Peer Review File

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Reviewer A

The present study, conducted by Sato et al, evaluated efficacies of systematic chemotherapy that was subsequent to immune-related interstitial lung disease. they found longer overall survival (OS) in patients with chemotherapy group compared with those without. Among patients with chemotherapy group, ILDs were recurred upto half of patients. Patients with recureent ILD showed shorter OS than those without ILD recurrence.

Although your article addresses an interesting topic in the area of lung cancer treatments, there were sever flaws in this manuscript.

Major

1. The small number of subjects without validation cohort precluded to make any conclusion.

Reply 1: We agree with the reviewer's comment. Limitation of this study was stated in the "Discussion" section, as the relatively small number of patients with ILD; however, similar findings have been reported from other studies. Previous studies have demonstrated the effectiveness of subsequent systemic cancer therapy for patients with chemotherapy-induced ILD and EGFR-TKI-induced ILD (ref. 22 and 23). The current study also demonstrated that OS in patients receiving systemic cancer therapy tended to be longer than in those without systemic cancer treatment (Fig. 2). There is an unmet need in the systemic cancer therapy for patients with ICI-related ILD, and we believe the current study includes useful information for readers of TLCR.

2. This study seemed to be biased from a problem called "immortal time bias", i.e. in the non-chemotherapy group every death counts from day one whereas in the chemotherapy group the patients have to survive quite a time before they can be included in the respective group. This favours the chemotherapy group. This Problem

is discussed in this manuscript (https://www.bmj.com/content/340/bmj.b5087). The "immortal time bias" severely affects the conclusion which can be drawn from your results, thus I decided that the manuscript has to be rejected.

Reply 2: We agree with the reviewer's comment. To minimize immortal time bias, we performed landmark analysis including only patients who were alive or whose ICI-related ILD was under control at 6 weeks after the onset of initial ICI-related ILD (n = 30, supplementary figure 1). Median OS in patients receiving subsequent cancer therapy was tended to be longer than that in patients who did not receive subsequent cancer therapy (22.0 months (95% CI: 7.3-NE) versus 5.5 months (95% CI: 2.2-NE); p = 0.165). We have created a new supplemental figure 1 to provide this additional information and have revised the second paragraph on page 8, lines 15-18 and the second paragraph on page 9, lines 18-22.

3. Related above, there should be several reasons that non-chemotherapy group did not received subsequent systematic chemotherapy; eg PS, lower spirometry, require high dose prednisolone, and rapid progression of their disease, and uncontrolled metastasis.

Reply 3: Because of the retrospective nature of the study, there were differences in the background of patients; however, there were no statistically significant differences in PS, systemic steroid use, grade of initial ILD and disease stage between the subsequent systemic cancer therapy group and the no subsequent cancer therapy group (Table 2).

4. As authors indicated in the Introduction: "previous studies have indicated that patients who discontinue ICIs due to irAEs have a worse prognosis than those who continue." This study enrolled several patients who continued ICIs despite of ir-ILD. These patients showed shorter survivals (Fig5)

Reply 4: In the current study, 5 out of 32 patients who had developed ICI-related ILD were rechallenged with ICIs. Similar to a previous report, 2 out of these 5 patients had long-term therapeutic effects (Fig. 5). Because high recurrence rate of ILD was observed in subsequent cancer therapy group, further study is warranted to elucidate biomarkers for recurrence of ILD. We have discussed these findings in the first paragraph on page 13, line 1-23. We cited reference 8 incorrectly and have corrected it.

5. The authors concluded safety and tolerability of systematic chemotherapy subsequent to ir-ILD. However, ir-ILD relapsed up-to 50% of the patients, though the severity were less than before. As the small number of the subjects, it was difficult to conclude or discuss with this topic in this manuscript.

Reply 5: In the "Abstract" and "Conclusion" section, we stated that safety of subsequent systemic treatment is uncertain because of the high risk of ILD recurrence and poor survival outcome following ILD recurrence. Please see the Abstract and the third paragraph on page 14, lines 21-23.

Reviewer B

This paper is a retrospective study on subsequent systemic therapy for non-small cell lung cancer patients with immune checkpoint inhibitor-related interstitial lung disease. This subject is a very important subject in clinical practice. I would like to praise the great efforts of the authors for the present study. But in my opinion, a substantial revision is needed to make this manuscript suitable for publication.

1. There is a question as to whether the relapse of ILD is due to the natural history of ICI related interstitial lung disease or due to subsequent treatment. To clarify this point, I suggest that you consider cases that have not been treated after ILD. In order to examine the prognosis, I think there is a reason for patients sufferd by ILD has not received subsequent treatment. Could you please clarify this point?

Reply 1: In the current study, 16 patients did not receive subsequent systemic cancer therapy after the onset of ICI-related ILD. In this no subsequent cancer therapy group, all but one patient recovered from ILD and no patients experienced recurrence of ILD. Therefore, we considered that systemic cancer therapy following ICI-related ILD caused the recurrence of ILD in 8 out of 16 patients (Table 2).

