Peer Review File

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Reviewer A:

The paper titled “ESMO guidelines for oncogene-addicted metastatic NSCLC. A personalized treatment for each patient is it now a reality?” is interesting. The oncogene addicted NSCLC ESMO guidelines present updated information regarding the latest breakthrough drugs for each molecular entity, and good algorithms to individually optimize the treatment for each patient, including special populations. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) In oncogene-addicted NSCLC (with the exception of KRAS-mutated), ICIs are usually administered at the failure of other treatment options, but administering single-agent immunotherapy in later disease phases may limit its efficacy. How to view this issue?

2) Please discuses molecular diagnostic assessment, potential biomarkers and radiological methods for response evaluation of ICI treatment.

3) More clinical trials on combination therapies and biomarkers for ICI therapy based on the specific differing characteristics of oncogene-addicted NSCLC need to be conducted.

4) What are the effects of oncogenic driver mutations on the efficacy of ICIs and the immune tumour microenvironment? It is recommended to add relevant content.

5) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Immunotherapy in oncogene addicted non-small cell lung cancer, Transl Lung Cancer Res, PMID: 34295674”. It is recommended to quote the article.

6) What is the efficacy and safety of first-line checkpoint inhibitors-based treatments for oncogene-addicted NSCLC? It is recommended to add relevant content.

Responses to Reviewer A

Comment 1: In oncogene-addicted NSCLC (with the exception of KRAS-mutated), ICIs are usually administered at the failure of other treatment options, but administering single-agent immunotherapy in later disease phases may limit its efficacy. How to view this issue?

Reply 1: Thank you very much for your comments and your time. Due to the word and citation limitations of the “Editorial Comment”, we only briefly assessed each topic. Since the article “Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023 Apr;34(4):339-357. doi: 10.1016/j.annonc.2022.12.009” has such a wide scope it is difficult to have a complete coverage of everything around ICIs in this population. We included the most important (and up-to-date data) by mentioning the recent results of the phase III trials

which discard the use of ICIs in the EGFR population, which is the one that has been more thoroughly explored, and a brief mention about the controversy in the rest of the mutations (lines 77-93 of the first-submitted version). The ALK data is scarce, and the rest of the mutations have almost non-existent data (as it is mentioned in the suggested article of point 5 "Immunotherapy in oncogene addicted non-small cell lung cancer, Transl Lung Cancer Res, PMID: 34295674". However, in order to increase the quality of the paper regarding this point, the section of lines 77-93 has been expanded with further explanation of other scenarios.
Changes in the text: Lines 110-112 on page 3 have been rewritten and expanded to 99-110 as advised.

Comment 2: Please discuses molecular diagnostic assessment, potential biomarkers and radiological methods for response evaluation of ICI treatment.
Reply 2: Due to the word and citation limitations, we only centered around citing the main studies which have implemented the different target therapy strategies on each mutation. If available, we would have doubled the number of references and citations. We have expanded the information regarding ICIs, and even briefly mention in the introduction more data regarding why ICIs data is controversial in this population. We think that the inclusion of more information (such as more biomarkers or radiological assessments such an iRECIST) is out of the scope of the editorial commentary since ICIs are not standardized in these patients, and in order to fit it into the word count we would have to eliminate information regarding other hot topics such as special populations or the evolution of NGS testing and could be a paper by itself (a paper centered around ICIs and oncogene-addicted NSCLC). We may explore this option in the future due to the need of updating this situation with the recent trial developments.
Changes in the text: Lines 22-26 in page 1 have been added to increase scope in the topic.

Comment 3: More clinical trials on combination therapies and biomarkers for ICI therapy based on the specific differing characteristics of oncogene-addicted NSCLC need to be conducted.
Reply 3: We have included in the text mention to this topic.
Changes in the text: Lines 108-110.

Comment 4: What are the effects of oncogenic driver mutations on the efficacy of ICIs and the immune tumor microenvironment? It is recommended to add relevant content.
Reply 4: We have included a brief mention of changes in the tumor microenvironment, but it is out of the scope of the editorial commentary to add further information since we are commenting on a specific text (Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023 Apr;34(4):339-357. doi: 10.1016/j.annonc.2022.12.009) and all the topics mentioned in it need to be briefly discussed. We have expanded as much as we could the controversy regarding the use of ICIs, and since

ICIs are not considered a standard in this population, we do not want to reduce information in other topics to more broadly assess ICIs.
Changes in the text: Lines 24-26 have been added to briefly increase the relevant content of this comment.

Comment 5: The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Immunotherapy in oncogene addicted non-small cell lung cancer, Transl Lung Cancer Res, PMID: 34295674”. It is recommended to quote the article.
Reply 5: We have cited 2 additional articles to increase the reference to ICIs topics in the introduction and in the paper discussion. Other reviewer has suggested to increase the scope of the introduction (not only regarding ICIs, but also general molecular characterization topics), which is in line with this comment, so we have expanded it by citing other topics.
Changes in the text: Lines 22-30 have been added to improve the introduction of the paper.

Comment 6: What is the efficacy and safety of first-line checkpoint inhibitors-based treatments for oncogene-addicted NSCLC? It is recommended to add relevant content.
Reply 6: It is out of the scope of this paper to include thoroughly first-line data in ICI based treatments for this populations, since barring particular cases such as KRAS, it is not a standard of care. We barely had space in the 2500 words to include a mention about the main targeted therapies and their approbatory trials, so including more ICI data would require for us to eliminate information regarding targeted therapies, which is the focus of this paper. Nevertheless, comments regarding some of the most important trials which combine ICI with other therapies (such as IMPOWER150 or KEYNOTE-789) were added and can be find throughout the article (for instance, lines 89-92)
Changes in the text: No main changes have been done. In the addition done in lines 99-101 due to other commentaries the topic has been briefly expanded.

Reviewer B:

This is a clinically relevant commentary article on ESMO guidelines for oncogene-addicted metastatic NSCLC. The paper is well-written and comments are up-to-date and have deep clinical insights. I suggest the authors to have a brief review on the clinical and molecular heterogeneity of NSCLC in the main text. The authors also need to analyze the limitations and knowledge gaps in prior studies in detail and suggest possible solutions in the final paragraphs of this paper.

Responses to Reviewer B

Comment 1: I suggest the authors to have a brief review on the clinical and molecular heterogeneity of NSCLC in the main text.
Reply 1: Thank you for your commentaries and your time. Regarding this point, we would have liked to expand the commentary with further topics, but it is very difficult to select the topics with a word limitation of 250. We did some brief annotations of this heterogenicity, but it is true that they may be insufficient. We have expanded in the introduction the commentary about the heterogenicity, with some clinical characteristics, but we cannot expand further since the limit would be overpassed.
Changes in the text: Added lines 26-30 in page 1 to add information of the suggested topics.

Comment 2: The authors also need to analyze the limitations and knowledge gaps in prior studies in detail and suggest possible solutions in the final paragraphs of this paper.
Reply 2: We have assessed different problematics on each mutation, but due to the 2500 word limit we could not assess every problematic. We have assessed the NGS vs single test problematic (lines 47-70), EGFR treatment beyond first line problematic (83-98). We have added (in line with comments from other reviewers) more insight into ICI controversies in this populations (lines 99-112), the controversies in CNS management in ALK patients (lines 124-132), controversies in special populations (178-191) … Regarding the suggestion of solutions to the problems, we have added some lines in the paper with suggestions of the next steps that should be explored in the future.
Changes in the text: Added lines 99-110 in page 3 regarding the ICI problematic/knowledge gaps, and lines 195-202 to suggest future investigational approaches.