenic therapy. Patients who have previously received other PD-1/PD-L1 targeting therapies or anlotinib will be excluded. The detailed eligibility criteria for the study are provided in *Table 1*. The Institutional Review Boards (IRBs) of each center have approved the trial, including Sun Yat-sen University Cancer Center (No. A2021-080-01), Zhejiang Cancer Hospital {No. IRB-[2020]62}, Guangxi Medical University Cancer Hospital {No. CS2020[11]}, Tianjin Medical University Cancer Institute & Hospital (No. E2020090), The Second People's Hospital of Neijiang (No. 2020-024-001), Henan Cancer Hospital (No. 2020022609), Qilu Hospital of Shandong University (No. 2020011), Xiangya Hospital Central South University (No. 202004075), Shandong Cancer Hospital & Institute (No. SDZLEC2021-041-01), and Shanxi Cancer Hospital (No. YW2020034). The complete list of the IRB names of 42 sites participating in

Table 1 Key inclusion and exclusion criteria of the R-ALPS study

Inclusion criteria

- Fully-informed written consent with well compliance

- Confirmed stage III NSCLC

- Expected survival time ≥3 months

- ECOG-PS: 0–1

- Completed at least two cycles of platinum-based concurrent/sequential CRT without PD

    (I)   Within 42 days between last radiotherapy and the first medication

    (II)   For sequential CRT, the interval between the end of the chemotherapy cycle and the start of radiotherapy should not exceed 6 weeks

    (III) Consolidation chemotherapy after radiotherapy was not allowed, however, chemotherapy before concurrent chemoradiotherapy was permitted

    (IV)   The total dose of radiotherapy was 60 Gy±10% (54–66 Gy). The minimum technical standard for radiotherapy is IMRT

- Adequate bone marrow, renal function, and hepatic functions

Exclusion criteria

- With EGFR, ALK, or ROS1 mutations

- Prior treatment with immunotherapeutic or anti-angiogenic drugs

- CT or MRI showed that the tumor had invaded major vessels, and was likely to cause fatal hemorrhage during the follow-up study

- AEs of CTCAE v5.0 ≥2 that had not completely relieved after previous radiotherapy or chemotherapy

- Presence of active bleeding or bleeding tendency

- Active or prior documented autoimmune or inflammatory disorders or history of active primary immunodeficiency

- History of another primary malignancy except for malignancies treated with curative intent and no known active disease ≥5 years before first dose of study medication

- Any co-existing medical condition that in the investigator's judgement will substantially increase the risk associated with the patient's participation in the study

R-ALPS, Radiotherapy and Anlotinib Let PD-L1 Superb; PD-L1, programmed death-ligand 1; NSCLC, non-small cell lung cancer; ECOG-PS, Eastern Cooperative Oncology Group performance status; CRT, chemoradiotherapy; PD, progressive disease; IMRT, intensity-modulated radiation therapy; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1; CT, computed tomography; MRI, magnetic resonance imaging; AEs, adverse events; CTCAE, Common Terminology Criteria for Adverse Events.

the study and their registration numbers can be found at Table S1.

In total, 534 patients will be enrolled at 42 sites in China. A complete list of the sites is available on ClinicalTrials.gov (NCT04325763). Recruitment began in May 2020 and is expected to be completed by March 2025.

Study procedures

All patients will be required to provide written informed consent before being enrolled in the clinical trial (available at https://cdn.amegroups.cn/static/public/ tlcr-24-362-1.pdf). The randomization will be done through the Interactive Web Response System (IWRS) integrated into the electronic case report form (eCRF). All randomization design aspects and patient allocation status will be conducted in a strict double-blind manner. After randomization, participants will receive either TQB2450 [1,200 mg infused on day 1, every 3 weeks (Q3W) for 36 cycles] and anlotinib (8 mg orally once daily on days 1–14, Q3W for 36 cycles) in experimental arm A; or TQB2450 (1,200 mg infused on day 1, Q3W for 36 cycles) and anlotinib placebo in experimental arm B, or placebos of both TQB2450 and anlotinib in the placebo control arm.

