TLCR TRANSLATIONAL LUNG CANCER RESEARCH
AN OPEN ACCESS JOURNAL FOCUSING ON CLOSING THE GAP BETWEEN "BENCH AND BEDSIDE"
IMPACT FACTOR 5.132

Peer Review File

Article Information: http://dx.doi.org/10.21037/tlcr-20-1117

Reviewer A:

This is a timely topic of interest to the radiotherapy community. The review is very well-written, and does a comprehensive job of describing the relevant literature relating to the mechanism of action of ICIs as well as their use in combination therapy alongside SABR. With respect to combination therapies combining ICI and RTs, it covered the relevant literature with respect to dose, fractionation, types of ICI to use, advantages and drawbacks of various sites of different immunogenicity, and single vs. multi-site treatments.
No major concerns, but just a few minor corrections:

Comment 1: Lines 120-122: The sentence should be broken in two: RT, in particular sterotactic ablative radiotherapy (SABR), has many postulated systemic immunomodulatory effects. This will be the subject of this review.
Reply 1: Noted.
Changes in text: Broken into two sentences as suggested. Now lines 121-123 in the revised manuscript.

Comment 2: Lines 160-162: The sentence should be broken in two: The benefit of ICIs in high PD-L1 expressing tumours is well established. However, this subset comprises ~30% (13) of patients with m-NSCLC.
Reply 2: Noted.
Changes in text: Broken in two sentences as suggested. Now lines 162-163 in the revised manuscript.

Comment 3: Lines 300-302: The first sentence should be broken in two: The optimal sequencing of RT and ICIs is yet to be definitively described in the clinic. However, preclinical data...
Also, in line 302, I think the reference to ICIs is wrong. It reads, "However, preclinical data suggests that ICIs are most effective ... in close sequence with ICIs ..." The second ICI should be RT, I think ("However, preclinical data suggests that ICIs are most effective ... in close sequence with RT ...").
Reply 3: Noted.
Changes in text: Broken in two sentences as suggested. Also, the second ICI has been changed to RT as suggested. Now lines 307-309 in revised manuscript.

Comment 4: Line 307: responds should be respond

Reply 4: Noted.
Changes in text: “responds” has been changed to “respond”, as suggested. Now line 314 in the revised manuscript.

Comment 5: Line 356: missing something after statistically significant. Should probably be "... a statistically significant increase in PFS to 19 months ..."
Reply 5: noted
Changes in text: Line has been changed to “a statistically significant increase in PFS to 19 months” as suggested. Now lines 363-364 in the revised manuscript.

Comment 6: Line 480: not sure what the end of this sentence means. Should it be something like "too large to treat with SABR completely?". So for large volume tumors?
Reply 6: Thank you for the comment. We had meant large volume tumours that are too large to treat with SABR.
Changes in text: We have removed “tumours that are too lage in volume to SABR in entirety.” and have replaced it with “large volume tumours”. Now lines 485-486 in the revised manuscript.

Comment 7: Line 492: missing a subject after "but": should be something like "... compared to conventional chemotherapy, but they are ..." or "their use is ..."
Reply 7: Noted.
Changes in text: inserted “their use is” after “but”, as suggested. Now line 499 in the revised manuscript.

Reviewer B:
The authors have provided a clear and concise review of literature associated with immunotherapy treatment of metastatic NSCLC and make a compelling case for further investigation into the potential for combination with stereotactic ablative radiotherapy**. I am happy to recommend that this review be published in its current form,** but do have some minor comments/suggestions for the authors to consider.

Comment 1: The authors have provided a clear and concise review of literature associated with immunotherapy treatment of metastatic NSCLC and make a compelling case for further investigation into the potential for combination with stereotactic ablative radiotherapy. In the mechanisms of resistance section the authors clearly describe the role of different immune cell subpopulations in ICI resistance. There is also growing evidence to support

that non-immune stromal cells within the TME play an important role in ICI resistance. For example, recent studies by Dominguez et al and Kieffer et al (both Cancer Discovery 2020) showed that cancer associated fibroblast gene signatures were significantly increased in NSCLC ICI non-responders.

Reply 1: Thank you for the comment. We primarily focused on the role of immune cells in the TME. We also acknowledge the emerging roles of non-immune cells in ICI non-responders, in patients being treated for NSCLC.

Changes in text: We have incorporated the reviewer's comment into the mechanisms of resistance section. See lines 240-244 in the revised manuscript).

Comment 2: The authors highlight the importance of optimal sequencing of radiotherapy and ICI treatments and suggest that this will need to be specifically optimised for different ICI modalities. Is there data to suggest that the results from pre-clinical studies are reflected in clinical trials? I.e. is there any data to support whether murine models are a reliable platform for carrying out studies to optimise treatment sequencing? Including a comment either for or against their suitability would be useful in the "Sequencing of RT and ICI" section.

Reply 2: Thank you for the comment. Sequencing with SABR and ICI is a novel area, that is being explored. There are currently no published clinical trials that we are aware of that examine this. As such we cannot comment on whether pre-clinical studies are reflected in clinical trials, or make a recommendation on the translatability of murine models. Sequencing with SABR and ICI (Pembrolizumab) is being investigated in m-NSCLC in the SABRseq phase I trial (NCT03307759). We are eagerly awaiting the results of this trial, and this has been mentioned in our manuscript.

Changes in text: no changes