

2023/8/16

Jin-Lei Wang

Editor-in-Chief

World Journal of Clinical Cases

Re: Manuscript reference No. 86340

Dear Dr Wang,

We thank you for the opportunity to resubmit a revised version of our manuscript titled, "Combination therapy with toripalimab and anlotinib in advanced esophageal squamous cell carcinoma: A case report," for publication as a case report in the *World Journal of Clinical Cases*.

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. The manuscript has been rechecked and the necessary changes have been made in accordance with the suggestions provided. The revised manuscript with revisions in the text shown using a yellow highlight is attached. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

In accordance with Reviewer #1's suggestion, we have added: Page 8, lines 1-2: "The combination of amlotinib and teraplizumab exerted a synergistic anti-tumor effect."

Page 8, lines 3: "induces a relatively immune-supportive tumor microenvironment"

Page 8, lines 3-4: "Furthermore, anlotinib promotes the differentiation and maturation of dendritic cells and thus enhances their ability to present tumor antigens to T cells."

Above changes and others are all highlighted with yellow color.

We hope that the revised manuscript is suitable for publication in the *World Journal of Clinical Cases*.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Responses to the comments of Reviewer #1

1. Fig.4 can be replaced to PET-CT data compared to pretreatment state shown in Fig.3.

Response: Thank you for your suggestions. After 6 months of treatment, we recommended that the patient undergo a PET-CT scan to better assess the tumor's response to the medication. However, due to the high cost of the PET-CT scan, the patient explicitly declined. Therefore, following the patient's achievement of CR, we conduct enhanced CT scans every 3-6 months to monitor tumor progression.

2. The authors should be discussed the mechanisms of two drugs resulted in disappearance of most ESCC, and further they can perform immunostaining of phosphorylated tyrosine kinase or PD-1/PD-L1.

Response: We have re-written the manuscript according to your suggestions.

Regarding the mechanistic queries you raised, we have modified certain sections of the paper based on existing research and highlighted these changes in yellow. However, due to the exceptional rarity of achieving complete remission in advanced ESCC through the combined administration of these two drugs, the specific signaling pathway by which the combination therapy affects

advanced ESCC, as well as its clinical feasibility, still necessitates further research to provide a valid explanation.

We also appreciate your suggestions concerning VEGFR or PD-1/PD-L1 immunostaining. Unfortunately, due to the relatively limited quantity of material obtained during the initial biopsy, immunohistochemical staining was not performed. If there arises a necessity for subsequent biopsies, we will be diligent in conducting immunohistochemical staining on the biopsy specimens to facilitate a more comprehensive analysis of the correlation between these markers and the effectiveness of the combination therapy.

Responses to the comments of Reviewer #2

1. The article deals with a very interesting subject regarding the combination of toripalimab and anlotinib as a treatment option for squamous cell carcinoma of esophagus. The whole set up of the article is very good fulfilling the requirements of the journal. The advanced squamous cell carcinoma of esophagus is a major issue firstly for the patient and additionally for the doctors surgeons and oncologists dealing with it. What is very interesting is that there was a complete response to treatment. My only concern is after the complete response did the patient had a surgery?

Response: We sincerely appreciate your recognition of our case. In this instance, the patient was diagnosed at an advanced stage. Despite achieving CR with the combination therapy of toripalimab and anlotinib, the extent of resection required for curative surgery was deemed too extensive, offering limited clinical benefit to the patient. Moreover, due to the patient's inclination towards

conservative treatment, surgical intervention was not performed after achieving CR. Meanwhile, we are highly interested in the issue you raised regarding the benefits of surgery for advanced or unresectable ESCC patients upon achieving CR. We have incorporated your perspective as one of the directions for our future research endeavors.