Peer Review File

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Reviewer A

This is a retrospective analysis of patients treated with immunotherapy, focusing on the prognostic impact of brain metastases, using patient-specific data from large prospective studies.

General Response

We sincerely appreciate the reviewer for the constructive comments and helpful suggestions, which have significantly improved our work. Below please find our response to each of these comments.

Minor points

In the abstract and text, the phrasing "trend towards" should be avoided. If the results are non-significant, one could say (for example) non-significantly greater (or lesser) or numerically greater (but not significantly so).

Reply: We have modified the text as suggested.

Changes in the text: (Line 64-65: in revised main text)

"Among patients with BM, patients with iBM (n=280) had a numerically longer OS (HR 0·66 [95% CI 0·41–1·07], p=0·090) than those with niBM (n=28)."

In the abstract the sentence "Findings were consistent with progression free survival) does not make sense.

Reply: We have deleted this sentence.

Changes in the text: (Line 69-70: in revised main text)

"…group. ~~Findings were consistent for progression-free survival.~~ Atezolizumab…"

Brain metastases are not a "complication" of NSCLC but rather a "consequence of"

Reply: We have modified the text as suggested.

Changes in the text: (Line 82-83: in revised main text)

"Brain metastasis (BM) is a frequent consequence of non-small cell lung cancer (NSCLC) (1), and…"

Major points

As the authors mention, there is likely selection biases in who underwent radiation vs. those who did not. The discussion describes patients with smaller lesions perhaps not being offered radiotherapy, which would make their results of radiation associated with greater survival more unexpected. However, it is also possible that patients with limited brain metastases (1 or a few) were more likely to undergo treatment, as brain radiation could be offered without whole brain radiation and conversely patients with innumerable brain metastases may have been offered immunotherapy without whole brain radiation in an effort to avoid that toxicity. Similarly, patients with limited extracranial disease (i.e. no extracranial
metastases) may have been more likely to undergo brain radiation in an effort to be more aggressive. These limitations should be recognized and discussed more. The lack of information on SRS vs WBRT should also be discussed and these treatments are very different and at least one study has shown poorer OS with WBRT vs SRS (Chang et al Lancet).

Reply: We have included the following statement in the Discussion section to describe the presence of selection biases and the insufficient information regarding SRS vs WBRT in this study.

Changes in the text: (Line 382-387: in revised main text)

"Secondly, there is a selection bias in the group of patients who received RT compared to those who did not. It is important to consider that patients with fewer and smaller BMs were more likely to receive treatment such as SRS. On the other hand, patients with more and larger BMs may opt for immunotherapy instead of WBRT to minimize potential toxicity. Similarly, patients with limited extracranial disease may have been more inclined to choose cranial RT as a more aggressive treatment approach."

(Line 390-392: in revised main text)

"Fourth, the 7 trials included in this study did not specify the type of cranial RT (SRS or WBRT). As a result, we are unable to compare the survival outcomes between patients who previously received WBRT or SRS for BM and those without BM."

As it stands, there is much redundancy within the discussion and with the discussion and introduction, with an overemphasis on describing the potential of brain radiation to improve survival Redundancies should be minimized to make the paper more streamlined

Reply: We thank the reviewer for this suggestion. We have revised the Discussion section to minimize redundancies and streamline the content.

(Line 293-303: in revised main text)

"~~Given the profound immune-modulatory effects of RT, combining PD-1/PD-L1 inhibitors and RT for the treatment of NSCLC is a burgeoning field of clinical research. Shaverdian and colleagues published one of the earliest clinical studies reporting a significant prolongation of overall survival in patients with pembrolizumab-treated NSCLC who had previously received RT compared with patients without previous RT (12). However, only 8 of the 97 included patients had a history of BMs, and the effect of previous cranial RT on the activity of pembrolizumab was not investigated. To date, most publications on the combination of cranial RT and PD-1/PD-L1 inhibitors have been small retrospective studies focusing on the effect of concurrent or consolidative cranial RT and PD-1/PD-L1 inhibitors on patient outcomes (12, 26, 27). This current study represents, to the best of our knowledge, a pilot investigation on the effects of previous cranial RT on the efficacy of anti-PD-(L)1 therapy based on the most compelling and largest pool of clinical data available.~~"

