Manuscript NO: 59162

October 11, 2020
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RE: Manuscript NO: 59162

Nso N, Antwi-Amoabeng D, Beutler BD, et al. Cardiac adverse events of immune checkpoint inhibitors: a systematic review and meta-analysis

Dear Na Ma and *World Journal of Cardiology* Editorial Office:

Thank you for your letter from October 5, 2020. My co-authors and I sincerely appreciate the thoughtful recommendations. We have incorporated all revisions into the manuscript, as described below.

Reviewer 1

This study aimed to estimate the incidence of cardiovascular irAEs among patients undergoing ICI therapy for various malignancies. The study is well design, and the paper is well written.

We sincerely appreciate the favorable review.

I only have some minor comments: 1. Page 9, data for the heterogeneous of incident of artial fibrillation (I2=0%, P=0.6) is not correct. Please check fig 7 and rewrite the results.

We apologize for the oversight and thank Reviewer 1 for the astute observation. We have corrected this error (Page: 9, Line: 19).

2. Please explain what the panel A and panel B in figure 7 stand for?

We agree that this was unclear. Panel A represents the initial analysis with heterogeneity. Panel B represents the homogenous results following implementation of Cochrane's leave-one-out method. This has now been clarified in the mauscript (Page: 9, Lines: 19 and 22).

3. The Incidence of atrial fibrillation is siginificant higher than other cardiac complicantions. The mechanisms for the increased risk of atrial fibrillation should be discussed.

We appreciate the thoughtful recommendation. It has been hypothesized that the connection between the sinoatrial node and autonomic nervous system plays an important role in the pathogenesis of ICI-related atrial fibrillation. We now discuss proposed mechanisms for ICI-related atrial fibrillation in greater detail (Pages 12-13, Lines: 19-23 and 1-3).

4. It is also important to explore what are the risk factors for atrial fibrillation in these patients (e.g age, sex, different kinds of ICI therapy)

We agree that this is an important point. Several of the studies included in the analysis did note that cardiovascular irAEs were more common in males, patients receiving multiple ICIs, and patients with pre-existing cardiovascular disease (Page: 12; Lines: 11-18). Unfortunately, however, raw data from the included trials were not available. We have added this to the "Limitations" section of the manuscript (Page: 13; Lines: 20-23) and note that it is an important area for further investigation.

Science Editor

1 Scientific quality: The manuscript describes a meta-analysis of the cardiac adverse events of immune checkpoint inhibitors. The topic is within the scope of the WJC. (1) Classification: Grade B; (2) Summary of the Peer-Review Report: This study aimed to estimate the incidence of cardiovascular irAEs among patients undergoing ICI therapy for various malignancies. The study is well design, and the paper is well written.

We are grateful for the favorable response from the science editor.

The Incidence of atrial fibrillation is significant higher than other cardiac complications. The mechanisms for the increased risk of atrial fibrillation should be discussed. The questions raised by the reviewers should be answered

We agree that this is an important point and now discuss the mechanisms for the increased risk of atrial fibrillation in further detail (Pages 12-13, Lines: 19-23 and 1-3).

The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement.

The signed conflict-of-interest disclosure form and copyright license agreement have been included with our revised submission.

(1) I found no "Author contribution" section. Please provide the author contributions.

Please find the "CRediT Author Contribution Statement" on Page 2 of the manuscript.

(2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

The original figures are now included in an attached PowerPoint document.

(3) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout

We apologize for this oversight and have added PMID and DOI numbers for each reference.

(4) I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text

An “Article Highlights” section has been added at the end of the main text.

(5) the author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author’s name, with no spaces

References are numbered according to the citation order in the text.

(6) please don’t include any *, #, †, §, ‡, ¥, @….in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as aP < 0.05, bP < 0.01 (P > 0.05 usually does not need to be denoted). If there are other series of P values, cP < 0.05 and dP < 0.01 are used, and a third series of P values is expressed as eP < 0.05 and fP < 0.01.

The above-referenced punctuation is not used in the manuscript. Superscript numbers are included where appropriate. P-values for statistical significance are cited as per the instructions.

Please note that one of our co-authors, Mark B. Ulanja, was included on the initial draft of the manuscript but was erroneously omitted on the BPG submission portal; this has been rectified.

We sincerely hope that our revised manuscript is now in suitable form for publication in *World Journal of Cardiology*. If there are any further recommendations, please contact us.

Sincerely,

Bryce D. Beutler