Peer Review File

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Reviewer A

The authors conducted a multicenter prospective observational cohort study evaluating the efficacy and safety of camerelizumab-containing neoadjuvant therapy for patients with local advanced esophageal squamous cell carcinoma. They demonstrated acceptable effectiveness and safety profiles in real-world ESCC patients. This manuscript will provide useful clinical information for readers. Several changes will improve the quality of this manuscript.

1. Only 66.3% of the included patients underwent surgical resection in this cohort. Did the authors include unresectable cases in this study? How many patients with initially resectable tumors were there? How many had unresectable tumors? How many patients were converted to be resectable? How many initially resectable cases turned out to be unresectable? Please provide a study flow diagram to demonstrate these findings.

Response: *Thanks for your comments. This was a prospective multicenter observational cohort study. All patients with histologically or cytologically confirmed esophageal squamous cell carcinoma (cTNM stage I–IVA) who had received at least one dose of camrelizumab-containing neoadjuvant therapy between May 2020 and March 2022 at 13 tertiary hospitals in Southeast China were screened for inclusion. Data on the resectability of tumors were not routinely recorded in the electronic medical record. The reasons for not undergoing surgery were described in the treatment sections. Notably, 37.0% (30/86) of patients chose to not undergo surgery after neoadjuvant camrelizumab-containing therapy in our daily practice. We sincerely hope our response will meet with your approval.*

Changes in the text: None.

2. The authors have not shown how they treat the patients who could not undergo surgery. Please provide the modality and the outcomes.

Response: *Thanks. Among the 86 who did not undergo surgery at the data cutoff (October 24, 2022), 17 (19.8%) were documented to receive chemotherapy plus radiotherapy, 10 (11.6%) were to receive immunotherapy alone or in combination with chemotherapy or radiotherapy, 6 (7.0%) were to received best supportive care, two (2.3%) were to have esophageal stent placement, two (2.3%) were to receive traditional Chinese medicine, and one was to undergo surgical resection later. By contrast, data on the subsequent treatment of the remaining 48 patients were not available in the medical record systems of the 13 study centers. Nevertheless, 23 patients died, 18*

patients lost to follow-up, while 45 patients were known to be alive. The estimated median OS was not reached (95% CI: 20.9, NR) months. We sincerely hope our response will meet with your approval.
Changes in the text: None.

3. There are no descriptions of ir-AEs in this cohort. Please provide the data.
Response: *Thanks for your comments. This was a prospective multicenter observational cohort study. Since the immune-related adverse events were not routinely documented in clinical practice, the corresponding data were not included in this study. We have added the information in the limitation section and sincerely hope it will meet with your approval.*

"Also, the immune-related adverse events were not routinely documented in clinical practice." (**Page 10 Lines 311-312**)

Reviewer B

The main advantages of the study include the new neoadjuvant regimen, a prospective character of the study and relatively large number of patients.
The construction of the study can be criticized for lack of uniformity of the treatment with inclusion of patients receiving only one dose of camrelizumab and patients who got the adjuvant therapy besides of the neoadjuvant one.
Nevertheless, this study presents something new.
Response: *Thanks for your comments. This prospective observational study aimed to investigate the real-life effectiveness and safety of camrelizumab-containing neoadjuvant therapy in ESCC patients. Accordingly, all patients with histologically or cytologically confirmed ESCC (cTNM stage I–IVA) who had received at least one dose of camrelizumab-containing neoadjuvant therapy between May 2020 and March 2022 at 13 tertiary hospitals in Southeast China were eligible for inclusion. This study may help to better understand the prescription patterns of camrelizumab, as well as real-world effectiveness and safety in the neoadjuvant therapy of ESCC. We have added some description in the Discussion section. Thanks again for your time and kind work.*

*"Nevertheless, this study may help to better understand the prescription patterns of camrelizumab, as well as real-world effectiveness and safety in the neoadjuvant therapy of ESCC." (**Page 10 Lines 314-316**)*

Reviewer C

Congratulations to you on your successful treatment of esophageal cancer using immunotherapy plus chemotherapy as the neoadjuvant management.

The entire article was well written with acceptable language, although there were some sentences needed to be rephrased. Also this is a hot topic being discussed in recent years.

However, there are several defects causing the consideration of publication doubtful. Listed as following:

(1) Your title is 'patients with locally advanced esophageal squamous cell ca.'. However the patients selected were from stage I (about 19 %). How would you define locally advanced?

Response: *Thanks for your comments. Indeed, there were three patients with stage I disease received camrelizumab-containing neoadjuvant therapy. To better defined the study population, we have deleted the words "locally advanced" throughout the manuscript, and hope our response will meet with your requirement.*

(2) Alright, if stage I was included, was there any difference on the effect of the neoadjuvant between the early and later stages (or among different stages)? Please stratify.

Response: *Thanks for your comments. We have stratified the pCR by clinical stage according to your suggestions. Due to the limited number of patients in the early-stage, the results were not mentioned in the main text. We sincerely hope our response will meet with your requirement.*

Changes in the text: None.

