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Reviewer A

Most patients with advanced hepatocellular carcinoma (HCC) do not have sustained disease control with 1st-line systemic therapy, particularly after tyrosine kinase inhibitors (TKIs). The second-line therapeutic landscape has changed in recent years, with various agents whose accessibility differs between countries (multi-kinase inhibitors such as regorafenib and cabozantinib, monoclonal antibodies targeting VEGF-R2, and antibodies directed against the immune checkpoints CTLA-4 and PD-1 (programmed death receptor-1). All these advances should not mask the singularity of HCC, mostly associated with chronic liver disease at cirrhosis stage of various etiologies. The relatively strict selection criteria used in the trials have resulted in a lack of data for many patients from common practice. So, this study is well justified.

Reply：Thanks for the evaluation. This is a real-world study. Macrovascular invasion and(or) extrahepatic metastasis are the main clinical characteristics of Chinese patients with hepatocellular carcinoma (HCC) after entering the second-line treatment. The aim of this study was to explore the efficacy and safety of regorafenib as second-line treatment for these patients with HCC. And we believe that our study has a certain clinical guiding value.

Changes in the text: None.

Introduction:

As the Authors point out, regorafenib (TKI) is the 1st TKI to demonstrate a benefit in survival after progression with sorafenib, following the results of the phase 3 RESORCE trial. But cabozantinib is the second TKI to be approved in this indication, following the results of the phase 3 CELESTIAL trial. It is important to note this, as well as ramucirumab (AM targeting VEGFR-2), which also showed a survival benefit in 2nd line after sorafenib in the REACH-2 trial, but in a specific population: HCC with alfa-fetoprotein (AFP) ≥400 ng/ml. It is also useful to note that despite a negative phase 3 trial, pembrolizumab was confirmed in this indication, based on a prolonged benefit on OS curves (KEYNOTE 240 study). The introduction needs to be simplified and the following data added.

Reply: Regorafenib (TKI) as the 1st TKI has been demonstrated a benefit in survival (phase 3 RESORCE trial). Cabozantinib as the second TKI (phase 3 CELESTIAL trial) and ramucirumab (AM targeting VEGFR-2) (REACH-2 trial) have also been studied in the HCC patients' trial.

Changes in the text: we have modified our text as advised (see Page 4, line 101).

line 113 - 114 (introduction), I would stay cautious; there are no controlled trials supporting the use of combination therapy as a second-line treatment.
Reply: We have carefully addressed the Reviewers' comments and revised our manuscript. Changes in the text: we have modified our text as advised (see Page 4, line 103-104).

Chapter method: it may be interesting to note the number of patients who received 1st systemic treatment, because in most real-life studies, these are only a minority.
Reply: Thanks for the suggestion, but we don't quite understand what you mean. The patients we collected were all patients who had previously received 1st systemic therapy. Searching for real-world studies on HCC, we already have a large amount of data.
Changes in the text: None.

In the results chapter, median OS under regorafenib is 9.6 months (n=63), line 190 – 191.
On page 239, it is specified that some patients received combination therapy (n=32). However, when we read the abstract, it talks about survival with regorafenib (i.e. monotherapy). Please clarify or modify the abstract.
Reply: It refers to the median survival time of all patients not only in the single drug group but also in the combination drug group. The research is more consistent with real-world settings. Therefore, we described the median survival time of all patients.
Changes in the text: None.

Line 253: it's interesting to include the results of the univariate analysis. The absence of Child-Pugh score as a prognostic factor is surprising.
Reply: We did not analyze data on Child-Pugh scores because more than half of the patients we collected had an A score (57/63) and a small number had a B score (6/63) that was not available for statistical analysis.
Changes in the text: None

Discussion: thanks for condensing the discussion
Line 279: it's important to note that switching to a second-line systemic treatment should theoretically concern most patients with advanced hepatocellular carcinoma (HCC), particularly after sorafenib. However, symptomatic disease progression and hepatic insufficiency are factors that may limit this sequencing, especially as the second-line drugs validated belong to the same therapeutic class.

