Peer Review File

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Reviewer A

Authors described that there were a few clinical trials to evaluate toxicity of combination therapy, however, this has been a very fundamental assessment of clinical trials and the conclusion they tried to lead was already shown in previous trials.

Reply
Thank you very much for your comments on our manuscript. As you have pointed out, evaluating toxicity of combination chemoimmunotherapy has been a very fundamental assessment of clinical trials and the conclusion we tried to lead was already shown in previous trials. As mentioned in the original and revised text, however, only one meta-analysis of adverse events caused by combination chemoimmunotherapy versus chemotherapy alone in the first-line treatment of non-small cell lung cancer has been published, and this report did not indicate which toxic symptoms and hematological toxicities occurred more frequently with the addition of immune checkpoint inhibitors compared with chemotherapy alone. Therefore, we believe that our meta-analysis can provide an important reference of the toxicity of combination chemoimmunotherapy for our clinicians in the management of lung cancer care.

Changes in the text
No additional description was included in the revised text.

Reviewer B

It was a great pleasure to review the manuscript 'Treatment-related adverse events of combination chemoimmunotherapy versus chemotherapy alone in first-line treatment for non-small cell lung cancer: A systematic review and meta-analysis of randomized clinical trials' by Takada K et al. This study is a meta-analysis investigating risk of treatment-related adverse events of combination chemoimmunotherapy for NSCLC. This paper is suitable for publication in the Journal of Thoracic Disease. Several concerns described below may improve their manuscript.

Major concerns:
1. This meta-analysis had some publication bias, and it should be considered as major concerns. In the discussion section, the authors mentioned that bias might be due to the discrepancy between actual clinical practice and RCTs. However, in my opinion, this explanation might be insufficient to support the reason why bias was caused. Please discuss in more detail and add some references.

Reply
Thank you very much for your comments on our manuscript. As you have pointed out, we think that there appear to be other causes of publication bias. In this meta-analysis, we only integrated the results of a mere 10 clinical trials, and if we exclude anti-CTLA-4 antibody, it comes down to 9 trials. While differences in drugs such as anti-PD-1 antibody and anti-PD-L1 antibody may affect the outcomes, the number of trials would be further reduced when conducting the analysis, so we have only analyzed the combined data of anti-PD-1 and anti-PD-L1 antibodies this time. It has been reported that there are particularly differences in the incidence rates of drug-induced pneumonitis between anti-PD-1 antibody and anti-PD-L1 antibody, so caution is needed when interpreting the results (Pillai RN et al. Cancer 2018).

Changes in the text
We have added this information in the revised text (page 19, lines 6–13).

Minor concerns:
1. In the discussion section (lines 238-244), "Although there are several treatment options for first-line therapy in the management of NSCLC without oncogenic driver alterations, including ICI monotherapy, ICI + chemotherapy, and chemotherapy alone, the previous and current meta-analyses indicated that patients treated with combination chemoimmunotherapy had the highest risk of treatment-related AEs among patients treated with ICI monotherapy, ICI + chemotherapy, and chemotherapy alone". I think that ICI + chemotherapy is identical with chemoimmunotherapy. If they indicate same therapy, please unify them.

Reply
In response to your comment, we have changed 'ICI + chemotherapy' to 'combination chemoimmunotherapy'.

Changes in the text
We have added this information in the revised text (page 16, lines 6 and 9).

2. With respect to mentioned above, "previous and current meta-analyses" were not added as references. Please add the references.

Reply
In response to your comment, we have added the references (Nishijima TF et al. The oncologist 2017, Luo W et al. J Cancer Res Clin Oncol 2018).

Changes in the text
We have added this information in the revised text (page 16, line 9).