Peer Review File
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Reviewer A

Comment 1: Thank you for submitting your manuscript relating to a meta-analysis of the evidence for the use of ICIs in EC. I have several comments detailed below. I think it is important to clarify that this study relates only to ESCC and not EC as a whole (if that is the intention) - this should be done in both the introduction and the methods i.e. patients with adenocarcinoma were excluded from the analysis.
Reply 1: Thank you for reviewing the manuscript; your suggestions help improve the study's usefulness. We have made it clear that advanced ESCC is the focus of the study in this paper, adjusting the title and subtitle and abstract. Modify the analysis for EC to the analysis for ESCC in Introduction and Methods.
Changes in the text: We change the “esophageal cancer” in the title and subtitle to “esophageal squamous cell carcinoma” (see Page 1, lines 2-5). We change the “EC” to “ESCC” (see Page 2, line 36-38) (Page 3, line 47-54) (Page 4, line 61-79). In the inclusion criteria, we added, "Histologic type is esophageal squamous cell carcinoma” (Page 6, line 106).

Abstract

Comment 1: I would reword ICIs 'including' rather than 'known as' - there any many different targets for ICIs
Reply 1: Thanks for this suggestion. We have modified the word.
Changes in the text: we have replaced "known as" with "including"(see Page 2, line 33).

Comment 2: duplication in 2nd and 3rd sentences
Reply 2: we have modified our text as advised.
Changes in the text: We deleted the 2nd sentence (see Page 3, lines 45-46).

Introduction

Comment 1: Platinum rather than cisplatin (oxaliplatin is an alternative to cisplatin following the REAL2 study), fluoropyrimidine rather than 5-FU (capcetabine can be interchanged with 5FU following the REAL2 study)
Reply 1: We appreciate this helpful suggestion. We have modified the sentence.
Changes in the text: We have modified the sentence, “Advanced ESCC patients receive chemotherapy regimens based on Taxane, Platinum, and Fluoropyrimidine as their first line of treatment because surgery is useless in this form of ESCC.” (see Page 4, line 62-64)

Comment 2: Need to briefly mention role of ICI in 1st line setting e.g. KEYNOTE-590
Reply 2: Thanks for this suggestion. We have briefly described the significant efficacy of ICI compared with chemotherapy in the first-line treatment of patients with advanced ESCC.
Changes in the text: In the Introduction section, we have added, “In KEYNOTE-590, which investigated first-line therapy for advanced ESCC, pembrolizumab as one of the ICIs combined

with chemotherapy improved overall survival in patients with advanced ESCC compared with placebo plus chemotherapy." (see Page 4, lines 68-71)

Comment 3: Should reference and name key studies (e.g. ATTRACTION-3) rather than review articles

Reply 3: Thanks again for your review. These comments are very helpful in improving the quality of the manuscript. We removed review articles and cited key studies as references as recommended.

Changes in the text: We have removed the review article and cited key studies as references, such as ATTRACTION-3, RATIONALE-302, etc. (see Page 4, line 68)

Methods

Comment 1: Was ipilimumab as search term? Studies exist e.g. https://www.thelancet.com/journals/lanhl/article/PIIS2666-7568(22)00116-7/fulltext and could be included in the analysis if combination regimens are eligible

Reply 1: Thanks for this suggestion. In the Methods section, we have added ipilimumab as the search term. Further analysis showed that RAMONA was a study of ipilimumab and nivolumab combination therapy in patients with advanced ESCC. Because there was no control chemotherapy group, it was not included in our study.

Changes in the text: We have added the search term "ipilimumab". (see Page 5, line 91)

Comment 2: Tislelizumab and Sintilimab should be search terms as they were used in the included studies (References 9 and 10)

Reply 2: Thanks again for your review. we have modified our text as advised.

Changes in the text: We have added the search terms "tislelizumab" and "sintilimab". (see Page 5, line 91)

Comment 3: Were the sencondary endpoints PFS, ORR and safety? If so, this should be stated.

