Memorial Sloan Kettering
Cancer Center

Tiago Villanueva MD
Associate Editor, The BMJ

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Dear Dr. Villanueva,

Thank you for your thoughtful review of our Manuscript (BMJ.2017.041528) entitled "Immune-related Toxicities in PD-1 and PD-L1 Immunotherapies: a Systematic Review and Meta-analysis." Below please find detailed responses to the comments from Editors and Reviewers.

In addition, we would like to inform you that Dr. Korenstein will be the corresponding author moving forward. We have updated the submission on the website and the manuscript to reflect this change.

Comments from Editors

Comment 1: *This is a mostly well done SR and MA which seems to closely follow Cochrane methodology. Perhaps the biggest limitation of this study is the use of RCTs only when the focus is on AEs. All included studies focused on AEs only as a secondary objective. Many studies were excluded as they did not meet the review study design criteria which may have otherwise contributed useful information, especially given the rarity of some of the events.*

Response 1: We agree with the biostatistician's point about this limitation, given that AEs are a secondary outcome in clinical trials. We elected to only include clinical trial data because of the relative rigor and reproducibility of the established rules for collection, grading and reporting of adverse events in therapeutic clinical trials. Further, we limited to only randomized controlled trials to enable comparison between checkpoint inhibitors and standard of care in a meta-analysis. We completely agree that future prospective observational studies will add to this literature but because these drugs are quite new there is not yet a robust observational literature

Deborah Korenstein MD, FACP
Director of Clinical Effectiveness
Chief, General Medicine Service
korenstd@mskcc.org

485 Lexington Avenue, New York, NY 10017 T 646.888.8139 F 929.321.1518
www.mskcc.org

NCI-designated Comprehensive Cancer Center

so we felt that clinical trial adverse events represented the best opportunity, at this point, to better understand drug toxicities. We have acknowledged this limitation now with additional statement, “Given the rapid anticipated growth in the number of patients treated with anti-PD1 agents, institutional cohort studies could provide more immediate insights into immune-related drug toxicities with an emphasis on not just short-term, but also long-term, adverse events, “ on Page 13 in the discussion section.

Comment 2: *Figure 2: I was unclear how authors got from the 1876 records to 1846 screened.*

Response 2: We apologize for the typographical error. We have now corrected this error in the figure.

Comment 3: *More detail is needed on the hierarchy of evidence. Data was taken from CT.gov and from the publication. What happened if the results from the two sources differed?*

Response 3: We thank the Editors for pointing out the lack of clarity. We made two changes to the main paragraph discussing data on Page 7 to further clarify this point. We removed a sentence that could lead to confusion and was redundant, “We identified outcomes of interest using both the publication identified in the review and study data posted on ClinicalTrials.gov.” We also added a sentence at the end of the same paragraph, “For studies with information available from both sources, we prioritized data from ClinicalTrials.gov over toxicity data from the publications.”

Comment 4: *There was a lot of zero event data, how was the accounted for in the meta-analysis? What method of estimation was used to best address this?*

Response 4: We thank the Editor for this important question. Studies that had zero events for both cases and controls did not contribute to the pooled OR estimate for an AE since an OR was not estimable for that specific study. We used the inverse-variance method, which weights the treatment effect of each study based on the inverse of its variance and does not include studies with zero total events. We added this issue as a limitation of the study at the bottom of page 14, as follows: “We also assumed that no events of a particular type occurred if none were reported and in our meta-analyses studies with zero events did not contribute to the pooled result. This may have led to errors in our pooled estimates, though the issue impacts the intervention and control arms equally.”

Comment 5: *There was inconsistency in the forest plots on the use of fixed and random effect meta-analysis which did not follow the approach described in the methods.*
It was a big assumption to make that non-reporting of an AE was a result of 'no events'.

Response 5: We apologize for the inconsistency and thank the Editor for pointing it out. The inconsistency in the forest plots has been fixed and the plots presented now reflect the approach described in the methods.

