Peer Review File
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Reviewer A

This is an interesting retrospective analysis on the effects of baseline cancer pain on the efficacy of immunotherapy in lung cancer patients. This report is the first research to assess the result of baseline cancer pain on survival in lung cancer patients treated with immunotherapy, and it also significantly adds to the literature on the impact of breakthrough cancer pain on survival among lung cancer patients treated with immunotherapy. As such, this is a noteworthy report, and it will be of interested to JTD readers. However, several issues must first be addressed.

Abstract

Comment 1: In the methods section, the word “recruited” should be replaced with something like “were included” since this was not a prospective study.

Reply: Thanks for your helpful suggestion. “Recruited” is really not very suitable for retrospective studies，so we've changed the “recruited” in the text to “were included”

Changes in the text: we have modified our text as advised (see Page 2, line 29)

Comment 2: 280 patients is repeated in the Methods and the Results section.

Reply: Thanks for your helpful suggestion. We've removed the duplicates from the results

Changes in the text: we have modified our text as advised (see Page 2, line 34-35)

Comment 3: Results of the cohort before propensity score matching should be presented in addition to, and prior to, the results of the propensity matching.

Reply: Thanks for your helpful suggestion. We think that there are many confounding factors in the data before PSM, table1 present is data on a patient's pre- and post-match basis, the elimination of confounding factors after matching makes the baseline situation comparable between the two groups and the results more reliable; therefore, we mainly analyzed the matched data. So the analysis results before matching were not added in the article.

Comment 4: The phrase “burst pain” is only used in the last line of the Abstract and once in the Discussion but it is never defined.

Reply: Thanks for your helpful suggestion. We've changed two places in this article from "burst pain" to "breakthrough pain" .

Changes in the text: we have modified our text as advised (see Page 2, line 44; Page 8, line169)

Comment 5: Introduction

The authors state pain reduced immunity but do not provide a citation for this.
Reply: Thanks for your helpful suggestion. We have added citations.
Changes in the text: we have modified our text as advised (see Page3, line56)

Comment 6: Methods
Again, the word “enrolled” should not be used for a retrospective study.
Reply: Thanks for your helpful suggestion. We have changed "enrolled" to "included"
Changes in the text: we have modified our text as advised (see Page 4, line 82)

Comment 7: Significance should be defined at <0.05 not at 0.05.
Reply: Thanks for your helpful suggestion. We've changed 0.05 to <0.05.
Changes in the text: we have modified our text as advised (see Page 6, line 116)

Comment 8:
Results
The first sentence is a near exact duplicate of the beginning of the Methods section, and it is more appropriate in the Results section so should be removed from the Methods section.
Reply: Thanks for your helpful suggestion. We have removed the sentence from the method.
Changes in the text: we have modified our text as advised (see Page4, line82-83)

Comment 9: A decimal should be added to 15% for immunotherapy plus targeted therapy to be similar to all of the other percentages that have a decimal place.
Reply: Thanks for your helpful suggestion. We have made the required changes
Changes in the text: we have modified our text as advised (see Page6, line129)

Comment 10: In the Relationship between pain and efficacy section, 2 decimals are used often, and these should be changed to have only 1 decimal place.
Reply: Thanks for your helpful suggestion. We have made the required changes
Changes in the text: we have modified our text as advised (see Page7, line143, 145)

Comment 11: Add a measure of statistical significance to the sentence “PR was achieved in seven (14.6%) of the 48 patients with 142 baseline cancer pain and 15 (31.25%) of the patients without baseline cancer pain.”
Reply: Thanks for your helpful suggestion. We have made a measure of statistical significance to the ORR%, had a P value in Page7, line145.

