# Peer Review File

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**Reviewer A**

I congratulate the authors for selecting a hot topic in early stage NSCLC. The manuscript appears as a sequence of part of the trials published or presented without a comprehensive and critical perspective on the different methodologies and the consequent potential criticisms for tomorrow's practice. I would therefore recommend the authors to revise the manuscript including all phase III presented and soon upcoming trials with a critical view and perspective on their heterogeneity and the clinical consequences of the available results.

Reply: Thank you for the valuable feedback. We agree these are very important points, and we have tried to briefly highlight these issues in our manuscript. Phase III trials evaluating perioperative immunotherapy are listed in Table 1. Salient features including the treatment schema and primary endpoints are included in the Table. Notable aspects of these trials such as the clinical benefit in relation to stage, histology and PD-L1 expression, where available, are included in the text on pages 4-6. We fully agree with the reviewer about providing a critical view of these results and have tried to highlight the clinical consequences of available data (lines 111-112) and issues that need to be addressed to further improve clinical outcomes, such as optimal management of adverse events to permit surgery as planned, development of biomarkers of response and toxicity for patient selection, use of combinatorial strategies to improve clinical outcomes, strategies to improve assessment of response such as the use of circulating tumor DNA, and optimization of study design to evaluate the relative benefits of pre- and post-operative therapy (lines 113-147).

Changes in the text: None.

**Reviewer B**

The text showed the findings of the main trials on perioperative immunotherapy.
It is a clean text with enough data for the reader to decide on the benefit of perioperative immunotherapy, with data posted so far.

Reply: We thank the reviewer for their kind feedback.

Changes in the text: None

**Reviewer C**

Thank you for submitting your work.
At line 50 you report that ICI may "eradicate micrometastasis" but I think it's not

completely correct. Indeed ICIs are known to be able to increase the survival of patients but it's not been yet clarified if it happens killing cells or helping the immunological systems. So you should modify the sense of that sentence.

Reply: Thank you for highlighting this important point. We have modified the sentence as described below and removed the phrase related to elimination of micrometastatic disease.

Changes in the text (Lines 40-42): Adding ICIs in the adjuvant setting can reverse the immunosuppressed environment associated with post-surgical stress, and potentially decrease the chances of disease recurrence by enhancing anti-tumor immunity, ultimately improving clinical outcomes as demonstrated in the IMpower-010 and KEYNOTE-091 trials.

You reportthe phenomen of the so-called "attrition to surgery" of 20% of patients submitted to neoadjuvant ICIs, but it's important to underly that another 20% of patients do not start/complete the adjuvant sistemic therapies foreseen. Also, this subgroup of pts are substantially undertreated so there may be at higher risk of relapse. So it's really important to better understand which may be the best selection of patients fit and able to sustain all the foreseen perioperative therapies

Reply: We completely agree with the reviewer's comment about patient selection and have highlighted the importance of developing biomarkers of response and toxicity (lines 123-136) to improve patient selection and maximize the chances of completing treatment as planned.

Changes in the text: None.

**Reviewer D**

The present Editorial Commentary, which focused on the Role of Immunotherapy in the Management of Resectable Non-Small Cell Lung Cancer. While this article is an interesting, it raises some suggestions.

1. It is recommended that you summarize the rate of discontinuation of surgery and delay in surgery by TRAE in each Phase III evaluating perioperative immunotherapy for potentially resectable NSCLC. (For example, consider listing it in one table).
2. Regarding as Table1, consider adding the ORR in the chemoimmunotherapy group.

Reply: The percentage of participants undergoing planned surgery (rather than the rate of discontinuation of surgery) is reported for all trials included in Table 1 and has been added as suggested. ORR prior to surgery was reported for only one of four trials listed in Table 1 and has been added as recommended. Additionally, the rate of major pathological response has been added to Table 1.

Changes in the text: Please see Table 1.

**Editorial Comments**

It is a great pleasure to read such a well-organized and written editorial commentary. The authors present several clinical trials on a timeline to give the reader a comprehensive understanding of the role of immune checkpoint inhibitors in the neoadjuvant, adjuvant, and perioperative settings for patients with non-small cell lung cancer. Last but not least, the authors objectively analyze the existing problems and give the referable solutions and directions for future research. We do believe this editorial commentary will be more enlightening to readers and colleagues. Many thanks to the authors' efforts. To further refine this commentary, below please see some minor suggestions.

1. "An exploratory analysis suggested that". Considering that readers may be confused by this statement without having read the Wakelee et al article, we suggest the authors specify that this is "an exploratory analysis of event-free survival according to major pathological response and pathological complete response".

Reply: Thank you for the suggestion. The sentence has been modified as suggested and reference to OS has been removed to improve clarity.

Changes in the text (Lines 83-85): An exploratory analysis showed an EFS benefit in the chemoimmunotherapy arm regardless of the degree of pathologic response.

2. "Treatment was associated with a manageable safety profile and 78% of participants in the chemoimmunotherapy arm completed surgery as planned". It should be "77.6%".

Reply: The figure has been corrected as suggested.

Changes in the text (Lines 106-108): Treatment was associated with a manageable safety profile and 77.6% of participants in the chemoimmunotherapy arm completed surgery as planned.

3.Please kindly confirm the originality of the Table 1. Permission is needed if they are reproduced or modified from a previously published paper.

Reply: Table 1 is original and not derived from a previously published paper. We have made changes to Table 1 in response to input from Reviewer D.

Changes in the text: Please refer to Table 1.

4. Conflict of Interest (COI) Form must be provided, as suggested by ICMJE: (http://www.icmje.org/conflicts-of-interest/). Each author should submit a separate

form and is responsible for the accuracy and completeness of the submitted information. COI form download link: https://cdn.amegroups.cn/static/public/coi_disclosure.docx.
Reply: COI forms are included with the submission.

Changes in the text: None.

Additional Changes:

1. Addition of results from the CheckMate 77T trial to the text (lines 95-102), which have been presented recently in abstract form.
2. Reference 18 has been added to cite the CheckMate 77T abstract.
3. Reference 19 (AEGEAN trial) has been updated since the abstract had been cited previously, but the full paper has since been published.
4. Minor grammatical corrections have been made throughout the manuscript.