

To the Vice Editor-in-Chief,  
*World Journal of Transplantation.*

Dear Na 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 Transplantation* number 56893, entitled **“Lenvatinib as first-line for recurrent HCC after liver transplantation: is the current evidence applicable to these patients?”**.

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.

***Science Editor:***

1 Scientific quality: The manuscript describes an opinion review of the Lenvatinib as first-line for recurrent HCC after liver transplantation. The topic is within the scope of the WJT. (1) Classification: Grade C and Grade C; (2) Summary of the Peer-Review Report: This paper focused on the treatment of HCC recurrence after liver transplantation by citing their own experience and reviewing the literature. And the topic of this paper was attractive and interesting. However, the case cited by the authors did not fit the topic of the paper well. The questions raised by the reviewers should be answered; and (3) Format: There is 1 table and 2 figures. A total of 55 references are cited, including 17 references published in the last 3 years. There are 4 self-citations. 2 Language evaluation: Classification: Grade A and Grade A. The language was edited by a native English speaker. 3 Academic norms and rules: The authors provided the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the Bing search. However, the highest single-source similarity index showed to be 11% in the CrossCheck report. The authors need to rephrase the repeated parts. 4 Supplementary comments: This is an invited manuscript.

The topic has not previously been published in the WJT. 5 Issues raised: 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 Re-Review: Required by Reviewer 05121731. 7 Recommendation: Conditional acceptance.

*Response: We submit now original figures using Power Point, and have addressed the issues each reviewer has done.*

Reviewer comments:

Reviewer #1:

-I consider this to be an adequate review of the topic. Even though the clinical case exposition is related to the subject, it does not fit in an opinion review.

*Response: Yes, we agree. However, we thought it might show more clearly the topic the opinion review underlines. As requested, we clarify this point. Please see the abstract and introduction (page 6, 2<sup>nd</sup> paragraph).*

-Question: Was the patient transplanted being 76 years old? It would appear to be an excessively old age to be the receiver of a transplantation.

*Response: No, age at transplant was 66. We corrected this in the manuscript (please see page 6, 2<sup>nd</sup> paragraph).*

Reviewer #2:

-This paper focused on the treatment of HCC recurrence after liver transplantation by citing their own experience and reviewing the literature. Tumor recurrence after LT remains a big problem concerning transplant HCC patients. Prompt diagnosis of tumor relapse has not been associated with improved survival or a reduction in cancer related mortality, because strong evidence regarding potent drugs that can hinder cancer progression still lacks. Therefore, the topic of this paper is attractive and interesting. In the paper, authors described a successfully treated patient with HCC who was diagnosed HCC in 2011, the patient suffered HCC recurrence and treated with repeated

ablations and finally liver transplantation in 2013. After LT, the patient consecutively suffered lung and adrenal metastasis at least five years after LT, both of the metastasis are removed by operation and confirmed by pathology. After that, the patient took lenvatinib without any adverse event for around two years. However, we deemed that the case cited by the authors did not fit the topic of the paper well. According to our experience, we speculate that removal of the solitary metastasis by operations in this case was essential to the excellent survival of the patient, but may not the use of lenvatinib. Much longer follow-up is still needed to ascertain the potential anti-tumor effect of lenvatinib. The case presented by the authors illustrated the importance of resection of the metastasis other than the utility of lenvatinib.

Nevertheless, considering the lack of potent drug, we agree with the notion that molecular targeted therapy may be effective in certain patients with recurrent HCC after LT, and lenvatinib can be used in case that the patient show intolerance to Sorafenib.

*Response: Yes, we agree that most of the survival benefit was not associated with lenvatinib. However, as reported in our opinion review, we underlined that other prognostic factors (such as time-to-recurrence) should be considered. Indeed, although surgical resection was proposed in this patient, he presented sequential extrahepatic recurrence in different locations in a short period of time. By taking all these facts into consideration is that we support the benefit of systemic treatment with lenvatinib. It is still uncertain whether the survival benefit is due to surgery or systemic therapy in this setting. Nevertheless, he has been receiving lenvatinib since 25<sup>th</sup> May 2019 (more than a year ago). As requested we added some comments on page 9, last paragraph, and page 10, 1<sup>st</sup> paragraph.*

-In paragraph 2, line 4 "On the contrary" is not appropriate, because the contents of the first and second sentences are not contrary.