Table 1. Pathological complete response (pCR) analysis stratified by clinical stage.

Variables	n/N	pCR (95% CI)
Clinical TNM stage		
I	0/3	0
II	4/24	16.7 (4.7, 37.4)
III	20/110	18.2 (11.5, 26.7)
IVA	11/27	40.7 (22.4, 61.2)
Unknown	1/5	20.0 (0.5, 71.6)
Clinical TNM stage		
I/II	4/27	14.8 (4.2, 33.7)
III/IVA	31/137	22.6 (15.9, 30.6)

(3) One of the operated patients died of post-operative bleeding. What was the bleeding site ?

Response: *Thanks. The patient died of upper gastrointestinal bleeding. We have added the corresponding information in the Results section.*

"There were 2 (1.2%) patients who died within 90 days postoperatively, 1 due to postoperative upper gastrointestinal bleeding and the other due to postoperative anastomotic leakage." (**Page 8 Lines 240-242**)

(4) Was there any conversion to conventional procedure?
Response: *Thanks. We have double-checked that three patients converted to conventional procedure.*

"Three patients had a conversion to conventional procedure. (**Page 7 Lines 215-216**)

(5) Was immunotherapy paid by your national insurance?
Response: *Thanks. In China, immunotherapy has been paid by the national insurance in the first-line treatment of advanced ESCC, but not in the neoadjuvant setting.*
Changes in the text: None.

(6) How did you decide to perform the adjuvant immunotherapy of chemotherapy?
Response: *Thanks for your comments. The decision to perform the adjuvant therapy was made based on the pathological staging at the joint discretion of treating physicians and patients.*
Changes in the text: None.

(7) How did you decide to perform the number of neoadjuvant cycles?
Response: *Thanks for your comments. Two to 4 treatment cycles have been recommended for neoadjuvant immunotherapy plus chemotherapy in the local guideline [1]. In our daily practice, most patients received two cycles of neoadjuvant therapy, and then underwent radiographical assessment to guide the further treatment decision-making.*
Changes in the text: None.

[1] Kang X, Qin J, Zhang R, et al. 2021 NCC/CATS/CSTCVS/STM expert consensus on perioperative immunotherapy for esophageal cancer. Ann Esophagus 2021;4:33.

(8) What was the rate of disease progression for every stage after the neoadjuvant therapy?
Response: Thanks. Ten (3.9%) patients had disease progression after neoadjuvant

therapy, including two with stage II diseases, four with stage III diseases, and four with stage IV diseases.
Changes in the text: None.

(9) PET scan was not mentioned. Is it an optional in your hospital?
Response: *Thanks for your comments. PET scan was optional as clinically indicated.*

"Positron Emission Tomography (PET)-CT was optional." (**Page 5 Lines 146-147**)

(10) The follow-up period is too short.
Response: *Thanks. This study mainly foucsed on the perioperative outcomes of camrelizumab-containing neoadjuvant therapy. We have already added the limitation in the discussion section.*

"The key limitation of this study is the relatively short follow-up time, thus not allowing for a comprehensive report on tumor recurrence/progression or survival. The long-term efficacy of camrelizumab-containing neoadjuvant therapy in patients with ESCC needs to be studied further." (**Page 10 Lines 306-309**)

The manuscript was well written with acceptable language (although some sentences have to be rephrased) and layout. Also this is a hot topic being discussed in the medical world.

However, there are some issues that need to be addressed, because (1) the title and the studied population did not match; (2) the follow-up period was too short.

The title is 'locally advanced...', but the patients selected were from stage I. The median follow-up period was 12.9 months.
Response: *Thanks. We have deleted the words "locally advanced" throughout the manuscript. Besides, we have already added the limitation of short follow up in the discussion section, as mentioned above.*

Reviewer D

The authors of the study conducted a trial to investigate the effectiveness and safety of camrelizumab-containing neoadjuvant therapy in patients with locally advanced ESCC in daily practice. Patients with at least 1 dose of camrelizumab-containing neoadjuvant therapy were included (combined with nab-paclitaxel plus platinum in the majority of patients). A prospective multicenter study (13 center in China) included 255 patients

between 2020 and 2022; 169 underwent surgical resection: 146 (86.4%) achieved R0 resection, and 36 (21.3%) achieved pathological complete response (pCR). Grades 3–5 adverse events were experienced by 14.5% of participants. The authors concluded that Camrelizumab-containing neoadjuvant therapy has acceptable effectiveness and safety profiles in real-life ESCC patients.

The investigation of novel systemic therapies for esophageal cancer patients is indeed relevant. I believe the investigators could have designed a better prospective trial with further standardization of the systemic therapy in order to determine effectiveness of the drug:

1.This is a single-arm non-comparative study with patients receiving both immunotherapy and chemotherapy. It is hard to tell which effect is related to each of the systemic therapies. In addition, different number of cycles of neoadjuvant therapy and different chemotherapy drugs were used in the included patients. Why have the authors decided to include such heterogeneity in a prospective trial? A comparative study including patients with and without Camrelizumab-containing neoadjuvant therapy might be more useful to determine the real effectiveness / safety of the drug. These issues should be discussed.

