

May, 11 2021

***Dear Editors-in-Chief***

Monjur Ahmed, FACG, FACP, FASGE, FRCP, MD, MRCP, Associate Professor

Florin Burada, MD, MSc, PhD, Doctor, Professor, Research Scientist

Rosa M Jimenez Rodriguez, MD, PhD, Doctor, Professor, Surgeon

**Re: Submission of a Revised manuscript to the WORLD JOURNAL OF GASTROINTESTINAL ONCOLOGY**

Thank you very much for giving us the opportunity to revise our *invited review* (Manuscript NO: 65638)

We would be grateful for the consideration of our revised manuscript "*Atezolizumab plus Bevacizumab versus Sorafenib or Atezolizumab alone for Unresectable Hepatocellular Carcinoma: Systematic Review*" (by Faiza Ahmed, Jennifer Onwumeh-Okwundu, Zeynep Yukselen, Maria-Kassandra Endaya Coronel, Madiha Zaidi, Prathima Guntipalli, Vamsi Garimella, Sravya Gudapati, Marc Darlene Mezidor, Kim Andrews, Mohamad Mouchli and Endrit Shahini) for publication in the *World Journal of Gastrointestinal Oncology*.

The authors have read and complied with author guidelines, and they all have seen and approved this manuscript for publication. None of the authors had a conflict of interest to disclose concerning this manuscript.

We are grateful to the Editors for their precious contributions and comments. We have revised our manuscript accordingly for grammar, style, structure and we hope that you will now find it suitable for publication in the *World Journal of Gastrointestinal Oncology*. In case of final acceptance, we agree to make this manuscript open-access.

The changes in the manuscript are identified in track change mode. Below you can find a point-by-point reply to the reviewers. We used red to denote revised or inserted text.

*Thank you for your precious time.*

We are looking forward to receiving your decision in due time.

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Reply to Editors:

#03475142

*"The manuscript was reviewed for publication in the journal. The aim of this manuscript was to compare the efficacy and safety of combination immunogenic chemotherapy of atezolizumab and bevacizumab as first-line therapy as opposed to sorafenib and atezolizumab monotherapies, for patients with advanced HCC. The results obtained indicated that treatment of HCC with atezolizumab-bevacizumab is effective in improving survival in patients with unresectable HCC. It is the reviewer's opinion that the review is interesting and that the manuscript is easy to follow for the readers.*

*However, it appears that there are a couple of concerns in the manuscript: "1) As the authors have discussed, this systematic review may be judged inadequate to provide strong recommendations due to the small number of included RCTs, two completed trials and two ongoing trials. This systematic review appears to be sort of premature. 2) The authors should emphasize the value of this review in more detail, compared to just reading the papers of two completed trials and two ongoing trials."*

We thank the reviewer for his valuable comments. It is true that our analysis was conducted on a few trials, but these studies were the only available ones at the time when we thoroughly searched multiple databases and wrote our systematic review. Accordingly, in the discussion section (second paragraph, page 22), as suggested by the reviewer we have added the sentence "...to determine which of the mentioned therapeutic regimens could be currently more promising regarding the efficiency and safety profile" to emphasize the value of our review.

#01798570

*"Finding more than four studies could make the comparison more exclusive."*

We thank the reviewer for his valuable comments. When we wrote our systematic review there were only two studies published comparing the Atezolizumab and Bevacizumab regimens to monotherapies (including Sorafenib agent) and two ongoing trials, as already mentioned in our paper.

The most recent papers published on this topic are herein reported (in parenthesis), and in truth, they were published just after the submission of our paper to this Journal.