Comment 12: There still must be some imbalances in arms, as the breakthrough pain group on propensity matching had numerous deaths immediately in the first weeks after the start of the study period that were not observed in the no pain group (shown in Figure 2).
Reply: Thanks for your helpful suggestion. We matched the baseline information, but we did not match some markers such as genes, underlying diseases, etc., because this

study is retrospective, less information is available, which may also affect patient efficacy and survival, and further exploration is needed in the future. So we added some content to the restrictive nature of the article.
Changes in the text: we have modified our text as advised (see Page 212, line 215)

Comment 13:
Discussion
In the first line of the first paragraph, “poor prognostic factor” has a different meaning than “negative prognostic factor.”
Reply: Thanks for your helpful suggestion. We have changed "poor prognostic factor" to "negative prognostic factor"
Changes in the text: we have modified our text as advised (see Page8, line167)

Comment 14: In the last paragraph, the statement is made that immunotherapy is not effective for small cell, which is not accurate.
Reply: Thanks for your helpful suggestion. We changed immunotherapy does not respond to small cell lung cancer to "small cell lung cancer is not sensitive to immunotherapy"
Changes in the text: we have modified our text as advised (see Page 10, line211-212)

Comment 15:
Table 1
Just like my above comment on arm imbalanaces shown in figure 2, there are clearly patient characteristic differences after propensity scoring. The authors should try to improve balance or otherwise, if not possible, then acknowledge these differences and the fact that the small patient numbers are likely driving these differences in the Discussion section.
Reply: Thanks for your helpful suggestion. We have performed PSM on the baseline of patients and compared the baseline of patients after PSM (>0.05). However, some baseline conditions were not included in the matching, so we've included some content in the restrictive sections of the article.
Changes in the text: we have modified our text as advised (see Page 212, line 215)

Reviewer B

This is a well conducted single-center, retrospective cohort analysis. The conclusions that baseline and breakthrough pain are prognostic clinical factors that influence efficacy of checkpoint inhibitors in patients with lung cancer are sound and informative. The methodology is sound and the variables that are matched are appropriate. The article is concisely written and the discussion focuses on the data generated and the clinical implications of this study. Overall, it makes a positive contribution to the literature.
A few additional considerations are discussed:

Comment 1: Throughout the manuscript- “PD-L1 mutation” is used where it is more appropriate to say “PD-L1 expression.” For example, page 5, line 130.
Reply: Thanks for your helpful suggestion. We have made the required changes
Changes in the text: we have modified our text as advised (see Page 6, line 111; Page6, line 132; Page8, line 160; Table 1)

Comment 2: In the “assessments” section, it would be helpful to have more information about how “baseline and breakthrough pain” were ascertained. For example, is there a standardized methodology across the institution where a pain scale is presented to every patient at their first visit and each subsequent visit? Were medication lists reviewed for pain medications to corroborate pain or lack thereof? More specific description of the ascertainment methods would be appreciated so that readers can understand how the patients were delineated in the pain or non-pain cohorts.
Reply: Thanks for your helpful suggestion. Modified as required. We included baseline and breakthrough pain protocols in the assessment.
Changes in the text: we have modified our text as advised (see Page 5, line 93-94)

Comment 3: In line 192 of the 7th page in discussion, the line: “Cancer pain has an immunosuppressive effect (with refs)” can be elaborated. I think this would be nice to expand on since it is effectively a component of the hypothesis. Whether this should be in the background or remain in the discussion can be left to the authors.
Reply: Thanks for your helpful suggestion. The relevant mechanism of cancer pain suppressing the immune mechanism has been added to the article
Changes in the text: we have modified our text as advised (see Page 9, line 191-194)

Comment 4: One major prevailing question is whether the presence of cancer pain is a surrogate for the amount of disease at baseline (ie baseline tumor burden). This is difficult to measure but plausibly patients with more disease will have more pain. These patients with high burden disease also traditionally have worse outcomes when treated with immune checkpoint inhibitors. Tumor burden has been difficult to measure and so I don’t expect the authors to account for this in propensity matching, but addressing this concept and the potential for tumor burden to be an interacting variable would be important. I will direct the authors to the following manuscript on the topic which may be helpful to discuss and reference (Dall’Olio, F.G., Marabelle, A., Caramella, C. et al. Tumour burden and efficacy of immune-checkpoint inhibitors. Nat Rev Clin Oncol 19, 75–90 (2022). https://doi.org/10.1038/s41571-021-00564-3)
Reply: Thanks for your helpful suggestion. We've added some discussion about this article to the restrictions in the discussion section of the article.
Changes in the text: we have modified our text as advised (see Page 212, line 215)