Comment 6: *These zero's were included in the MA I think - this may not be true. The non- reporting of the event might be for the reason of selective non-reporting (see Saini et al. 2014 in The BMJ). This was also not reflected under the selective reporting domain in the RoB assessment which was listed as low risk for all studies.*

Response 6: We agree with the Editor that selective non-reporting could be a reason for zero events. In terms of the MA, as described above, studies with zero total events were not included in the calculation of pooled estimates. In risk of bias assessments, we had to rely on the primary outcomes. We agree that with regard to selective reporting the risk of bias assessment regarding the primary outcomes may apply poorly to toxicity data, but we have no way to assess selective reporting of toxicity data. For this reason, we have added a footnote to Appendix Table 1 (Risk of Bias), stating that the Selective outcome reporting domain applies to primary outcomes and not to toxicity data.

Comment 7: *Another editor said this is an important topic and it would be good to know the spectrum of adverse events and their relative frequencies. He added the list of adverse events is known and published RCTs aren't best placed to give an unbiased report of frequencies. He would have preferred inclusion of many more MAB therapies and of non-randomized studies.*

Response 7: We appreciate the support from the editor on this important topic. We would like to explain the choices we made to be selective and only address the monoclonal antibodies that are directed at PD-1 and PD-L1 and only include RCT's for our meta-analysis. First of all, checkpoint inhibitors are unique in their mechanism of action compared to other monoclonal antibodies and as a result, the adverse events associated with their use differ. As a result, a broader understanding of the adverse events associated with monoclonal antibodies was beyond the scope of this study.

We agree that well conducted prospective cohort studies with larger populations of patients treated with checkpoint inhibitors could offer important insights into the incidence and nature of immune medicated adverse events, but given the relatively recent introduction of these agents, such post-approval studies are only forthcoming. The publications that are currently available tend to focus on specific adverse events such as neurological or cardiac events resulting from immune activation. We now include these references in the discussion on page 14 with addition of the following sentence: “Similar attention has been turned to less frequent, but significant toxicities impacting the neurologic, cardiac, and ocular systems.” Such reporting remains crucial in a rapid understanding of these novel therapies, but cannot provide a balanced review of adverse events related to these drugs in general.

Comment 8: *Another editor thinks that this is an important paper He does not think that this is niche, as more patients are now being treated with immunotherapies and physicians with many specialties will see them (many are immune mediated and systemic). While these agents are better tolerated than usual chemotherapeutic agents, they pose different risks. He said you should address the fact that RCTs only identify short-term toxicities.*

Response 8: Thank you for this suggestion. We have now clarified the short time frame available for toxicity assessment in these studies. Specifically, we now write on page 13 in the discussion, “With a focus on acute or short-term adverse events captured in clinical trials, our study may have underestimated the prevalence of late-developing or persistent immune-related toxicities.”

Comment 9: *As the experience with these agents grow, we are uncovering more adverse effects, and manufacturers may not have a record of any prior instances. These adverse effects are being reported to FDA and regulatory bodies. Is there a way you can access the data? This could be a separate paper, or a separate section. You could also do a literature search for case reports of toxicities associated with immunotherapies, and include a small section about these in their paper (it should not replace or overshadow the MA from RCTs).*

Response 9: We appreciate this interesting suggestion and agree it would be helpful to access such data. Unfortunately, data from post-marking surveillance are not routinely made publically available. We hope that

investigators will make such information available in the future, but this is not something that we could access for this study. We did include more in the discussion and additional references to case reports and case series chronicling neurological and cardiac toxicities now on page 14. “Similar attention has been turned to less frequent, but significant toxicities impacting the neurological and cardiac systems.”

Comment 10: *Another editor was supportive. He said that even though these adverse effects have been published in specialist journals until now, it is plausible to suspect that more and more oncological patients will therefore be seen by a non-specialist with related complaints, so he acknowledges it could thus be worth to present these findings to general readers.*

Response 10: Thank you for your supportive comments.

Comment 11: *Another editor thinks it is very timely and important, and not only GPs but also oncologists should learn and pay attention to AEs caused by immunotherapy. The authors should specify it only identifies short-term toxicities.*

Response 11: Thank you for this suggestion. We have now explicitly commented on the relative limited follow-up for adverse events in currently published randomized studies. On page 13 in the discussion, we now state, “With a focus on acute or short-term adverse events captured in clinical trials, our study may have underestimated the prevalence of late-developing or persistent immune-related toxicities.”

