Peer Review File

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Reviewer A

I think your data showed the impact of 2nd-line immune checkpoint inhibitors following platinum-based chemotherapy on survival and medical expenses in patients with advanced non-small cell lung cancer comparing with targeted therapy and cytotoxic chemotherapy well. In particular, the analysis regarding the nationwide database of large population might reflect real practice well.

Reply: Thanks for your positive review.

Reviewer B

In the paper "Effects of second-line ICI use among advanced NSCLC patients", Ji et al. set out two investigate two elements: cost and treatment outcomes of immunotherapy in Korea. Although both aspects are not new, they are important to record as (i) they may differ regionally and (ii) they set the bar for therapeutic improvements, since immunotherapy is now the de facto standard. As such, this paper further solidifies our existing knowledge about treatment outcomes and associated costs.

My two main points of critique are:

- Given the sheer volume of publications in the space of immunotherapy outcomes (both trial and real-world) and cost analyses, I think the link with previous work is not comprehensive enough.

- Currently, the analysis of the expenses is too superficial. The authors showed some differences in expenses between the groups (split by cancer related vs total cost) but did not drill down how these differences came to be. For example, after discounting the costs of the therapy itself, what other expenses were different between the groups? This is important to bring across the message (which I think this paper aims to do) that the treatment itself (incl. accompanying costs) is expensive, and not attributable to other (confounding) factors.

Reply: We agree with your opinion. Regarding comparing medical expenses, ITS analysis is also a time-series method that excludes and corrects for variables that change over time. Other confounding variables in Table 5 are corrected. Nevertheless, there was a limitation in that it did not accurately explain the cause of the cost difference; therefore, this has been described as a limitation of this study. **(Page #13 , Line #239).**

However, our study is a comprehensive investigation of all lung cancer patients in Korea, and there has been no study of this scale in Korea before. Even if there have been many previous studies, the results can vary significantly depending on race and environmental factors. From this perspective, the results from our nationwide study in Korea help validate previous studies' findings in different regions, races, and environments.

In addition, there are several other minor points to be addressed:

- Title:
- The title does not make clear that this manuscript primarily deals with expenses of immunotherapy.
Reply: We agree with your comments. Therefore, we have changed the title to "**Clinical and financial impact of immune checkpoint inhibitors following platinum chemotherapy in patients with advanced or metastatic non-small cell lung cancer: A nationwide population-based study".**

- Abstract
- The abbreviation USD was not defined.
Reply: Thank you for pointing this out. "USD" has been changed to "$", and the 1000-dollar unit has been changed to K to improve readability.

- Methods
- For the logistic regression, indicate how the variables were dichotomised and how censoring was handled.
Reply: We apologize for the confusion by the errors in the notation. Survival analysis was used in both the overall survival and disease progression analyses. For disease progression, if the regimen was changed again in the second regimen, that date was defined as the date of disease progression. The Table and relevant text in the Methods have been revised accordingly.

- Maybe I've missed it, but I couldn't find the reference point that was used for OS and PFS. Was it starting from second line treatment? Or first line treatment?
Reply: OS was measured from the timing of initial diagnosis until death and PFS was measured based on the treatment maintenance period of second-line treatment.

- Can smoking status be included in the analysis? This is known to be an important factor, and potentially confounds the results listed in Table. 3. If this information is not directly available, perhaps some other variable that acts as a surrogate thereof?
Reply: Data related to smoking history were collected from participants who underwent the national health examination. However, due to a significant amount of missing data, smoking history data could not be included in this analysis. Additional analysis was conducted on 4,644 individuals with smoking history data, and these findings have been provided in supplementary tables. This information has also been added to the methods section. **(Supplementary Table S2,3).**

- Results
- Throughout the paper, I would suggest indicating expenses in units per $1000 USD to improve readability.
Reply: Thank you for the suggestion. "USD" has been changed to "$", and the 1000-dollar unit has been changed to K to improve readability.

- In Fig. 1:
- The figure is difficult to read, please improve the resolution.
Reply: Following your comments, we increased the resolution (600dpi) of the image and

changed the file extension to a PNG file.

- It looks like the negation in the diamond "Having chemotherapy regimens not used for NSCLC or other cancer diagnostic codes except for C34" is incorrect. Please double check.
Reply: We agree with your opinion. The negation in the sentence in the yellow diamond led to the wrong direction, so I corrected it to the right direction.

- The blue square box, point 4) "Patients with history of 2nd line chemotherapy". Is this correct? Wouldn't that exclude patient that received ICI monotherapy from 2nd line treatment?
Reply: Thank you for the comment. The study subjects were patients with advanced NSCLC who received 2 or more lines of chemotherapy, and the study group also included patients who received ICI monotherapy as the 2nd line of treatment. Therefore, we believe that the sentence is correct.

- In Fig. 2,
- Please indicate in the caption what is control in panel a.
Reply: To reflect your opinion, the caption was changed to ICI group and non-ICI.