The treatment will be continued until the patient develops intolerable toxicities, progressive disease (PD), death, withdrawal, or the end of the trial.

Over the course of the study, treatment response will be examined according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) (27) using enhanced computed tomography (CT) of the chest and upper abdomen, and magnetic resonance imaging (MRI) of the brain at baseline, and then every 2 cycles (6 weeks) throughout the 36 cycles, and every 12 weeks thereafter until the onset of PD. The efficacy will be further confirmed with the immune RECIST (iRECIST), which means that patients who have PD according to the RECIST v1.1 criteria will be further evaluated to confirm the same according to the iRECIST criteria. In patients who discontinue treatment for reasons other than PD, imaging evaluation will be performed based on the above-mentioned timeline until progression, death, initiation of another antitumor treatment according to the care standards, or the end of the study. During and after the study, follow-up will be proactively conducted regarding treatment-related adverse events (AEs) of the participants until they are resolved, return to baseline or are deemed irreversible, loss to follow-up, or withdraw study consent. For participants who refuse to return to the site for evaluation, routine follow-ups by phone will be performed every 3 months. The investigators of this trial will be responsible for further treatment after the end of the study of participants with PD.

The safety assessment during the R-ALPS study will include physical examination, Eastern Cooperative Oncology Group performance status (ECOG-PS), continuous evaluation of AEs, and clinical laboratory profiles. *Table 2* summarizes the study procedures. The principal researchers or authorized research assistants will complete the eCRF for each participant to collect data throughout the trial. All observed AEs and toxicities will be recorded in the eCRF and graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0) to summarize their relationship to all study treatments and procedures.

Maintenance treatment after dCRT

All participants should complete the first medication on day 14–42 after the last radiotherapy.

- ❖ Patients in the experimental arm A (Group T + A) will be administered: TQB2450 1,200 mg, intravenously, once every 21 days; anlotinib 8 mg, orally, once daily for 14 days and 7 days

off. Therefore, anlotinib will be administered regularly. If a dose is missed during the course of the medication and the time from the next medication is less than 12 hours, no additional replacement dose will be taken.

- ❖ Patients in the experimental arm B (Group T) will be administered: TQB2450 1,200 mg, intravenously, once every 21 days; and anlotinib placebo (8 mg), orally, once daily for 14 days and 7 days off.
- ❖ Patients in the placebo control arm (Group P) will be administered: TQB2450 placebo 1,200 mg, intravenously, once every 21 days; anlotinib placebo (8 mg), orally, once daily for 14 days and 7 days off.

One treatment cycle will take 21 days, and participants will receive no more than 36 cycles (108 weeks). Participants who have disease control [complete response (CR), partial response (PR), or stable disease (SD)] as assessed by the investigator and tolerable AEs may continue to participate in the R-ALPS study voluntarily until the clinical benefit is lost, or the adverse effects of treatment become intolerable. No other antitumor therapy will be administered during this trial.

Collection of biomaterials for translational research

An accompanying translational research project will investigate the mechanisms underlying potential tumor-specific immune effects that might be induced by the combination of PD-L1 and anti-angiogenic therapy and will explore potential biomarkers for such a treatment combination. To this end, the investigators will collect blood samples at baseline and at the time of PD. Tumor tissue samples will be collected at baseline and in cases of re-biopsy after PD during the study treatment, if possible. Although the collection of baseline tissue is mandatory, the collection of all other biomarker samples is voluntary, meaning that eligible patients can still be enrolled in this study if they do not consent to the collection of biomaterials.

