

Peer Review File

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Reviewer A

The Editorial Commentary "Dual PD-1/PD-L1 and CTLA-4 inhibition strategies: tailoring immunotherapy for metastatic NSCLC" provides an interesting reflection on the role of dual PD(L)-1/CTLA-4 inhibition in PD-L1-negative NSCLC. Undoubtedly, one of the most complex issues in the treatment of metastatic NSCLC is in PD-L1-negative patients, where neither immunotherapy nor chemoimmunotherapy has demonstrated a clear superiority over classical platinum-based chemotherapy. Therefore, the authors' article critically addresses this point of NSCLC treatment and their reflections I believe may be of great help to readers.

The article is well written and the language that does not require editing. The references are correct, and the tables are a great summary of the clinical trial results. However, on reading the article a number of changes are needed which would clarify certain points in the manuscript and also increase its quality in my view.

The changes I suggest are as follows:

- Title: acronyms should not be used in titles such as NSCLC.

Reply: We thank the reviewer for the careful review. As suggested, we have changed the title as "Dual PD-1/PD-L1 and CTLA-4 inhibition strategies: tailoring immunotherapy for metastatic Non-small cell lung cancer".

- Overall, the editorial is too long. I think there are certain parts that are easy to summarise which would be between lines 8-33 and 45-60. This would allow the article to read more smoothly.

Reply: We thank the reviewer for the careful review of the manuscript. There was a lot of repetition of the same context in the areas pointed out by Reviewer A. We have deleted and summarized some text in lines 8-33 and 45-60 (Deleted lines 19-21, 29-30, 45-53, and summarized lines 28, 35-36 of the CCO-24-20-peer-review version).

- Line 28: add the reference.

Reply: We appreciate the reviewer's suggestion. As suggested, we have added the article on the effect of ITx in patients with non-high PD-L1, particularly negative PD-L1, to the references (References 2-4).

- Lines 36-37: it would be very interesting, for example, to provide data from the KEYNOTE-407 clinical trial in which the analysis in PD-L1 negative shows no difference between chemotherapy and chemoimmunotherapy.

Reply: We appreciate the opportunity to clarify this point. We agree with the importance of the data from the KEYNOTE-407 clinical trial. In PD-L1 negative subgroup (<1%), it seems that the benefit of chemoimmunotherapy was not evident compared with PD-L1 high subgroup ($\geq 50\%$) and PD-L1 non-high subgroup (1-49%). However, the analysis in PD-L1 negative shows a difference in OS (HR: 0.61 [95% CI: 0.38-0.98]; median OS: 15.9 versus 10.2 months) and PFS (HR: 0.68 [95% CI: 0.47-0.98]; median PFS: 6.3 versus 5.3 months) between chemotherapy and chemoimmunotherapy. This does not mean that there is no difference between chemotherapy and chemoimmunotherapy in the PD-L1-negative subgroup of the KEYNOTE-407 clinical trial.

- NEPTUNE trial: the main problem with this clinical trial and the rest is that when analysing the results, dual inhibition is not compared with chemoimmunotherapy (especially in PD-L1 negative patients), so it would be useful to express this point at some part in the article.

Reply: We appreciate the reviewer's helpful suggestions. This problem reviewer A pointed out is the limitation of this clinical trial and all the previous clinical trials. Therefore, we have added the following text in the conclusion paragraph (lines 137-138) that dual ITx and chemoimmunotherapy were not directly compared, instead of in the limitation paragraph of this clinical trial. "In previous clinical trials, including Cheng et al.'s study, dual ITx is not directly compared with chemoimmunotherapy regardless of PD-L1 expression."

- Conclusions: should be clearer, stating that currently dual inhibition does not represent a real clinical option in the treatment of metastatic NSCLC PD-L1 negative.

Reply: We thank the reviewer for the insightful comment. As requested, we have added the following text to the conclusion paragraph (lines 138-139). “At present, dual ITx does not exclusively represent a clinical option in the treatment of PD-L1-negative metastatic NSCLC.”

- Table 2: indicate the HR confidence intervals.

Reply: We appreciate the reviewer’s suggestion. As suggested, we have added the article the HR confidence intervals to Table 2.

In summary, if the authors make the right changes, I consider this to be a subsidiary article for publication in the journal in my view.

Reviewer B

In my opinion the Comment on: Cheng Y that was made by the authors are impressive and important, I was really pleased to read it.

I have no comments

Reply: We thank the reviewer for the positive comment.