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Peer Review File

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Reviewer A

Comment 1: The study by Matsumoto et al. is a systematic review to clarity the efficacy and safety of ICIs in NSCLC patients with pre-existing ILD. They found that frequency and severity of ICI-related ILD was higher in patients with pre-existing ILD. They also reported that ORR was associated with the treatment line of ICI. The risk of ICI-related ILD was not associated with the pattern of pre-existing ILD (UIP pattern vs. non-UIP pattern). The findings in this study have been reported elsewhere and was not novel. In addition, they compared the impact of ICI monotherapy between 1st-line and 2nd-line or later. However, very few NSCLC patients received ICI monotherapy as 2nd-line treatment in clinical practice.

Reply 1: We thank you for the thoughtful and constructive comments. As you pointed, this study may show a few new findings, because Zhang et al. have published in Chest during our researching. However, we emphasize the differences in the following points.

First, our meta-analysis added seven studies in addition to the study by Zhang et al., including about three times as many patients with pre-existing ILD (543 patients vs. 179 patients). It is important facts that similar results were shown in much more patients.

Second, they concluded that the ICIs had favorable efficacy in patients with pre-existing ILD and ICIP was often mild and easily manageable. This conclusion may result from the high percentage in patients recovered from ICIP in supplementary e-Table 4 in Chest; however, those patients included some severe patients who received steroid pulse therapy and immunosuppressants and finally needed home oxygen therapy. Hence, it may be risky to interpret that ICIP is often mild and easily manageable. We concluded that ICIs should be administered cautiously in patients with pre-existing ILD, and then emphasize the risks of pneumonitis more than Zhang et al. We added the differences from the study by Zhang et al. in discussion section (see Page 14, line 259-264).

As your proper point, ICIs have been used less frequently as 2nd-line treatment in clinical practice. For instance, patients with pre-existing ILD sometimes avoid ICIs as 1st line treatment considering the failure of initial treatment due to pneumonitis, and then ICIs are administered after the 2nd-or later-line. As the results of our study, we cannot actively recommend the use of ICIs for patients with pre-existing ILD

regardless of treatment lines, considering the frequency of ICIP. Especially on 2nd-or later-line treatment, the risk of ICIP may outweigh ICI benefits. We added the last message in conclusion section (see Page 17, line 309-311).

Changes in the text: We revised and added the sentences in discussion (see Page 14, line 259-264) and conclusion section (see Page 17, line 309-311).

Reviewer B

Comment 1: As mentioned in the Discussion, I had the impression that the novelty was diminished by the fact that a meta-analysis of the same argument has already been reported in Chest. I can't come up with many strange ideas to improve it, but I think it is true that it has become less interesting.

Reply 1: We thank you for the thoughtful and constructive comments. As you pointed, this study may have a few novel findings and we are aware that the similar results are shown to some extent. However, we also suggest the differences in the following points.

Our meta-analysis added seven studies in addition to the study by Zhang et al., including about three times as many patients with pre-existing ILD (543 patients vs. 179 patients). It's important that the similar results were shown despite such difference in the number of patients.

Then, they concluded that the ICIs had favorable efficacy in patients with pre-existing ILD and ICIP was often mild and easily manageable. This conclusion may result from the high percentage in patients recovered from ICIP in supplementary e-Table 4 in Chest; however, those patients included some severe patients who received steroid pulse therapy and immunosuppressants and finally needed home oxygen therapy. Hence, it may be risky to interpret that ICIP is often mild and easily manageable. We concluded that ICIs should be administered cautiously in patients with pre-existing ILD, and then emphasize the risks of pneumonitis more than Zhang et al. We added the differences from the study by Zhang et al. in discussion section (see Page 14, line 259-264).

On the other hand, we cannot actively recommend the use of ICIs for patients with pre-existing ILD in any line, considering the frequency of ICIP. Especially on 2nd-or later-line treatment, the risk of ICIP may outweigh ICI benefits. We added the last message in conclusion section (see Page 17, line 309-311).

Changes in the text: We revised and added the sentences in discussion (see Page 14, line 259-264) and conclusion section (see Page 17, line 309-311).

Comment 2: The next problem I felt this time was that, as you mentioned in the Discussion, the race of the papers selected may have a significant impact.
Almost all of the studies used are Japanese, and the only different paper by Byeon et al seems to be from Korea, so I think this is a meta-analysis of East Asia.
If the readership of this journal were exclusively from East Asia, the current level of explanation might be sufficient, but if we take into account the fact that there are readers from other regions with different racial backgrounds, it is not clear how the meta-analysis of East Asia would be able to explain the results.
Japanese and East Asians are more hypersensitive to pulmonary toxicity to immune checkpoint inhibitors due to I felt that a little supplement might be necessary to add that this might be reflected in the present results.

Reply 2: We thank you for the great suggestion. As a result of systematic review, we could not gain the data of ICIP in non-Asians with pre-existing ILD. Therefore, we cannot discuss risks and benefits of ICIP in such population. As you pointed, in terms of the absence of studies in patients except for Asians, Asians may be more likely to develop ICIP compared to patients in other countries (JTO 2018;13(12):1930-1939). We added this fact to limitation section with the article (see Page 16, line 296-297).

Changes in the text: We revised and added a part of limitation section (see Page 16, line 296-297) and added an article to reference section (see Page 25, line 465-467).