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25th April 2020

Title - Efficacy and Safety of Lenvatinib for Patients with Advanced Hepatocellular Carcinoma: A Retrospective, Real-World Study Conducted in China

Reference# 55265

Dear Editor-in-Chief,

Thank you for giving us the opportunity to revise this manuscript and we appreciate your help and guidance. According to your suggestions, we have made extensive modifications to the manuscript and supplemented extra data to ensure this is more comprehensive and generalizable. Detailed point-to-point responses are provided below. We hope these changes are met with your approval but if you have any further issues, please don't hesitate to contact me directly.

Best wishes

Haitao Zhao

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Responses to reviewers' comments

1st Reviewer

1. The author decided the title of this study `Efficacy and Safety of Lenvatinib for Patients with Advanced Hepatocellular Carcinoma: A Novel Real-World Study Conducted in China'. This study was a single-center, small number, and retrospective study. So, this title is exaggerated to mention a real-world clinical study in China, especially from the point of view in the effect of lenvatinib treatment for HBV related HCC patients.

Response - As you will know, the hierarchy and cone of evidence are changing and we, as clinicians and researchers are rightly being encouraged to intercalate real-world evidence into clinical studies. You are right, this is a small, retrospective study which involved patients from only a single center; however, we elongated the cone bridging

gaps between methodologies, thereby changing dynamics. The size of the study does not negate the implications nor the fact that it is not actually a standard design. As such, we feel that the term ‘real-world’ applies, although we maintained a tentative approach by using the term ‘conducted’ which explicitly restricts. That said, we have added the word ‘retrospective’ to the title in order to ensure the reader begins without an *exaggerated* understanding of this research.

2. The author mentioned therapeutic response predictions based on AFP and gene mutation. But, this paper does not show the profile of AFP in the enrolled patient. Please show the detailed data.

Response - According to your suggestion, we have provided added this very necessary knowledge to Table 1.

3. The author mentioned therapeutic response predictions based on AFP and gene mutation. Please show your opinion based on the relationship between tumor shrinkage and gene mutation, especially.

Response - Gene sequencing provides insight into potential gene mutation signatures related to the lenvatinib effect and we have explained this within the manuscript. Unfortunately, the small number of archived tumor samples prevented us from carrying out correlative statistical analyses. That said, this study does suggest that some genes (and potentially intervention-related mutations) might be used to prompt the use of lenvatinib, which is consistent with the RESORCE Biomarker Study [1].

[1] Teufel M, Seidel H, Köchert K, et al. Biomarkers associated with response to regorafenib in patients with hepatocellular carcinoma[J]. Gastroenterology, 2019, 156(6): 1731-1741.

4. Abbreviation 2.3 Further analysis of baseline characteristics ECOG-PS, BCLC 1-2 Spelling miss 3.2 Assessment of efficacy and AEs during the entire treatment period ALBI grade I…1, II…2, III…3 palmar-plantar erythrodysaesth Asia by diarrhea in two patients.

Response - These issues have been corrected.

2nd Reviewer

1. The idea is very excellent and manuscript had language editing and there are some grammar mistakes.

Response - The manuscript has been revised thoroughly by all authors to ensure it succinct and accurate. One of the authors (Samuel Seery) is a native English speaker with doctoral degree in population health sciences. Sam edited the English carefully to ensure that our ideas are expressed in standard, scientific English language. Sam

has also provided a separate English language editing certificate to clarify.

2. The list of abbreviation not found and some abbreviations not found as DCR, AEs,PFS,RFA,ECOG-PS scores,MVI and EHS,FGFRs, VEGF and FGF

Response - Thanks for pointing this out, we have corrected this accordingly.

3. Methods: ECOG-PS score, ALBI stage, Child-Pugh class and BCLC stage needs references and hcv patients you should how to diagnose and what investigations you made for the undiagnosed cases

Response - We have added the references for each of these terms. We have also provided a detailed description of the diagnostic process for HBV infections according to your advice.

4. as regards results (diarrhea in two patients) was written by mistake. Base line AFP is NOT mentioned and follow up level should be mentioned and what about the cases with normal AFP

Response - We have corrected this issue according to your suggestion. We have also supplemented Table 1. to include these data.

5. Discussion: the first paragraph is mentioned previously in the result, you should focus on discussion only

Response - We have revised the manuscript according to your suggestion, thank you.

