Peer Review File

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Reviewer A

Comments:

Comment 1: Be consistent with AFP-positive/negative (not “APF+” or “AFP-“). Can also use the abbreviations used in the original paper (APHC/ANHC)

Reply: We agree that this will improve the readability of the present manuscript and have changed this abbreviation. We are now using APHC/ANHC throughout the manuscript.

Changes in the text: all “AFP-positive/negative” or “APF+/AFP-“ have been changed to APHC/ANHC

Comment 2: Mention the TGF/IL-6 ligands from endothelial cells against TAM-SPP1+ cells. This will tie in to Figure 1

Reply: Thank you for this comment, we added some details on this important signaling pathway.

Changes in the text: (see lines 78-80)

Reviewer B

Comments:

Comment 1: I suggest the authors add relevant references that also studied the role of TAM in HCC TME in neoadjuvant/ICI treatment setting, such as:

1.Mi, Haoyang, et al. "Multi-scale spatial analysis of the tumor microenvironment reveals

features of cabozantinib and nivolumab efficacy in hepatocellular carcinoma." Frontiers in immunology 13 (2022): 892250.

2. Ho W J, Zhu Q, Durham J, et al. Neoadjuvant cabozantinib and nivolumab convert locally advanced hepatocellular carcinoma into resectable disease with enhanced antitumor immunity[J]. Nature Cancer, 2021, 2(9): 891-903.

Reply: Thank you for pointing out these important references, they have been inserted as new references no. 6 and 7.

Changes in the text: see lines 27-30

Reviewer C

Comments:

Comment: The authors commented on a recent article published on Cell Discovery and suggested new opinions, in general well written.

Reply: Thank you very much for your time in reviewing this manuscript and for the favourable response.

Reviewer D

Comments:

Comment 1: As well reported in Figure 1, a crucial role in the immunosuppressive mechanisms and immune evasion, is played by Regulatory T cells (also called CD4+ CD 25+ Foxp3 Regulatory T cells). This subset T cell population largely expresses CTLA4 and PD1 and is, therefore, a potential target of current ICIs, as well described in a comprehensive recent review (Hepatocellular carcinoma in viral and autoimmune liver diseases: Role of CD4+ CD25+ Foxp3+ regulatory T cells in the immune

microenvironment. World J Gastroenterol. 2021 Jun 14;27(22):2994-3009.).

Reply: We thank the reviewer for this point and have inserted a comment, the above-mentioned review paper is referenced as new reference no.19.

Changes in the text: see lines 111-113

Comment 2: In light of the well-described intricate mechanisms linking microenvironment immune cells and tumor-associated neoangiogenesis, the authors should also recall the recent very promising results of concluded and ongoing clinical trials showing an increased objective response and overall survival obtained with a combination treatment strategy based on tyrosine kinase inhibitor plus ICIs, as described in a recent comprehensive review (TKIs in combination with immunotherapy for hepatocellular carcinoma. Expert Rev Anticancer Ther. 2023 Mar;23(3):279-291.).

Reply 2: Thank you for providing this clinical perspective; we have added a comment regarding this.

Changes in the text: see lines 33-36