Peer Review File

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Reviewer A

The primary objectives of the study are to validate on real-world data the benefit of the chemo-immunotherapy regimen in limited-stage SCLC and to find predictive biomarkers. These objectives are relevant because PD-1/PD-L1 blockade has little data in the setting of limited stage, in addition there is a need to better delineate which sub-group drives the benefit of these drugs in the overall population through feasible blood-based biomarkers.
This study brings valuable data in this setting as well as useful hypotheses. The main revision to be done would be to test a better method to get cutoff values for the biomarkers.

Detailed comments below

Title:
The study included only patients receiving either anti-PD-1 or anti-PD-L1 drugs, no anti-CTLA-4 or whatsoever. Maybe "Efficacy and safety of first-line PD-1/PD-L1 blockade in limited-stage small cell lung cancer" would be more appropriate?
Reply: Thank you very much for your comment, we have modified our title as advised.
Changes in the text: Page 1, line 1

Abstract:
Minimum safety data should be presented in the results section.
Reply: Thank you very much for your comment, we have modified our text as advised.
Changes in the text: Page 2, line 56-57

Methods:
The authors explain well in the introduction treating of first line limited stage SCLC with ICI is not routine practice, however they retrospectively screened 63 patients receiving this kind of regimen in their centers.
Can they provide more information about the reasons leading to offer ICI to these patients, and if this implies some selection bias? For instance, was it within the context of prospective clinical trials of ICI in this setting?
Reply: Thank you very much for your comment.
1. The reasons leading to the offer of ICIs: Although first-line immunotherapy was not a standard treatment regimen for LS-SCLC, immunotherapy has been validated to significantly improve survival in patients with ES-SCLC. And numerous preclinical studies have demonstrated the potential synergy between chemoradiotherapy (CRT) and ICIs. Based on these, our clinical practitioners often mention immunotherapy when recommending treatment options to patients. Every patient who chose immunotherapy did so voluntarily and signed an informed consent form.
2. Regarding selection bias, we provide the following explanation: We strictly adhered to the inclusion and exclusion criteria when enrolling patients. We checked the medical records of each patient and did not find any patients who had participated in prospective clinical trials.

And we employed propensity score matching to minimize selection bias.
Changes in the text: Page 4, line 119-121

RECIST: which version? 1.1? iRECIST?
Definition of DCR: evaluated at what time from treatment initiation? (everyone is at least SD if you perform a scan 2 weeks after baseline)
Reply: Thank you very much for your comment. The response was evaluated in accordance with the RECIST v1.1. As you said, the timing of evaluation can significantly influence the DCR calculation. Patients in clinical practice cannot be scanned as frequently as those in clinical trials. Often, we conduct a comprehensive reassessment after two treatment cycles. We have collected the optimal response during the first-line treatment of each patient.
Changes in the text: Page 4, line 126-128

The ROC method is used to determine cutoffs; however it is not detailed for which endpoint. In the case of survival (censored) data it might not be the optimal method. You could maybe get better cutoff values from implementation of the maxstat package in survminer (R).
Reply: Thank you very much for your comment. I'm very sorry for the misdescription. The method we used actually was from survminer (R). The optimal cut-off value of NLR, LMR, PLR, SIRI, SII, and PNI were determined by the 'surv_cutpoint' function.
Changes in the text: Page 4, line 145-146

Results:
If the design of the study was from the start based on propensity matched cohort, then what is the added value of reporting analyzes performed on the full non-matched population?
Reply: Thank you very much for your comment. Analyzing the full non-matched population provides valuable insights into the broader patient population and allows for a comprehensive understanding of the study cohort beyond the propensity-matched subset. This approach offers a more inclusive perspective and enables researchers to assess the generalizability of findings beyond the matched cohort. Additionally, it facilitates comparisons with other studies that may have employed different methodologies or included diverse patient populations.

"In addition, not similar to the overall PFS outcomes, females (HR=0.39 [0.14, 1.09], p=0.072), and patients with the primary left site (HR=0.71 [0.40, 1.24], p=0.229) and tumor size ≥ 5cm at initial diagnosis (HR=0.56 [0.30, 1.02], p=0.059) failed to obtain PFS benefit from immunochemotherapy (Fig. 1D)." : In my opinion there is nothing to be said about these subgroups. Sample sizes are likely to be too small to demonstrate an interaction, but there does not seem to be any. The effect of the treatment seems to be consistent in these subgroups even if some are underpowered to get a significant value.
Safety section: were they any fatal adverse events (treatment related, or not = any non-cancer - related death)?
Reply: Thank you very much for your comment, we have modified our text as advised.
Changes in the text: Page 5, line 185-187; Page 6, line 206-208

Discussion:

LIPI appears as a promising and feasible predictive biomarker in your study. It is not significant for OS but as said in the method section you could maybe get a better cutoff value and it seems to go the same way as PFS. One of your conclusions may be that LIPI is worth exploring in a prospective manner and should be a stratification variable for clinical trials in this setting.

