Peer Review File

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Reviewer A

Comment 1: In this Editorial manuscript, the Authors discuss the results of the phase II trial evaluating the use of camrelizumab (a PD-1inhibitor) plus apatinib (an VEGFR-2 inhibitor) and hepatic artery infusion chemotherapy for hepatocellular carcinoma (HCC) in Barcelona Clinic Liver Cancer stage C (BCLC-C).

Hepatic arterial infusion chemotherapy (HAIC) is a locoregional treatment that directly administer different chemotherapy agents (including epirubicin, doxorubicin, 5-Fu, gemcitabine, platinums) into the tumors via the hepatic artery and that has been previously explored in combination with systemic agents in the management of intermediate or advanced HCC cases and in those with PVTT as a traditional treatment intervention mainly in some Asian countries. However, this promising approach is not endorsed by the guidelines of the European Society of Liver Diseases and the American Association for the Study of Liver Diseases.

I have only a comment, of clinical relevance. It should be recalled that the use of HAIC can be associated with liver function deterioration thus precluding the use of systemic agents (TKIs, ICIs, anti-VEGF) that require a preserved liver function (usually Child-Pugh A class). Thus, the authors should also recall that in future clinical trials, the combination therapies using HAIC should be compared with a combination treatment strategy based on TKIs plus ICIs (without HAIC) that recently demonstrated very promising efficacy and safety as well-summarized in a recent comprehensive review discussing the pathogenic rationale of this combination treatment strategy and the risk of adverse events such as immune-related adverse events as well as the risk of liver function deterioration thus requiring an optimal patients selection, as recently discussed (TKIs in combination with immunotherapy for hepatocellular carcinoma. Expert Rev Anticancer Ther. 2023 Mar;23(3):279-291. doi: 10.1080/14737140.2023.2181162.). This is a crucial point for future clinical trials to compare OS (which could be also affected by liver function deterioration) and the safety of the treatment strategies with and without HAIC.

Reply 1: We highly appreciate the reviewer's comment and thank you for the time taken to critically assess our study. We have followed your recommendations and we have included a a paragraph referring to your suggestion (see Page xx, line xx).

Changes in the text 1: "It is important to emphasize that the use of HAIC can be associated with liver function deterioration thus precluding the use of systemic agents (tyrosine kinase inhibitors, immune checkpoint inhibitors or anti-VEGF) that require a preserved liver function (usually Child-Pugh A class). In future clinical trials, combination therapies using HAIC should be compared with a combination treatment strategy based on tyrosine kinase inhibitors and immune checkpoint inhibitors (without HAIC). This combination has recently shown very promising efficacy and safety, in a comprehensive review analyzing the pathogenetic rationale of this combination treatment strategy and the risk of adverse events (immune-related adverse events or risk of liver function impairment), which requires optimal patient selection (Expert Rev

Anticancer Ther. 2023 Mar;23(3):279-291. doi: 10.1080/14737140.2023.2181162). This is a crucial point for future clinical trials comparing OS (which could also be affected by impaired liver function) and safety of treatment strategies with and without HAIC".

Reviewer B

Authors give an interesting overview on the available first-line options and the ongoing prospective concerning immunotherapy for HCC.

Comment 1: In order to give to the readers a complete overview about first-line therapies, authors should mention also LEAP-002, COSMIC-312, RATIONALE-301 trials presenting their results, limitations and food for thought.

Reply 1: We share with the reviewer the suggestion to include the results of these three studies because they are of great relevance among the different alternatives and combination of treatments in the management of unresectable advanced hepatocellular carcinoma (see Page 3-4, line 97-106).

Changes in the text 1: "Different randomized clinical trials have attempted to demonstrate the usefulness of different combinations of chemotherapy with the aim of improving oncologic outcomes in patients with advanced unresectable hepatocellular carcinoma. The addition of pembrolizumab to lenvatinib as first-line therapy for advanced hepatocellular carcinoma did not meet prespecified significance for improved overall survival and progression-free survival versus lenvatinib plus placebo. In the COSMIC-312 study, first-line cabozantinib plus atezolizumab did not improve overall survival versus sorafenib. On the other hand, in RATIONALE-301 trial, tislelizumab demonstrated overall survival benefit that was noninferior vs sorafenib, with a higher objective response rate, while median progression-free survival was longer with sorafenib".

Comment 2: Please specify somewhere that apatinib and rivoceranib are the same drug.

Reply 2: We have clarified in the manuscript the that apatinib and rivoceranib are the same drug (see Page 3, line 82).

