Peer Review File

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Reviewer A

In this manuscript, the authors performed a comprehensive bioinformatic analysis using several cohorts of hepatocellular carcinoma patients and identified clinical significance of ARID1A expressions. The paper represent a strong interest in the context of HCC diagnosis and contributed to the discovery of novel therapeutic targets. I don't have major comments, only suggest authors to:

1. include proper references on recent biomarker research on HCC, such as:

Chen, Krista Y., et al. "Clinical Outcomes in Fibrolamellar Hepatocellular Carcinoma Treated with Immune Checkpoint Inhibitors." Cancers 14.21 (2022): 5347.

Ho, Won Jin, et al. "Neoadjuvant cabozantinib and nivolumab convert locally advanced hepatocellular carcinoma into resectable disease with enhanced antitumor immunity." Nature Cancer 2.9 (2021): 891-903.

Mi, Haoyang, et al. "Quantitative Spatial Profiling of Immune Populations in Pancreatic Ductal Adenocarcinoma Reveals Tumor Microenvironment Heterogeneity and Prognostic Biomarkers." Cancer research (2022).

Reply 1: Thank you for your responsible attitude towards the manuscript. According to your advice, we have added relevant description about recent biomarkers on HCC in introduction section in our revised manuscript. We mark the additions in red. All the suggested references have been cited properly. (see Page 4-5, line 78-86)
Changes in the text: Page 4-5, line 78-86

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2. Include the cohort sizes from cBioPortal and TCGA.

Reply 2: Thanks for your comment. Due to our negligence, the cohort sizes from cBioPortal and TCGA was not clearly indicated. In Result section, we illustrated the cohort sizes from cBioPortal, including patients who received sorafenib treatment from the cBioPortal (L172, L190). According to your advice, we have illustrated the cohort sizes from TCGA in Methods section in our revised manuscript (see Page 7, line 163). We mark the additions in red, and we also note the cohort size from cBioPortal in the Figure1and Figure2.

Changes in the text: Page 7, L163: 338 patient samples.

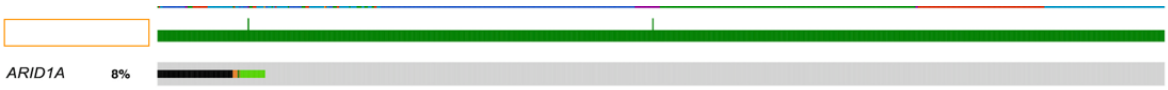
Reviewer B

1. Please check if more references should be cited in the following sentences since you mentioned "studies".
   - Regarding the efficacy of sorafenib treatment, previous studies have demonstrated a 3- to 5-month median survival of HCC patients, and it is necessary to explore the underlying mechanisms of sorafenib resistance.
   - According to published studies, activation of the PI3K/Akt signaling pathway serves as a potential mechanism related to acquired resistance to sorafenib

Reply: Thanks. We have checked carefully and corrected it in the revise manuscript.

2. Figures and tables

(1) Please check if any description should be added in Figure 1A.

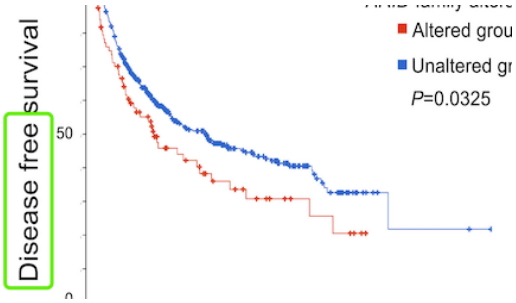


Reply: Thanks. We have checked and revised Figure 1.

(2) Please add "%" to the description of y-axis in Figure 1D, 3C, 5 (OS parts), 6, 7C-7E, 8B-8C and 8E.

Reply: Thanks. We have checked and revised all figures

(3) Please revise all "Disease free" to "Disease-free" in Figures 1

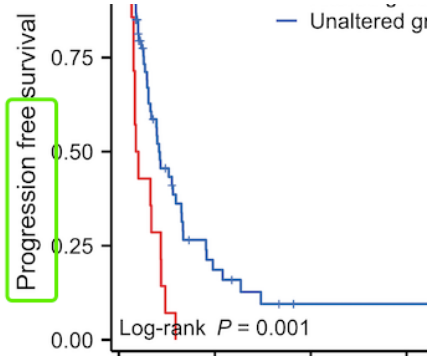


Reply: Thanks. We have checked and revised Figure 1.