Comment 12: *Another editor said these results are worth highlighting as clinicians are unaware of what to look for and can be caught on the back foot. Absolute risk rates are worth knowing. He did wonder if it might be better if the control group subtracted rates of SAE were reported i.e. the excess risk, but we dont have a true placebo group.*

Response 12: We appreciate this suggestion and agree that excess risk would be useful to report. However, given that the included studies did not have true placebo groups, we feel that we do not have the correct data to report excess risk. However, we do report absolute rates of organ complications in the text (page 10) and in Appendix Table 2 and we report absolute rates of musculoskeletal toxicities in Table 1.

Comment 13: *Other editors were concerned with the lack of post-surveillance observational data.*

Response 13: We agree that longer-term observational data will be critical for informing a full understanding of the toxicities of these drugs. However, little such information is available and in order to perform a meta-analysis, we needed a consistent and systematic method for data collection. We therefore did not include any such data, although in the future it will certainly further our understanding of the toxicities associated with these agents.

Comments from Reviewers

Reviewer 1

Comment 14: *Were the PD1/ PDL1 levels reported in the published studies? If yes, It would be important to correlate PD-1/ PD-L1 levels with the levels and type of immune-related toxicities*

Response 14: We thank the Reviewer for this interesting question. Adverse event data is not available by the PD-1 status of tumors on ClinicalTrials.gov or in the published reports, so we were unable to perform this analysis. While the data available from phase I and phase II studies on anti-PD-1/anti-PD-L1 monoclonal antibodies suggest that the development of adverse events is not dose dependent, as seen with traditional cytotoxic chemotherapy, we agree that in the future it would be interesting to look further at the question of PD1/PDL1 levels.

Comment 15: *The authors have described the presence of muscle-related toxicities as a novel side-effect associated with checkpoint inhibitors. These findings need to be discussed further - what would be the possible mechanisms of checkpoint inhibition that would lead to bone, muscle and joint toxicities?*

Response 15: We appreciate this insightful suggestion and have now expanded discussion of the issue on page 12. Specifically, the manuscript now reads: “These problems are not surprising given that autoimmune diseases commonly have musculoskeletal manifestations. Inflammatory arthritis from checkpoint inhibitors has already been recognized in the rheumatology community; these adverse events are likely to grow in prevalence over time.”

Reviewer 2

Comments 16: *This work would be highly valuable to the clinicians to be*

aware of the potential side effects of the treatment and encourage patients to report all the symptoms that they might develop during the course of the treatment.

Response 16: We thank Reviewer 2 for these supportive comments.

Reviewer: 3
Comments 17: *Do the imAEs have tumor type specific (or dependent) incidence?*

Response 17: We appreciate the Reviewer's interesting question. Unfortunately the answer is not known. Our analysis would suggest that the development of an adverse event is agnostic to tumor type, given that there was little heterogeneity in event rates across studies that included patients with different tumor types. However, there is some speculation that prior therapy or exposure might increase the risk for some patients. For example, radiation to the neck in head and neck cancer may lead to higher rates of hypothyroidism, but whether this increases the risk of immune-mediated hypothyroidism with checkpoint inhibitors is unclear at this time. Our study was not designed to evaluate these nuances, though we look forward to future studies for better clarity.

Comment 18: *Can you stratify the imAE of PD-1 and PD-L1 blockade? Antibodies targeting these two proteins essentially affect the same pathway theoretically. However, the applications of these antibodies were considered differentially in reality. Hence, comparison of adverse effects for them will add significance to this study.*

Response 18: We appreciate the Reviewer's attention to this important detail. For the purposes of this study, we combined the two types of monoclonal antibodies into the analysis. This was based on prior published reports of similar adverse event profiles between the two. (Weber, JS et al. Toxicities of Immunotherapy for the Practitioner, Journal of Clinical Oncology, 2015 Jun 20; 33(18): 2092-2099). Further, with 11 of 13 studies evaluating the efficacy of the anti-PD-1 agents nivolumab and pembrolizumab, the ability to detect any meaningful difference between the two drug types would likely be small. We acknowledge this in our limitations on page 15, "Given the wide variation in drug and dose across studies we

were unable to perform subgroup analyses to examine these factors. However, we found little heterogeneity across studies for toxicity outcomes, suggesting little difference based on the specific agent or the drug dose."

