**Peer Review File**
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**Reviewer A**

I have read and reviewed the submitted manuscript "Preoperative administration of camrelizumab combined with chemotherapy for borderline resectable esophageal squamous cell carcinoma (BRES-1): A single-arm, open-label, phase II study". This appears to be the same announcement that I was able to find in the Journal of Clinical Oncology (https://ascopubs.org/doi/abs/10.1200/JCO.2023.41.4_suppl.360). I worry that the authors have a serious design flaw that should likely be addressed prior to enrollment as it deals with sample size (see below).

Major Points:
1. The pathological CR rate of 10% for squamous cell carcinoma of the esophagus is extremely low. The value in the CROSS trial ~30% overall and nearly 50% in the squamous patients. Therefore, as the CROSS trial is currently considered first line therapy for esophageal cancer patients, then this should be the used to aid in sample size determination. The authors even state pCR of 45-56% in their references, yet choose 10%. Why?
**Reply 1:** First, we apologize for the mistakes we made. The pCR rate of esophageal squamous cell carcinoma after neoadjuvant chemotherapy is generally less than 10%. The pCR rate of neoadjuvant immunotherapy combined with chemotherapy for esophageal squamous cell carcinoma patients is between 20% and 50%. The pCR rate mentioned in this paper is an estimated value based on previous studies (https://ascopubs.org/doi/10.1200/JCO.2021.39.3_suppl.220).
Title: Neoadjuvant PD-1 blockade in combination with chemotherapy for patients with resectable esophageal squamous cell carcinoma. Our study referred to the pCR rate of 28% from this study, in which camrelizumab was also used as a neoadjuvant immunotherapy.
**Changes in the text: (**Sample Size Calculation section: paragraph 1, lines 3-4**)**

2. Why was Camrelizulmab chosen? This is not an FDA approved drug for esophageal cancer.
**Reply 2:** Camrelizumab has shown good efficacy in trials on the immunotherapy combined with chemotherapy for esophageal cancer (e.g., NICE study, ESCORT study), but there is still a lack of data for patients with borderline resectable esophageal cancer. Therefore, camrelizumab was selected as the investigational drug for this clinical study.

Minor Points:
1. The statement at line 59 is not entirely accurate and a bit misleading. References 9-12 include not one, but 2 meta-analysis. Therefore, stating that "several clinical trials

have compared efficacy of neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy…" could be better phrased. Please consider this in the re-write of this sentence.

**Reply 2.1:** We apologize for our carelessness. For the sake of the rigor of the article, we have made corresponding changes in the article.

**Changes in the text:** (Introduction section: paragraph 2, lines 12-13)

2. It is unclear of why the endpoints and expected date to finish the study are stated. Was this study completed based upon the originally calculated sample size? If so, state it. As the manuscript is being reviewed in February 2024, it makes it seem that the study is not over.

**Reply 2.2:** The study was not complete and the sample size was calculated based on our predicted pCR rate. Enrollment was ongoing at the time of submission of this protocol.

3. Line 203, this is the future tense. Is the study completed? If so, was surgery scheduled for 3 to 4 weeks after completion of neoadjuvant therapy?

**Reply 2.3:** The study was not complete. In our updated protocol, 3-4 weeks was changed to 3-6 weeks, which means that all patients underwent esophagectomy 3-6 weeks after neoadjuvant therapy.

**Changes in the text:** (Abstract section: paragraph 2, line 4)

4. To be clear, there was no follow-up imaging unless recurrence was suspected?

**Reply 2.4:** We apologize for our oversight. Chest CT was required for all follow-up patients because the follow-up data needed to be evaluated according to the patient's imaging examination.

**Changes in the text:** (Follow-Up section, paragraph 1, lines 2-6)

5. The IRB approval number should be stated.

**Reply 2.5:** We added the IRB approval number to the text.

**Changes in the text:** (Ethics approval of the research section, paragraph 1, line 7)

**Reviewer B**

Thank you for the opportunity to review this manuscript outlining a phase 2 study investigating the utilization of immunotherapy utilizing camrelizumab perioperatively for esophageal cancer. In the intro the authors suggest that immunotherapy has been shown to have promising results and neoadjuvant phase of clinical trials. However it is important to note that there is no definitive evidence of its preoperative benefit as of yet. Though the NICE trial seems to support neoadjuvant immunotherapy, the population analysis was not really an intention to treat analysis but an efficacy population study. An intent is to treat analysis would suggest that the outcomes are fairly similar to the cross trial. Regardless I do think there is a role in investigating immunotherapy as an adjunct to perioperative treatment. The authors years certainly seem to outline the perioperative regimen that is reasonable. There are studies seems to be limiting it to squamous cell cancer which I think is reasonable given the patient population in China. They do note that under the ethics contact that the ethics committee of XXX University school of medicine will review the studies. I am not sure

if XXX is intended or there is a name of the school that is supposed to be in the section. I will also consider as an adjunct following circulating tumor cells as a marker of efficacy for the trial but otherwise the trial seems to be reasonable schema.
**Reply:** As you previously mentioned, considering the unique characteristics of esophageal cancer in China, this study aimed to assess the efficacy of immunotherapy specifically in esophageal squamous cell carcinoma patients. The primary endpoint was the pCR rate, while other markers were not included as a reference. However, this does not imply their lack of significance. XXX University is a placeholder for the name of the school, as the editor anonymized our workplace due to the need for a blind review.

