BMJ - Decision on
Manuscript ID
BMJ.2017.041528

Body: 18-Nov-2017

Dear Dr. Baxi

Manuscript ID BMJ.2017.041528 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 and discussed it at our manuscript committee meeting. 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 report from the manuscript meeting, 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.

Tiago Villanueva
Associate Editor
tvillanueva@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: John Fletcher (chair), Jamie Kirkham (statistician), Elizabeth Loder, Georg Roggla, Sophie Cook, Jose Merino, Daoxin Yin, Tiago Villanueva

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- Our statistician made the following comments:
This is a mostly a 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 focussed 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 rarety of some of the events.
More specific comments:
Figure 2: I was unclear how authors got from the 1876 records to 1846 screened
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?
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?
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'. 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.

- 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-randomised studies.

- 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. 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).

- 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.

- 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.

- 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.

- Other editors were concerned with the lack of post-surveillance observational data.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
The article has done a thorough review of literature to look at potential cytotoxic effects of PD1 and PDL1 checkpoint inhibitor therapy. These results are important given the increasing importance of checkpoint inhibition therapy in the treatment of cancers.The manuscript has been well-written and the results have been discussed to a satisfactory amount. A few additions/ modifications, if incorporated, would increase the impact of the article:
1) Were the PD1/ PDL1 levels reported in the published studies? If yes, It would be important to correlate PD1/ PDL1 levels with the levels and type of immune-related toxicities
2) 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?

Additional Questions:
Please enter your name: Aparna Rao

Job Title: Postdoctoral Associate

Institution: university of Pittsburgh

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:
The authors in the present work have done a systematic review and meta-analysis of immune mediated toxicities of anti-PD1 and anti-PDL1 inhibitors. The results of the study highlights increased rates of hypothyroidism, pneumonitis and colitis with anti-PD1 agents compared to standard therapy and inconsistent data with reported musculoskeletal problems.

The authors had done an extensive literature survey including all the known available databases and independently assessed the data and drawn consensus among the investigators. The authors have cited their exclusion criteria and limitations of their study in a precise manner.

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.

Overall recommendation: Accept for publication

Additional Questions:
Please enter your name: Sangeetha Surianarayanan

Job Title: Post-doctoral researcher

Institution: University of California, San Francisco

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Reviewer: 3

Recommendation:

Comments:
Title: Immune-related Toxicities in PD-1 and PD-L1 Immunotherapies: a Systematic Review and Meta-analysis
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In this paper, the authors performed a systematic literature/clinical trial review on the adverse effects of PD-1/PD-L1 checkpoint inhibitor blockade in comparison with standard treatments. In 13 studies that were selected, they examined the organ-specific imAE, immune-relevant effects, and musculoskeletal toxicities. The result suggested that organ-specific imAE has a higher percentage in PD-1 treated patients than that in standard treatment, albeit at the low rate. Systematic analysis of adverse effects of the PD-1/PD-L1 blockade will provide an insightful reference for future checkpoint blockade application. This paper encompasses comprehensive presentation of adverse effects as well as related statistic analysis. However, the potential influence is not well highlighted in a detailed manner, which might render readers to question the significance of this study. Some concerns were listed as below:

Concerns:

1. Do the imAEs have tumor type specific (or dependent) incidence?

2. 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.

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

4. 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?

Minor revision:

1. How many records were identified? 2485 or 2486?

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

3. You might want to explain the ‘weight’ in the figure more in detail.

Overall, acceptance for publication is suggested after the above-mentioned revisions.

Additional Questions:
Please enter your name: Qingtai Su

Job Title: postdoc fellow

Institution: Baylor Institute for Immunology Research

Reimbursement for attending a symposium?:

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A fee for organising education?:

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Funds for a member of staff?:

Fees for consulting?:

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Reviewer: 4

Recommendation:

Comments:
This represents an important area in medicine: understanding the toxicities of immunotherapies. The authors correctly state that the list of indications and list of IO therapies are quickly expanding. They have clearly listed the methods, which appear thorough and correctly done for a meta-analysis. The conclusions accurately reflect the results as written in the manuscript.

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.

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.

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".

Overall, this represents an important addition to the literature as it compares the rate of adverse events of immune therapy to non-immune therapy. There certainly are limitations to the study but I think this is worth publishing.

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

Job Title: Clinical Instructor

Institution: Huntsman Cancer Institute, University of Utah

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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