Patients did not receive subsequent systemic therapy for a variety of reasons. Thirteen patients did not receive subsequent systemic therapy at a physician's discretion, one patient for deterioration of PS, one patient did not recover from ILD and one patient had complete remission of lung cancer.

To make this clear, we revised the first paragraph on page 13, lines 7-15.

2. On page 8, "Two patients in the ILD recurrence group who were rechallenged with

ICIs had long-term therapeutic effects even after ICI discontinuation." Regarding this description, one case is true, but the other does not. Please reconsider the expression.
Reply 2: We agree with the reviewer's advice. Therapeutic effects of 2 patients were sustained at the data cutoff even after ICI discontinuation and PFS of these patients were 17 and 7 months, respectively. We have revised the third paragraph on page 11, lines 8-11.

Reviewer C

How best to approach the treatment of lung cancer in the setting of patients that develop drug-induced lung disease remains an unclear area. The authors report on the outcomes of patients with drug-induced lung disease who were rechallenged with lung cancer treatment vs those who were not. This is overall an important area. I think the article could be improved in the following ways:

1. While the term ILD is overall correct, would favor the use of drug-induced lung disease or something similar to make clear to the readers that these are patients with out a history of ILD prior to lung cancer treatment. Along those lines please comment if any of these patients had a history of prior ILD or CT findings c/w interstitial lung abnormalities as such may affect the risk of developing pneumonitis.
Reply 1: We agree with the reviewer's comment. We changed ILD to ICI-related ILD or drug-induced ILD.
Three out of 16 patients in subsequent cancer therapy group and none of 16 patients in no subsequent cancer therapy group had interstitial lung abnormalities before initial ICI treatment. In these 3 patients, 2 had the recurrence of ICI-related ILD after the subsequent cancer therapy. Interstitial lung abnormalities might be the risk of the recurrence of ICI-related ILD after subsequent cancer therapy. We included additional data in Table 1 and have revised the second paragraph on page 14, lines 8-12 to include this possibility.

2. The last two sentences of the background section of the abstract need to be clarified. "Few treatment options" - does this mean cancer treatment options? I assume so but this should be specified as could be interpreted as ILD treatment options. I think evaluating "safety and efficacy" are difficult to do in the limitations of a retrospective study - perhaps better would be evaluate differences in OS in patients who were re-challanged with cancer treatment.
Reply 2: According to reviewer's comment, we changed "few treatment options" to "few cancer treatment options".

We agree with the reviewer's advice. Indeed, we evaluated differences in OS between patients with and without systemic cancer therapy after the onset of ICI-related ILD and found that the median OS tended to be longer in the systemic cancer therapy group than in the no systemic cancer therapy group (Fig. 2). As mentioned in the discussion section, subsequent systemic cancer therapy seemed to be effective for patients with ICI-related ILD; however, its safety is uncertain because 8 out of 16 patients had recurrence of ICI-related ILD in the subsequent treatment group.

3. The term "systemic treatment" is slightly confusing - the authors should clarify that this term refers to cancer treatment and not ILD treatment

Reply 3: We agree with the reviewer's comment. We changed "systemic treatment" to "systemic cancer therapy" or "systemic cancer treatment.

4. In the last sentence of the results section of the abstract, would lead with the duration of survival for the recurrent ILD group (again as per above would favor a different terms like recurrent pneumonitis)

Reply 4: Thank you for your valuable advice. We changed "recurrent ILD" to "recurrent ICI-related ILD".

5. More information is needed as to how a diagnosis of ILD (or as per above drug induced lung disease) was determined

Reply 5: ICI-related ILD was diagnosed by the attending physician at each institution, and chest CT scans were reviewed by two independent respiratory physicians and one radiologist. As mentioned above, 3 out of 16 patients in subsequent cancer therapy group and none of 16 patients in no subsequent cancer therapy group had ILA before initial ICI treatment. Because of the difficulty to distinguish between exacerbation of ILA and ICI-related ILD, regardless of whether patients had ILA at baseline, we diagnosed ICI-related ILD if patients had pneumonitis after the initiation of anti-PD-1 therapy.

We have revised the first paragraph on page 8, lines 1-8 to include how we diagnosed ICI-related ILD.

6. Why were some patients re-challenged with cancer treatment and not other? The bias here would be helpful to address as a confounder

Reply 6: We agree with the reviewer's comment. We have investigated the reasons why patients did not receive subsequent systemic cancer therapy and we found there was a variety of reasons. Thirteen patients did not receive subsequent systemic therapy at a

physician's discretion, one patient for deterioration of PS, one patient did not recover from ILD and one patient had complete remission of lung cancer. We added the reasons why patients with ICI-related ILD did not receive subsequent systemic cancer therapy and mentioned these reasons might affect the prognosis of patients with ICI-related ILD on page 13, lines 11-15.