- Is there a particular reason for choosing to restrict the analysis to one year? If not, please provide additional follow-up information to improve the statistical estimates.
Reply: Thanks for your valuable feedback. There is no special reason to limit the period to one year. As per your opinion, we conducted new analysis with follow-up observation for 2 years or longer. And brief descriptions regarding the Kaplan-Meier curves are commented in 3.2 Survival outcomes section. **(Page #11, Line #193)**

- Improve Fig. 4. For example, the x-axis scale and ticks are missing. Disambiguate the intervals (2013.1 ~ 2016.7). I guess this this is supposed to mean year.month, but if I interpret it literally as a decimal it means 2013 + 0.1 * 365 days. Please indicate the actual data points, and annotate the different lines. It is not clear from the figure caption what they mean.
Reply: Thank you for the suggestions. To improve readability, we have added a major grid line and labelled the x-axis as year-month.

- In Table 1, clarify what is the number +/- after. One standard deviation or two standard deviations?
Reply: We apologize for the lack of clarity. The +/- symbol in Table 1 represents one standard deviation.

- In Table 2:
- first row second column: the comma should be a period (i.e., 16.7).
Reply: We have corrected the punctuation.

- In the caption, list which test was used to compute the p-value.
Reply: In Table 2, the p-values for the differences in OS (Overall Survival), PFS (Progression-Free Survival) durations, and cost between groups were calculated using Analysis of Variance

(ANOVA). This detail has been added to the 'statistical analysis' subsection of the methods section and as a caption to the Table.

- Discussion:
- The authors write that they “found changes in the patterns of chemotherapy drug prescriptions after coverage expanded“. These patterns were not discussed before. Please detail these patterns in the results.
Reply: Thank you for the valuable comments. We have described in brief the pattern of chemotherapy drug prescription after coverage expansion. (**Page #12 , Line #210**).

- It would help to indicate the typical re-imbursement price (per year) for ICB itself, to put the costs in perspective.
Reply: We have elaborated on these findings in Section 3.4, titled "Trends in Chemotherapeutic Use and Medical Expenses." **(Page #12, Line #213).**

- In Sec. 4.3, Comparison with similar research: The current discussion is not comprehensive enough. For example, the five-year overall survival of some of these clinical trials are now in. It would be nice to compare the results with those reported [e.g., JTO 16, pp. 1718-1732 (2012), but probably you can find many more papers]. There are also various real world outcomes available in addition to those reported in the introduction [e.g., Front Oncol. 13: 1182748 (2023) just to name one]. The current findings should be placed in the context of those similar reports. Ideally, in the context of the corresponding regions, (e.g., Asia-Europe-Africa-Americas).
Reply: Thank you for the comment. Following your suggestion, we have added relevant references and sentences in 4.3 **(Page #14, Line #246).**

- Conclusion
- The authors write “Therefore, the development of valuable biomarkers to increase treatment effectiveness in patients with NSCLC”[(l. 285-287). This does not logically follow from the previous sentence: there may be other (confounding) factors that explain the difference in expenses.
Reply: We agree with your opinion. We intended to state that further studies should be conducted to precisely select the patients with advanced NSCLC who may benefit from ICI administration rather than TT. We have removed this sentence because it was inappropriate.

Reviewer C

This manuscript addresses an important health economic issue in recent anti-cancer treatment after insurance reimbursement of expensive ICIs. My evaluation is that the paper is publishable with minor scientific revisions.

Minor comments
1) In Table 2, if “medical expense (USD)” means the annual medical expenses of a patient or individual, the authors should be described it in the Table.
Reply: Thank you for the positive review. Regarding your comment, for better clarity of

meaning, “Medical expenses” has been changed to “Personal annual medical expenses”. **(Table 2).**

2) In Table 5, please spell out β and SE in footnotes.
Reply: Following your suggestion, we have expanded these statistical terms in the footnotes. **(Table 5)**

3) In Figure 1, the sentence “Having chemotherapy regimen not used for NSCLC or other cancer diagnostic codes except for C34” seems to be inconsistency. The authors need to re-written to remove potential confusion.
Reply: We agree with your suggestion. The negation in this sentence in the yellow diamond leaded to the wrong direction, so I corrected the right direction. **(Figure 2)**

4) In Figure 1, the authors ruled out the patients who were treated by atezolizumab as second-line settings. Please explain why you did not include those patients who received atezolizumab in the text.
Reply: Thank you for the comments. Approval for reimbursement for atezolizumab was granted by the Korean NHIS in 2019, unlike that for other ICIs (nivolumab in 2016-07 and pembrolizumab in 2017-08). Given that this study included study subjects until December 2020, atezolizumab was excluded due to insufficient study period.

5) The y-axis label of Figure 5 seems to be incorrect. Please check it and revise it, if necessary. If a two-headed arrow shows ＄4,560.6, that's not consistent with the scale of the graph.
Reply: We apologize for the confusion. The graph scale was originally in Korean Won (1,000 KRW) but has now been converted to US dollars.

6) If the authors got an Ethical Committee approval, please describe it in the text.
Reply: The study was approved by the Institutional Review Board of the NHIS Ilsan Hospital (NHIMC 2022-10-015). This has been described in **Page #17, Line #329.**

7) The authors showed the criteria to identify the population with stage IIIB or IV (Line 122–128). If it is possible that the criteria include the patients with IIIA NSCLC who were not indicated for the definitive radiotherapy and underwent some palliative chemotherapy, the authors should describe it.
Reply: Thank you for the comment. We have added the small possibility of including stage IIIA patients in the limitation section. **(Page #13, Line #235).**