

Reviewer A:

Major Points

1. **I have major concerns, essentially regarding the placebo arm. Durvalumab post chemoradiation was first published for PFS in NEJM in November 2017 and subsequently FDA approved in February 2018. The OS data came out again in NEJM in December 2018. To my knowledge, NMPA approved durvalumab on December 12, 2019. However, the authors claim that the study was approved because at the time of application, durvalumab had not been approved and was not available. While that may be true, the protocol should have been amended to omit the placebo arm once it was approved (NMPA 12/12/2019).**

Response: We thank the expert for the careful reading and questions. The first patient in this study was enrolled on May 26, 2020, recruitment of the placebo control arm was completed in September 2022, and enrollment in the other two arms (experimental arm A and experimental arm B) was completed on May 12, 2023.

Considering that durvalumab has not been covered by health insurance and high co-pay since it was launched in China in December 2019, its accessibility was far from meeting clinical needs, and observation after dCRT was still the standard treatment for locally advanced/unresectable NSCLC in China at that period, a placebo control arm was set up in this study. All eligible participants declined treatment with durvalumab before fully informed and consented to participate in this study (please see **page 7, line 116**; and **page 14, line 270**).

In addition, another randomized, double-blind, placebo-controlled, phase III trial (GEMSTONE-301) conducted by us as the primary participant, with enrollment between August 30, 2018 and December 30, 2020, also had a placebo control group, but neither interfered with patients' initial treatment decisions (1).

2. **I also have a hard time understanding how the enrollment of this study started in May 2020 and the placebo arm completed accrual in May 2023. Although NMPA approval may not translate into direct availability to patients (i.e. insurance issues, high co-pay), I feel that this study is borderline unethical.**

Response: We thank the expert for the question. This trial was one of the earliest studies on the combination of immunological and anti-angiogenic therapy for NSCLC in China, and the NMPA approved this trial base on national conditions at that period. The protocol was approved by the human research ethics committees of all study sites, including Sun Yat-sen University Cancer Center, Zhejiang Cancer Hospital, Guangxi Medical University Cancer Hospital, and Tianjin Medical University Cancer Institute and Hospital.

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 vs. experimental arm B (please see **page 12, line 223**).

That is, the first patient in this study was enrolled on May 26, 2020, recruitment of the placebo control arm was completed in **September 2022**, and enrollment in the other two arms (experimental arm A and experimental arm B) was completed on May 12, 2023 (please see **page 14, line 271**).

Considering that durvalumab has not been covered by health insurance and high co-pay since it was launched in China in December 2019, its accessibility was far from meeting clinical needs, and observation after dCRT was still the standard treatment for locally advanced/unresectable NSCLC in China at that period, a placebo control arm was set up in this study. All eligible participants declined treatment with durvalumab before fully informed and consented to participate in this study (please see **page 7, line 116**; and **page 14, line 270**).

3. **For this study to be published, I would suggest the authors to attach the informed**

consent form (that should have clearly stated the approval of durvalumab) as a supplementary material.

Response: We thank the expert for the constructive suggestion. Given that durvalumab has been approved by the NMPA for the maintenance treatment of patients with stage III NSCLC after concurrent chemoradiotherapy at the time, our study encourages the patients to receive the standard immunotherapy. If the patients decide to decline the maintenance therapy with durvalumab and may be eligible for the study inclusion will be approached and invited to participate when they arrival at the medical site. All patients will be required to provide written informed consent before being enrolled in the clinical trial. We have added the informed consent form of this study (v4.0, September 16, 2022) to the supplementary materials, which clearly states that approval for the use of durvalumab (please see supplementary material [TQB2450-III-05-ICF, **page 5/14**]).

Minor Points

There are numerous grammatical mistakes throughout the manuscript. Please fix and make sure you have it checked by a native speaker/language review service. Some examples are shown below.

Response: We thank the expert for the careful review. we do invite an editor who is a native English speaker to help polish the article. These changes will not influence the content and framework of the paper. And here we did not list the changes but tracked in revised paper.

a. Drug names should not be capitalized mid-sentence. It is distracting. Please fix anolitinib but also for atezolizumab, bevacizumab and sintilimab.