3rd Reviewer

1. This is a report of a retrospective study on a systemic therapy, lenvatinib, in hepatocellular carcinoma patients in China. Results from this real-world study are comparable to existing data. The use of this systemic therapy medication appeared safe and effective. The analysis of genetic mutation in the treatment response is quite intriguing. Perhaps a prospective study could further investigate this topic. The "strict" eligibility criteria were quite vague; authors did Not specify inclusion criteria specifically, though exclusion criteria were somewhat hinted--31 patients excluded due to prior treatment w/ another "anti-tumor therapy" and 26 were excluded due to additional concurrent "anti-tumor therapy," which I assume is another systemic therapy. They need to clarify by stating that the so called "anti-tumor therapy" is systemic therapy, since they appeared to include patients with locoregional therapy.

Response - We have attached complete details about our eligibility criteria to the Supplementary materials. We have also revised the related segment within the Methods section and adjusted Figure 1. accordingly. We hope this adequately

addresses the issues raised.

2. One major issue with the omission of the inclusion criteria is the indication of systemic therapy vs locoregional therapy in hepatocellular carcinoma treatment. It appears based on the results and statistical analysis, one could infer that BCLC stage B and stage C patients were included. However, systemic therapy was recommended in stage C, not stage B in the original BCLC classification. It is scientifically sound (and clinically beneficial) to go beyond the guidelines. However, the authors should explain the rationale of rendering lenvatinib to BCLC stage B patients. Was it due to tumor progression?

Response - Systemic therapy is advocated for stage C according to current clinical guidelines. However, some patients with BCLC stage B are also intolerant of chemoembolization and other potential radical treatments. Likewise, there are patients who progress despite previous TACE therapy, and therefore through shared-decision making some stage B patients choose first-line systemic treatments such as lenvatinib. In the REFLECT trial, 22% of patients with BCLC stage B, were administrated with lenvatinib which is a larger proportion of patients who are unsuitable for TACE. Other real-world studies also included some patients with BCLC stage B, ranging from 23%-35%. As such, we have provided a detailed description of this within the method section and have discussed this within the manuscript, as advised.

3. The authors mentioned that the diagnosis of HCC was based on either histological evidence or radiographic evidence. What was the percentage of either method? Did some patients have both histological evidence and radiographic evidence of HCC? Among those who had received biopsy, what was the histological grade distribution (poorly differentiated, moderately differentiated, vs well differentiated, etc.)? What radiographic classification was used? The study period which ended in December 2019 was recent enough for the authors to go back and re-examine these questions.

Response - According to clinical guidelines such as American Association for the Study of Liver disease, European Association for the Study of the Liver (EASL) and Asian-Pacific Association for the Study of Liver, the diagnostic approach for HCC is based on imaging studies, restricting the role of histopathology to only certain situations. However, we agree with your suggestions and have added a detailed description to Table 1. and to the results. A detailed description of histological grade distribution has also been attached as supplementary materials which we felt is necessary because of dissimilar descriptions and tumor diversity.

4. One issue in the monitoring tumor response is the use of imaging. The author mentioned that RECIST 1.1 was used, which was published in 2009. Perhaps the authors should consider the addition of more up-to-date imaging criteria such as LI-RADS 2018.

Response - Presently, the RECIST 1.1 assessment tool is widely applied to consider tumor responses, in almost all clinical trials [1]. The LI-RADS (2018) on the otherhand, is advocated by the American College of Radiology (ACR) can standardize liver imaging terminology, image acquisition, sign interpretation, reporting, and data collection [2]. Although the LI-RADS (2018) focuses on the collection and processing of images, the RECIST 1.1 was designed specifically to assess tumor changes. However, we have adjusted the manuscript to ensure this is determining factor on tool selection is explicit.

[1] Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., ... & Rubinstein, L. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer, 45(2), 228-247.

[2] Chernyak, V., Fowler, K. J., Kamaya, A., Kielar, A. Z., Elsayes, K. M., Bashir, M. R., ... & Tang, A. (2018). Liver Imaging Reporting and Data System (LI-RADS) version 2018: imaging of hepatocellular carcinoma in at-risk patients. Radiology, 289(3), 816-830.

5. One question regarding the analysis of the results is the presence of hepatitis B infection. Does it make a difference in the treatment response vs those without hep B? It is unclear if the authors thought about this question regarding the highly prevalent viral infection among the Chinese population.

Response - The reviewer raises an interesting question here. In the REFLECT trial, a significant difference was observed between the HBV and non-HBV groups. Likewise, the global research community has also observed differences in terms of broad ethnicities e.g., between Asian-Pacific and Western populations. However in our study, comparing differences between patients with or without HBV infection was not possible due to the limited number of patients' number and relative ethnic homogeneity. Having said that, we take this comment on board and have revised to discussion to include more details about several RWS studies in this field conducted in Japan. Thanks for this advice, please read the manuscript for further details.