(4) Please check if any description should be added to indicate what red, orange and yellow bars represent in the legend of Figure 2A.

Reply: Thanks. The result can be obtained by the length of the bar, not by the color.

(5) Please revise all “Progression free” to “Progression-free” in Figures 2, 3.



Reply: Thanks. We have checked and revised Figure 1.

(6) Please unify p values below in your main text with Figure 2B.

Table S1. As shown in the survival analysis in **Figure 2B**, genomic alterations of the *ARID* family predicted poor prognosis of HCC patients who underwent sorafenib treatment in terms of both progression-free survival (PFS: *P*=0.0011, 1.91 months versus 4.18 months) and OS (*P*=0.0161, 8.4 months versus 17.6 months). Specifically, the subgroup analysis revealed that a single *ARID1A* alteration also displayed satisfactory efficacy in predicting the prognosis of patients who received sorafenib treatment (PFS: *P*=0.0082, 2.54 months versus 4.18 months; OS: *P*=0.0220, 8.4 months versus 15.2 months).

Reply: Thanks. We have checked and revised Figure 2 and main text.

(7) The total numbers are inconsistent in Figure 3A. Please check.

Reply: Thanks. Figure3A was analyzed using the online database. The patients numbers are inconsistent between the PFS and OS analysis. We have checked this data again.

(8) Please confirm all cell images in Figure 4 are original and created/made by the authors.

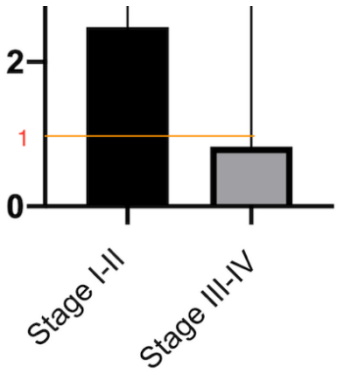
Reply: Thanks. We confirm all cell images in Figure 4 are original and created/made by the authors.

(9) Please provide explanation for “****” in Figure 5, 7B.

Reply: Thanks. We have provided related explanation in legends.

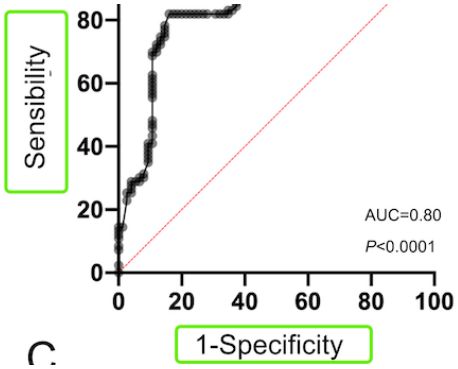
(10) Please revise the height of the bar "Stage III-IV" as the data is 1.02.

- In addition, as shown in **Figure 7B**, ARID1A expression was lost with disease progression (mean score of expression differences between tumor and normal tissue: stage I-II: 2.34; stage III-IV: 1.02; *P*<0.0001).



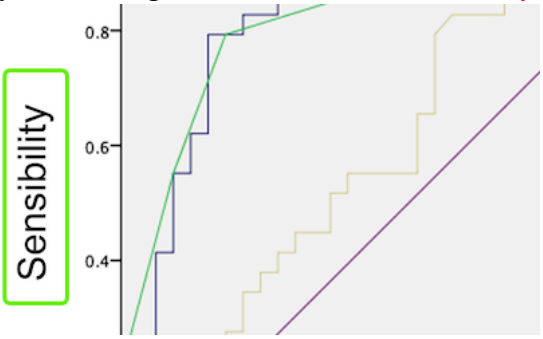
Reply: Thanks. We have made the relevant modifications in Figure7.

(11) The description of x/y-axis of Figure 8B should be "100-Specificity, %" and "Sensitivity, %". Please revise.



Reply: Thanks. We have made the relevant modifications in Figure8

(12) The y-axis of Figure 8F should be "Sensitivity".

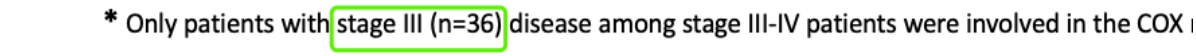


Reply: Thanks. We have made the relevant modifications in Figure8

(13) It is suggested add a unit after Age in Table 1.

Reply: Thanks. We have made the relevant modifications in Table1.

(14) Table 1: The number of stage III patients is n=35 in your main text. Please unify.



Reply: Thanks. We have made the relevant modifications in Table1.