*Response: Yes, we agree. We changed for "Moreover"(please see paragraph 2 Line 3 &4).*

*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 Transplantation.*

Yours Sincerely,

Dr Federico Piñero MD MSCE, on behalf of all co-authors

To the Vice Editor-in-Chief, World Journal of Transplantation, Baishideng Publishing Group Inc, Dear Na 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 Transplantation NO.: 56893, entitled "Lenvatinib as first-line for recurrent HCC after liver transplantation: is the current evidence applicable to these patients?". 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:

1.Key words should include "Hepatocellular carcinoma" Response: We appreciate your remark; hepatocellular carcinoma was added to the key words.

2.The introduction portion need further modification, for example, the second paragraph the first sentence described that prompt diagnosis did not improve survival, should be the result of no available effective drug or therapy, and that is the significance of this review, and second sentence described that earlier recurrence after LT was associated with poor prognosis, these two sentences

should not be in the same paragraph. There are same problems exists in other paragraph. Response: We appreciate your remarks; changes have been made in order clearer. Also as suggested this paragraph and others were divided, as suggested (page 5).

3.Improvement is needed to make the presentation more precisely and understandable, for example, "In some series there was not a comparison group or adjusted treatment effect for prognostic baseline variables at recurrence diagnosis. " should be changed to "In some series, treatment effects were assessed without a control group or adjustment for prognostic baseline variables". And in this paragraph, logistic between sentences needs to be strengthened. Response: We changed as suggested (page 7, last paragraph).

4. Based on the case presented by the authors and review of the current literature, this work proposed that TKIs such as lenvatinib might be useful in transplant HCC patients, but need to be verified in the near future. HCC recurrence after LT remains a severe problem, because lack of potent drug or treatment strategy. Therefore, the information provided by the present work is helpful and important for the doctors. The quality of the paper needs further improvement as I mentioned in 2 and 3, the authors need thoroughly revise the whole manuscript. Response: We appreciate your comments. In regard with your suggestions, changes have been made not only in particular sentences, but also along the whole manuscript.

Reviewer #2: I consider this to be an adequate review of the topic. Even though the clinical case exposition is related to the subject, it does not fit in an opinion review. Question: Was the patient transplanted being 76 years old? It would appear to be an excessively old age to be the receiver of a transplantation. Response: We tried to introduce a clinical case scenario from the real world setting in order to give a practical message. We know that it does not exactly fit within an Opinion Review, but we thought that it may be more didactic and

illustrative. The patient was 66 years old and a perfect candidate for a liver transplantation. We clarified this point (page 6).

Reviewer #3: -This paper focused on the treatment of HCC recurrence after liver transplantation by citing their own experience and reviewing the literature. tumor recurrence after LT remains a big problem concerning transplant HCC patients. Prompt diagnosis of tumor relapse has not been associated with improved survival or a reduction in cancer related mortality, because strong evidence regarding potent drugs that can hinder cancer progression still lacks. Therefore, the topic of this paper is attractive and interesting. In the paper, authors described a successfully treated patient with HCC who was diagnosed HCC in 2011, the patient suffered HCC recurrence and treated with repeated ablations and finally liver transplantation in 2013. After LT, the patient consecutively suffered lung and adrenal metastasis at least five years after LT, both of the metastasis are removed by operation and confirmed by pathology. After that, the patient took lenvatinib without any adverse event for around two years. However, we deemed that the case cited by the authors did not fit the topic of the paper well. According to our experience, we speculate that removal of the solitary metastasis by operations in this case was essential to the excellent survival of the patient, but may not the use of lenvatinib. Much longer follow-up is still needed to ascertain the potential anti-tumor effect of lenvatinib. The case presented by the authors illustrated the importance of resection of the metastasis other than the utility of lenvatinib. Nevertheless, considering the lack of potent drug, we agree with the notion that molecular targeted therapy may be effective in certain patients with recurrent HCC after LT, and lenvatinib can be used in case that the patient show intolerance to Sorafenib. Response: We appreciate your comments and thoughts. It is widely described the poor prognosis associated with recurrent HCC after liver transplantation. This case was rare one, presenting HCC recurrence with isolated extrahepatic location (1st recurrence in the lung) and following with other sequential locations (adrenal). The patient is still

receiving lenvatinib today (14th September), thus almost 16 months of benefit upon survival. By taking all these facts into consideration is that we support the benefit of adjuvant treatment with Lenvatinib, although we know it may be a consequence of other co-interventions (surgical resection). We added this point on page 7. -In paragraph 2, line 4 "On the contrary" is not appropriate, because the contents of the first and second sentences are not contrary. Response: The heading "On the contrary" has been removed and modified (please see paragraph 2 Line 3 &4). 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 Transplantation. Yours Sincerely, Dr Federico Piñero MD MSCE, on behalf of all co-authors