Peer Review File

Article Information: https://dx.doi.org/10.21037/tlcr-21-419

Reviewer A

Comment 1: A very interesting and clear paper - concise and well-written. No major issues. But one minor concern is the decision to accept abstracts. Conference abstracts are notoriously premature (or worse, simply wrong) - and rarely reflect final published results (peer-reviewed). I would not have accepted abstracts.

Reply 1: We are grateful for your deliberate responses to our manuscript. As you commented, some readers would like to know the result from the analysis excluding conference abstract though the other readers might like analysis including conference abstracts. After the discussion in our author group, we decided not to eliminate conference abstract from our main analysis and decided to conduct a sensitivity analysis by removing conference abstract. The results of the sensitivity analysis excepting the conference abstracts did not conflict with our main analysis with the conference abstract. The manuscript has changed according to this comment (Page 14, line 232) and Supplementary Figure 2 was added. Thank you.

Reviewer B

Comment 1: Authors have done an important meta-analysis on the the best chemotherapy combination with ICI. ICI plus chemotherapy is the standard of care in patients with NSCLC especially in patients with PDL-1 expression of 0-49%. the patients with PDL-1 50% or greater respond well to ICI only. It is unclear why authors excluded the patients with PDL-1 <1%. To improve the quality of this manuscript, those patients would be included in the study. If authors believe that grouping those patients with the patients with PD-L1 1 - 14% would influence the results, they can make a separate groups i.e. group 1 (<1%), Group 2 (1-49%), and do separate analysis and this will help us to know if the same combination of chemo+ immunotherapy or a different combination is more beneficial in those sub-set of the patients. It is not reasonable to exclude those important group of patients.

Reply 1: We appreciate precious advice to enhance our manuscript. Current major guidelines such as NCCN and ASCO distinguish patients with PD-L1 expression <1% from >1%. These guidelines usually categorize patients into three groups: PD-L1 high expression (>= 50%), PD-L1 low expression 1-49%, and PD-L1 no expression < 1%. Furthermore, some major large-scale trials also separately grouped patients with PD-L1<1% and >1% (KeyNote-041. Lancet. 2019 May 4;393(10183):1819-1830. // KeyNote-021. Lancet Oncol. 2016 Nov;17(11):1497-1508.) To our understanding, our patient category using the cutoff, PD-L1 of 1%, seems fairly reasonable. Therefore, in the current manuscript, we focused on patients with PD-L1 expression 1-49%. As you correctly recommended, the analysis of patients with PD-L1 expression <1% is meaningful. Nonetheless, it takes months to perform such analysis. We eventually made a difficult decision not conducting the subgroup analysis focusing patients without PD-L1 expression because the re-submission deadline was set in three weeks. We would like to conduct such meta-analysis next time. Thank you again for the thoughtful comments for us.

Comment 2: Page 12, line 202, what does it means by " decrease risk of PFS"?

Reply 2: Following your advice, the wording was changed in the manuscript (Page 14, line 237). Thank you.

Comment 3: Page 13, line 219, please explain why "it is controversial whether ICI mono therapy or a combination with ICI is better"?

Reply 3: We noticed that this sentence is confusing and deleted this sentence (Page 16, line 258). Thank you for the careful reviewing.

Comment 4: Page 14, line 241, please clarify why it is difficult to continue long-term treatment with dulanermin?

Reply 4: We noticed that this sentence is confusing and deleted this sentence (Page 17, line 284). Thank you for your comment to clarify the manuscript.

Reviewer C

Comment 1: Dr Fukuda et al. reported the best regimens for chemo-naive incurable non-squamous non-small cell 1 lung cancer with a programmed death-ligand 1, tumor proportion score 1%-49% (A network meta-analysis).
It's a well analyzed review paper.
However, a similar review paper has been published in JTO.
Dr Liu et al. have reported the systematic review and network meta-analysis (NMA) comparing the efficacy and safety profiles of currently available IO combinations of first-line immunotherapy. They suggested that pembro-chemo and nivo-ipi-chemo appear to be superior first-line immunotherapy combinations for advanced NSCLC patients with positive and negative PD-L1 expression, respectively (Liu et al. Efficacy and safety of first-line immunotherapy combinations for advanced non-small-cell lung cancer: A systematic review and network meta-analysis. J Thorac Oncol. 16:1099-1117, 2021.).

Reply 1: Thank you for reviewing our manuscript. Dr. Liu et al. had recently reported efficacy and safety of first-line immunotherapy combinations for advanced non-small-cell lung cancer. We acknowledge that their paper descripted a well-coordinated network meta-analysis on the topic that we touched in the current manuscript. However, our study differed from their report in the following points. Our manuscript evaluated some single-agent regimens including single-agent atezolizumab and single-agent pembrolizumab, while their article reported limited number of combined treatment options. According to recent guidelines (NCCN and ASCO), both single agent regimen (i.e. pembrolizumab) and combined ICI regimens (i.e. platinum doublet plus pembrolizumab) are recommended. Therefore, many readers may be interested in the safety and efficacy of single-agent regimens, which Dr. Liu et al. did not evaluate. Besides, since we included a larger number of regimens, our analyses eventually included 26 original reports for the main model and 63 original reports for the separate model, whereas only 16 reports were included in the paper by De Liu et al. Although we highly appreciate Dr. Liu's article, we would like to emphasize that our analysis had another message for readers. Thank you again for the thoughtful comments for us.

Reviewer D

Comment 1: This analysis demonstrated the clinical utility of adding PD-1 inhibitors to platinum-based chemotherapy for non-small cell lung cancer with PD-L1 expression of 1-49%. The results from individual clinical trials cannot conclude the therapeutic effect on this subgroup. Also, it is hard to plan a new randomized study for this subgroup. Therefore, I felt that a method like this study was very useful. However, I felt that further improvements were needed to be accepted.

Reply 1: We are grateful for your deliberate responses to our manuscript.

Comment 2: For clinicians who actually decide the treatment regimen for advanced lung cancer patients, Fig. 3 of this paper seems to be the most useful information. The authors also conclude this paper based on the analysis results using the 26 clinical trials shown in Fig. 3. The 26 trials appear to meet all the Inclusion criteria listed in Methods, but this list of 26 trials is important and should be presented. The presentation should also include the treatment regimen and the number of cases in each group.

Reply 2: As you commented, the previous manuscript did not present sufficient data to know which article is classified to models. Based on your suggestion, Table 1 was modified to tell which trial was used for the main analysis with 26 trials and the additional analysis. We believe readers can distinguish 26 trials that were used for the main analysis from those that were not. You can see the regimens used for the main analysis from the modified Table 1. The total number of patients evaluated in the main model was 7,142 as shown in the manuscript (Page 14, line 221). We sincerely appreciate for your careful reviewing.

Comment 3: Differences in the antibodies used cannot be ignored when performing an analysis that defines a patient group based on PD-L1 expression. In the discussion, the evaluation when using different PD-L1 antibodies should be mentioned.

Reply 3: As you rightly commented, differences in the antibodies cannot be ignored. This

considerable limitation was added to our limitation section (Page 18, line 300). Thank you for your advice.