Peer Review File

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Reviewer A

This is an original article regarding the efficacy and safety of a relatively unknown immunotherapy - namely tislelizumab in locally advanced NSCLC. The manuscript is mostly well written, but there are a couple of changes that need to be done before consideration of publication:

- Please changes all times that "the operation" was used to "surgery" since this is a more academically accepted term
Reply:we have modified our text as advised (see Page 2, line 7,see Page 5, line 22,see Page 9, line 14,see Page 9, line 15)

- When noting the percentages of patients, please also show the total amount of patients. For example: 5/12 (41.67%) patients in line 151 on page 7.
Reply:we have modified our text as advised

- Line 116 on page 6: by all patients instead of by the patients
Reply:we have modified our text as advised(see Page 13, line 8)

- Paragraph 2.2 on treatment options is very unclear. Which patients are "others" that received only neoadjuvant chemotherapy. All patients received neoadjuvant tislelizumab right?
Reply: All patients received neoadjuvant tislelizumab combined with chemotherapy.

- Correct typo in line 152 on page 7: tweleve --> twelve
Reply:we have modified our text as advised(see Page 8, line 19)

- Correct line 165 on page 7: the rest --> others
Reply:we have modified our text as advised(see Page 9, line 11)

- Paragraph 2.3.2 10% residual tumor cells is also MPR, please change to "10% or less"
Reply:we have modified our text as advised(see Page 7, line 21)

- Introduction: maybe change the first sentence, you cannot be 100% sure that lung cancer "has always been a tumor with highest morbidity and mortality". Suggestion to change to "lung cancer is one of the malignant tumor with the highest...". With a source, please. For example Cancer statistics Ferlay 2020 GLOBOCAN
Reply:we have modified our text as advised(see Page 4, line 2)

Reviewer B

The article entitled "Efficacy and safety of neoadjuvant tislelizumab combined with

chemotherapy in locally advanced non-small cell lung cancer" is a research into the efficacy of an anti-PD1 drug in the neoadjuvant treatment of non-small-cell lung cancer (NSCLC). This is undoubtedly a very novel topic that broadens our knowledge of such a current field as neoadjuvant lung cancer and the possible implications that this has on the survival and quality of life of patients. Undoubtedly, although it is a very limited cohort of patients, I believe that the article could be well received by readers and may help to increase knowledge in the clinical practice of the scientific community.

First of all, I believe that the article is well structured and easy to read, with a language that does not need revisions. There are no major errors that limit the quality of the article and should be corrected. The introduction is what the article needs (in the absence of a series of changes specified below). The methodology is adequate to achieve the objectives set out by the authors. Likewise, the results, although there are parts that the authors should specify, are also correct, being similar to the articles that have already been published on neoadjuvant therapy in NSCLC. The references are a point that the authors should correct because they need to be updated. Probably, since the authors wrote the article until it was submitted to the journal, there have been a number of publications that have not been included. Finally, the figures and tables are as indicated, although given that to complete the introduction a figure on the action of tislelizumab would be much appreciated.

Revisions found to be appropriate are indicated below. No major revisions are noted as necessary, although given the large number of minor changes suggested, a great deal of effort is required to make them:

- Title: specify that this is a study of a retrospective cohort of patients so that readers entering the article can understand that it is not a clinical trial.
Reply: We have modified our text as advised (see Page 1, line 2)

- Abstract: specify in the conclusion that further studies are needed to confirm the findings.
Reply: We have modified our text as advised (see Page 2, line 18-19)

- Introduction, line 49: replace "primary lung cancer" with "lung cancer".
Reply: We have modified our text as advised(see Page 4, line 2)

- Introduction, line 51-52: talk about worldwide data, not in a single country.
Reply: We have modified our text as advised(see Page 4, line 2-4)