Editorial Office's comments

1. The manuscript had language editing, but there are some grammar mistakes. 4 tables and 6 figures. 25 references were cited, including 21 latest references from 2017-2020. self-citation. 2 Language quality: 3C. The author declared that the manuscript was edited by a native English speaker. Academic norms and rules: Retrospective Study. Signed informed consent, IRB, BRC and Conflict-of-Interest statement files are complete and qualified. Copyright license agreement file is not qualified. Bing search and CrossCheck are eligible. 4 Others: With financial support. Corresponding author has published 11 articles in BPG. Unsolicited manuscript.

Response - This has been addressed, please see the response to the 2nd reviewer's first

comment. A language editing certificate has also been provided for your consideration.

Editorial Office Director

1. Recommend for potential acceptance. 1. Scientific quality: I have checked the comments written by the science editor, and I basically agree with the science editor. The topic of the paper is the lenvatinib for patients with advanced hepatocellular carcinoma, and is within the scope of the WJG. This is a report of a retrospective study on a systemic therapy, lenvatinib, in hepatocellular carcinoma patients in China, which is very excellent, but the authors need to revise the manuscript according the reviewers' suggestions.

Response - Thank you for your positive comments on our manuscript. We really appreciate your time and effort. According to suggestions, we have supplemented data and corrected all mistakes in our previous draft.

2. The questions raised by the reviewers should be answered. 2. Language quality: 3C. One of the authors is a native speaker, but the reviewer 04737401 pointed out that there are some grammar mistakes, the language need to be edited. Academic norms and rules: I have checked the documents, including biostatistics review certificate, institutional review board approval form or document, informed consent form(s) or document(s), conflict-of-interest disclosure form, and copyright license agreement, all of which are qualified. No academic misconduct was found in the CrossCheck investigation and the Bing search. 4 Supplementary comments: (1) Unsolicited manuscript. (2) With 7 financial support. (3) Corresponding author has published 11 articles in BPG journals.

Response - This has been addressed.

Company Editor-in-Chief

1. I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report and the Criteria for Manuscript Revision by Authors.

Response - We have tried our best to modify our manuscript to meet the journal's requirements. Although, should you require further amendments, please feel free to contact me directly.

2. However, the quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the

English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240.

Response - This has been addressed.

Based on these comments and suggestions, we have made careful modifications to the original manuscript, and have carefully proof-read to fix typographical and grammatical errors. We believe that the manuscript has been greatly improved and hope it has reached your magazine’s standards.

Thank you very much for your feedback and we look forward to hearing from you.

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17th May 2020

Title - Efficacy and Safety of Lenvatinib for Patients with Advanced Hepatocellular Carcinoma: A Retrospective, Real-World Study Conducted in China

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Best wishes

Haitao Zhao

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Responses to reviewers' comments

1. However, I still think it's vitally important to mention certain key inclusion criteria in the manuscript (e.g., BCLC B and C, Child A and B), especially given that there is no work count limit. This should be easily taken care of by two to three sentences. Without mentioning the specifics, the phrase "strict eligibility criteria" sounds like a cliche.

Response – Thank you for your valuable suggestion. We have revised the details about the eligibility criteria in the manuscript. Please check it.

'Patients were included with Barcelona Clinic Liver Cancer (BCLC) stage B (not applicable for TACE, or progressed on locoregional therapy) or BCLC stage C, Child-Pugh score A-B, Eastern Cooperative Oncology Group performance status

(ECOG-PS) 0- 2 (please see Supplement S1 for details).'

2. I agree that RECIST is superior than LIRADS 2018 in terms of the study purposes. Is there a reason why the authors elected to use RECIST 1.1 rather than mRECIST?

Response -Thank you for your valuable suggestions. mRECIST is also a widely used criteria in the evaluation of hepatobiliary carcinoma, but the evaluation of tumor using mRECIST always demand the professional image skill and uniform image examination, and the process of evaluation is also complex. RECIST 1.1 criteria measures tumor size changes more directly and does not consider necrosis during tumor treatment, so it is more objective than the mRECIST standard. Presently, most clinical trials use RECIST 1.1 standards to evaluate the tumor size changing. Considering the respective feature and the non-uniformed clinical materials of this study, the RECIST 1.1 may be more suitable for the evaluation of our RWS study to reduce potential bias.

3. In terms of the effect hepatitis B had on the treatment response, perhaps a simple chi square or Fisher exact test would do--a total sample size of 54 would suffice. Just by eyeballing their Table 3, there appears to be some differences, and it'd be interesting to find out if these would be statistically significant or not.

Response – We agree with your suggestions and have added a statistical comparison to Table 3. However, we didn't find a significant difference between the all patients group and HBV related group.

Based on these comments and suggestions, we have made careful modifications to the original manuscript. We believe that the manuscript has been greatly improved and hope it has reached your magazine's standards.

Thank you very much for your feedback and we look forward to hearing from you.