Response: *Thanks. This is a prospective multicenter observational cohort study including all patients with histologically or cytologically confirmed ESCC (cTNM stage I–IVA) who had received at least one dose of camrelizumab-containing neoadjuvant therapy between May 2020 and March 2022 at 13 tertiary hospitals in Southeast China. This study may help to better understand the prescription patterns of camrelizumab in the neoadjuvant setting, as well as real-world effectiveness and safety of camrelizumab-containing neoadjuvant therapy in ESCC patients. Thanks again for your time and kind work.*

Changes in the text: None.

*"Nevertheless, this study may help to better understand the prescription patterns of camrelizumab, as well as real-world effectiveness and safety in the neoadjuvant therapy of ESCC." (**Page 10 Lines 314-316**)*

2.Patients were staged with CT, MRI, and/or endoscopy. Please expand on why PET-TC and EUS were not used for staging.

Response: *Thanks for your comments. Enhanced chest CT scan, magnetic resonance imaging (MRI), and/or esophageal endoscopy were routinely used for staging, while PET-TC and EUS were optional as clinically indicated in our daily practice.*

Changes in the text: None.

3.Most tumors were located in the middle thoracic esophagus (71%). It is striking that 45% of the surgical patients underwent Ivor Lewis esophagectomy (making difficult to obtain adequate proximal margins). Please comment on how the surgical approach is decided in these patients.

Response: *Thanks. In our daily practice, the surgical approach was decided by the operative surgeon based on the patient's condition with the reference to the Clinical Society of Clinical Oncology (CSCO) guidelines. In general, McKeown esophagectomy and three-field lymph node dissection were recommended for patients with upper-thoracic tumors, McKeown esophagectomy or Ivor Lewis esophagectomy was for patients with middle-thoracic tumors, while Ivor Lewis esophagectomy was for those with lower-thoracic diseases or Siewert type I esophagogastric junction cancer. Thanks for your time and kind work. We sincerely hope our response will meet with your requirement.*

Changes in the text: None.

Reviewer E

I offer the followig comments/criticisms and suggestions for revision.

This multi center study from China reports on the efficacy and safety of camrelizumab-containing neoadjuvant therapy in squamous cell cancer of the esophagus. This study follows a recent systematic review On the topic of neoadjuvant chemoimmunotherapy in esophageal cancer published in JAMA. The results in terms of R0 resection and CPR are very similar. This systematic review significantly limits the impact of the present manuscript and the authorsa need to provide some justification as to why their findings are novel and/or add significantly to our current understanding.

Response: *Thanks for your comments. This prospective observational study mainly foucsed on the real-life effectiveness and safety of camrelizumab-containing neoadjuvant therapy in ESCC patients. Accordingly, all patients with histologically or cytologically confirmed ESCC (cTNM stage I–IVA) who had received at least one dose of camrelizumab-containing neoadjuvant therapy between May 2020 and March 2022 at 13 tertiary hospitals in Southeast China were eligible for inclusion. This study may help to better understand the prescription patterns of camrelizumab, as well as real-world effectiveness and safety in the neoadjuvant therapy of ESCC. Thanks again for your time and kind work.*

Changes in the text: None.

*"Nevertheless, this study may help to better understand the prescription patterns of camrelizumab, as well as real-world effectiveness and safety in the neoadjuvant therapy of ESCC." (**Page 10 Lines 314-316**)*

I also note that in the above mentioned systematic review, 7 studies are included that enrolled 277 patients from China where camrelizumab-containing neoadjuvant therapy was used. This is very similar to the 255 cases reported here and this leads me to question if any and how many of the pateints in the present report have previously been reported in the literature?
In a study with median follow-up of only 12.9 months, reporting survival data has very little clinical relevance and this should probably be eliminated from the manuscript.

Reviewing the literature on the results of chemoimmunotherapy in the neoadjuvant setting for esophageal cancer, there is a systematic review published in JAMA in 2022 that summarizes all of the published Phase II and III studies. These include 27 studies involving 815 patients with very similar results in terms of response rates and outcomes. This significantly limits the impact of the current report. Of note, the JAMA systematic review included 8 trials using camrelizumab from China including 277 patients. I am concerned that this manuscript includes patients previously reported in the other 8 published trials.

Ge F, Huo Z et al, JAMA Network Open. 2022;5(11):e2239778. doi:10.1001/jamanetworkopen.2022.39778
Response: *Thanks for your comments. This was a prospective multicenter observational cohort study including all patients with histologically or cytologically confirmed ESCC (cTNM stage I–IVA) who had received at least one dose of camrelizumab-containing neoadjuvant therapy between May 2020 and March 2022 at 13 tertiary hospitals in Southeast China. We declare that no patients previously reported in other published trials were included in this study. Thanks again for your time and kind work.*
Changes in the text: None.