Reply: Thank you very much for your comment. LIPI has standardized classification criteria. LIPI categorizes the population into three different prognostic groups: good (dNLR≤3 and LDH≤ULN—upper normal limit), intermediate (dNLR> 3 or LDH>ULN), and poor (dNLR> 3 and LDH>ULN). Although we have not found the value of LIPI for OS in multivariate analysis, we discussed in the manuscript that based on previous research results and our finding, LIPI may have some predictive value.

Changes in the text: Page 4, line 142-144

Reviewer B

The authors have done a significant effort in the implementation described in this publication. Methodology used has been defined to minimize differences between treatment groups and allow the comparison between them. Despite the efforts done to allow the comparison, I think that there are still some aspects to be reviewed.

1. As described by authors in the introduction, 'due to the lack of adequate data, it is not recommended to offer immunotherapy to patients with LS-SCLC. Despite this, numerous preclinical studies have demonstrated the potential synergy between chemoradiotherapy (CRT) and ICIs, serving as the basis for combining these therapeutic approaches. [10-12] Currently, the utilization of concurrent or consolidation ICIs alongside with CRT remains relatively restricted, with only three phase II clinical trials reporting outcomes for LS-SCLC.[13-15]'.
Based on the current evidence and recommendation for use of ICIs in patients with LS-SCLC, the main concern is about representativeness of patients receiving ICIs in combination with CRT in term of clinical practice.

Reply: Thank you very much for your comment. As you said, existing clinical studies on LS-SCLC were exploring the efficacy of combined radiochemotherapy and ICIs. However, due to the complexity of real-world clinical research, some patients are unable to undergo thoracic radiotherapy. For these reasons, we adjusted the design strategy, primarily comparing the differences between the immune and non-immune groups. Although this may lead to higher heterogeneity, it also demonstrates the effectiveness in a broader population. Regarding the comparison between the ICIs+CRT group and the CRT group, we also conducted the subgroup analysis, and the results suggested benefits in both OS and PFS, which have reference significance for the subsequent conduct of clinical research.

Changes in the text: Page 5, line 185-186; Page 8, line 278-289

2. The covariates used for matching included age, sex, PS, smoking status, primary site, Lymph Node stage (N stage), TNM stage, and history of radiotherapy, thoracic chemoradiation, and PCI. Which means that a total of 10 variables, and some of these variables were categorical with more than two categories, are included in the logistic regression model to derive propensity scores. However, the sample size was limited to 87 patients receiving first-line EP alone and 63 patients receiving first-line EP in combination with ICIs. The study sample size is probably too

small to properly apply the propensity score matching and derive comparable treatment groups.

Reply: Thank you very much for your comment.

We collected patient data from three provincial medical centers over nearly two years, making it a relatively large-scale retrospective study. Unfortunately, due to a lack of indication support, the sample size included in our study is relatively small. According to previous studies, LS-SCLC patients indeed constitute only a small fraction of lung cancer patients. The two mentioned Phase II clinical trials investigating the efficacy of first-line CRT+ICIs in LS-SCLC patients included only 40 and 50 patients, respectively. In our study, we included 63 patients who received ICIs, which is a relatively decent sample size.

With a limited sample size, there may be challenges in achieving well-balanced treatment groups, especially when matching multiple covariates, as in our study. Despite these limitations, we believe that our study provides valuable insights into the potential benefits of combining EP with ICIs in the treatment of LS-SCLC. Moving forward, large-scale studies are needed to further evaluate the efficacy and safety of this treatment approach. We appreciate your feedback and will consider it in the interpretation of our study findings.

Changes in the text: Page 7-8, line 263-277

3. The limited sample size can also limit the validity of subgroup analysis or the assessment of factors associated with endpoints. Results derived from regression models must be interpreted with caution due to the limited generalizability of results obtained with this limited sample size.

Reply: Thank you very much for your comment. We acknowledge that the small sample size can indeed constrain the validity of subgroup analysis and the assessment of factors associated with endpoints. We have adjusted the presentation of the subgroup-analysis results in the Results section.

Regression models derived from such a limited sample size must be interpreted with caution. Considering these limitations, we agree that it's important to interpret our findings cautiously and recognize the inherent constraints imposed by the sample size. And we will emphasize the need for larger, more representative studies to validate and corroborate our findings. Additionally, we will consider these limitations when discussing the implications of our study results and their relevance to clinical practice. Your insights are valuable, and we appreciate your thoughtful consideration of these limitations in our study.

Changes in the text: Page 5, line 185-187; Page 9 line 317-318

4. Differences obtained in study outcomes are presented in HR and confidence interval for median OS and PFS. 95% CI obtained in treatment groups are huge and there is a significant overlap between treatment groups. Results presented should be reviewed and interpretated with caution due again to the limited sample size.

