

Cellular Based Treatment Modalities for Unresectable Hepatocellular Carcinoma

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Dear Professor Lian-Sheng Ma,

Thank you for reviewing our article titled, “Cellular Based Treatment Modalities for Unresectable Hepatocellular Carcinoma”. We were thrilled to learn that it has been conditionally accepted for publication and appreciate the helpful comments and suggestions provided by the reviewer and your editorial team. We have carefully reviewed all the comments and suggestions and revised our manuscript accordingly. Below you will find detailed replies to each reviewer comment and the appropriate reference to the changes made within the manuscript itself. In summary, we have incorporated a description of the variety of tumor infiltrating lymphocytes and their roles in cancer immunity. We have also added a figure outlining the variety of treatment modalities used for the treatment of HCC ranging from tyrosine kinase inhibitors to immune checkpoint inhibitors and various cellular based options. All authors have contributed to and agree on the content of this manuscript. The manuscript has not been published previously and is not currently under consideration elsewhere.

Sincerely,

Editor's comment and suggestions:

Reviewer #1

The authors described nicely about current treatment of HCC with the details of etiology, incidence, disease staging, systemic medications including kinase inhibitors, antibodies and adoptive cell transfer. The manuscript is well written.

1. The authors described about current treatment of HCC by the drugs kinase inhibitors and antibodies, which are not brief, as well as adoptive cell therapy. However, the title only reflected cellular based treatment therefore it should be modified to match story of the manuscript as a whole. If the authors wish to briefly discuss about the systemic treatments other than cellular components a few tables of currently used drugs could be given rather giving quite a long discussion on them.

Authors' response: *Thank you. In our opinion we believe that a thorough yet brief introduction of the kinase inhibitors and antibodies is critical for readers in order to understand the current FDA approved therapies and their limitations. Approval of these agents as first and second line treatments has been based on different quantitative measures including but limited to overall survival (OS), progression free survival (PFS), and overall response rate (ORR); description of these elements allows for thorough understanding and the initiative to investigate cellular based modalities for the future treatment of HCC.*

2. For cell therapy, it would be more interesting for a minireview to have a picture/diagram of the cells used for adoptive transfer and the molecular strategies involving T cell receptor and chimeric antigen receptor for examples.

Authors' response: *We have described the structure of CAR-T and TCR engineered T cells in detail within the manuscript. We have also described the key differences between the two (MHC restriction), and introduced readers to various tumor associated antigens, which are essential to designing effective T-cell based immune therapies. Figure 1 is now included, which illustrates the available modalities used to target advanced hepatocellular carcinoma.*

3. More details should be given about the specific types of TILs currently defined such as CD8, Th17, and gamma delta T cells.

Authors' response: *Thank you for presenting us with this information. We have included the specific types of TILs in the manuscript based on your suggestion. References 95-99.*

4. Minor comments: There might be perhaps typo errors such as 'Alpha-fetoprotein (AFP) is a glycoprotein "compromised" of 591 amino acids....'. Please check thoroughly

***Authors' Response:** Thank you for pointing out this error. We have extensively reviewed the entire manuscript for grammatical errors and ensure it is free of typo errors to the best of our ability.*

Reviewer #2

This paper summaries immunotherapeutic treatments of hepatocellular carcinoma (HCC), but I do not think the authors provides much unique views. I suggest the authors should focus on one or two topics either in basic study or clinical problem and then give much deep thinking.

***Authors' Response:** Thank you for the comments. Given the broad topic of the invited manuscript "Cellular Based Treatment Modalities," we included a variety of different treatment modalities that are being utilized in clinical and pre-clinical models. We believe that it is imperative to introduce readers to the traditional treatment modalities first, before continuing with the emerging immunotherapeutic agents, which are paving the way for a possible revolutionary change in the treatment of HCC. In addition, our paper has included an extensive and up to date compilation of clinical trials focusing on CAR-T, TCR engineered T cells and cancer vaccines and oncolytic viruses.*

Reviewer #3

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and is unfortunately associated with an overall poor prognosis and high mortality. The authors briefly introduced the currently approved systemic treatment options and present clinical and experimental evidence of HCC immunotherapeutic treatments. Further, the authors provided an up-to-date compilation of ongoing clinical trials investigating T cells, cancer vaccines and oncolytic viruses. The data is comprehensive and interesting. So I would suggest it publish in WJCO if the authors can address the following concerns. 1. Where are the references?

***Authors' Response:** Thank you for the comments, we are glad that you enjoyed our manuscript. The references were subsequently added after the initial file upload did not include the references. All subsequent reviewers were provided with a complete list of references in the appropriate requested format.*

Science editor's comment: The authors should add some figures or tables

***Authors' Response:** Upon reviewing the comments it is noted that "there are no tables and figures" was mentioned. Our original document includes 3 tables, which we hope were not accidentally overlooked. The 3 tables remain in place upon revision. We have also included a new figure labeled "Figure 1."*

Editor-in-chief comment: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

***Authors' Response:** Thank you for taking the time and effort to review our manuscript in its entirety. We are glad to hear that the manuscript is conditionally accepted, and have made all revisions which we believe to be appropriate.*