Comment 19: *A graph illustrating the incidence of organ-specific or musculoskeletal imAE will convey the comparison more efficiently and concisely.*

Response 19: Thank you for this suggestion. We attempted to make such a graph but the wide range of adverse event rates from 0.1% for hepatitis to up to 22% for back pain, makes visualization on a single graph difficult. We therefore opted to present the rates in the text and in tables.

Comment 20: *In Langer et al 2016, the PD-1 blockade was added on top of carboplatin and pemetrexed. Can you justify your comparison of imAE between the PD-1 antibody and standard treatment as stated in your objective?*

Response 20: We thank the Reviewer for pointing out the distinction. Our inclusion criteria specified any RCT that compared a standard arm to an arm that included an anti-PD-1 agent. This study, although unique in including chemotherapy in both the standard and intervention arms, met this criterion. In our meta-analyses, results from Langer did not appear as an outlier and we believe that inclusion of this study did not bias our results. In addition, we used a random effects model to account for heterogeneity among studies in the meta-analysis, which helps to mitigate large differences in study event rates.

Comment 21*: How many records were identified? 2485 or 2486?*

Response 21: We apologize for the typographical error. We identified 2486 studies and have made corrections to make this number consistent throughout the PRISMA diagram and the text.

Comment 22**:** *Suggestion for abbreviation as inconsistency appeared in the text: imAE for immune-mediated adverse effect and irAE for immune-related adverse effect.*

Response 22: Thank you. We have referred to these toxicities as immune-related adverse events and irAE throughout the text to be consistent.

Comment 23 *You might want to explain the 'weight' in the figure more in detail.*

Response 23: Thank you for this suggestion. The weight is calculated from the inverse of the variance of the effect estimate for each study. We have added an explanation to the methods section on page 8, which reads "Studies were weighted based on the inverse of the variance of the effect estimate."

Reviewer: 4
Comment 24: *Evaluating the side effects of immunotherapy across trials is challenging as the authors list in the conclusions and limitations sections. Not only can there be variation between investigators in assigning CTCAE criteria, but each study also has different criteria for defining irAE. Indeed, reported toxicity tables in many of the cited studies include (AST/ALT elevations simultaneously with hepatitis). This should be further discussed as another potential source of uncertainty regarding the quality of data.*

Response 24: Yes we absolutely agree with this important point and have added further limitation to explicity state this in the discussion on page 13. "This could lead to potential uncertainty regarding the quality of the data, which will need to be addressed moving forward for studies of immunologic agents."

Comment 25: *Another limitation that merits additional discussion is the variance in the control groups. This meta-analysis lumped all of the control groups together. However, there is a significant difference in adverse events between single-agent chemotherapy vs doublet chemotherapy vs everolimus. This does bias the control group comparison and needs to be discussed further in the discussion section.*

Response 25: We thank the Reviewer for this comment and agree that this represents possible bias. We did look for relevant control group differences before performing meta-analysis for each outcome. For two particular toxicities, rash and pneumonitis, there was an increased risk associated with specific targeted therapies so we separated those drugs in the meta-analysis and display them separately. In other cases, because immune-mediated toxicities occur via a unique mechanism, we believe that comparison to any other control is reasonable. The relative consistency of findings across studies supports this approach. We discussed this issue in

the Limitations section on page 15: “In addition, we combined all non-immunotherapy agents into one category of “control”, including both traditional chemotherapy and two targeted agents, cetuximab and everolimus. We performed a subset analysis separating targeted from non-targeted control therapy. Risks of pneumonitis and rash differ for targeted therapies compared to traditional chemotherapy and odds ratios differed across control therapies, so targeted agents are presented separately. For other outcomes there was no heterogeneity based on comparator so all studies are presented together.”

Comment 26: *For consistency with other manuscripts, I suggest changing "serious" in table 2 to "Grade 3-5". This is the common way of reporting and is less subjective to interpretation than "serious".*

Response 26: Thank you for this suggestion. We have now clarified the category in Table 1, “Incidence of musculoskeletal toxicities.”

Yours truly,

Shrujal Baxi

Deborah Korenstein