7. In the first section of the results, it says "of these patients, 16 (7%) received systemic therapy" - this should be clarified as it appears to be in reference to the 32 patients that developed pneumonitis and if this is the case it would be 50%

Reply 7: Thank you for the valuable advice. According to the reviewer's comment, we changed 7% to 50%.

8. While it is noted that no patients died of ILD, further detail as to respiratory-related morbidity would be helpful

Reply 8 We agree with the reviewer's comment. We have revised the first paragraph on page 10, lines 7-11 to add more details about the relapsed ICI-related ILD.

9. The sentence after the reference to table 3 in the results is incomplete

Reply 9: Did the reviewer mention "Tumor responses to systemic cancer therapy and radiographic patterns of ILD recurrence"? This is the heading and we apologize to confuse the reviewer. We have changed the heading to make it simple.

10. Would consider expanding the discussion to include how ILD in general may be a risk factor for poor cancer outcomes

Reply 10: We are thankful for the reviewer's valuable advice. We have revised the second paragraph on page 11, lines 14-19.

Reviewer D

The authors present data on 32 patients who developed ILD after treatment with PD1 inhibitors, and were either retreated after the onset of ILD (n=16) or did not receive further treatment after onset of ILD (n=16).

However, it remains unclear why patients in one group were exposed to further treatment, while the other group was not treated further. There might be an unknown bias here, which makes interpretation of survival data problematic. For example, initial response to PD1 inhibitor might have played a role in the decision-making

regarding re-treatment, the authors do not present data to this regard. However, breaking down survival data in each group with regards to initial response (or any other aspect that may have played a role in deciding on further treatment), would reduce the already low number of patients to the level of case reports. Altogether, the low number of cases leads to a questionable relevance of the data presented. Therefore, the manuscript is not recommended for publication in TLCR.

Reply 1: We apologize for the lack of the information about initial response to PD-1 inhibitors. There were no differences in initial response to anti-PD-1 treatment between two groups. Also, we could not find any significant differences in terms of age, sex, smoking status, ECOG-PS, disease stage, histology, line of anti-PD-1 therapy, PD-L1 expression, type of anti-PD-1 therapy, baseline interstitial lung abnormality, grade of the initial episode of ICI-related ILD, or radiological features. As mentioned in discussion section, limitation of this study was the relatively small number of patients with ILD. Previous studies have demonstrated similar findings as the effectiveness of subsequent systemic cancer therapy for patients with chemotherapy-induced ILD and EGFR-TKI-induced ILD (ref. 22 and 23). Along the same lines, the current study showed that subsequent systemic cancer therapy might be effective in patients with ICI-related ILD. We added initial response to anti-PD-1 treatment to Table 1 and have revised the first paragraph on page 9, lines 8-12.

Reviewer E

The author analyzed the subsequent therapy of patients with ICI-related ILD. Post-treatment for patients with chemotherapy-related ILD is clinically very difficult to determine, and this study may contribute to the choice of treatment strategy.
I would like to request additions and corrections regarding the following points.

1. It will be helpful to the reader to provide data that suggests which patients with ICI-related ILD should be treated with subsequent therapy.
Describe whether there is a difference in patient background between patients with and without Recurrent ILD. In particular, are there any differences in the grade of initial ILD, radiologic futures, and steroid doses?

Reply 1: Thank you for the reviewer's valuable comment. We could not find any significant differences in background between patient with and without the recurrent of ICI-related ILD (supplementary Table 1). In general, patients with ILD and ILA have a higher risk of drug-induced ILD. Indeed, 2 out of 3 patients with ILA at baseline had recurrent ICI-related ILD. Patients with baseline ILA might have a higher risk of the recurrence of ICI-related ILD

and subsequent systemic cancer therapy should be avoided. According to the reviewer's comment, we have created a new supplementary Table 1 to provide this additional information. Also, we have revised the first paragraph on page 10, lines 2-4 and the first paragraph on page 14, lines 8-12 to discuss this possibility.

2. The author stated that the OS in patients with subsequent systemic therapy group was longer than patients without subsequent systemic therapy. It was also stated that there was no difference in patient background between the two groups.
However, there may be a bias in choosing whether or not subsequent treatment will be given.
Please explain whether there was differences in steroid dose, ILD outcome, and the after effect of respiratory failure between the two groups. I think it is better to explain as much as possible why subsequent systemic therapy was not given.
Reply 2: Thank you for the reviewer's valuable comment. We collected patient data to investigate the reasons why patients did not receive subsequent systemic cancer therapies after the onset of ICI-related ILD. We found a variety of reasons, such as physician's discretion, deterioration of PS, not recovering from ILD and complete remission of NSCLC. These reasons for not treating patients with ICI-related ILD might affect their prognosis. We have revised the first paragraph on page 13, lines 11-15 to discuss this possibility.