Reply: Sorafenib inhibited tumor growth and angiogenesis through targeting both the RAF/MEK/ERK pathway and receptor tyrosine kinases. Regorafenib is a multitarget and small-molecule tyrosine kinase inhibitor (TKI), which has multiple effects such as inhibiting tumor proliferation, mitigating vascular proliferation, and reversing immune tolerance. The anti-tumor mechanism of the two drugs is not the same. Most patients enrolled in RESORCE and CELESTIAL trial were one-line Sorafenib and second-line Cabozantinib or Regorafenib. Our study had strict entry criteria (hepatic sufficiency: Child-Pugh score of ≤ 7 points). And in our results, the median OS of patients using regorafenib as second-line treatment in the first-line sorafenib group and first-line nonsorafenib group were 9.5 months and 9.6 months, respectively (P=0.9766). There was no statistical difference between the 2 groups in OS (P=0.9766). Our results have clinical significance.
Changes in the text: None.

Line 294, the authors report survival results similar to those of resorce, but it's also worth pointing out that half of the patients received combination therapy.
Reply: This study refers to research conducted in real-world settings. This approach aligns more closely with actual clinical practice and enables better evaluation of the effectiveness and safety of drugs or treatment methods in the real world. Combination therapy is more common in the clinical treatment of liver cancer patients. By recording the number of patients receiving initial systemic treatment, we can obtain more accurate data and analyze the effectiveness and side effects of drugs or treatment methods in practical applications. This is crucial for guiding clinical practice and developing treatment strategies to ensure that patients can achieve better treatment outcomes and safety.
And in the real world, there are a variety of treatments. Our findings are more reflective of the real world and reflect the methods of treatment on survival which were described in our article. However, our study has a certain limitation. It is a retrospective study, and future studies will be conducted.
Changes in the text: None.

line 345: to support their statements, the authors can cite this study: Yoo C, Byeon S, Bang Y, Cheon J, Kim JW, Kim JH, et al. Regorafenib in previously treated advanced HCC: Impact of prior immunotherapy and adverse events. Liver Int. 2020;40(9):2263-71
Reply: According to the suggestion, we have added the references to the article.
Changes in the text: we have modified our text as advised (see Page 9, line 300-302).

line 410: chemoembolization is a high-risk treatment in this setting of vascular invasion; radioembolization is more appropriate for advanced HCC with limited vascular invasion (*E Garin: Trans-arterial Radioembolization Dosimetry in 2022 Cardiovasc Intervent Radiol. 2022*). It is better to modify this part.

Reply: TACE or hepatic arterial infusion chemotherapy (HAIC) is a treatment for chemoembolization. As per the suggestion, we have modified the relevant description in the diccussion.

Changes in the text: we have modified our text as advised (see Page 11, line 359).

Reviewer B

The aims of this manuscript were to evaluate the efficacy and safety of regorafenib as second-line treatment for patients with hepatocellular carcinoma and macrovascular invasion and(or) extrahepatic metastasis. The results were not novel. However, only Chinese patients with chronic hepatitis B were included. This might provide more or less local information. Unfortunately, the manuscript was not well organized.

Reply: Most patients with advanced hepatocellular carcinoma (HCC) do not have sustained disease control with 1st-line systemic therapy, particularly after tyrosine kinase inhibitors (TKIs). Regorafenib is a multitarget and small-molecule tyrosine kinase inhibitor (TKI), which has multiple effects such as inhibiting tumor proliferation and mitigating vascular proliferation. Regorafenib has established itself as a second line treatment of HCC through A phase III clinical study of regorafenib (RESORCE) that confirmed regorafenib can significantly improve the overall (OS) and progression-free survival (PFS) of patients with unresectable advanced HCC in second-line treatment compared with placebo.

However, there are not only ethnic differences between Chinese and Western patients but also different pathogenic factors for liver cancer. In addition, whether different first-line treatment protocols can affect the efficacy and outcome of secondline regorafenib treatment has not yet been reported. Third, macrovascular invasion and(or) extrahepatic metastasis are the main clinical characteristics of Chinese patients with liver cancer after entering the second-line treatment. However, whether patients with macrovascular invasion and/or extrahepatic metastasis can benefit from the combination therapy and its safety remains unclear. In view of these issues, Thus, the purpose of this study was to evaluate the efficacy of regorafenib as second line treatment for real world Chinese patients with HCC patients with macrovascular invasion and/or extrahepatic metastasis. Therefore, this study is innovative.

Changes in the text: None.

1. Introduction:

The contents from line 80 to 117 need to be rewritten in concise form. Most of these contents belonged to the section of discussion.

