

To the Editor-in-Chief,

World Journal of Gastroenterology,

Dear Lian-Sheng Ma,

Dear Editors and Reviewers:

On behalf of the co-authors, we greatly appreciate your assistance and helpful comments in reviewing our manuscript World Journal of Gastroenterology NO.: 65904, entitled **"Trial eligibility in advanced hepatocellular carcinoma: does it support clinical practice in underrepresented subgroups?"**

We have carefully reviewed your comments and have edited the submission as noted in the attached revision copy highlighting each change (marked version) in the new manuscript version. In addition, we have responded reviewer comments, in a point-by-point response.

Reviewer comments:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This manuscript raised and well discussed the need for representing more subgroups based on clinical practice.

Response: We would like to thank the reviewer for his/her comments. We have further revised English grammar with www.grammarly.com.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: MANUSCRIPT TO BE REVIEWED: Trial eligibility in advanced hepatocellular carcinoma: does it support clinical practice in underrepresented subgroups? By Federico Piñero and Leonardo da Fonseca. (Manuscript number 02993003) GENERAL COMMENT: I enjoyed reading this paper. The authors discuss a very important topic in systemic treatment of hepatocellular carcinoma. The populations studied in clinical trials do not include lesser fit, older patients and those with important comorbidities. These patients are subject to regulatory restrictions in many countries and are often excluded from treatment. The authors thoroughly review these categories and present evidence in favor or against systemic therapy. The paper is very well written and includes the newest drugs, including checkpoint inhibitors and bevacizumab. Both the hepatologist and the clinical oncologist will find this paper very useful in their everyday practice and in choosing the right drug for the right patient. The flow charts provided in the two figures are easy to use and particularly helpful. I have only a few minor comments to improve readability and recommend publication in the Journal.

SPECIFIC COMMENTS: INTRODUCTION:

- Line 16: I suggest “no other organ failure” instead of “adequate organic function”.

Response: *Done as requested.*

- Line 21: "with less than 50% liver involvement" instead of "without more than 50% of liver involvement"

Response: Done as requested.

- Line 32 "a PDL-1 inhibitor" will be enough instead of "an ICI blocking the programmed cell-death -PD-L1- inhibition". Everybody knows what is a PDL-1 inhibitor.

Response: Done as requested.

ELDERLY: - line 16: In their field-practice study Iavarone et al. found that elderly patients more frequently discontinued treatment at multivariate analysis. In these patients half dosing sorafenib was associated with increased survival while discontinuation negatively affected the outcome. This is a relevant finding and suggests that an early reduction of the dose in this population would be the best strategy. I suggest to add a comment on this point.

Response: We added this important reagent on page 9, as suggested.

- line 27: do the authors suggest that an assessment of Clinical Significant Portal Hypertension is mandatory before starting treatment? If this is the case which tool should be used? (ultrasonography plus endoscopy would be enough? Transient Elastography?, LSPS ratio?, Baveno criteria?)

Response: We added this important reagent on page 10, as suggested, focusing on clinical evaluation of the presence of clinically significant portal hypertension.

We do not recommend the use of transient elastography to better select patients for the systemic therapies for HCC. The most important clinical variables are those showing already clinically significant portal hypertension.

FIGURES AND TABLES:

- Fig.1 Lenvatinib: tumor <50% instead of > 50%

Response: In fact, the figure shows exclusion criteria for Lenvatinib. Not inclusion criteria. So we preferred to show this data already clarified in the written section. As suggested, we added a comment on the figure's note.

- TABLE 1: MVI trunk: does it mean neoplastic PVT (Portal Vein Thrombosis)?

Response: As suggested, we added a comment on the table's note.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Thank you very much to let me for reviewing this comprehensive review which was described the overall systemic treatment options in first and second line treatment in for the advanced hepatocellular carcinoma. Manuscript is well preparation and written well.

Response: We'd like to thank the reviewer's comments.

Reviewer #4:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The inclusion criteria used in clinical trials do not support the use of novel therapies in several real-world scenarios involving

underrepresented subgroups, such as patients with unpreserved liver function, other comorbid conditions, a history of solid-organ transplantation, autoimmune disorders and those with a high risk of bleeding. This article discussed treatment strategies in these subgroups and is of promotional significance to improve the level of HCC treatment. It is recommended to publish.

Response: We'd like to thank the reviewer's comments.

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor: 1 Scientific quality: The manuscript describes an Opinion Review of the Underrepresented subgroups in HCC. The topic is within the scope of the WJG. (1) Classification: Grade B, B, C and C; (2) Summary of the Peer-Review Report: Manuscript is well preparation and written well. I suggest to add a comment on discontinuation negatively affected the outcome. Some sentences need to be rephrased. The questions raised by the reviewers should be answered; (3) Format: There is 1 table and 2 figures; (4) References: A total of 51 references are cited, including 21 references published in the last 3 years; (5) Self-cited references: There are 6 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated. 2 Language evaluation: Classification: Grade A, A, B and B. 3 Academic norms and rules: No academic

misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJG. 5 Issues raised: (1) The language classification is Grade B. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>; (2) 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. 6 Recommendation: Conditional acceptance.

Response: We appreciate your remarks and suggestions. We have only included 5 self-references, as requested. We have done additional English grammar revision using www.grammarly.com. Now we send in requested files figures and tables. Also, reviewing references we included new ref number 21, which includes important and key points from a very recently published paper.

We would like to thank all the reviewer's comments and suggestions; including these changes have improved the manuscript.

We have carefully considered each of the Editor and reviewer's suggestions and believe this report to be novel, interesting and of appropriate subject matter to the readership of *World Journal of Gastroenterology*.

Yours Sincerely,

Dr Federico Piñero MD, Msc, PhD, and Leonardo da Fonseca, MD.