- Introduction and discussion: it is important that studies talk about the recent clinical trials published in the New England Journal of Medicine NADIM II and KEYNOTE-671 in both the introduction and the discussion. Along with this, as is done in the discussion with the CheckMate-816 study, the authors' results should be compared with those of these studies. Including a comparative table between the studies and the results would be very interesting.
Reply: We have modified our text as advised. We added some data from NADIM II and KEYNOTE-671(see Page 12, line 7-14)

- Methods: This treatment has not been approved in clinical practice. Was it used in a clinical trial? Please specify.
Reply: Our research is aim to investigate the efficacy and safety of neoadjuvant tislelizumab combined with chemotherapy in the treatment of locally advanced non-small cell lung cancer. And Tislelizumab combined with carboplatin and paclitaxel (or nab-paclitaxel) has been approved as the first-line treatment for advanced squamous cell carcinoma of the lung.

- Methods, line 88-89: specify that patients were studied in a multidisciplinary committee. Change the meaning of the sentence.
Reply: We have modified our text as advised and change the meaning of the sentence(see Page 7, line 15)

- Methods: genes should be indicated in italics (EGFR and ALK).
Reply: We have modified our text as advised.

- Methods and results: How was the re-evaluation performed by imaging, PET-CT or CT? Please specify.
Reply: The patients will be performed by imaging, PET-CT or CT before starting neoadjuvant therapy and after completing three cycles of neoadjuvant therapy. And we will evaluate the treatment effectaccording to the Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

- Methods, line 113-114: specify the approval protocol number of the study.
Reply: The approval protocol number of the study is 2022KY021

- Methods, treatment options: supplementary material could be included with the specific regimens used in each patient, with doses.
Reply: We have modified our text as advised. Specific regimens and doses of relevant drugs are given in the treatment options.

- Methods: replace "PCR" with "pCR".
Reply: We have modified our text as advised and replace all "PCR" with "pCR".

- Results: Why were all patients of squamous subtype? Pre-and post-treatment PD-L1 values are not mentioned. It is essential to indicate this and to analyze the response according to this value.
Reply: This is a retrospective study, and we only selected patients with squamous non-small cell lung cancer. We have made modifications to the inclusion criteria in the article. It's a good advice. Part of our patients did not complete the pre-and post-treatment PD-L1 values. May be we need some time to complete the pre-and post-treatment PD-L1 expression.

- Discussion: pCR is higher in the study than the reference clinical trials. Is there an explanation for this?
Reply: This is a small sample size study, excellent pathological complete response (pCR) rate may be derived from selection bias and further large-scale prospective studies are needed in the

future to validate our research results.

- Discussion, line 249-250: this sentence should be more cautious, change the meaning.
Reply: We have modified our text as advised replace "At present, there is no clear conclusion regarding the impact of neoadjuvant immunotherapy on the feasibility and safety of surgery." with "At present, the impact of neoadjuvant immunotherapy on the feasibility and safety of surgery is being explored.".

- Conclusions: indicate that clinical trials are needed with this anti-PD1 in this indication.
Reply: We have modified our text as advised.(see Page 14, line 18)

- Conclusions, line 271: replace "good" with "favourable".
Reply: We have modified our text as advised and replace "good" with "favourable".(see Page 14, line 15)

In summary, I think this is a very good study that needs a number of important changes to be published. Given the number of changes needed, although none of them is a major change, I think it is essential to make a thorough correction of the manuscript.

Reviewer C

The manuscript written by Chen and associates addressed efficacy and safety of neoadjuvant PD-1 inhibitor, tislelizumab, combined with chemotherapy in locally advanced non-small cell lung cancer (NSCLC).
This paper deals with an interesting topic and shows excellent results of neoadjuvant tislelizumab with chemotherapy; however, there are several concerns and flaws for general readers to understand and utilize the current results.

