Reviewer’s report

Title: Natural History and Outcome in Chinese Patients with Gastroenteropancreatic Neuroendocrine Tumours: A 17-year Retrospective Analysis

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Reviewer: Michael Postow

Reviewer's report:

Redman et al. review advances in immunotherapy for melanoma. They start with a description of IL-2 and then discuss immune checkpoint inhibitors with a subsequent focus on special clinical scenarios such as brain metastases, adjuvant therapy, combinations, and biomarkers. The review is well written and thorough. I left a number of detailed comments which are just intended as discretionary areas for possible improvement of the manuscript.

1. In the introduction's 2nd to last paragraph, the authors should add that CTLA-4 inhibits T cells through a number of different mechanisms. (in addition to just outcompeting CD28 for binding to B7.1)

2. Citations 10 and 11 appear in the "Anti-CTLA-4 Therapy" section discussing early phase trials. It would be better to cite the early work at the NCI (Prieto et al. Clin Cancer Res 2012 provides a summary of these three early NCI trials if helpful), rather than the phase II trials currently mentioned.

3. When quoting the median OS and the 1- and 2-year OS for the MDX010-20 study (ipi with gp100), it would be helpful to be more precise in mentioning if the numbers mentioned are for the ipilimumab alone arm or the ipi + gp100 arm. Understandably, there was no significant difference.

4. In the paragraph describing the pooled long-term ipi OS data starting with the "follow-up extended to 10 years and suggested…", I think it's better to state "durable overall survival" (instead of "durable responses").

5. The authors should consider adding 2-3 sentences about tremelimumab in the CTLA-4 section. Likely just mentioning some response rates in phase II and explanations as to why the phase 3 study may not have shown an OS benefit would likely suffice.

6. Citation 22 should be Hamid et al. NEJM 2013.
7. In the adjuvant ipilimumab section's last paragraph, the term "advanced" in describing melanoma (and superiority of anti-PD-1 over ipilimumab) may be a bit confusing when coming right after the adjuvant discussions since PD-1 in the adjuvant setting is just now being compared to ipilimumab and other control arms in other trials. It would be best to replace "advanced" with "established, unresectable metastases" to be most specific about the disease setting where the superiority of PD-1 over ipilimumab has been shown.

8. In the adjuvant ipilimumab section, I would include one sentence about the 5 treatment-related deaths.

9. The follow-up time for citation 41 should be included in that sentence since a 30% relapse rate is time dependent and inevitably would likely increase as follow-up increases.

10. The authors mention pembro vs. placebo is actively accruing patients, but it would be helpful if this exact, precise language was used to describe the pembro vs. high dose IFN study, if indeed this study is also already accruing patients as well.

11. When discussing checkmate 064, the authors should mention the 47.7% and 22.6% ORR refers to ORR at a later timepoint (~6 months).

12. The authors may want to now wish to include the low dose ipilimumab + pembrolizumab data that were presented at the SMR meeting in 2015.

13. In discussing ipilimumab + GM-CSF, the authors should mention specifically that it was longer "overall" survival, instead of just "survival," given the lack of an obvious PFS difference.

14. I'm not sure citations 51 and 52 are both necessary. Citation 52 is the more mature data and would likely be sufficient alone.

15. In describing citation 58, the authors should include a caveat that the number of treated patients is still very low with the IDO + pembrolizumab combination.

16. In describing the PD-L1 results from checkmate 067, I would still caution the language "PD-L1 status might help select for patients to give anti-PD-1 monotherapy". In patients with PD-L1 + tumors, the response rate was still higher in patients receiving the combination vs. monotherapy. More general, cautious language is least likely to be offensive in this controversial area.
17. In discussing the mutational load possible biomarker, the authors may want to consider citing Levi Garraway's recent publication on the topic (Van Allen Science 2015).

18. At the end of the conclusion's first paragraph, the authors could cite "Horvat et al. Journal of Clin Oncol 2015 and Weber et al. ASCO 2015" to make their point even more strongly that treating side effects of ipilimumab and nivolumab, respectively, does not compromise outcomes.

19. In the first sentence of the last paragraph of the review, I'd recommend being more conservative with the declaration combination CTLA-4 and PD-1 is more effective than monotherapy. Perhaps apparent ORR and PFS, but it's important the authors include a mention that we still await OS data from the phase III checkmate 067 study.

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