Response: Thanks for your advice. We have made correction according to the request. We also carefully proof-read the manuscript to minimize grammatical and typographical errors.

b. Introduction first word. Typo? Did you mean “Approximately”?

Response: Thank you for your careful review. I'm apologized for our negligence in reviewing the manuscript and confusion about the misspelling in the INTRODUCTION section. We have corrected the mistake in this section on **page 5, line 65**.

c. Stage should not be capitalized mid-sentence.

Response: Thanks for your advice. We have made correction according to the request, and we hope the revised manuscript could be acceptable for you.

d. Line 131. Did you mean “Over the course of the study”?

Response: Thanks for your advice. We have made correction according to the comments.

e. Line 243. Did you mean “lost to follow up”?

Response: We feel sorry, but we can not locate the correction in **L243**.

f. Line 256. Remove “remain”.

Response: Thanks for your advice. We have made correction according to the comments.

g. References. 11 and 14 does not belong to this manuscript. Please reconsider.

Response: Thank you for your careful review. About **Ref. 14**, we have replaced the reference according to the comments. The **Ref. 11** is the citation of the IMpower150 trial, which reported the enhanced efficacy of anti-angiogenic and immunological therapy in combination with chemotherapy in patients with metastatic NSCLC, and we thought it can be retained.

Reference

1. Zhou Q, Chen M, Jiang O, et al. Sugemalimab versus placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III non-small-cell lung cancer in China (GEMSTONE-301): interim results of a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2022;23:209-19.

Reviewer B:

1. **This protocol paper is worthy of publication. I have a few questions regarding the eligibility criteria. The authors mention that patients were eligible after the completion of chemoradiation (CRT). What is the definition of completion of CRT?**

Response: We sincerely appreciate the reviewer for your comments and encouragement. The definition of completion of CRT refers to complete at least two cycles of platinum-based concurrent/sequential chemoradiotherapy without progression. For sequential chemoradiotherapy, the interval between the end of the chemotherapy cycle and the start of radiotherapy should not exceed 6 weeks. The consolidation chemotherapy after radiotherapy was not allowed, however, chemotherapy before concurrent chemoradiotherapy was permitted. The first administration of this study should be done within 42 days of completion of CRT. The detailed information about definitive chemoradiotherapy for the study are provided in the tables, please see **Table 1**.

2. **How many cycles of chemotherapy and what dose of radiation are required for patients? The authors should provide a clear explanation.**

Response: Thank you for your question. The inclusion criteria of this study required the participant to complete at least 2 cycles of platinum-based concurrent/sequential CRT without progression, the total dose of radiotherapy was 60 Gy \pm 10% (54 Gy–66 Gy). The minimum technical standard for radiotherapy is intensity-modulated radiation therapy. Due to the limitation of space, this part can be found in **Table 1** (*Key inclusion and exclusion criteria of the R-ALPS study*), and **supplementary material** (*TQB2450-III-05-ICF [v4.0 2022-09]*).

Reviewer C:

1. **There is significant interest in the combination of immunotherapy and VEGF inhibition, particularly given the pembro/ram trial currently recruiting in the US. The trial is therefore of interest to the broader lung cancer community, to demonstrate the efficacy of this strategy in the limited stage setting. The English needs to be significantly improved, and might benefit from a formal English editing service.**

Response: We appreciate your interest in our protocol manuscript and comments. We do invite an editor who is a native English speaker to help polish the article. These changes will not influence the content and framework of the paper. And here we did not list the changes but tracked in revised paper. We hope the revised manuscript could be acceptable for you.

2. **In the abstract, would specify for anlotinib more than just "multi target TKI" - if the VEGF activity was the primary thing to drive interest in this molecule, would state that upfront.**

Response: We thank the expert for the constructive suggestion. We have enriched the description of anlotinib in the *ABSTRACT* section, according to the recommendation (please see **page 3, line 41**).