1) As mentioned in the section of 2.1 clinical data, this study was a retrospective study. Excellent pathological complete response (pCR) rate is considerably derived from selection bias. The authors should emphasize this as a critical limitation of study. The pCR is also affected by the way of pathological examination; however, the details about that are not described clearly. Conclusively, the excellent results are preliminary and should be validated in the well-designed prospective studies.
Reply: We have modified our text as advised (see Page 10, line 17-18).Pathological complete response (pCR) is often used as one of the study endpoints in clinical trials of neoadjuvant therapy and is defined as the absence of residual tumor cells after assessment of resected tumor tissue and regional lymphocytes. The specific steps are as follows: 1. Measure the longest diameter of the tumor (cm); 2. According to the longest diameter of the tumor, take at least one pathological section every 1cm for HE staining; 3. Calculate the viable tumor cells remaining on each section. The proportion of necrosis, stromal tissue and inflammatory cells; 4. Count the proportion of residual tumor cells in each section and take the average value, which is the average proportion of residual tumor cells. If there are no residual tumor cells, the patient is considered to have achieved pCR.

2) This study protocol included the patients who were not expected to achieve the ideal radical resection, as shown in the section of 2.1 clinical data. I could not understand why all patients could achieve R0 resection despite 2 of 12 patients showed increasing of the tumor from baseline marginal resectability.
Reply: This is a study with a small sample size, and the higher R0 rate may be due to selection bias.Postoperative pathology confirmed negative margins in all patients.

3) Although 9 of 12 patients had cN2 disease, was histological confirmation performed? The cN2 status might be determined only by imaging study.
Reply: The status of cN2 is mainly determined through imaging studies.Among the 9 patients only part of patients was histological confirmation performed before surgery.

4) All the patients had squamous histology, suggesting some biases. The authors should comment the biased characteristics in this study population.
Reply: Because tislelizumab combined with carboplatin and paclitaxel (or nab-paclitaxel) has been approved as the first-line treatment for advanced squamous cell carcinoma of the lung.In our research, we just only selected the patients had squamous histology.We have made modifications to the selection criteria.(see Page 6, line5-6)

5) There are many typos including no space before parentheses and unnecessary space in parentheses.
Reply: We have modified our text as advised.

Reviewer D

General comments:
This article reported the good efficacy and safety of neoadjuvant tislelizumab combined with chemotherapy in patients with locally advanced non-small cell lung cancer.
This theme is one of the hot topics of perioperative immunotherapies for resectable NSCLC.
However, some modifications would be needed for publication.

Comment 1:
Page 4, line 59-61 in Introduction, the authors described “Compared with adjuvant therapy, neoadjuvant therapy has more advantages, including better tolerance, shrinking of primary lesions, reduced clinical stage, increased chances of radical surgery, and reduced postoperative recurrence (5,6).”. However, this sentence considered to be overstated. The both benefits of the pooled analysis of adjuvant therapy and neoadjuvant therapy for 5-year survival rate were approximately 5%, and which has more advantages is controversial. Authors should modify the sentence for appropriate meaning.
Reply:we have modified our text as advised.(see Page 4, line 14-15)

Comment 2:
Page 4, line 68-70 in Introduction, the authors described “Studies have reported that neoadjuvant immunotherapy is superior to adjuvant immunotherapy in prolonging survival,

reducing distant recurrence, and inducing anti-tumor immunity (11).". However, this sentence also considered to be overstated. The reference is only one preclinical study data. Clinically, it is not known whether neoadjuvant or adjuvant immunotherapy is better at prolonging survival. Authors should modify the sentence for appropriate meaning.
Reply: We have modified our text as advised. (see Page 4, line 22)

Comment 3:
Page 4, line 77-78 in the Introduction, the authors described "which is used as adjuvant therapy in patients with advanced non-small cell lung cancer and has shown good safety and antitumor activity (14).". In the reference (14), Tislelizumab was not used as adjuvant therapy but used as 1st line therapy for advanced squamous NSCLC. Authors should modify the reference or sentence appropriately.
Reply: We have modified our text as advised.(see Page 5, line 10-11)