Changes in the text 2: "…daily oral rivoceranib (formerly apatinib, a VEGFR-2 inhibitor), …".

Reviewer C

This is a nice summary of a recent trial of immunotherapy plus VEGFR-2 inhibition as well as a discussion of the current state of immunotherapy, targeted therapy, and hepatic artery infusion chemotherapy treatment of patients with BCLC-C HCC.

Comment 1: Line 6 – an VEGFR-2 inhibitor better as "a VEGFR-2 inhibitor"

Reply 1: Thanks for your review. We have followed your recommendations and changed "and" for "a" (see Page 2, line 34).

Changes in the text 1: "..., plus apatinib (a VEGFR-2 inhibitor),..".

Comment 2: Line 11 – Hepatocellular carcinoma represents 75-85% of all liver cancer cases.
Reply 2: Thanks for your review. We have followed your recommendations and changed the sentence (see Page 2, line 40).
Changes in the text 2: "Hepatocellular carcinoma represents 75%–85% of all liver cancer cases".

Comment 3: Line 13 – please point out which new recommendations are included in the BCLC group update.
Reply 3: Thanks for your review. We have followed your recommendations and point out one of main new recommendations included in the BCLC group update (see Page 3, line 42).
Changes in the text 3: " The last update by the BCLC group on prognosis and treatment strategies was recently published including some new recommendations, such as the use of TARE in patients with a BLCL-B".

Comment 4: Line 15 – change to systemic chemotherapy is often recommended.
Reply 4: Thanks for your review. We have followed your recommendations and changed the sentence (see Page 2, line 45).
Changes in the text 4: "For patients classified as BCLC-C, systemic chemotherapy is often recommended".

Comment 5: Line 19 – needs editing
Reply 5: Share with the reviewer that this sentence needed a new edition to improve compression (see Page 2, line 48-50).
Changes in the text 5: "Currently, the preferred initial treatment for unresectable or metastatic HCC is the combination of atezolizumab (an anti-PD-L1 agent) and bevacizumab (a VEGF inhibitor) due to its enhanced survival advantages compared to sorafenib".

Comment 6: Line 20-22 – Per my reading of reference #9, that study shows increased PD-L1 on tumor cells and increased PD-1 expression (NOT PD-L1) on CD4+ cells. I do not see where it specifically shows that PD-L1 expression by endothelial cells is modulated though I could have missed that. It rather shows that VEGFR-2 is expressed mainly by the HCC cancer cells and endothelial cells. I would recommend editing this sentence to more accurately reflect the findings of the paper.
Reply 6: Coincidimos con el revisor en que este párrafo necesita una aclaración respecto al mensaje del estudio que se menciona (see Page 2, line 52-53).
Changes in the text 6: "This combination therapy shows increased PD-L1 on tumor cells and increased PD-1 expression on CD4+ cells".

Comment 7: Line 30-32 – Recommend editing this for clarity. As written it could be

read as prior sorafenib treatment resulted in an ORR of 15% whereas the authors intend to point out the ORR with nivolumab treatment.
Reply 7: Thanks for your review. We have followed your recommendations and changed the added that nivolumab was the group with best results (see Page 3, line 67).
Changes in the text 7: "The CheckMate 040 study investigated the effectiveness and safety of various dosages of nivolumab in 262 participants, some of whom had been previously treated with sorafenib with an objective response rate (ORR) of 15% in the dose-escalation phase and 20% in the dose-expansion phase with nivolumab treatment(11)".

Comment 8: Line 30 – Nivolumab is a generic drug name and likely does not need to be capitalized here.
Reply 8: We have followed your recommendations and not capitalized Nivolumab (see Page 2, line 64).
Changes in the text 8: nivolumab.

Comment 9: Line 46 – the use of notable to describe improvement in PFS is ambiguous. Perhaps leave out vs. state if this was statistically significant.
Reply 9: We have followed your recommendations and deleted notorious to avoid confusions Page 3, line 83-84).
Changes in the text 9: "The camrelizumab-rivoceranib combination showed animprovement in median PFS …"

Comments 10: Line 61 – instead of saying HAIC "could not become a standard treatment" perhaps say it is not currently a standard treatment.
Reply 10: We have followed your recommendations and changed it is because as you mention it is not currently a standard treatment (see Page 4, line 109-110).
Changes in the text 10: "At the moment, HAIC it is not currently a standard of treatment for patients with advanced HCC…".

Comment 11: Line 98 – change "es" to "is"
Reply 11: We have followed your recommendations and changed it (see Page 5, line 154).
Changes in the text 11: "The sample size is limited …"