Reply 3: Thank you for your comment. As advised, we have stated in the text that the secondary endpoints in the study were PFS, ORR and safety.

Changes in the text: we added, "The secondary endpoints were PFS, ORR and safety." (see Page 6, lines 109-110)

Results

Comment 1: does this not show that there is a difference in any grade TRAEs?

Reply 1: Thanks again for your review. We reviewed the data of any grade TRAEs again, proving that there were differences in any grade of TRAEs.

Changes in the text: We have changed the "there was no statistically difference in TRAEs of any grade observed" to "there were statistical differences in TRAEs of any grade observed". (see Page 9, lines 163-164)

Comment 2: Was there a difference according to histology i.e. ESCC vs adenocarcinoma? We may expect ESCC to have better outcomes with ICIs. If the focus of the manuscript is only on ESCC, then this does not need to be addressed.

Reply 2: We have made it clear that advanced ESCC is the focus of the study in this paper. As for

histological differences, we may conduct further research in the future.
Changes in the text: We change the “esophageal cancer” in the title and subtitle to “esophageal squamous cell carcinoma” (see Page 1, lines 2-5). We change the “EC” to “ESCC” (see Page 2, line 36-38) (Page 3, line 47-54) (Page 4, line 61-79). In the inclusion criteria, we added, "Histologic type is esophageal squamous cell carcinoma” (Page 6, line 106).

Comment 3: It is worth commenting either in the methods or results, that the ORIENT-2 study included assessment of both TPS and CPS
Reply 3: Thank you for your comment. The ORIENT-2 study included assessment of both TPS and CPS, which made a great contribution to our analysis of PD-L1 expression.

Discussion
Comment 1: Duplication of sentences in line 178-180.
Reply 1: we have modified our text as advised.
Changes in the text: We deleted the 3rd sentence. (see Page 10, lines 191-192)

Comment 2: Is the study only in ESCC? As stated above, this should be clearly defined earlier in the manuscript.
Reply 2: Thank you for your comment. We have made it clear that advanced ESCC is the focus of the study in this paper.
Changes in the text: We change the “esophageal cancer” in the title and subtitle to “esophageal squamous cell carcinoma” (see Page 1, lines 2-5). We change the “EC” to “ESCC” (see Page 2, line 36-38) (Page 3, line 47-54) (Page 4, line 61-79). In the inclusion criteria, we added, "Histologic type is esophageal squamous cell carcinoma” (Page 6, line 106).

Comment 3: Need to reference the study being referred to
Reply 1: Thanks for this suggestion. we have referenced the study being referred to.
Changes in the text: we have referenced the study on pembrolizumab. (see Page 11, line 211)

Comment 4: Expand discussion on Checkmate-648 and relate back to PD-L1 expression
Reply 4: Thanks for this suggestion. We have reviewed the Checkmate-648 study and further discussed the relationship between PD-L1 expression and survival benefits.
Changes in the text: we have added, “The effect of PD-L1 expression on treatment outcomes has also been further investigated in the checkmate648 trial. In patients with TPS $\geq$ 1% or higher, both immune combination regimens had a better survival benefit compared with chemotherapy. In patients with TPS $\leq$ 1%, no significant survival difference was observed between the regimens, but the proportion of patients with objective response to immune combination therapy was more than that in the chemotherapy group, indicating that longer follow-up may be required to determine changes in overall survival. Similar results were also obtained in comparing patients with CPS $\geq$ 1 and CPS < 1. It is proved that both TPS and CPS have certain guiding significance for advanced ESCC.” (see Page 12, lines 230-239)

Comment 5: The manuscript would benefit from further discussion about the use of PD-L1 as a biomarker. From your results, it does not appear to be a good biomarker of outcome.