Comment 4:
Page 5, line 88-90 in Methods section, the authors described "These patients are not expected to achieve the ideal radical resection of lung cancer, or the operation is more difficult, and they are treated with neoadjuvant tislelizumab combined with chemotherapy.". In this study, the targeted patients were inoperable at initial evaluation, therefore, the term neoadjuvant chemotherapy does not seem appropriate. The operation in this study was the conversion surgery in salvage surgery for inoperable NSCLC patients. The authors should clearly state this point.
Reply: We have modified our text as advised.(see Page 6, line 1)

Comment 5:
In the Methods section, Although the trial is described as a retrospective study, this study appears to be a prospective study, not a retrospective study, based on the study design and inclusion and exclusion criteria.
Reply: Our study is a retrospective study, and all patients were included before the establishment of this study according to the inclusion criteria.

Comment 6:
Page 6, line 130 in Methods section, "complete pathological response (PCR)" is probably a misspelling of "pathological complete response (PCR)".
Reply: We have modified our text as advised.(see Page 7, line 19)

Comment 7:
Page 6, line 129-133 in Methods section, do the PCR and MPR criteria also include lymph node assessment?
Reply: The PCR and MPR criteria include lymph node assessment

Comment 8:
Page 7, line 139 in Methods section, "complete pathological response (PCR)" should be modified to "PCR", because it is the second notation.

Reply: We have modified our text as advised.(see Page 8, line 6)

Comment 9:
Authors should describe the method of statistical analysis in the Methods section in relation to the results that are statistically analyzed.
Reply:we have mentioned the method of statistical analysis in the section of 2.5 Statistical Analysis.

Comment 10:
Page 11, line 263 in Discussion section, “The first study” is probably a misspelling of “First, this study”.
Reply: We have modified our text as advised.(see Page 14, line 7)

Comment 11:
All patients have pathological response in Figure 2. The results are too good to be true, although there is bias being considered by a small number of patients. Did you exclude patients who could not be operated on in the end? The author should show the information about PD-L1 expression.
Reply: All the patients who could not be operated on in the end was be excluded. Part of our patients did not complete the pre-and post-treatment PD-L1 values. May be we need some time to complete he pre-and post-treatment PD-L1 expression.

Reviewer E

I enjoyed reading the article.
The current study investigated clinical efficacy and showed good outcomes.
However, I have several questions.
1. I couldn't figure out what this study newly added to the results of the previous studies using tislelizumab in neoadjuvant chemotherapy for NSCLC (e.g. RATIONALE 304). Please clarify.
Reply: RADIONALE 304 Study: A phase III, open, multicenter, randomized study comparing the efficacy and safety of tirelizumab (anti PD-1 antibody) combined with platinum and pemetrexed chemotherapy alone in first-line treatment of stage IIIB or IV non-small cell lung cancer (nsq NSCLC) patients. While our research is aim to assessing the phase descending and surgical rate of tislelizumab combined with chemotherapy in patients with locally advanced lung cancer.

2. Did the authors investigate PD-L1 expression in the preoperative specimens? It would be nice if you look at PD-L1 expression and efficacy.
Reply: Part of our patients did not complete the pre-and post-treatment PD-L1 values.May be we need some time to complete he pre-and post-treatment PD-L1 expression.

3. I thought the exclusion criteria description were confusing. Did authors plan to exclude the patients who could not tolerate three cycles of the neoadjuvant therapy? Did authors exclude the case that failed to live longer that 6 months after the surgery? Please clarify.

Reply: We excluded patients who were unable to tolerate three cycles of neoadjuvant therapy and who failed to live longer that 6 months after the surgery, without dropouts.

4. Please consider to add postoperative survival data as it has been more than two years since the clinical study started.
Reply: Patients included in our study were from January 1, 2021, to November 30, 2022. Some patients have insufficient follow-up time, but we can provide existing follow-up data if needed. Also, I found several grammatical errors. Please proofread the manuscript again.