Besides, the various authors also included other immunotherapy regimens in their analyses, whereas our study represents an in-depth and focused study of selective therapeutic regimens; also, other additional articles investigated solely the cost-effectiveness aspects regarding these combination therapies, therefore our study is unique and different from the others (*Lim H, Ramjeesingh R, Liu D, Tam VC, Knox JJ, Card PB, Meyers BM. Optimizing Survival and the Changing Landscape of Targeted Therapy for Intermediate and Advanced Hepatocellular Carcinoma: A Systematic Review. J Natl Cancer Inst. 2021 Feb 1;113(2):123-136. doi: 10.1093/jnci/djaa119; Castet F, Willoughby CE, Haber PK, Llovet JM. Atezolizumab plus Bevacizumab: A Novel Breakthrough in Hepatocellular Carcinoma. Clin Cancer Res. 2021 Apr 1;27(7):1827-1829. doi: 10.1158/1078-0432.CCR-20-4706; Sangro B, Sarobe P, Hervás-Stubbs S, Melero I. Advances in immunotherapy for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2021 Apr 13:1-19. doi: 10.1038/s41575-021-00438-0; Casadei-Gardini A, Tada T, Shimose S, Kumada T, Niizeki T, Cascinu S, Cucchetti A. Is Atezolizumab Plus Bevacizumab for Unresectable Hepatocellular Carcinoma Superior Even to Lenvatinib? A Matching-Adjusted Indirect Comparison. Target Oncol. 2021 Mar;16(2):249-254. doi: 10.1007/s11523-021-00803-8; Sharma R, Motedayen Aval L. Beyond First-Line Immune Checkpoint Inhibitor Therapy in Patients With Hepatocellular Carcinoma. Front Immunol. 2021 Mar 15;12:652007. doi: 10.3389/fimmu.2021.652007; Celsa C, Giuffrida P, Stornello C, Grova M, Spatola F, Rizzo GEM, Busacca A, Cannella R, Battaglia S, Cammà C, Cabibbo G. Systemic therapies for hepatocellular carcinoma: the present and the future. Recenti Prog Med. 2021 Feb;112(2):110-116. doi: 10.1701/3559.35371; Shek D, Read SA, Nagrial A, Carlino MS, Gao B, George J, Ahlenstiel G. Immune-Checkpoint Inhibitors for Advanced Hepatocellular Carcinoma: A Synopsis of Response Rates. Oncologist. 2021 Apr 5. doi: 10.1002/onco.13776; Rizzo A, Ricci AD, Brandi G. Atezolizumab in advanced hepatocellular carcinoma: good things come to those who wait. Immunotherapy. 2021 Apr 6. doi: 10.2217/imt-2021-0026; Su D, Wu B, Shi L. Cost-effectiveness of Atezolizumab Plus Bevacizumab vs Sorafenib as First-Line Treatment of Unresectable Hepatocellular Carcinoma. JAMA Netw Open. 2021 Feb 1;4(2):e210037. doi: 10.1001/jamanetworkopen.2021.0037; Wen F, Zheng H, Zhang P, Liao W, Zhou K, Li Q. Atezolizumab and bevacizumab combination compared with sorafenib as the first-line systemic treatment for patients with unresectable hepatocellular carcinoma: A cost-effectiveness analysis in China and the United states. Liver Int. 2021 May; 41(5):1097-1104. doi: 10.1111/liv.14795. Epub 2021 Feb 8. PMID: 33556230; Chiang CL, Chan SK,*

*Lee SF, Choi HC. First-Line Atezolizumab Plus Bevacizumab versus Sorafenib in Hepatocellular Carcinoma: A Cost-Effectiveness Analysis. Cancers (Basel). 2021 Feb 24;13(5):931. doi: 10.3390/cancers13050931).*

*3) Comments from Science Editor/Company Editor-in-Chief: "...The authors should provide the Biostatistics Review Certificate, and the PRISMA 2009 Checklist. 5 Issues raised: (1) The authors did not provide original pictures. 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; and (2) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words)."*

We thank the Science Editor and Company Editor-in-Chief for their valuable comments. As requested, we have provided the PRISMA 2009 Checklist, the original figure documents as well as the "Article Highlights" section at the end of the main text. However, some images can't be converted into powerpoint format since they have been exported from a specific website that doesn't allow any further modifications (i.e. figure 2, that has been exported from mapchart.net ( <https://mapchart.net/> ) and also Risk of Bias figures 3 & 4 which were created using Cochrane robvis visualization tool). Moreover, we have shortened the title as per your suggestion. Besides, we added in the material and methods section the PROSPERO number of registration which was pending (CRD42021237736). The request of a Biostatistics review does not apply to our type of study as we have included only the information that was available within the published trials. We did not use any SPSS system or Revman 5.3 software to present any mathematical calculations or analysis.