Peer Review File

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Reviewer A

The authors should cite state-of-the-art studies that evaluate the efficacy of combinatory therapy of nivolumab and cabozantinib to treat hepatocellular carcinoma (Clinical trial ID. NCT03299946):

1. Mi, H., Ho, W. J., Yarchoan, M., & Popel, A. S. (2022). Multi-scale spatial analysis of the tumor microenvironment reveals features of cabozantinib and nivolumab efficacy in hepatocellular carcinoma. Frontiers in immunology, 13, 892250.

2. 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.

Reply:

we have modified our text as advised, both suggested articles were included as references (see page 2 line 39).

Changes in the text:

The following paragraph was included:

" Analysis of the tumor microenvironment (TME) in patients with localized or locally advanced HCC, treated first with preoperative cabozatinib (40mg daily for 2 weeks) followed by combined treatment with cabozatinib and nivolumab (240mg IV every 2 weeks for 8 weeks), revealed potential immunoestimulatory effects of this drug. The two-week treatment with isolated cabozatinib resulted in an increase in memory and effector T cell subtypes within the CD4+ and CD8+ populations compared to baseline samples. Interferon-γ, granzyme B, and Ki-67-positive cell subtypes were included among these populations and are signatures associated with antitumor activity. Cabozatinib treatment also led to reduced levels of CXCL1, a chemokine ligand associated with CXCR2 and mediated by VEGF signaling, linked to immunoresistance and the confinement of T-cells within the TME. A higher density of immune cells, such as lymphocytes, is associated with tumor response when treated with the combination of cabozatinib and nivolumab. On these studies, 5 out of 12

patients (42%) who underwent surgery had major or complete pathological responses. These findings indicate that cabozatinib promotes a favorable environment for an immune response through both systemic and localized effects."

Reviewer B

The authors state the relationship between efficacy and safety in patients with advanced hepatocellular carcinoma treated with Cabozantinib, Nivolumab, and Ipilimub. The editorial is comprehensive and informative.

I have the following concerns.

1) Line73: Please add the data of median overall survival and median progression free survival.

Reply:

We added data regarding median overall survival and median progression frees survival (see page 4 line 102).

Changes in the text:

The median OS (95% CI) was 20.2 months (ranging from 13.1 to 32.2 months) in the doublet arm and 22.1 (15.2 to not reached) in the triplet arm. The median PSF (95% CI) was 5.1 months (2.8 to 10.9) with the doublet therapy and 4.3 months (3.6 to 11.9) with the triplet combination.

2) Lines 96-97: Line breaks are not necessary.

Reply:

We changed the text removing the line break (see page 4 line 116).

3) Line 125: Hepatic event should be specified.

Reply:

We added the description of hepatic events (see page 5 line 152).

Changes in the text:

The majority of these events involved elevations of serum transaminases, with one case of bilirubin elevation associated with cholangitis.