(Line 321-336: in revised main text)

"~~In line with this speculation, we found that OS was better in patients with iBM than those without BM, while it was similar between patients with niBM and those without BM. The survival advantage of patients with iBM over those without BM was not observed in the chemotherapy group. We also compared the survival outcomes between patients with iBM and niBM. The results indicated that patients with iBM had a trend toward improved OS than those with niBM in the atezolizumab group, However, no difference in OS was observed between iBM and niBM patients in the chemotherapy group. The small sample size of patients with niBM may have limited our power to detect significant survival differences in the atezolizumab group. Some previous studies have shown that the ICIs combined with cranial RT prolonged OS for patients with NSCLC BM than ICIs alone (15, 28). A previous retrospective multi-institutional study showed that anti-PD-(L)1 therapy combined with upfront cranial RT prolonged OS for patients with brain-metastatic NSCLC than anti-PD-(L)1 therapy alone (15). Another retrospective multicenter analysis demonstrated that recent cranial RT within 3 months of the initiation of ICI treatment improved the survival of patients with NSCLC BM compared with ICI treatment alone (28). Taken together, these findings suggest the potential of the combination of cranial RT and immunotherapy to augment anti-tumor immunity for patients with NSCLC BM.~~"

The lack of specifics on PFS is a major limitation (i.e. intracranial vs extracranial progression)

Reply: We have discussed this limitation in the Discussion section.

(Line 395-397: in revised main text)

"Sixth, the 7 trials included did not provide specific information about the sites of the progressive disease (i.e. intracranial vs extracranial progression). Therefore, intracranial PFS or extracranial PFS could not be analyzed."

Reviewer B

The results of this study are intriguing.

In the analysis of individual patient data from seven prospective trials, authors demonstrated the prolongation of OS in patients with BM compared to patients without BM in the group of patients receiving atezolizumab. This benefit was not observed in patients receiving CHT alone. Further, in the Atezolizumab group, patients with irradiated BM had better OS than patients w/out BM. This difference was not observed for patients with non-irradiated BM vs patients w/out BM.

Indeed, this is very intriguing and hypothesis-generating finding.

However, as Authors stated, it is very small proportion of patients who had no cranial irradiation for BM. We cannot exclude that there were any undetected variables that impact on the unfavorable prognosis of these patients. Additionally, with such a small number of patients the statistical power is low.

In a new updated RPA for BM, the PD-L1 status was included as one of the predictors of survival. In at least two of the included trials, only patients with PD-L1 positive results were included. I know, that with PSM, the results unchanged, but this would be interesting to include only PD-L1 status to check the results (some other included variables not necessarily impact on the OS of patients with BM).

Atezolizumab improved survival in metastatic NSCLC. This would be relevant to check, how this drug improved OS for all patients (from 7 trials), for BM patients (irradiated and non-irradiated), and for patients w/out BM. This probably won't change a main message from this study; however, this will further strengthen a message that both cranial RT + IO are needed, and non IO only.

Reply: We thank the reviewer for the valuable comments and suggestions. We appreciate the reviewer's interest in further analyzing the data based on the PD-L1 status and exploring the impact of atezolizumab on overall survival (OS) for different patient groups (all patients & patients with BM & patients without BM).

However, we would like to kindly clarify that the reviewer's questions are beyond the scope of our research. We want to assure you that our study still supports the message that both cranial RT and IO are essential for improving treatment outcomes, as mentioned by the reviewer.

In fact, numerous previous studies have extensively investigated the impact of IO including atezolizumab on OS in both all patients and subgroups of patients with and without BM (PMID: 30780002, 34590048, 34265431, 30642441, 37729600). The results consistently showed that IO treatment improved OS for all patients, patients with BM, and those without BM.

