Peer Review File

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Reviewer A

The authors present and review potential steps forward in improved neoadjuvant immune-based treatment in curable NSCLC. It is very well written and insightful.

Reply: We thank Reviewer A for their positive comments.

My only comment and suggestion are very minor. Line 34 states NADIM II (published NEJM 2023; ref. 8) led to the phase III CM 816 (published NEJM 2022). It should refer to and reference the phase II non-randomized trial NADIM (Provencio et al Lancet Oncology 2020 or Provencio et al JCO 2022).

Reply: We thank the reviewer for catching the oversight.
Changes in the text: We now reference the 2020 study from Lancet Oncology as well as a 2018 study from Forde et al.

Reviewer B

In complex, this is a well-organized and written commentary. Here below some minor suggestions

Reply: We thank Reviewer B for the positive comments.

I agree in defining immunotherapy a "pillar", but targeted therapies should be mentioned as well.

Reply: We agree that targeted therapy is a pillar of cancer therapy.
Changes in the text: We have revised our opening sentence to include targeted therapy as a pillar of cancer therapy.

"...including lung, breast, colon, and urothelial cancers." This list is too short, and not in all the cases of the mentioned malignancies there is a PD-L1 overexpression. I suggest to remove this list of examples.

Reply: We agree with the reviewer.
Changes in the text: We have removed the list of examples.

The dichotomy PD-L1 on tumor cells and PD-1 on immune cells is useful in terms of simplification, but we know that both molecules can be expressed by a variety of cell types.

Reply: We agree with the reviewer that PD-1 and PD-L1 expression patterns are complex. Meticulously reviewing the biology of the PD-1 axis is outside the scope of this commentary, especially since the NeoCOAST trial focused on incorporating other immunomodulatory agents.
Changes in the text: We added the word “primarily” when describing PD-L1 expression patterns.

"...one-third of patients to achieve long-term survival" this estimation is too optimistic, especially as the authors use a reference of nivolumab in the second-line setting.

Reply: We agree that this assessment was overly optimistic and not supported by the citation.
Changes in the text: We have revised our statement and now cite 5-year outcomes from KEYNOTE-189 (Garassino et al. JCO 2023).

"neoadjuvant nivolumab neoadjuvant" please correct

Reply: We regret this typo.
Changes in the text: A duplicate “neoadjuvant” was removed.

Changes in the text:
"CD73 is a cell surface molecule that has been shown to increase regulatory T and NK cells" how can a cell surface molecule increase cells? Does it increase their number or their activity?

Reply: We agree that this comment lacked clarity.
Changes in the text: We have extensively revised this sentence to provide the presumed mechanism of CD73 blockade.

"...randomized to receive a single cycle (28 days) of durvalumab..." does this mean that patients receive only one injection of durvalumab with/without the investigational drugs?

Reply: The reviewer’s interpretation is correct.
Changes in the text: No changes were made to the main text of the manuscript. In our figure, the day 15 line was removed. The figure legend was updated to include the dosing regimen.

"Notably, pathological assessment of resection specimens demonstrated that combination immunotherapy with durvalumab and either oleclumab, monalizumab, or danvatirsen improved the rates of MPR as compared to durvalumab alone. Specifically, the rates of MPR were 11.1% (3/27 patients) in the durvalumab monotherapy arm, 19.0% (4/21 patients) in the durvalumab + oleclumab arm, 30.0% (6/20 patients) in the durvalumab + monalizumab arm, and 31.3% (5/16 patients) in the durvalumab + danvatirsen arm. While the combination immunotherapy arms improved MPR rates, our ability to draw definitive conclusions about clinical significance is limited by the trial’s small size and short-term follow-up"
I agree on this paragraph, I would just put the limitation of the small sample size at the beginning of the paragraph.

Reply: We agree that a major weakness of the NeoCOAST trial is the small sample size.
Changes in the text: We revised the sentence to acknowledge the limitiations earlier. did not

change the location of the trial's limitations as we felt it was important to first discuss the findings of the trial before commenting on its limitations.

"In the NeoCOAST trial, MPRs were more frequent in patients with PD-L1 > 1%..." please check if the right statement is PD-L1 > 1 or PD-L1 ≥ 1.

Reply: We thank the reviewer for his/her careful attention to detail. The statement should read PD-L1 ≥ 1.
Changes in the text: We updated the text accordingly.

Reviewer C

Overall, this is a well-written article. No major changes.
line 38 - remove duplicate "neoadjuvant" before nivolumab.

Reply: We regret this typo.
Changes in the text: A duplicate “neoadjuvant” was removed.

Reviewer D

The manuscript is well written and the figures are explicative as well.

Reply: We thank Reviewer D for the positive feedback.

Reviewer E

The authors reviewed novel immunotherapy combination treatments in the neoadjuvant setting. The manuscript is well written. Although there are several questions to be solved, such as “whether patients who achieved pCR with perioperative IO can omit adjuvant IO?”, this manuscript refers to existing evidence and future clinical trials.
One minor comment on Figure should be answered.

1. Regarding NeoCOAST-2, Neoadjuvant chemoimmunotherapy period includes 4 vertical lines. Though, it includes four cycles of treatment, it should be 5 lines or the date of the final line should be Day 64 (cycle 4 day 1) instead of Day 84.

Reply: We thank the reviewer for catching this error in our figure.
Changes in the figure: We added a fifth line to accurately denote each cycle of therapy.

Reviewer F

The authors provide a good perspective on novel immunotherapy combinations in neoadjuvant landscape for non-small cell lung cancer. I have the following suggestions for the authors:
Line 34: Forde et al. NEJM 2018 tested neoadjuvant nivolumab with improved outcomes leading to phase 3 Checkmate 816 clinical trial. Meanwhile, NADIM II was run in parallel with CheckMate 816 by the Spanish oncology group. So, I would include the Forde et al. publication crediting as precursor to CheckMate 816. Also note, NADIM II included adjuvant treatment with nivolumab for 6 months which was not included in the Checkmate 816 trial. I think this needs to be brought forth by the authors for the reader.

Reply: We thank the reviewer for identifying the lack of clarity in our writing and citations.
Changes in the text: In line 34, we now reference Forde et al. NEJM 2018 as well as Provencio et al. Lancet Oncology 2020.

Line 42: I would include additional adjuvant checkpoint inhibitor therapy duration for the reader

Reply: We thank the reviewer for this helpful suggestion.
Changes in the text: We added the duration of adjuvant therapy to the text.

Line 89: Please include last shot description of the COAST trial for the reader since this was in stage III unresectable setting

Reply: We agree it would be helpful to introduce the COAST trial.
Changes in the text: The text was revised to include a description of the COAST trial.

Line 121: The only randomized study comparing different treatment.'s of immmunochemotherapy in the neoadjuvant setting is the neoSCORE trial which demonstrated higher MPR rate for patients who received 3 cycles compared to 2 cycles neoadjuvantly. I would encourage the authors to include the study in the discussion on optimal number of treatment cycles for neoadjuvant strategy.

Reply: We agree that the neoSCORE trial should be discussed.
Changes in the text: The text was revised to include a discussion of neoSCORE trial results.