Reply: As per the suggestion, we have revised the introduction.

Changes in the text: we have modified our text as advised (see Page 3-4, line 81-109).

2. Methods:

(a) Exclusion criteria duplicated the meaning already described in inclusion criteria.

Reply: As per the suggestion, we have revised the description.

Changes in the text: we have modified our text as advised (see Page 5, line 145-147).

(b) Since difference in the interval of imaging and/or tumor marker AFP evaluation such as one month vs. 6 months will significantly influence on the results of disease control rate (DCR), the authors should describe the exact interval and method(s) to determine DCR as complete response (CR), partial response (PR), or stable disease (SD). In clinical practice, only overall survival and side effects are the main concerns for both the patients and the physicians. Both DCR and progression-free survival (PFS) are mainly applied in the clinical trial for the possibility to fasten the time for approval of new drug.

Reply: According to the suggestion, we have added the exact interval and method(s) in the methods.

Changes in the text: we have modified our text as advised (see Page 4-5, line 133-135).

(c) The contents from line 228-231 in section of results should be placed in section of methods to describe what kind of drug(s) was(were) applied in the first-line non-sorafenib group.

Reply: Thanks for the suggestion, we have revised the results section and added it to the methods section.

Changes in the text: we have modified our text as advised (see Page 4, line 123-127).

(d) The contents from line 241-244 in section of results should be placed in section of methods.

Reply: Thanks for the suggestion, we have added the relevant content in section of methods. Changes in the text: we have modified our text as advised (see Page 4, line 129-133).

3. Results:

(a) This section was too redundant and duplicated the contents of Table 1 and 3.

Reply: We have revised the contents of Table 1. The data in Table 3 has been summarized and simplified, so no changes have been made.

Changes in the text: we have modified our text as advised (see Page 6, line 171-172).

(b) The sentence of "The OS of the 63 patients with HCC … (Figure 1A)" should be revised as "The OS of the 63 patients with HCC with macrovascular invasion and/or extrahepatic metastasis being administered regorafenib as second-line treatment was 9.6 months (Figure 1A)".

Reply：As per the suggestion, we have made revisions.

Changes in the text: we have modified our text as advised (see Page 6, line 176-178).

(c) The meaning of Figure 1C was questionable unless the exact interval and method(s) to determine DCR were clearly described.

Reply：We have described the exact interval and method(s).

Changes in the text: we have modified our text as advised (see Page 4-5, line 133-135).

(d) The relationship between OS and age, ECOG score, AFP, tumor invasion range, treatment order, and treatment methods can be concisely described in one paragraph.

Reply：This part of the result is more than enough to be superfluous in a single graph. But we put these results together in the same section.

Changes in the text: we have modified our text as advised (see Page 6-7, line 182-212).

(e) Figure 2 and 3 can be described as supplement data or deleted.

Reply：Although there was no statistical significance in mOS between the age and ECOG groups, it was also the main content of the study. And we've watered down that part.

Changes in the text: None.

(f) Figure 5A and 5B can be deleted unless the authors analyzed patients with or without macrovascular invasion excluding those with extrahepatic metastasis and versa.

Reply：As per the suggestion, we deleted figure 5A and 5B.

Changes in the text: we have modified our text as advised (see Page 23, line 652-655).

(g) Since regorafenib is an oral medication, the word “orally” can be deleted in paragraph of “Dose of regorafenib”.

Reply：Thanks for the suggestion, we have modified the colloquial description.

Changes in the text: we have modified our text as advised (see Page 7, line 223-225).

(h) The reason for the patient to stop regorafenib should be clearly described.

Reply：The main reasons for patients to stop regorafenib were disease progression, intolerance, and death. As recommended, we also added reasons for patients to decrease the dose of regorafenib.

Changes in the text: we have modified our text as advised (see Page 7, line 225-226).

4. Discussion:

(a) This section was too redundant and frequently duplicated descriptions in section of methods and should be rewritten in concise form.

Reply: We have made some revisions in the discussion section.

Changes in the text: we have modified our text as advised (see Page 8-10, line 244-336).

(b) It was not suitable to discuss DCR in this section unless the exact interval and method(s) to determine DCR were clearly described.

Reply: We have described the exact interval and method(s).

Changes in the text: we have modified our text as advised (see Page 4-5, line 133-135).