We acknowledge the need for further research to fully explore the potential benefits for patients. Unfortunately, our access to the data in Vivli ended on 11/29/2023, which prevented us from performing the requested analysis. Due to this limitation, we were unable to include the specific analysis in our study. We apologize for any inconvenience caused by the limitations in our analysis.

Changes in the text: none

Reviewer C

This study provides valuable insight that cranial RT may prime an effective systemic immune response to immunotherapy, from pooled analysis of individual patient data from seven prospective trials involving atezolizumab for the treatment of NSCLC. It also showed that neurologic safety profile of atezolizumab in patients who had previously received cranial RT for NSCLC was generally acceptable.

As authors noted, the small sample size of patients with niBM may be one of the major limitation, nevertheless quite better survival (OS HR 0.45) in patients with iBM than those with niBM or without BM is an impressive result for many readers

1. It would have been better if BM characteristics (such as number of baseline BM and the diameter of the largest BM) were taken into consideration during the PSM matching analysis, but as the authors described, it is also unfortunate that there was no information currently available. Is there any additional information available, such as extracranial disease burden potentially usable for PSM?

Reply: We thank the reviewer for this comment. Unfortunately, the seven trials included in the present study did not collect information on BM characteristics (such as number of baseline BM and the diameter of the largest BM) and extracranial disease burden. We acknowledge that the lack of information on baseline BM characteristics, such as the number and diameter of the largest BM, is a limitation of our study, which we have mentioned in the Discussion section. Additionally, we regret that there was no available information on extracranial disease burden

for potential use in the PSM analysis, and thus, we were unable to include these factors in our PSM matching analysis. We understand that considering these additional variables would have provided a more comprehensive analysis. We apologize for any confusion caused by the absence of this information.

2. Is there a hypothesis for a mechanism that can explain atezolizumab treatment and cranial RT synergism?

Reply: We have included the following statement in the Discussion section to discuss potential mechanism that can explain atezolizumab treatment and cranial RT synergism.

(Line 351-358: in revised main text)

"One possible mechanism for the synergism between atezolizumab treatment and cranial RT is their combined effect on the immune system and tumor microenvironment. Cranial RT can enhance the release of tumor antigens, making them more accessible to the immune system. Atezolizumab, by blocking the PD-L1 pathway, can further enhance the immune response, preventing cancer cells from evading immune detection and destruction. This combined approach has the potential to increase tumor cell killing and promote a stronger anti-tumor immune response, potentially improving treatment outcomes for patients. It is important to note that further research is still needed to fully understand the mechanism and optimize the combination of atezolizumab treatment and cranial RT for maximum efficacy and safety."

3. Is the HR used in the description of Fig 2C, 2D, 3C, and 3D in the text correct? Isn't it just simple HR?

(line 218, 220, 253, 255)

Reply: Yes, it's correct. The term "adjusted HR" refers to the hazard ratio that has been adjusted for multiple variables in the multivariate analysis.

4. additional few minor points to be corrected

line 103: demonstrtaed

line 107: fulfil

line 216: figure 1c and 1d -> 2c and 2d

line 239: Figure 3G and 3H -> 2G and 2H

reference 15: XXXX ?

Reply: We thank the reviewer for carefully checking our manuscript. We have addressed the minor points that need correction.

(Line 102: in revised main text)

"Several case reports have demonstrated the extracranial…"

(Line 106: in revised main text)

"To fulfill this unmet need, we…"

(Line 215: in revised main text)

"Figure 2C and 2D shows the Kaplan-Meier survival curves for…"

(Line 238-239: in revised main text)

"…after PSM (Supplementary Table 5 and Table 6, Figure 2G and 2H)."

(Line 459-461: in revised main text)

"15. Guo T, Chu L, Chu X, Yang X, Li Y, Zhou Y, et al. Brain metastases, patterns of intracranial progression, and the clinical value of upfront cranial radiotherapy in patients with metastatic non-small cell lung cancer treated with PD-1/PD-L1 inhibitors. Transl Lung Cancer Res 2022;11:173-87."