Reply: Thank you very much for your comment. We acknowledge the wide 95%CI observed and the significant overlap between treatment groups, which may raise concerns about the precision of our estimates. These findings indeed reflected the limitations imposed by our study's small sample size. As such, we agree that caution is warranted when interpreting and generalizing the results. We will ensure to thoroughly discuss these limitations in our interpretation of the results.

Changes in the text: Page 7-8, line 263-277

5. Conclusion provided by authors are probably too optimistic describing that the study has demonstrated encouraging clinical effectiveness and acceptable safety when utilizing first-line PD-1 inhibitors or PD-L1 inhibitors in combination with CRT. The limited sample size, the restrictive sample of patients included in the study (i.e. ECOG<2) and potential lack of representativeness are limiting the study.

Reply: Thank you very much for your comment. Indeed, the conclusion provided may have been overly optimistic given the limitations of the study, including the limited sample size and the restrictive inclusion criteria. These factors undoubtedly impact the generalizability and effectiveness of our findings. We revised the text to reflect a more balanced interpretation of the results, emphasizing the study's limitations. We appreciate your valuable feedback, which will contribute to enhancing the clarity and accuracy of our study's conclusions.

Changes in the text: Page 7-8, line 263-277

Reviewer C

1. As the authors said, the standard treatment of limited stage SCLC is chemotherapy, thoracic RT, and PCI. However, 38.6% of patients in this study population did not receive thoracic RT and 94% of patients did not receive PCI. All patients in this study have good general conditions with a performance status of 0 or 1, but the proportion of patients who did not receive thoracic RT and PCI is too high. Even if propensity score matching was performed, I think this study has a problem in selecting patient groups.

Reply: Thank you very much for your comment. Regarding the issue you raised about patient population selection, we can provide the explanation. Treatment decision-making in real-world clinical practice exists the complexity. First, it's important to note that the treatment decisions for each patient are influenced by various factors, including individual clinical characteristics, patient preferences, and physician judgment. Some patients refuse radiotherapy due to old age, emphysema, or pulmonary fibrosis. Some patients are concerned about the potential severe side effects of combined radiotherapy, chemotherapy, and immunotherapy, leading them to refuse radiotherapy. Second, radiotherapy requires patients to visit the radiotherapy department for further treatment after discharge, and the course of treatment is relatively long. Some patients did not undergo radiotherapy after discharge due to inconvenience. Lastly, based on the NCCN guideline, PCI is not the optimal choice for LS-SCLC, and there is still controversy. Therefore, we chose to include all individuals who received EP chemotherapy. Analyzing the full population provides valuable insights into the broader patient population and allows for a comprehensive understanding.

Changes in the text: Page 7, line 229-230; Page 8, line 278-289

2. As can be seen in Reference No. 13-15 of this paper, there are already three prospective studies that analyze the effect of addition of ICI in patients with limited stage SCLC. The patient population in this study is heterogeneous. And, because significant proportion of patients did not receive standard treatment, this paper has a lot of bias. Moreover, this is retrospective study. Therefore, we can acquire any further significant results from this study.

Reply: Thank you very much for your comment. We acknowledge that our patient population is heterogeneous, and we recognize the potential biases associated with the significant

proportion of patients who did not receive standard treatment. Although propensity score matching and subgroup analysis were utilized to minimize selection bias, we acknowledge the limitations inherent in retrospective analyses. We provide a comprehensive discussion of these limitations in the manuscript.

However, phase III clinical trials for LS-SCLC have only just begun, requiring a longer research period to obtain survival outcomes. We collected patient data from three provincial medical centers over nearly two years, making it a relatively large-scale retrospective study. The two mentioned Phase II clinical trials investigating the efficacy of first-line CRT+ICIs in LS-SCLC patients included only 40 and 50 patients, respectively. In our study, we included 63 patients who received ICIs, which is a relatively decent sample size. Retrospective studies can be used to explore potential associations or propose new research hypotheses, as well as to provide supplementary evidence for clinical trials. We believe that despite these limitations, our study contributes valuable insights and complements the existing literature on this topic.

Changes in the text: Page 7-8, line 263-289; Page 9, line 320-323

3. Throughout the paper, abbreviations are not properly defined.

Reply: Thank you very much for your comment, we have modified our text as advised. If there are any inaccuracies remaining, please point them out.

Changes in the text: Page2-3

4. In Methods section, the description about the treatment is too poor. A brief explanation of the chemotherapy regimen, radiation therapy dose, radiation therapy field, etc. is needed.

Reply: Thank you very much for your comment, we have modified our text as advised.

Changes in the text: Page 3, line 110-114

5. The letters in the Figures are too small.

Reply: Thank you very much for your comment, we have modified our figures as advised.

Changes: Figures in the re-submitted files