April 26th, 2022
Prof. Hiten RH Patel, BM BCh, BSc, FRCS, PhD
Prof. Stephen Safe, PhD
Editors-in-Chief
World Journal of Clinical Oncology

Dear Prof. Patel, and Safe:

We are pleased to re-submit for publication our review article titled: ***"Immunotherapy for advanced hepatocellular carcinoma: from clinical trials to real-world data and future advances"***.

We are grateful to the editors and reviewer for providing insightful feedback on our manuscript. We have carefully reviewed the recommendations and have revised our manuscript accordingly. Addressing each of their comments has certainly improved our manuscript. Detailed responses to the reviewers' comments are provided below.

Reviewer #1:

Suggestion 1.1:
The section of "clinical trials" has three subheadings: "effectiveness, safety and economy", and put "Immunotherapy combination with locoregional ablation" under "Combination Therapy" in "Effectiveness". The safety conclusions in the monotherapy and combination therapy should be placed under "Safety", and " Immunotherapy in LT " should be placed under "real-world data".

Response:
Thank you for this suggestion. We have not explicitly defined the 3 subheadings you suggest in "clinical trials" as "effectiveness, safety and economy", as the 'economy' section is more fitting for "Real world data" and also because the 'safety' section is relatively short and would not balance out with the section on efficacy which includes "monotherapy", "combinations", and "adjuvant/neoadjuvant setting". We have restructured the combination therapy section to include both "ICI duplet combinations" and also the "Immunotherapy combination with locoregional ablation" section; as a result, the numbering of tables 3-4 have been switched and edited accordingly. We have moved the main safety conclusions regarding monotherapy and combination therapy from those respective paragraphs to the section on "Safety". Some core safety facts and explanations of the suggested clinical context for these regimens are maintained in former paragraphs to maintain a logical

flow for the reader. We have now moved the "Immunotherapy in LT" section from “Future directions” to "Real-world data”.

Suggestion 1.2:

It is recommended to list each clinical trial, including Phase, intervention measures, and start- end times of the experiment , outcomes, etc.

Response:

Thank you for your comment. We have reviewed the entire manuscript and tried to ensure that the necessary information is summarised and presented briefly for each trial without expanding the word count significantly – the exception to this being noteworthy practice-changing trials.

Suggestion 1.3:

The article is too long, and the content of the full text need to be simplified.

Response:

Thank you for your suggestion. We have deleted and simplified content where possible whilst trying to maintain core information.

Reviewer #2:

Suggestion 2.1:

More efforts should be spent on the incidence, exposure risk factors and the immunotherapy regarding aHCC in the ‘INTRODUCTION’ part.

Response:

Thank you for your suggestion. We have added further information on the incidence and risk factors for aHCC. We have maintained the information on TKIs as this encompasses noteworthy historical information on the emergence of systemic regimens that contextualises the subsequent development of ICI approaches in the field.

Suggestion 2.2:

When introducing the background of immunotherapy on HCC, it should be more precisely on this part and more detailed on the immune-microenvironment of advanced HCC.

Response:

Thank you for your suggestion. We use the subsequent transition paragraph on "Immunogenicity in HCC" to elaborate on more specific information on immunotherapy specifics in aHCC. We have now summarised and referenced further information pertaining to recent advances on the tumor immune microenvironment characterization in aHCC (see references 23-28). We have added a sentence in paragraph 3 of introduction to highlight the rationale for immunotherapy in advanced-stage disease (i.e., systemic immune recognition).

Suggestion 2.3:

After reviewing the ICI monotherapy, combined ICI immunotherapy and ICI immunotherapy with other therapeutic agents on aHCC, no needs to further stress the irrelevant points on HCC. Cause this review focuses on the immunotherapy of advanced HCC, the main body is advanced HCC.

Response:

Thank you for your suggestion. The first sentence from the paragraph on "ICIs in the adjuvant/neoadjuvant setting" has been added to explicitly clarify that this paragraph does not allude to advanced stage disease ubiquitously; this sentence does not contain any bibliography. The remainder of the text in this section is only 84 words, plus Table 4. Reference 64 is the only reference discussed in this section of the text and comprises a phase II trial on the use of immunotherapy for perioperative treatment of intermediate/advanced-stage HCC patients. This paragraph is very short and yet provides critical information to aid the reader's holistic understanding on the use of ICIs in HCC, albeit the disease not necessarily defined as 'advanced' stage in this context. Table 4 is comprehensive and of great value to readers interested in this field and is hence maintained even though trials summarised may not ubiquitously include advanced-stage HCC patients.

Suggestion 2.4:

Similarly, only references regarding the treatment on advanced HCC could be maintained in this review, the remaining parts should be ignored.

Response:

Thank you for your comment. We have reviewed the entire manuscript and to ensure that all references are for advanced-stage HCC. With the exception of reference 64 in the section regarding "ICIs in the adjuvant/neoadjuvant setting", as well as those trials discussed in the respective table for this paragraph (Table 4), there are no other references regarding non-advanced-stage HCC patients. The

section on "ICIs in the adjuvant/neoadjuvant setting" is very brief and is maintained for the purpose of comprehensiveness.

Reviewer #3:

Suggestion 3.1:
As a review summarizing the recent progress, the latest data should be used. In the section of INTRODUCTION, more recent literatures should be cited and updated.

Response:
Thank you for your suggestion. Additional and more recent references have been added to the introduction and subsequent transition section on immunogenicity in HCC. At the same time, we have ensured to maintain references to the original works as necessary.

Suggestion 3.2:
Authors' own viewpoint should be presented. For instance, advantages, limitations and prospects of clinical trials and real-world studies could be commented. Some potential synergism should be discussed.

Response:
Thank you for your suggestion. We have expanded on further author opinions including in the "cost-effectiveness" and "discussion and conclusion" sections. The real-world studies have been commented extensively already with authors' opinions and reflections on the significance of this data presented and summarised throughout. Noteworthy drug synergisms are highlighted in the 'ICI+VEGF', 'ICI + locoregional ablation', and in the 'future directions' section for each of the 'ACT', 'vaccination' and 'virotherapy' points. We offer the main take away conclusions for each of the sections under "clinical trials" including 'monotherapy', 'ICI duplets', 'ICI+TKI', and 'ICI+VEGF' by elaborating on the principles and recommended clinical context for the use of each of these regimens in 1st- and 2nd-line treatment setting for aHCC.

Language Quality: *Rated as "Grade B (Minor language polishing)" by all three reviewers.*

On reviewing the manuscript, we agree with this assessment of language quality. The entire manuscript has now been proofread and edited by a native English speaker for linguistic corrections.

We hope that with these revisions, our work is felt appropriate to publish in *World Journal of Clinical Oncology* and perceived as educational to the Journal's readership. Thank you again for inviting us to submit a revision of our work to your journal. We would be pleased to answer any additional concerns or questions you may have.

Sincerely,

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