Peer Review File

Article Information: https://dx.doi.org/10.21037/jgo-21-414

Reviewer A

In this manuscript, Xia et al. described the CP Score, BCLC stage, and MELD Score in a Hispanic-majority cohort receiving various second-line therapies for advanced HCC after first-line systemic therapy. Most patients in the cohort had CP-B cirrhosis or BCLC stage C HCC. Males patients were correlated with significantly decreased survival and young adults were corollate with significantly greater prevalence of HCV cirrhosis. In terms of second-line therapies received, mPFS with IO (CheckMate-040) and TKI (CELESTIAL and RESORCE trials) improved survival when compared to BSC. The detailed comparison between IO and TKI therapies was particularly interesting. There are some minor questions for the authors:

Comment 1: Table 2 indicated that patients receiving IO and TKI had an HR of 3.26 and 3.1 respectively which is higher than the HR of patients who received BSC therapy. Is this data consistent with the conclusion that TKI and IO can improve survival?
Reply 1: Thank you for this comment, and we apologize for this confusion. The statistical analysis was repeated with careful attention to ensure the inverse function was appropriately applied. We corrected the hazards ratios for the IO to BSC and TKI to BSC comparisons. Table 2 has also been updated accordingly.
Changes in the text:
Page 2, lines 44-49: We updated the hazard ratios and rounded the p-values (p-values were unchanged after this analysis).
Page 9, lines 213-216: Same as above, we updated hazard ratios and rounded p-values.
Table 2: updated analysis

Comment 2: Why is the baseline divided into groups Age <60 and Age> 60? It seems that the focus of the research is on the mPFS of the three treatments, IO, TKI, and BSC. Would it be informative to establish baselines based on these groups as well?
Reply 2: We agree with the reviewer and modified Table 1 to establish baselines based on treatment.
Changes in the text:
Page 2, line 44: Cohort analysis updated CP scores
Page 8, line 181-182, 187: Deleted previous analysis of table 1, and replaced with new analysis of table 1.
Table 1: stratified by treatment group

Comment 3: Following the second question, Table 3 compares the side effects, including nausea, fatigue, diarrhea, etc., of IO, TKI, and BSC treatments. It will be informative to also provide a summary of the basic characteristics of the three treatment groups, such as HCC diagnosis age, other diagnosis HCC stages, etc.

Reply 1: Thank you for this comment. The revised Table 1 now is formatted by treatment group to show each group's baseline data, which follows a similar format to Table 3.
Changes in the text: No changes made in text.

Comment 4: How are the 58 patients receiving each treatment allocated? Would patients in a healthier state be preferentially allocated to one of the groups? Would that confound the results of your study? For instance, if patients in a better condition, such as being younger, are more likely to be assigned to IO and TKI treatment would that increase the survival rate in those groups?
Reply 4: Thank you for this comment. Second-line treatment was selected by physician's choice based on NCCN guidelines. As this is not a randomized study, but a retrospective analysis, the groups were not balanced in regards to Child Pugh Status (Table 1). This IO group had more B patients versus TKI group had more A patients versus BSC had more B/C patients. This can possibly impact survival as well. Patients in each group has a similar stage for HCC, BCLC B: IO 85.2%, TKI 83.3%, BSC 84.0%. Given this small cohort, a larger randomized study would address these biases.
Change in text:
Page 6, lines 136-137 – added physician's choice per NCCN Guidelines to methods
Page 12-13, lines 302-311 – above added to manuscript
Page 15, lines 358-360 — added NCCN Guidelines reference

Comment 5: Finally, while this cohort mainly represents Hispanic patients in a South Texas tertiary referral cancer center, it may be necessary to supplement the discussion with data from studies focused on other regions or ethnicities, in addition to the South Korean (Asian) studies described in discussion, to be more representative.
Reply 5: Thank you for the comment. We added text including a US-based study assessing IO vs non-IO efficacy, that has a cohort with HCV majority and based on U.S. population, more representative of our cohort.
Change in text:
Page 11, Lines 273-281: added text about this US based study
Page 15, lines 368-370: added new reference

Reviewer B

The authors provide real-world data on the 2nd line therapy of HCC. They compared TKI vs IO regimens and did a subgroup analysis on age, liver function and other parameters. Overall, such data is important since patient populations in trials often differ from real-world patient populations regarding ethnicity and other confounding factors, which is nicely discussed here.
The major limitation of the paper is the very small sample size of patients receiving 2L treatment. Only 2 patients on regorafenib and only 4 patients on cabozantinib were included, while no patients on ramucirumab or pembrolizumab was included. This may lead to a bias of the results when comparing TKI vs IO outcomes and the feasibility of the performed subgroup analyses needs to be checked carefully by a statistician. Yet, a further subgroup analysis on efficacy would be very intersting, e.g. how does the IO cohort perform related to CP status?

Better performance of IO in the cited Korean studies could also be due to the high prevalence of HBV in this population, which in general responds better to IO treatment than non-viral HCC.

Minor points:
Comment 1: do not use "gender" when referring to biologic sex
Reply 1: Thank you for this comment. We have changed “gender” to “sex.”
Changes in text: Page 8, line 184 and line 193

Comment 2: it is suggested not to write "patients receiving first-line therapy" (e.g. l. 34) as this sounds misleading, but to speak of patients enrolled into this study
Reply 2: Thank you for this comment. We modified the sentence to resolve the confusion.
Changes in the text: Page 2, Line 43. We replaced “Of the patients receiving first-line therapy” with “In our cohort”.

Comment 3: - the title of the paper should be amended to reflect the focus on nivo, rego and cabo treatment and to indicate the small sample size (e.g. "a single center experience")
Reply 3: We modified the title as advised. We also modified a sentence in the methods to specifically reflect which TKIs and IO were used at our cancer center.
Changes in the text:
Page 1, lines 2-4. We changed the title from “Real-world comparison of second-line therapy tyrosine kinase inhibitors versus immunotherapy for advanced hepatocellular carcinoma in patients with varying liver dysfunction” to “Second-line treatment with nivolumab, cabozantinib, regorafenib or best supportive care in patients with advanced hepatocellular carcinoma: Analysis at a Hispanic-majority NCI-designated cancer center”

Page 6, line 135-139. We replaced the former sentence “Second-line therapies included cabozantinib, regorafenib, nivolumab, pembrolizumab, ramucirumab” with the following: “Of the five FDA-approved second-line therapies, as a result of physician’s choice for treatment based on National Comprehensive Cancer Network (NCCN) guidelines, patients received nivolumab (IO; immunotherapy) and regorafenib and cabozantinib (TKI; tyrosine kinase inhibitor) at our center during the time frame of this retrospective study.”