Reply 5: Thanks again for your review. These comments are very helpful in improving the quality of the manuscript. Most of the studies included in our study on PD-L1 expression levels only assessed CPS or TPS. Some patients with PD-L1-negative tumors also responded to ICI to a certain degree, which may have contributed to the reduced difference between the two groups. But PD-L1 remains an important biomarker and CPS may be more appropriate than TPS.

Changes in the text: In the Discussion section, we have added, “But in gastroesophageal adenocarcinoma, CPS proved to be a more appropriate indicator than TPS. A TPS of 5% had a longer duration of response compared with 10%, and there was no significant difference in overall survival, suggesting that the benefit in a population with tumor cell TPS ≥ 1% may not be driven by a subgroup with TPS ≥ 10%. In a study of patients with advanced squamous non-small cell lung cancer, TPS ≥ 50% was associated with a greater OS benefit with nivolumab in the second-line treatment, and different immunotherapy regimens may be explored in the future based on different PD-L1 expression levels.” (see Pages 12-13, lines 239-246)

Reviewer B

Comment 1: It is not clear if the authors are discussing combination (Chemo+PDL1inhibitors) or mono therapy. Mono therapy is most effective in PDL1 high (>0.5 at least) patients.

Reply 1: Thank you for your comment. TPS ≥ 50% have been shown to be superior in the treatment of patients with advanced NSCLC. However, there is no evidence that TPS ≥ 50% is the most effective monotherapy in advanced ESCC. We discuss PD-L1 expression levels and survival benefits further in the discussion.

Changes in the text: In the Discussion section, we have added, “But in gastroesophageal adenocarcinoma, CPS proved to be a more appropriate indicator than TPS. A TPS of 5% had a longer duration of response compared with 10%, and there was no significant difference in overall survival, suggesting that the benefit in a population with tumor cell TPS ≥ 1% may not be driven by a subgroup with TPS ≥ 10%. In a study of patients with advanced squamous non-small cell lung cancer, TPS ≥ 50% was associated with a greater OS benefit with nivolumab in the second-line treatment, and different immunotherapy regimens may be explored in the future based on different PD-L1 expression levels.” (see Pages 12-13, lines 239-246)

Comment 2:PDL1 inhibitors were not approved prior to 2015 - please identify the date range for the search.

Reply 2: Thanks again for your review. We have modified the date range for the search.

Changes in the text: As advised, we replaced "as of February 1, 2022" with "from January 1, 2015, to February 1, 2022".(see Page 5, lines 91-92)

Comment 3:please explain the criteria for inclusion and exclusion of the articles, e.g, only English language? only standard approved therapies by [name of the regulatory bodies e.g., FDA, EMA, CDE] and other criteria. So that will describe as to why only 5 articles were selected

Reply 3: Thanks for this suggestion. We have selected five articles based on inclusion and exclusion criteria. We included studies containing ESCC and English was the only language. ICIs used in the study require FDA approval, and study endpoints include OS, PFS, ORR, and safety. Studies with

data lacking and no control chemotherapy arms were excluded, and five articles were selected.
Changes in the text: We have adapted the inclusion and exclusion criteria, we have added, "ICIs for clinical trials have been approved by the Food and Drug Administration (FDA)", “English is the only language of publications” and “Histologic type is esophageal squamous cell carcinoma”. (see Pages 5-6, lines 100-106)

Reviewer C

Comment 1: Thanks for this work which analyse data regarding the impact and safety of ICIs in the second line setting for esophageal cancer which is a topic of interest.
The metanalysis provide an interesting overview of the results of the most important trials in this setting. However, as the authors had mentioned, the study present limitations such as the few studies included and heterogeoeus that do not allow to make such comparisons.
Reply 1: Thank you for your recognition of the value of our research and suggestions. According to the current study, which has preliminarily obtained the results that ICIs have longer survival and better safety in the second-line treatment of advanced ESCC, more relevant studies are expected to be published to improve the evidence-based medical evidence for this study.
Changes in the text: None.