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Review Comments

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Reviewer A

Well written comprehensive review. Minor comment that a small paragraph on literature search strategies should be included after introduction.
Reply: Thank you. This section was added as suggested.

Reviewer B

1. Introduction - Lurbinectedin is now also approved in the second line setting and so this introduction should be revised. Both topotecan and lurbinectedin are FDA approved agents in second line.
Reply: Thank you. The approval came after the paper was submitted. The paper has now been updated.

2. Line 72 – insert word “study” following retrospective
Reply: Thank you for catching this. Added.

3. Lines 100-102 – consider revising taking into account that both lurbinectedin and topotecan are now FDA approved for second line treatment of SCLC
Reply: Updated.

4. Lines 162-164 – would revise now that lurbinectedin is also FDA approved.
Reply: Updated.

5. In the irinotecan section could consider discussing liposomal irinotecan which is being investigated in SCLC and which has some preliminary data.

Reply: The preliminary data were added, as suggested.

6. Lines 240-242 – was intracranial response rate available to suggest that responses to temozolomide were actually seen in active, untreated brain metastases. Assuming these were active untreated brain metastases versus previously treated and stable brain metastases.
Reply: Yes, this is referring to untreated brain metastases and the sentence was restructured for accuracy and clarity.

7. Lurbinectedin section - Since this is now FDA approved as second line therapy would suggest discussing it earlier in the manuscript and editing parts of the manuscript to reflect this new FDA approval.
Reply: Yes, this has been moved to follow topotecan and updated.

8. In the phase I study of lurbinectedin plus doxorubicin which was discussed and on which outcomes were reported, how many patients had platinum sensitive versus resistant SCLC?
Reply: This was added (12 sensitive, 15 resistant)

9. Lines 265-269 - update median OS and other data based on the most up to date information from the recent Lancet Oncology publication in May 2020.
Reply: Yes, this was updated.

10. Consider making PARP inhibitor one section and discussing the talazoparib monotherapy data in SCLC.
Reply: This data was added, thank you.

11. Consider making temozolomide plus PARP inhibitors a separate section.
Reply: There did not seem to be enough to justify two separate sections so we opted to leave these together.

12. Lines 295-300 - this did not compare the two treatments, but rather compared SLFN-11 positive versus negative within each treatment arm and thus should be revised. Should be mentioned there was no difference in PFS or OS for temozolomide monotherapy when comparing SFLN-11 positive versus negative.
Reply: Thank you for calling attention to the misphrasing, this has been clarified.

13. Make sure when PFS and OS are mentioned in body of manuscript that it is clear whether this is median or mean, etc.
Reply: Thank you.

14. 361-363 – this sentence (end of line 361 through first part of line 363) can be removed as was mentioned verbatim above.
Reply: Yes, removed.

15. When discussing CheckMate 032 would suggest highlighting this was immunotherapy naïve patients and could consider discussing the limited data in the randomized portion available for patients who progressed on nivolumab and subsequently received nivolumab plus ipilimumab.
Reply: this caveat was added

16. Immunotherapy regimens discussed - May want to discuss whether or not these have any place in the current therapeutic landscape where immunotherapy is now part of initial first line treatment in combination with platinum plus etoposide. In effect, is retreatment with PD-1/PD-L1 inhibition plus/minus CTLA-4 inhibition likely to be beneficial at all following progression on platinum etoposide immunotherapy.
Reply: Yes, agreed and this has been added.

17. Immunotherapy regimens – would highlight that the nivo, pembro, nivo plus ipi and atezo studies discussed in the manuscript were in immunotherapy naïve patients.
Reply: Yes, clarified.

18. Lines 401 – 402 – When discussing CheckMate331 data on PFS in the two treatment arms, would suggest providing HR and p-value for this comparison.
Reply: Yes, quite telling. This was added.

19. For CheckMate451 consider providing data on the nivolumab monotherapy maintenance arm.
Reply: This was added.

20. Lines 422-423 – were these side effects grade 3 only, or grade 3 and higher? I noticed you mentioned grade 3 AEs and grade 5 AEs. Were there no grade 4 AEs?
Reply: Correct, there were no grade 4. This was clarified and the section was updated to reflect the interval publication.

21. Table 1 – were these median PFS and median OS?
Reply: Yes, updated.

22. Instead of NTP and TCP consider just putting neutropenia and thrombocytopenia
Reply: This was changed

23. Table 2 – I would double check the RR mentioned for the three regimens as I think these RRs are too high (not accurate).
Reply: Yes, not sure how this error was made but it has been corrected.

Reviewer C

I have read with interest the review titled “Salvage Therapy in SCLC”. The authors summarized the treatment options for relapsed SCLC in this review.

Major comments:

For a meaningful review, a timely topic is needed. The general progress of the field of SCLC are relatively few in recent years. I suggest the author focus on one specific filed for the relapsed SCLC.

Reply: Thank you for the comment. With the recent approval of lurbinectedin in 2020, we do feel the topic is more timely now.

Reviewer D

This review provides an overview of the current standard of care and response to experimental therapies for small-cell lung cancers (SCLC). The paper reviews curated studies to understand what other agents may potentially increase efficacy of relapsed SCLCs. While resistance mechanisms are certainly of interest in the SCLC field, the review lacks the author's perspective on how the results from these trials can guide future trials and experimental studies in relapsed SCLC. Overall, the review is concise and well-organized. The following are major concerns:

1. Tables summarizing the clinical trials for the target-therapy and immunotherapy sections in text would be helpful.

Reply: An additional table was added as suggested.

2. While the authors did mention the first pivotal immunotherapy study, Impower133, the authors should also report the most current immunotherapy combination results, such as KEYNOTE-604, where the combination regimen did not show a statistically significant improvement in overall survival, but in PFS for ES-SCLC patients. The authors should offer their perspective of the implications of these discordant results - "lessons learned".

Reply: This is an interesting topic but is being addressed in a separate manuscript and did not seem to fit in this narrative review on salvage therapy.

3. In-depth discussion or speculation on potential resistance mechanisms explaining the results throughout the text would be helpful.

Reply: This has been mentioned now in the conclusion with appropriate references to summary papers, as this was not the focus of this narrative review.

4. The review focusses on relapsed SCLC yet there is a lack of discussion on what resistance mechanisms or hypotheses have been generated in this field.
Reply: This has been mentioned now in the conclusion with appropriate references to summary papers.