Peer Review File

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Reviewer A

Comment1:
"Regarding preoperative chemotherapy, many clinical trials were stopped prematurely because of the early establishment of postoperative chemotherapy" Reference is missing
Answer1:
Thanks for the suggestion, I have added the Reference (Ref No 3,4).

Comment2:
" Given the clinical disadvantages of preoperative treatment, it has actively been used in limited situations". Explain the "clinical disadvantages"
Answer2:
The reviewer's point is correct. The clinical disadvantages were not mentioned above, but were mentioned later. This sentence is confusing and has been removed.

Comment3:
The author says the addition of immunotherapy to neoadjuvant treatment might guarantee "cure" to a percentage of patients. I think it is a bit of an overinterpretation, since OS was not a primary endpoint of CM816. I would rather talk of increased pathological responses and their correlation with event free survival and prognosis. Moreover, the topic of the perioperative strategy should be better introduced: if a percentage of patients are "cured" (according to the author), why should patients need an adjuvant component?
Answer3:
Thanks for pointing this out. When we mentioned the expectation of "cure" by ICI, we were referring to stage IV lung cancer. However, as you point out, this may be an overstatement and is causing confusion, so I will remove it.
I agree with the reviewer's point. As I discuss below, the biggest question is whether there is any benefit in adding postoperative adjuvant ICI therapy for patients who have achieved pCR with preoperative treatment. Although additional analysis of this study or another new study is needed to entirely answer this question. An exploratory analysis of EFS by treatment showed that EFS in the group that achieved pCR was very good in both the CheckMate-816 and Keynote-671 trials, and there seemed to be no difference in the results between the two treatment strategies. This suggests that pCR cases may not require additional postoperative treatment.

Comment4:
"Losing the opportunity for surgery in patients with operable lung
60 cancer is the last thing that attending physicians want in clinical practice" and "EFS by treatment showed that EFS in the group that achieved
148 pCR was very good in both the CheckMate-816 and Keynote-671 trials" are too colloquial

Answer4:
Following the reviewer's suggestion that it was colloquial, we have rewritten the sentence.(see, line 58 to 59, line 143)

Comment5:
"OS data were immature; however, 24-month OS was observed in
80.9% of the patients in the pembrolizumab group and 77.6% in the placebo group (HR, 0.73; 95% CI: 0.54–0.99)". Immature but not significant
Answer5:
As the reviewer noted, I inserted "Immature but not significant." (see, line 77)

Comment6:
"Preoperative treatment in patients with advanced disease is more likely to
cause unresectability" reference missing
Answer6:
In accordance with the Reviewer's comment, I added Reference (Ref 10).

Comment7:
"EFS by treatment showed that EFS in the group that achieved pCR was very good in both the CheckMate-816 and Keynote-671 trials, and there seemed to be no difference in the results between the two treatment strategies.
Contrarily, in the patient population that did not achieve pCR, the hazard ratio of
chemotherapy and ICI to chemotherapy alone was 0.84 (95% CI: 0.61–1.17) in the
CheckMate-816 and 0.69 (95% CI: 0.55–0.85) in Keynote-671"
Please disclose the limitation of inter-trial comparison.
Answer7:
In accordance with the reviewer's suggestion, I noted that there are limitations since this is a comparison of different trials. (see, 142)

Comment8:
Here I would focus on the prognostic impact of the grade of pathological response. In the KN, for instance, patients who achieve complete pathological response have longer EFS (with or without pembro in the adjuvant setting) than patients who don't achieve it. Pembro seem to be more beneficial when complete pathological response is not achieved (clear separation of the curves).
Answer8:
I strongly agree with the reviewer's opinion. In the KN trial, patients who did not achieve a pCR seemed to have a longer EFS in the Pembro group than in the placebo group. I have inserted the following sentence to emphasize this: Of note, in the Keynote-671 trial, patients who did not achieve pCR with pembrolizumab had a longer EFS than those who received placebo. (see, line 147-149)

Comment9:
Discuss AEs in the adjuvant setting (supplementary, table S8) and their potential long-term

impact.

Answer9:

In accordance with the reviewer's suggestion, I have added the following sentence: Because perioperative ICI therapy is accompanied by postoperative ICI administration, attention should also be paid to trAEs during postoperative ICI administration. In the KN671 study, 10% of patients experienced grade 3 or higher trAEs during postoperative pembrolizumab administration. (see, line 174-177)

Comment10:

From line 121 to 128, too much focus on advanced disease.

Answer10:

I followed your advice and removed the following sentence: ICIs have been evaluated for their use in metastatic NSCLC, including as single agents, in combination with chemotherapy, and in combination with other ICIs.

Comment11:

Reference to AEGEAN and NEOTORCH is mandatory.

Answer11:

In accordance with the reviewer's suggestion, I added References (Ref No 15 and 16). The following sentence was newly added accordingly: Many trials targeting perioperative ICI and chemotherapy combination therapy in patients with clinical stage II or higher disease have been conducted. (see, line 182 to 184)

Reviewer B

Commen1:
The editorial by Dr Murakami presents an analysis of the pre and post-operative use of chemo/IO in resectable NSCLC.
The data available are well presented and put in context.
My major comment is that there could be more depth in the editorial. Why would a neo adjuvant approach be beter. Is it because of the abundance of neo-antigens or are other factors related to the effect. And is it relevant to have 4 courses of chemo/IO?
Answer1:
Thank you for pointing this out. I think it is a very important point. I rewrote it as follows: Regarding perioperative treatment, preoperative ICI could maximize the efficacy of immunotherapy when the primary tumor is still present and has a high neoantigen burden. The presence of the whole tumor enables a broad T cell response owing to exposure to a large repertoire of tumor antigens. This approach theoretically allows intact tumors, lymphatic vessels, and draining lymph nodes to successfully prime T cells, efficiently activate systemic tumor immunity, and control small distant metastases. ICIs can be used in combination with chemotherapy in neoadjuvant therapy to enhance neoantigen release and promote a more robust immune response. (see, 45-52). However, it is difficult to answer the question of whether four courses of chemotherapy is necessary, as you pointed out, and we have avoided discussing this question in this text. Although not based on scientific evidence, four courses of platinum-based chemotherapy is widely used in advanced lung cancer, and considering that no additional postoperative platinum-based chemotherapy is required, four courses is acceptable for preoperative treatment.

Comment2:
Minor remarks
line 33: add "only" 5%
Answer2:
As suggested, I added "only" (see, line 28)

Comment3:
line 1323 mPR should be MPR
Answer3:
As suggested, I changed.

Reviewer C

Comment1

The authors report a study in which the use of perioperative pembrolizumab is assessed. Their results have shown a treatment gateway for patients with large tumors and lymph node metastases who are not suitable for definitive surgery as treatment initially, these patients may be candidates for surgery after preoperative ICI therapy, with potential to improve therapeutic outcomes, as shown in the paper

As it cannot be otherwise, it would be desirable for these results to be seen in other populations.

Reply:

Thank you for reviewing my manuscript.