Peer Review File

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Reviewer A:

Reviewer A Comments: *This is a well written and comprehensive review of use of ICI in lung cancer we have some suggestions*

Reply: We are pleased that the reviewer found our manuscript well written and comprehensive. We are also very grateful for their insightful comments/suggestions which we think have made this review much stronger. We have addressed/included all suggestions in our revised manuscript. Please see a point by point response to each comment below.

1) ***Reviewer A Comment:*** *Unfortunately, science moves fast nowadays, when the authors wrote the review, the standard of care for adjuvant therapy for NSCLC was only chemotherapy, now with the data from ADAURA the bar is higher for CPI entering the neo or adjuvant arena because we know that they can to show benefit on top of TKI for EGFR mutant patients, maybe a paragraph acknowledging that will help to have a complete review.*

   Reply 1: We agree with the reviewer that the field is moving rapidly, and it is important to acknowledge that the bar has been elevated following the data from ADAURA. A paragraph was added in the "Neoadjuvant immunotherapy for operable non-small cell lung cancer" section to acknowledge the added benefit of adjuvant targeted therapy. Changes are tracked directly in the revised manuscript (Pages 8 and 9).

2) ***Reviewer A Comment:*** *Also the topic is NEO adjuvant Immuno, I understand that we have to have a good introduction but to have several pages reviewing stage III and stage IV first and second line data in NSCLC lung cancer only to say that thanks to that there should be a role for CPI in neoadjuvant arena maybe too much, the readers will get tired reading a review of CPI instead to going to the point of what is offered Neoadjuvant immunotherapy.*

   Reply 2: We thank the reviewer for this insightful comment and agree we can be more succinct. The section entitled "*Immunotherapy for locally advanced and metastatic non-small cell lung cancer*" has been significantly shortened to provide a concise introduction to the relevance of neoadjuvant

immunotherapy. Changes are tracked directly in the revised manuscript (Pages 5 and 6).

3) ***Reviewer A Comment:*** *When the authors present, Forde, NADIM, NEOSTAR they should be more balanced, looks like they are a "home run" and that is not the truth , later they discussed some weaknesses of these trials, but when they comment the trial they should not omit in each of that the side effects, the DEATHS (controversial some of them apparently NOT related with CPI but who knows???) and weaknesses of this small studies.*

   Reply 3: We agree with the reviewer that these are all important details to include. Accordingly we have now included more details regarding adverse events, deaths and study weaknesses for all of the following studies:
   - Forde et al: Changes tracked directly in the revised manuscript (Page 9)
   - NEOSTAR: Changes tracked directly in the revised manuscript (Page 10)
   - LCMC3: Changes tracked directly in the revised manuscript (Page 11)
   - NADIM: Changes tracked directly in the revised manuscript (Page 11)

Reviewer B:

Reviewer B Comments: *I congratulate the authors for their review of neoadjuvant immunotherapy in NSCLC. It is very comprehensive and well written. My comments below:*

Reply: We thank this reviewer for their enthusiasm and support for our manuscript. We have included/addressed all suggestions in a revised manuscript and believe that these thoughtful suggestions have made the manuscript much stronger. Please see a point by point response to each reviewer comment below

1) ***Reviewer B Comment:*** *Regarding biomarkers, this comment by the authors starting on line 487:*
   "Although the Forde et al study did not show a strong correlation between PD-L1 status and MPR, it did reveal a higher TMB with tumors achieving MPR compared to those who did not (80). Two other recent studies with atezolizumab also validate this concept, supporting TMB assessment as an appropriate measure of response to immunotherapy (147, 148)."

   - TMB is not currently considered an appropriate measure of response to immunotherapy. Please remove or rephrase.

Reply 1: We agree with this insightful comment. This statement was removed for clarity: *"Two other recent studies with atezolizumab also validate this concept, supporting TMB assessment as an appropriate measure of response to immunotherapy."* Changes are tracked directly in the revised manuscript (Page 21, Line 646).

2) ***Reviewer B Comment:*** *Regarding safety of ICI, starting on line 499:*
"Immune checkpoint inhibitors increase the system's natural tumor killing response, which can lead to immune-related adverse events involving many organs such as the lung, the intestines, the skin and the endocrine system (150, 151). These side effects are usually benign or treatable, but can rarely lead to serious or life-threatening events, prompting rapid recognition and initiation of treatment by specialists in the field (152)"

- This paragraph is VERY important. Since we are discussing patients who have a better prognosis and survival than currently approved indications for ICIs (in the metastatic setting), long lasting adverse events such as hypothyroidism, adrenal insufficiency, some cases of colitis, etc. are to be considered when evaluating the cost/benefit of this approach. I suggest the authors expand on the safety aspect of these agents and its importance in the neoadjuvant setting.

Reply 2: We agree with the reviewer and we appreciate this important suggestion. Further details regarding adverse events related to ICI has been added to this paragraph. Changes are tracked directly in the revised manuscript (Page 22).