Efficacy endpoints

The primary endpoint of the R-ALPS study is PFS assessed by the independent review committee (IRC) calculated as the time from randomization to PD or death from any cause, whichever occurs first. The secondary endpoints are OS, calculated from the date of randomization to death of any cause; ORR (proportion of patients who achieve CR or PR), DCR (proportion of patients who achieve CR, PR, or SD); duration of response (DOR), defined as the interval

Table 2 Summary of scheduled assessment

Procedure	Point in time								
	Screening inclusion	Treatment (36 cycles)							Post-treatment
	Day −14 to 0	C1D1	C1D21	C2D1	C2D21	C(2n+1)D21	C(2n)D21	Withdrawal	C(n+4)D21
Informed consent, eligibility criteria, demographics, medical and disease history	×			×					
Collection of biomaterials	×								
EGFR, ALK, and ROS1 detection	×								
CBC for TMB	×							×	
ADA analysis		×		×		×			
Physical examination	×	×	×	×	×	×	×	×	×
QoLQ	×			×			×	×	×
ECOG-PS	×			×			×	×	×
Pregnancy test	×							×	
Tumor imaging	×				×		×	×	×
12-lead ECG	×		×		×	×	×	×	×
Pulmonary function tests	×				×		×	×	×
CEA, SCC antigen, and Cyfra21-1	×				×		×	×	×
CBC, serum chemistry panel, CK-MB, and cTn	×		×		×	×	×	×	×
Thyroid and coagulation function test	×		×		×		×	×	×
Assessment of AEs	×	×	×	×	×	×	×	×	×

CnDn, cycle number and day number; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1; CBC, complete blood count; TMB, tumor mutation burden; ADA, anti-drug-antibody; QoLQ, Quality of Life Questionnaire; ECOG-PS, Eastern Cooperative Oncology Group performance status; ECG, electrocardiograph; CEA, carcinoembryonic antigen; SCC, squamous cell carcinoma; CK-MB, creatine kinase and its MB isoenzyme; cTn, cardiac troponin; AEs, adverse events.

from the date of first recorded CR or PR to the date of the first recorded PD according to the RECIST v1.1 criteria or death of any cause, whichever occurs first; AEs, and 6-, 12-month PFS assessed by the investigator. In addition, the frequency, nature, severity, and causal relationship of AEs will be evaluated using the CTCAE v5.0 criteria to assess the safety of the treatment regimens. The planned biomarker analysis of biomaterials collected during the trial is an exploratory endpoint of this study.

Statistical analysis

The data management and statistical analysis of the R-ALPS study will be carried out by Department of Biostatistics, School of Public Health, Nanjing Medical University, using SAS v9.4 (SAS Inc., Cary, NC, USA). All statistical analyses will be carried out in line with International Conference on Harmonisation (ICH) Guidelines "Statistical Principles for Clinical Trials", and "Structure and Content of Clinical

Study Reports".

Sample size calculation

The sample size calculations have been revised since the trial was registered owing to the requirements of the regulatory agencies. The original sample size calculations were based on a comparison of experimental arm B versus the placebo control arm. The sample size calculations were subsequently revised at the request of the regulatory agencies to enable a comparison of experimental arm A versus experimental arm B. Both the original and updated sample size calculations are detailed below.

Based on previously published results (1), the expected median PFS in the placebo control arm is 6 months, and the PFS in the experimental arm B is assumed to extended to 9 months compared with the placebo control arm. A difference between treatment groups regarding the primary endpoint, PFS, will be detectable with a power of 80% using a log-rank test at a two-sided α of 0.05, assuming a dropout rate of 10%, follow-up phase of 18 months, and an accrual period of 16 months. Based on these assumptions, the estimated total sample size yielding the necessary number of 200 events is 222 cases (111 per arm). To adjust for dropouts, the target sample size was set as 124 cases in each of the two arms.

The original protocol was to follow the ratio of 1:1:1 among the three groups, that is, a total of 372 cases in three arms (with 124 cases per arm). However, to meet the review requirements of regulatory agencies, an analysis of experimental arm A versus experimental arm B was added to ensure sufficient power in the study protocol v4.0. Assuming that the PFS in experimental arm A is extended to 12.5 months, the sample size ratio is 1:1, the power is 80%, the final sample size of the two arms (experimental arms A and B) is 410 cases. That is, based on the original 124 cases in each group, and additional 81 cases will be needed in each experimental group. In summary, the revised sample size of this study is 534 cases, with 205 cases in each of the experimental arms A and B and 124 cases in the placebo control arm.

