Peer Review File

Article information: https://dx.doi.org/10.21037/tlcr-24-264

REVIEWER A

Comment 1:
As reported by the authors themselves, a limitation arises from the dataset's focus on first-line treatments, which primarily includes patients enrolled in RCTs in the early years of immunotherapy (2016-2017). In a time where immunotherapy is predominantly used in the first line setting, this limitation becomes significant, and the data obtained may not reflect the real-world evidence. It might be useful to add more recent data (2020-2022) if possible, to better evaluate the evidence collected.

Reply 1:
We agree with the reviewer's assessment. However, the survival data we utilized from the Netherlands Cancer Registry is updated yearly, which does take some extra processing time. This has caused a delay in obtaining more recent data. Our aim was to ensure a follow-up period of at least 2 years, which is why we didn't include data from further years in our analysis. Unfortunately, we don't have access to the updated survival dataset from 2023 at the time of the study completion. Nevertheless, we will expand the discussion of this point further.

Changes in the text:

- Discussion, Page 12, Lines 208-212: Nevertheless, incorporating data from patients treated in more recent years (2021-2022) could provide a more comprehensive assessment of real-world evidence. However, due to the annual update process of survival data from the Netherlands Cancer Registry, it was not possible to access more recent survival data to ensure that patients were followed for at least two years at the time this work was completed.

Comment 2:
It may be useful to provide more detailed information about the type of immune checkpoint inhibitors used, by specifying them in the introduction and differentiating the data reported in the results.

Reply 2:
We appreciate the reviewer's perspective and agree that insightful information regarding the type of ICI used can bring more context on the setting of our study. We have made changes to the main text, as well as adding a supplementary table with detailed information on ICI type.

Changes in the text:

- Results, Page 9, Line 147-148: The most commonly prescribed ICI was Pembrolizumab as monotherapy (43.9%), followed by Pembrolizumab as a combination with two chemotherapeutic agents (34.7%).
- Results, Page 10, Line 158-159: The most commonly prescribed ICI was Nivolumab as monotherapy (53.2%), and Pembrolizumab as monotherapy (20.3%).
- Table B.1 was added to the supplemental material.

REVIEWER B

Comment 1:
Throughout, the expression “patients with lung cancer” is more common than “lung cancer patients”.
Reply 1:
We concur with the reviewer's assessment that using the words “patients with lung cancer” allows us to define the patients not in function of their disease, but in terms of their person.
Changes in the text:

- The term has been changed throughout the manuscript provided by yellow shading.

Comment 2:
Why does not the number of people match “Results section on Page 3, lines 128-130 in 6816 patients” and “Figure 2 in 6815 patients”?
Reply 2:
The reviewer rightly points out that there is a difference between the numbers reported in the result section in the main text and in Figure 2. After reviewing the original dataset, we concluded that this was a typo in the year 2019, where in Figure 2 indicated 2437 patients started treatment in this year, whilst in the original dataset there were 2438. A total of 6816 patients were included.
Changes in the text:

- Figure 2 was updated and reflect the correct number of patients (6816)

Comment 3:
In Figure 2, you describe that 2019 and beyond may have a lower median OS due to COVID-19. To make this discussion more robust, it may be advisable to present it for chemotherapy as well.
Reply 3:
Thank you for your insightful comment. We agree that including data on chemotherapy-only treated patients would enhance the robustness of our discussion regarding of the potential impact of COVID-19 on survival outcomes. Unfortunately, we do not currently have access to updated survival data specifically for chemotherapy-only treated patients beyond 2019. Nonetheless, we acknowledge the value in considering such data and will endeavor to incorporate it into future analyses when it becomes available. However, we consider this is an important point and will add this consideration to the discussion section.
Changes in the text:

- Discussion, Page 12, Lines 219-222: In addition, we did not have access to updated survival data for patients with lung cancer who underwent chemotherapy-only treatments between 2019 and 2020. This limitation hampered our ability to test this hypothesis in patients treated with systemic therapies other than ICIs.

Comment 4:
I recommend labeling the vertical axis of the KM in Figure 3.
Reply 4:
We appreciate the detailed review of our manuscript. We agree with the comment from the reviewer, and we modified the figure accordingly.
Changes in the text:

- We have added the label in the Y axis of Figure 3.

Comment 5:
In the Figure 3, you mention "Time period (years)", is it correct that this is HR for each 1-year increase? If so, using something like "Time period - 1 year increase" would be easier to understand.
Reply 5:
We share the reviewer's viewpoint, rephrasing this way the HR might provide an easier understanding.
Changes in the text:

- We have changed the labeling of the HR of Figure 3.

Comment 6.
This data holds information from January 2016 to December 2020. However, since those who received their first ICI therapy in January 2020 can only be followed for 12 months, their OS after 2019 may not be adequately evaluated. In fact, the recent population has a shorter follow-up period in Figure 3. This also needs to be added to the discussion. However, if it is difficult to add it due to character limitation, etc., please give priority to it because I also think that the impact of population differences by RCT is significant.
Reply 6:
Thank you for your thoughtful comment. While we appreciate your concern regarding potential differences in follow-up periods among patients receiving their first Immune Checkpoint Inhibitor therapy, we respectfully disagree with the assertion that this discrepancy significantly affects the evaluation of overall survival beyond January 2020.
Firstly, we ensure that the patients had a minimum follow up time of 2 years by stablishing the date of data censoring and end of the study as 31st December 2022. Secondly, the proportional hazard assumption inherent in the Cox regression model employed in our analysis accounts for differences in patient follow-up durations. This statistical technique allows for the comparison of survival outcomes while adjusting for differences in follow-up times among patient groups by computing the time contributed by both the patients who experience the events and the ones who are censored. Moreover, in RCTs, the Hazard Ratio for Overall Survival is commonly evaluated using the same statistical technique, given that patients in these studies are rarely enrolled simultaneously or followed for identical durations. Therefore, we consider that our analysis adequately addresses any potential bias arising from differences in follow-up durations among patients.
However, we consider that it is relevant to make this point clearer. In order to achieve this we made additions to the methods section
Changes in the text:

- Methods Page 8, Lines 130-136: Survival analysis was performed to observe changes in median OS over the years. The Kaplan-Meier method, with 95% confidence intervals, was used to calculate median OS. To ensure each individual had the opportunity for at least two years of follow-up, the censoring date was set at two years after the treatment initiation date of the last patient included in the study (December 31st , 2022). Consequently, survival time was defined as the interval between the ICI treatment start date until either death or the censoring date. To account for individual and group differences in follow-up times, we calculated hazard ratios using four Cox proportional hazards regression models.

REVIEWER C

Comment 1:
The reviewer thinks that a limitation of this study is that this study does not examine biomarkers other than PD-L1, such as Tumor Mutational Burden (TMB) and Tumor-Infiltrating Lymphocytes (TILs) while it compares with previous RCTs. The authors should consider adding this statement in limitation part with references.

Reply 1:
We acknowledge and thank the reviewer's observation regarding the limitation of our study in not examining biomarkers beyond PD-L1.

Changes in the text:

- Page 12, Lines 214-217: Moreover, we lacked information on variables known to be indicative of treatment efficacy, such as Tumor Mutation Burden (TMB) and Tumor-Infiltrating Lymphocytes (TILs). This limitation impeded our ability to account for these crucial tumor characteristics, thereby hampering our ability to limit confounding biases [9][10].