Peer Review File

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Reviewer A

This study by Qu and colleagues was a single arm phase II trial assessing the efficacy (primary endpoint response) and safety of camrelizumab and apatinib as first line or second line treatment for advanced unresectable esophageal squamous cell carcinoma. The findings of this study are clearly written. My comments below:

Comment 1: Though the sample size is small, are you able to separate out response outcomes according to line of treatment?
Reply 1: Due to the small number of participants in our study, we have provided a detailed presentation of tumor regression for each patient in Figure2.

Comment 2: Line 32 - "…inhibitor with high affinity" - Do you mean "high affinity" for binding to PD1 receptor?
Reply 2: Yes.

Comment 3: Line 230 - "second" should be "secondary"
Reply 3: We have made correction according to the Reviewer's comments (see page 8, line235).
Changes in the text: Adjust "second" to "secondary".

Comment 4: Line 298-299 - Please elaborate on what is "liver protection symptomatic treatment"?
Reply 4: We have made correction according to the Reviewer's comments (see page 10, line306-307).
Changes in the text: We have made the targeted treatment for liver protection more specific and adjusted it to "use liver protective drugs such as adenosine methionine and diammonium glycyrrhetinic acid.".

Comment 5: Line 301 - Should specify if anti-allergy symptomatic treatment resolved the rash entirely.
Reply 5: The patient did indeed continue treatment after complete remission. We have made correction according to the Reviewer's comments (see page 10, line309).
Changes in the text: We have adjusted it to "....the treatment was continued after complete remission through anti-allergic symptomatic treatment.".

Comment 6: Line 303 - Please clarify what oral hormone symptomatic treatment means. I am unclear why that was used for immune related hepatitis.
Reply 6：According to the toxicity management guidelines related to immune checkpoint inhibitors, glucocorticoid therapy is recommended for liver toxicity above G2.
Changes in the text: ....glucocorticoid treatment (prednisone acetate,1mg/kg) ....(see page 10, line 312).

Comment 7: Line 307 - Why could Crohn's not be excluded? Wouldn't there have been a colonoscopy performed if you were concerned regarding this? Also again, please clarify what 'oral hormones' are and why that would apply to Crohn's.

Reply 7: After the patient developed diarrhea, the patient went to a comprehensive hospital for examination and treatment. Considering that glucocorticoids could alleviate both Crohn's disease and immune related diarrhea, it was recommended that the patient take prednisone orally, and the patient did not provide colonoscopy or pathological reports for the diagnosis of Crohn's disease. Therefore, we truthfully described our ideas. If there is a need to modify or add relevant content, we hope experts can continue to provide valuable feedback.

Comment 8: Line 313 - Can you quantify amount of proteinuria instead of "+++".

Reply 8: We have made correction according to the Reviewer's comments (see page 10, line320).

Changes in the text: Adjust "+++" to "3+".

Comment 9: Line 321 - Did this patient experience toxicities as opposed to just being of 'old age'?

Reply 9: This patient has received multiple cycles of chemotherapy in the past, which is also one of the reasons for the patient's repeated liver dysfunction. We have already mentioned this in the article, not only because of old age.

Comment 10: Line 370 - "Our clinical trials…" - Would suggest changing to "our study" or "the current study", as I think you are referring to this study, but "our clinical trials" sounds as if you are referring to other trials.

Reply 10: We have made correction according to the Reviewer's comments (see page 12, line377).

Changes in the text: Adjust "Our clinical trials" to "our study".

Reviewer B

Comment 1: First, the title needs to indicate the clinical research design of this study, i.e., a single-arm, open-label, prospective study.

Reply 1: We have made correction according to the Reviewer's comments (see page 1, line3-4).

Changes in the text: We have adjusted the title of the article to "Camrelizumab combined with apatinib for unresectable, metastatic esophageal squamous cell carcinoma: a single-center, single-arm, prospective study".

Comment 2: Second, the abstract needs some revisions. The background did not analyze why camrelizumab combined with apatinib is potentially safe and effective and what the knowledge gap is on this research focus. The methods need to describe follow up procedures and measures of efficacy and safety outcomes. The results need to briefly

summarize the clinical characteristics of the patient cohort. The conclusion needs more comments for the clinical implications of the findings.

Reply 2: We have made correction according to the Reviewer's comments (see page 1, line34-37; page 2, line 46-51). For the conclusion section, we hope to retain the original content.

Comment 3: Third, in the introduction of the main text, a brief review on the available treatment strategies for unresectable, metastatic esophageal squamous cell carcinoma is needed and please analyze why camrelizumab combined with apatinib is potentially safe and effective.

Reply 3: We have made correction according to the Reviewer's comments (see page 3, line96-97). Camrelizumab combined with Apatinib has been recognized in the treatment of cancer such as lung cancer and liver cancer. Our focus is on the effectiveness and safety of Camrelizumab and Apatinib in advanced esophageal squamous cell carcinoma. Based on the efficacy and safety of this treatment method in other cancers, it may also achieve good results in advanced esophageal squamous cell carcinoma.

Changes in the text: We have added treatment methods currently available for advanced metastatic esophageal cancer.

Comment 4: Fourth, in the methodology of the main text, please describe the estimation of sample size and follow up procedures of this study. In statistics, please describe the handling of missing data.

Reply 4: In the initial research application, we estimated to include 30 patients. After screening, we included 29 patients in our study for final statistical analysis. During the follow-up process, we focused on the imaging evaluation after every two cycles and the adverse reactions that occurred during treatment. We described this on page 8, lines 248 to 252.

Comment 5: Finally, several related papers should be reviewed and cited: 1. Xu Z, Zhang Y, Yu YH. Successful treatment of advanced alveolar soft part sarcoma with camrelizumab combined with apatinib: a case report. Ann Palliat Med 2021;10(1):785-792. doi: 10.21037/apm-20-2275. Cong X, Chen J, Zheng W. The combination of camrelizumab and apatinib obtained ongoing partial remission for a patient with osimertinib-resistant non-small cell lung cancer: case report. Ann Palliat Med 2021;10(3):3469-3474. doi: 10.21037/apm-19-462. 3. Kanamori K, Koyanagi K, Ozawa S, Yamamoto M, Ninomiya Y, Yatabe K, Higuchi T, Tajima K. Multimodal therapy for esophageal squamous cell carcinoma according to TNM staging in Japan—a narrative review of clinical trials conducted by Japan Clinical Oncology Group. Ann Esophagus 2023;6:32.

Reply 5: Considering the Reviewer's suggestion, we have carefully read each literature and have benefited greatly. Considering that adding new research content would result in a larger amount of modified space, we hope to retain the original content. Thank you again to the experts for providing us with the opportunity to learn together.