Interim analysis

An independent data monitoring committee (IDMC) consisting of two independent oncologists and one statistician has been established to conduct interim data analyses and assess patient risks and benefits. A safety and effectiveness analysis will be performed by IDMC during this trial. The effectiveness analysis will focus primarily on PFS and will be triggered when 70% (286 cases) of the total PFS events have occurred. Based on the results of the interim analysis, the IDMC will provide a recommendation to the CRO or its delegates, who will be responsible for formally deciding whether the study should be terminated or continued.

Methods of statistical analysis

All statistical analyses will be prespecified and will follow the intention-to-treat (ITT) principle. The primary endpoints will be analyzed using the Kaplan-Meier method. The two-sided significance level is set to α =0.05. Descriptive analyses will be performed of secondary endpoints. Chi-squared tests and t-tests will be used for intergroup comparisons of ordinal or dichotomous variables and continuous variables, respectively. Cox proportional hazards regression will be used to estimate the hazard ratios of factors associated with survival outcomes. Safety analysis will be performed for all participants who have received at least one dose of the study medication, including a description of relative and absolute incidence of AEs and severity grade based on the CTCAE v5.0 criteria. The AE summary tables will provide the number and percentage of participants with AEs and the 95% Clopper-Pearson type confidence intervals for the event rates.

Trial status

Considering that durvalumab has not been covered by health insurance since it was launched in China in December 2019 and requires a high co-payment, its accessibility is currently far from meeting clinical needs. All eligible patients had declined treatment with durvalumab prior to being recruited and providing informed consent to participate in this study. The first patient was enrolled on May 26, 2020. Recruitment of the placebo control arm was completed in September 2022, and recruitment of the other two arms was completed on May 12, 2023.

Discussion

Despite recent advances in the treatment of stage III NSCLC, survival rates need to be improved. Combination therapy, including ICIs and anti-angiogenic agents, is expected to improve the prognosis. A growing number of preclinical studies have demonstrated that PD-L1 and anlotinib complement each other and play synergistic roles in antitumor therapy. Anlotinib, a multitargeted anti-

angiogenic agent can normalize tumor blood vessels and improve the immune microenvironment of tumors (28). Furthermore, decreased expression of PD-L1 by endothelial cells leads to an increase in VEGFR2 expression, suggesting a potential regulatory role for PD-L1 in tumor angiogenesis (29-31). However, the clinical potency of the combination of anti-angiogenic therapy and PD-L1 in stage III NSCLC is still unclear.

This phase III trial is designed to examine the efficacy and safety of TQB2450 with or without anlotinib maintenance therapy in patients with stage III NSCLC who have not progressed after prior dCRT. The development of the R-ALPS study will provide new insight into the interaction between immunotherapy and anti-angiogenic therapy, thereby expanding the treatment options for patients with locally advanced or unresectable NSCLC. Participant recruitment for the trial was completed in May 2023, and an interim analysis will be conducted in the future.

Acknowledgments

Footnote

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The protocol will be established according to the ethical guidelines of the Declaration of Helsinki (as revised in 2013). The Institutional Review Boards (IRBs) of each center have approved the trial, including Sun Yat-sen University Cancer Center (No. A2021-080-01), Zhejiang Cancer Hospital {No. IRB-[2020]62}, Guangxi Medical University Cancer Hospital {No. CS2020[11]}, Tianjin Medical University Cancer Institute & Hospital (No. E2020090), The Second People's Hospital of Neijiang (No. 2020-024-001), Henan Cancer Hospital (No. 2020022609), Qilu Hospital of Shandong University (No. 2020011), Xiangya Hospital Central South University (No. 202004075), Shandong Cancer Hospital & Institute (No. SDZLEC2021-041-01), and Shanxi Cancer Hospital (No. YW2020034). The complete list of the IRB names of 42 sites participating in the study and their registration numbers can be found at Table S1. Written informed consent will be obtained from all patients or guardian participants before being enrolled in the clinical trial.

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