**Reviewer C**

This is a protocol paper.
This study is prospective phase II trial, which investigates the efficacy of neoadjuvant treatment including chemotherapy and immune-check point inhibitor (camrelizumab) for patients with borderline resectable esophageal squamous cell carcinoma.

There are a few minor points to be revised.
1. On page 3 and 9, the authors wrote “XXX university”. What is that?
**Reply 1:** XXX University is a placeholder for the name of the school, as the editor anonymized our workplace due to the need for a blind review.
2. On page 4, line 100, what is “atria”?
**Reply 2:** Thanks you for pointing out our spelling error. We have changed "atria" to "atrial fibrillation".
**Changes in the text:** (Endpoints of the Study section, paragraph 3, line 3)

**Reviewer D**

The authors are conducting the phase II study to evaluate the safety and efficacy of camrelizumab combined with chemotherapy in patients with borderline resectable esophageal squamous cell carcinoma. The primary endpoint is pCR rate.
I think that this is an intriguing study for borderline resectable esophageal cancer.
However, I have a few comments.

Introduction:
Several references are missing, such as references about the ESCORT trial and the NICE trial.
**Comment 1:** Introduction:
Several references are missing, such as references about the ESCORT trial and the NICE trial.
**Reply 1:** I apologize for this carelessness, and the corresponding references have been inserted.
**Changes in the text:** (Introduction section, paragraph 3, lines 5-6)

Methods:

 In borderline resectable esophageal cancer, tumors sometimes can be regarded unresecatable when tumors do not respond well to neoadjuvant therapy. In such cases, which type of additional therapy is performed? If tumors are regarded resectable after additional therapy, can surgeons perform esophagectomy?

**Reply 2.1:** After two periods of neoadjuvant therapy, we evaluated the eligibility of the patient for surgery based on CT scans. When the tumor has a poor response to neoadjuvant therapy, we recommend that the patient continue 1-2 periods of neoadjuvant therapy for the greatest benefit. Surgery eligibility was then evaluated again, and patients with resectable tumors who underwent esophagectomy were not excluded from the study. Patients who were considered to have unresectable tumors were given additional radiation therapy, at which point they were excluded from the study. After radiotherapy,patients were given the option of esophagectomy as one of the alternative surgical options.

 I think that the authors should evaluate survival such as progression-free survival and overall survival as the secondary endpoint.

**Reply 2.2:** I agree with you. OS and DFS were added as endpoints in our revised protocol version a few months ago.

**Changes in the text:** (Endpoints of the Study section, paragraph 2, lines 2-3)

Discussion:

Several references are missing in Discussion section, too.

**Reply 3:** We apologize for these mistakes. We have inserted the corresponding references in the discussion section.

**Changes in the text:** (Discussion section, paragraph 1-2)

**Reviewer E**

This is a protocol paper of neoadjuvant camrelizumab combined with chemotherapy for borderline resectable esophageal squamous cell carcinoma.

I considered that this study is insightful and valuable. There are some points to be addressed before publication.

(Minor point)

1. In introduction, there were no references regarding the ESCORT trial and the NICE trial in line 66-67. Please attach the references.

**Reply 1:** I apologize for this carelessness, and the corresponding references have been inserted.

**Changes in the text:** (Introduction section, paragraph 3, lines 5-6)

2. I considered that borderline resectable esophageal cancer could be challenging to classify as cT3br or cT4b depending on the patients. Moreover, there is a possibility that the diagnosis to the same case may be different depending on the evaluators. The

difficulty of the diagnosis is considered to be one of the limitations in this study. The authors should add this point in limitation.
**Reply 2:** Thank you for your constructive suggestions. In fact, all enrolled patients were selected by the thoracic surgeon following collaborative discussion. However, as you correctly noted, precise tumor staging remains one of the limitations inherent in this study. Thank you once again for your invaluable advice, and we have duly incorporated this limitation into the article.
**Changes in the text:** (Strengths and Limitations section, paragraph 1, lines 7-9)

**Reviewer F**

The authors demonstrated the protocol for a clinical trial to evaluate the benefit and safety of preoperative chemotherapy including camrelizumab for borderline resectable esophageal cancer. In the field of esophageal cancer, immune checkpoint inhibitors have been shown to be effective, but reports to date have limited their use to treatment of unresectable esophageal cancer or as adjuvant chemotherapy. As the authors pointed out, the benefit of preoperative immune checkpoint inhibitor has been reported in animal experiences or in the field of other cancers, and the treatment modality is promising for esophageal cancer as well.

In this report, protocol of the clinical trial is described in detail, and there are no major problems with the protocol.

In the background and discussion, the JCOG9204 and JCOG9907 trials are cited to explain the evidence for preoperative chemotherapy, but I suggest mentioning the JCOG1109 trial, a trial that noted the long-term prognostic benefit of preoperative chemotherapy over preoperative chemoradiotherapy.
Thank you for your constructive suggestions. The JCOG 1109 findings primarily demonstrated the superiority of the three-drug regimen over the two-drug regimen. However, there was no significant difference in OS or PFS between patients who received neoadjuvant chemotherapy and those who received neoadjuvant chemoradiotherapy.