TRANSLATIONAL CANCER RESEARCH

Peer Review File

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Response to reviewer:

Comment 1：Originality. Although the topic is interesting, a quick search on PubMed identified at least 2 published articles on the same topic. I am not sure if we need a third article publishing on the same topic unless it can add something above and beyond what was already published.

Reply 1: Special thanks to you for your comments. The difference between our study and the other two meta-analysis is that we are focusing on the correlation between TMB and OS, and our conclusions about TMB and OS are not the same as that of the two articles. Wu Y et al. found that patients with high TMB had significant improved OS of pan-tumors. However, in their subgroup analysis they found that there was no significant difference in OS between non-small-cell lung cancer patients with high TMB and low TMB. On the other hand, we don't think that we could get the conclusion that high TMB significantly improved OS in pan-tumor, because of the high heterogeneity (I-squared=72.6.0%). And we found that high TMB had significant improved OS in non-small-cell lung cancer. (HR=0.50, 95% Cl: 0.38-0.64, I-squarely: 18.3%) And as for the study of Zhu J, et al, they focused on comparing the prognosis

of patients with high TMB between immune therapy and chemotherapy, while our study focused on comparing the prognosis of patients received immune therapy between high TMB and low TMB patients. What's more, we added some contents about TMB and objective response rate (Line 274-283).

Changes in the text: Line 274-283

Comment 2: Confusion between predictive value and prognostic value. To understand a predictive value, there needs to be a control group receiving no treatment. Predictive value can be said to exist if there is a significant interaction between TMB level and the treatment. Based on what the authors are presenting, they are dealing with just a prognostic value of TMB since all patients were treated with ICI. This needs to be clarified.

Reply 2: Special thanks to you for your comments. We think that predictive biomarkers could indicate the sensitivity to a particular treatment, and predict the efficacy of a certain treatment, while prognostic biomarkers could indicate the benefit of the prognosis, which are used to assess the risk of disease recurrence, metastasis, death and so on. The purpose of our study is to discuss whether TMB has predictive value in predicting the efficacy of ICIs. We compared the efficacy of ICIs between patients with high TMB and low TMB, and we found that the efficacy of the two groups is different. Thus, we think TMB can predict the efficacy before patients

revive ICIs. And for fitting the theme of our study better, we changed our title (Line2-4).

Changes in the text: Line2-4

Comment 3：To understand the prognostic value of TMB across several studies, ones need to know whether the HR in each study has been adjusted for other known prognostic factors (such as performance status, line of treatment etc.) before adding to meta-analysis. A table showing this information will be useful for readers to know the factors adjusted for in each study.

Reply 3: As Reviewer suggested that we have supplemented the Characteristics of included trials (Table 1 and Table 2).

Changes in the text: Table 1 and Table 2.

Comment 4: The HR for OS was 0.61 (95% CI: 0.4-0.92) with p value < 0.001 is considered statistically significant. Why did the author conclude that this was not significant?

Reply 4: Special thanks to you for your comments. Our submitted version showed that although the pooled HR value of the OS and high TMB was 0.56 (95% CI: 0.40-0.92), the I-square value was 87%, which meant that the heterogeneity was too

high. Thus, we concluded that patients with high TMB could not be considered to have better OS in pan-tumor. During revised the manuscript, we added some latest data of 2020, and got the new results (polled HR=0.56, 95%CI: 0.44~0.70, I-squared=72.6%), and the heterogeneity could not be ignored. Thus, we still do not think that patients with high TMB are related to better OS in pan-tumor (Line 161-180).

Changes in the text: Line 161-180

Comment 5: In the abstract “magnificent” is a wrong word used.

Reply 5: We are very sorry for our incorrect writing, and we have corrected as required (Line 100).

Changes in the text: Line 100

Comment 6: Throughout the paper, language editing is needed.

Reply 6: We are very sorry for our incorrect writing, and we have corrected as required.

Comment 7: The authors should mention a paper by Hellman et al N. Engl J Med 2019 which showed that high or low tumor mutation burden is not predictive of ICI efficacy. This is a large randomized study and is very important to include or at least discuss why their analysis still shows prognostic value of TMB.

Reply 7: Special thanks to you for your comments. Our study did not include the data of the study by Hellman et al because this article compared the efficacy between the nivolumab plus ipilimumab group with chemotherapy group. It did not meet our inclusion criteria. The study by Hellman et al found that regardless of TMB, the prognosis of immunotherapy was better than that of chemotherapy. While the purpose of our study is to explore whether there is a difference in efficacy of immunotherapy between patients with high TMB and patients with low TMB.