Peer Review File

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Comment to Reviewer A

We wish to express our appreciation to the Reviewer A for their insightful comments on our paper. We believe that the comments have helped us substantially improve our manuscript.

Comments 1:

The substance of the article is on the results of the NeoCOAST trial published in 2021. There are some merits in the content. And there are some good discussions on the author's insight into the results.

Nevertheless, I find the article not easy to read. In particular, there are long paragraphs of complex data and content that are lumped together. References are not always consistently identified for easy reference. For example, NeoCOAST trial was not clearly numbered in the manuscript, and the reader has to look at the list before finding the reference.

I would suggest the author to break down some of the mor chunky paragraphs into logical sections for smaller paragraphs, so as to organize the information better. Can also make sure important references are clearly numbered.

Reply 1:

We thank the Reviewer A for their valuable comment and apologize for the difficulty in reading our manuscript. As Reviewer A indicates, our manuscript may not be easy to read. As recommended by Reviewer A, we have added the NeoCOAST trial itself in the reference list and have provided the reference number (#20); consequently, the reference numbers after #20 were revised appropriately.

In addition, we separated some paragraphs into smaller paragraphs according to the discussion points. Moreover, we included references as much as appropriate, and if needed, described the trial names in addition to the reference numbers in the revised main text.

Change in the text 1:

1. We united the paragraph as described in Line 46–47 in the revised manuscript.
2. We divided the paragraph as described in Lines 53–54, 118–119, 124–125, and 143–144 in the revised manuscript.

3. We provided the reference number (#20) of the NeoCOAST trial, as written in Lines 55, 72, and 109 and added this article in the reference list (as described in Lines 240–242) in the revised manuscript. Consequently, previous reference numbers were revised appropriately as written in Lines 86, 163, 167, 245, 247, and 255.
4. We added the descriptions of the reference numbers to clarify which articles were referred to, as written in Lines 78–79, 105, 108, and 147 in the revised manuscript.
5. We added the trial name, as written in Lines 95, 126, 144, 159, and 172 in the revised manuscript to clarify which trial's findings were being discussed in that context.
6. We added a new, referenced article and numbered it #24, as written in Lines 138 and 249–251 in the revised manuscript.

Comment to Reviewer B

We wish to express our appreciation to the Reviewer B for their valuable comments on our paper.

Comments 1:

Congratulations to the authors for this well-done comment on the NeoCOAST study.

Most of the studies on neoadjuvant IO for resectable lung cancer employed mono-ICI with or without chemotherapy. The analysis of the safety profile and adverse events is an important business also for the surgeon, because in some cases severe TRAEs could stop the surgical treatment.

The tables provide an good overview on the main studies.

Congratulations to the authors.

No revisions are needed.

However, new IO are coming on the counter and an extensive analysis and clinical trials are required.

Reply 1:

We thank the Reviewer B for their valuable comments. We hope our manuscript contributes to future improvement of lung cancer treatment.

Change in the text 1:

Nothing.

Comment to Reviewer C

We wish to express our appreciation to the Reviewer C for their insightful comments on our paper. We believe that the comments have helped us substantially improve our manuscript.

Comments 1:

When referring to IO in advanced NSCLC, why mention the results from 6 ears ago, while the current standard of care of IO in 1st line stays unmentioned? Especially since the neoadjuvant approaches are based on these advanced stage experiences.

Reply 1:

We thank Reviewer C for their valuable comments. As Reviewer C indicates, IO is currently used as first line therapy and as the most important, key drug for patients with advanced NSCLC. We described the history of IO for advanced diseases to neoadjuvant settings. We did forget to mention the present standard of treatment for advanced disease. We added a new sentence to explain that IO is used in first line therapy as mono-therapy or in combination with chemotherapy.

Change in the text 1:

We added a new sentence:

"Currently, IO agents are used in first-line therapy as mono-therapy or in combination with cytotoxic chemotherapy and have become the most important, principal drug for the treatment of patients with advanced NSCLC." as described in Lines 40–42 of the revised manuscript.

Comments 2:

Line 46 "tremendous improvement in postoperative prognosis": there is no OS benefit mentioned in ref 7. What improvements are ment here?

Reply 2:

We apologize for the ambiguity. The 'prognosis' in this sentence meant 'disease-free survival'. To clarify this, we have revised the sentence.

Change in the text 2:

We have revised the sentence from "First, these agents were introduced as adjuvant treatments and they resulted in tremendous improvement in postoperative prognosis if patients had tumors with PD-1/PD-L1 expression (7)" to

"First, these agents were introduced as adjuvant treatments and they resulted in tremendous

improvement in postoperative disease-free survival if patients had tumors with PD-1/PD-L1 expression (7)," as described in Lines 48–50 of the revised manuscript.

Comments 3:

A long evaluation of NeoCOAST follows. Althought it is mentioned that MPR and cPR rates fall short, itis not mentioned that the durvalumab mono arm falls short of expected outcomes in general, which is an important issue when evaluating results between arms in this trial.

Reply 3:

We thank Reviewer C for their valuable comment. We have described the hypothesis of the expected outcomes, not only for the durvalumab mono arm, but also for the dual IO arm in this manuscript (Lines 80–94 in the revised manuscript), considering the peak time for immunity promotion by IO agents.

Change in the text 3:

Nothing.

Comments 4:

On one hand, the author states that dual IO is promising based on this phase 2 data of the NeoCOAST, but the standard of care is currently IO+chemo based on the CM-816. On- the other hand, the author states that dual IO+chemo may be too toxic (line 102-103 and 168-171). This seems to contradict each other, especially as is also mentioned that the NeoCOAST-2 will evaluate the dual IO+chemo.

Reply 4:

We thank the Reviewer C for their valuable comment and apologize for the ambiguity. In this paragraph, the context we had hoped to convey was that "the use of dual IO + chemotherapy for neoadjuvant setting should be carefully considered". Indeed, dual IO may be promising in terms of therapeutic efficacy, such as radiological and/or pathological response, but patients also risk missing the chance to undergo surgery due to severe AEs. Even the CM-816 regimen, mono IO + chemotherapy, carries the risk that patients will miss the chance to undergo surgery due to the severe AEs; dual IO + chemotherapy should have increased risk. To clarify these concerns, we have revised the last paragraph, as noted below.

Change in the text 4:

We revised the sentence from "Considering the results of the KEYNOTE-671 trial (22) and AEGEAN trial (23), the results of the NeoCOAST-2 trial are promising" to "Considering the results of the KEYNOTE-671 (22) and AEGEAN trials (23), the results of the NeoCOAST-2 trial may be promising in terms of pathological response," as described in Lines 162–164 in the revised manuscript.

We revised the sentence from "such dual-IO + cytotoxic agents as perioperative therapy can be expected to have better efficacy, but induce severe TRAEs, and consequently, patients will be incapable of surgery" to "As such, dual IO + cytotoxic chemotherapy as perioperative therapy can be expected to have better efficacy from the aspect of therapeutic response, but may induce severe TRAEs, and consequently, patients will be incapable of undergoing surgery," as described in Lines 172–175 of the revised manuscript.

Comments 5:

Also, what about the CM-816 arm of ipi/nivo which was prematurelay stopped?

Reply 5:

As Reviewer C indicates, the ipi/nivo arm in the CM816 trial was prematurely stopped. The data were immature and no data are shown in the article or Supplementary Appendix. Thus, we excluded the data concerning this arm from our manuscript.

Change in the text 5:

Nothing.