BMJ - Decision on
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Body: 26-Dec-2017

Dear Dr. Baxi

Manuscript ID BMJ.2017.041528.R1 entitled "Immune-related Toxicities in PD-1 and PD-L1 Immunotherapies: a Systematic Review and Meta-analysis"

Thank you for sending us your paper. We sent it for external peer review again. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the reviewer's comments, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Yours sincerely,

Tiago Villanueva
Associate Editor
tvillanueva@bmj.com

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** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:
Thanks for clarifying the method of estimation used in the manuscript. However, I was surprised the authors opted for the inverse-variance approach when this has been shown to be one of the most biased estimators with rare event data. Why not use the Peto odds method also implementable in Revman. The authors appear to be following a Cochrane approach – this is documented in section 16.9 of the Handbook.

For transparency, can the funnel plots please be included as supplementary material

The authors report "The median treatment time in the investigational arm ranged from 3 to 8 months". Can you present the median and range (as for follow-up time).

Table 1. I do not understand the new footnote "‡Applies to primary outcomes only and not to toxicity outcomes". Using this version of the Cochrane RoB assessment you are assessing the study as a whole (i.e. all outcomes) not just primary outcomes. However, the efficacy outcomes are not of interest to this review so you could define your selective reporting assessment RoB criteria (as a method) for the toxicity outcomes only because this will impact the analyses within this review. I believe an assessment can be done because you have defined very specific AE review outcomes of interest, e.g. colitis.

"Further because toxicity outcomes were not collected and reported differently we could not assess their selective reporting." I don't totally agree with this statement – how do you know toxicity outcomes were not collected? You cannot assume this if they were not reported, this is part of the purpose of the selective reporting bias domain. If you know the outcome was not collected (confirmed by the author) then bias is unlikely (but perhaps a missed opportunity to record data on this outcome)- but there is no suggestion of this confirmation.

How was overall RoB judged?

Table 2: use of dagger and double dagger. In Table 2, can confidence intervals also be provided for the incidence rates (same for all other rates).

In some cases the subgroups being considered seems to be producing very different results. For example in Figure 4, the single study with everolimus control seems very different than studies with a different control – does it therefore make sense to provide an overall pooled effect estimate for these two groups? This is important as the main subgroup (containing most studies) seems to be exhibiting very little heterogeneity and hence a fixed effect MA maybe OK. Higher levels of heterogeneity are observed for some of the latter outcomes such as Fatigue and therefore random effects MA is probably the best approach if pooling these studies is deemed sensible. Why have fixed and random effects forest plots been shown? Statistical packages such as STATA allow both fixed and random pooled effects estimates to be shown on one plot if this is what you want to show.

For data extraction – prioritisation was made of the data included in CT.gov. What was the rationale for this as a trial may have been registered in a different trial registry. Is it because all studies are not yet published? Also, if the data differed in the publication, how was this issue dealt with as it is possible that registry data is not up to date.

"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." I do not agree with this statement. If the event rates truly are 0 in both arms then the meta-analysis is unaffected and this is not an error.

However, it's possible that the non-reporting occurred because there were more harms in the intervention group and the non-reporting occurred as it masks the beneficial effect of the interventions. If this is the case then this would underestimate the harmful effect of treatment so the meta-analysis would be biased. So if the non-reporting is based on the results, I don't think it does effect both arms equally. How about just make a statement of this nature "A limitation of this analysis is that we assumed that the non-reporting of "AE" data was the result of either no events or the outcome was not measured. If a selective non-reporting mechanism was present, such that the AE data was

measured but not reported based on the results, then there is the possibility that the harm of intervention maybe underestimated [cite Saini 2014 BMJ]

Additional Questions:
Please enter your name: Jamie Kirkham

Job Title: Senior Lecturer in Medical Statistics

Institution: Unicersity of Liverpool

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 2

Recommendation:

Comments:
Immune-related Toxicities in PD-1 and PD-L1 Immunotherapies: a Systematic Review and Meta-analysis (revision review)

In this revised manuscript, the authors had performed thorough examinations and clarified multiple statements (pointed out by me and other reviewers). The errors presented in the first draft were corrected correspondingly. My major concerns were addressed by the authors one way or the other. For example, a graph illustrating the incidence of organ-specific or musculoskeletal imAE was previously expected; the author discussed the difficulty and disadvantage of using the graph to present the rates. Overall, the concerns were addressed. Thus acceptance for the publication is suggested. Thanks.

Additional Questions:
Please enter your name: Qingtai Su

Job Title: postdoctoral fellow

Institution: Baylor Research Institute

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 3

Recommendation:

Comments:
This manuscript offers a balanced discussion regarding the incidence of irAE seen between standard of care therapy versus newer immunotherapy agents. The major limitations of their approach are well described (ex. differences in diagnosis from hepatitis to AST elevations etc). This is valuable information for the medical community and is well described. A particular strength is the use of ClincialTrials.gov data. This manuscript is acceptable in its current published form.

Additional Questions:
Please enter your name: Benjamin L. Maughan

Job Title: Clincial Instructor, Genitourinary Oncology

Institution: Huntsman Cancer Institute, University of Utah

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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Funds for research?: No

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