6 July 2021

Dear Prof. Monjur Ahmed, Prof. Florin Burada and Prof. Rosa M Jimenez Rodriguez, Editor in Chief of World Journal of Gastrointestinal Oncology, and Reviewers,

Please find a revised review manuscript entitled, "The prospect of lenvatinib for unresectable hepatocellular carcinoma in the new era of systemic chemotherapy" by Takuya Sho et al.

We are most grateful to you for the helpful and constructive comments and suggestions on the original version of our manuscript entitled "The prospect of lenvatinib for unresectable hepatocellular carcinoma in the new era of systemic chemotherapy" (Manuscript ID: 66501). We have addressed the reviewers' comments and revised the manuscript accordingly. The changes are underlined in the text, and point-to-point response is described below.

Reviewer: 1

Comments to the Author

This a well-written review paper on the prospect of lenvatinib for treatment of unresectable hepatocellular carcinoma (HCC). The paper adds to the growing literature on potential use of lenvatinib for systemic treatment for patients with advanced HCC. I don't not have any major concerns, except a few minor comments listed below.

Comment 1;

Instead of using abbreviations like "Sor" and "Len" why don't you use the more recognizable names, "sorafenib" and "lenvatinib" for easy comprehension of the text?

Response to Comment 1;

We appreciate reviewer's suggestion. According to the reviewer's suggestion, we used the words, "sorafenib" and "lenvatinib", in the whole text as the standardized words.

Comment 2;

In general, there are way too many abbreviations in the text, which should be reduced to about 4-5 abbreviations, unless they are well-known like "OS" for overall survival, or they are gene names.

Response to Comment 2;

We are grateful for reviewer's suggestion. According to the reviewer's suggestion, we reduced too many abbreviations in the revised manuscript.

Comment 3;

Based on these results, Sor, Len, and Atezo+Bev could be administered to patients with unresectable HCC as first-line systemic chemotherapy." Authors should please make it clear that this is not a consensus agreement, but rather their opinion.

Response to Comment 3;

We apologize for the confusion. According to the reviewer's comment, we added the following sentence "The 2020 AASLD and the 2021 European Society for Medical Oncology (ESMO) liver treatment options depending on BCLS stage specify atezolizumab+bevacizumab as first-line systemic therapy in stage B with TACE unsuitable HCC and stage C. In addition, even with the latest version of the treatment algorithm in the Clinical Practice Guidelines for HCC 2020 in Japan, the first-line drug therapy for unresectable hepatocellular carcinoma is atezolizumab+bevacizumab combination therapy. Sorafenib and lenvatinib, which were previously the first-line treatments, are now the second-line treatments. Regorafenib, ramucirumab, and cabozantinib can be used as third-line treatment." in Introduction section (Page 6).

Comment 4;

Page 10, last paragraph, "The proof of concept," should be "The proof-of-concept".

Response to Comment 4;

We appreciate the reviewer's suggestion, we changed the sentence from "proof of concept" to "proof-of-concept" in Page 11.

Comment 5;

Page 11, referencing issue "{Kudo, 2020 #8}" and Page 12 "{Kawamura, 2020 #10}".

Response to Comment 5;

As the reviewer pointed out, we corrected the references in Page 11 and Page 12 by editorial rule.

Reviewer: 2

Comments to the Author

Comment 1;

Please make the following statement in introduction section more easy to understand and digestible [Systemic chemotherapy is the only therapeutic option in patients with Child-Pugh grade A at Barcelona Clinic Liver Cancer (BCLC) stage C (advanced stage) and stage B (intermediate stage) in parallel with HCC unsuitable for locoregional therapy].

Response to Comment 1;

We appreciate the reviewer for the helpful comments and suggestions. We added the following sentences "Since the publication of the American Association for the Study of Liver Diseases (AASLD) practice guide-lines on the management of hepatocellular carcinoma (HCC) in 2005, the BCLC staging system has come to be widely accepted and is also being used for many clinical trials. It takes into account factors such as tumor burden, liver function and general health to determine prognosis and the best therapy. Patients at an early stage are those with HCC ≤5 cm or up to three nodules <3 cm each (BCLC stage A). Patients exceeding these limits, without vascular invasion or extrahepatic spread, fit into the intermediate stage (BCLC stage B). Patients with evidenced by a performance status ≤2 and/or an aggressive tumor pattern (vascular invasion or extrahepatic spread) correspond to an advanced stage (BCLC stage C). Systemic chemotherapy is the only therapeutic option in patients with Child-Pugh grade A at BCLC stage C and stage B with unresectable HCC" about BCLC staging and stage B or C in Introduction section (Page 4) to make the explanation clear.

Comment 2;

I Give more details [Therapeutic options for extrahepatic metastases and vascular invasion have been added]

Response to Comment 2;

We are grateful that the reviewer brings an important point. Prior to the development of the MTA, patients in the advanced stage had a survival time of approximately 6 months. Sorafenib has enabled treatment of advanced stage HCC. According to the reviewer's suggestion, we added the following sentence "Therapeutic options for extrahepatic metastases (e.g. lung, lymph node or bone) and vascular invasion (e.g.

portal vein tumor thrombus) have been demonstarated" in Introduction section (Page 5).

Comment 3;

I recommend rewrite the introduction section provided that it should reflect the problem of unrespectable HCC and available therapeutic options from past to present in simple and smooth methods.

Response to Comment 3;

We appreciate the reviewer for the helpful and constructive comments and suggestions. We have rewritten the introduction section by adding the systemic chemotherapy drugs currently in use and clarifying the problems and treatment options for unresectable HCC.

Comment 4;

What mm or cm or inches or criteria [a large tumor mass such as beyond up-to-7?

Response to Comment 4;

We appreciate the reviewer for the important question. We stated the following sentence "Beyond Up-to-7 has a sum of the maximum tumor diameter (cm) and the number of tumors exceeding seven." in the section of 2-2 (Page 9).

Comment 5;

Is the following statement true? [two or more consecutive progressions in the liver (tumor number increases before the previous TACE procedure]

Response to Comment 5;

We appreciate the reviewer for the helpful comments and suggestions. The respective section in the JSH (The Japan Society of Hepatology) guidelines was revised to define TACE failure as an insufficient response after ≥2 consecutive TACE procedures. In addition, the appearance of a higher number of lesions in the liver than that recorded at the previous TACE procedure (other than the nodule being treated) was added to the definition of TACE failure/refractoriness.

Comment 6;

{Kawamura, 2020 #10} page 12 ? please edit it

Response to Comment 6;

As the reviewer pointed out, we corrected the reference in Page 12 by editorial rule.

Response to All Comments from Reviewers;

We are truly honored and astonished by the kind comments from both reviewers.

We believe that we have sufficiently revised our paper in accordance with the comments of the reviewers. We hope that you will find this revised manuscript acceptable for publication in the World Journal of Gastrointestinal Oncology and look forward to hearing from you at your earliest convenience.

Yours sincerely,

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