World Journal of Gastroenterology

Manuscript NO 48028: Hepatocellular carcinoma in research and clinical practice

Authors: Daniel Neureiter, Sebastian Stintzing, Tobias Kiesslich, Matthias Ocker

Dear editor,

Thank you for the valuable reviewers' comments. Please find a specific point-to-point reply to each comment.

Looking forward to your positive evaluation, we remain with best regards,

Yours,

Daniel Neureiter, Sebastian Stintzing, Tobias Kiesslich, Matthias Ocker

Reviewer 1 (03724099):

We thank the reviewer for the positive evaluation. Typos were corrected throughout the manuscript.

Reviewer 2 (03475479):

We thank the reviewer for the positive evaluation.

Reviewer 3 (00058381):

We thank the reviewer for the positive evaluation.

The outlook section of the manuscript was revised. Language and typos were corrected throughout the manuscript.

Reviewer 4 (02904354):

We thank the reviewer for the critical and valuable comments.

1. Title was changed to "Hepatocellular carcinoma: therapeutic advances in signaling, epigenetic and immune targets". The suggested references were added to the introduction section.

2. New parts e.g. on c-Met, PVTT (see below) and vitamin K (see answer to reviewer 5) were added. The presentation of different issues of HCC is comprehensively completed so that a reorganization of the manuscript is not necessary in our opinion now.
3. Smoking was removed from the list of risk factors.
4. The role of Met inhibitors was added to the suggested section in the manuscript: "Several other targets for inhibition of receptor tyrosine kinase function in HCC were investigated. Hepatocyte growth factor (HGF) and its receptor c-Met are commonly overexpressed in HCC and have been linked to poor prognosis and resistance to e.g. sorafenib treatment[18-20]. c-Met is targeted by several multi-kinase inhibitors like gefitinib or cobazitinib and more recently also selective inhibitors like capmatinib or tepotinib entered clinical trials but results for studies in HCC are still pending[21-23]. Other less selective compounds with c-Met inhibition properties like crizotinib, brivanib or foretinib did not lead to significant prolongation of overall survival (OS) in phase III studies or were not investigated in HCC patients yet[21, 22, 24, 25]."
5. The role of sorafenib in patients with PVTT was further discussed as suggested: "Esp. the use of sorafenib in patients with portal vein tumor thrombosis (PVTT) remains controversial[27]. In a study with 30 patients with advanced HCC and PVTT treated with sorafenib monotherapy, a disease control rate of 33.3% was achieved, including thrombus revascularization in a small number of patients. Yet, OS and progression-free survival (PFS) still remained disappointing with only 3.1 and 2.0 months, respectively[28]. In combination with TACE, sorafenib was able to induce a significant survival benefit compared to TACE only in patients with type B (13 vs. 6 months) or type C (15 vs. 10 months) in a stud enrolling 99 patients[29]. Similar results were obtained in combination with radiofrequency ablation (RFA)[30]. Still, prospective randomized controlled trials on sorafenib or regorafenib monotherapy in this setting are missing and the effect of the combination approach is probably overruling the currently available results[27]."
6. Abbreviations are spelled out at first occurrence.
7. Typo and language corrections were done throughout the manuscript.
8. Sentence was changed to "Animal models, however, still represent standard models for early drug development approaches."

Reviewer 5 (00182114):

We thank the reviewer for the critical and valuable comments.

1. The sentence was changed to "All of these compounds are recommended for patients with preserved liver function, i.e. Child-Pugh score 5, 6 and 7[26]." The recommended reference was added.
2. We added a statement on vitamin K and sorafenib synergy: "Interestingly, vitamin K was shown to enhance the antitumor effects of sorafenib via reduction of expression of des-γ-carboxy prothrombin (DCP), a proangiogenic growth factor that can also trigger signaling via c-Met and which is commonly upregulated after sorafenib treatment[31, 32]."
3. CD44v9 is proposed as another prognostic biomarker for HCC, while the section in our manuscript discussed biomarkers that are predictive for specific treatment options. Recent data (Wada F et al., Cancer Sci 2018;109:2801-10) also indicate a role in hepatic artery infusion chemotherapy (HAIC), but currently no data is available on its use with targeted agents or immunotherapies.

Similarly, only limited information (2 publications) are available for HPCAL1 and HCC. This marker was also proposed as a diagnostic or prognostic biomarker, but was not yet clinically validated and its role as a predictive biomarker for specific therapies is not known.
We did therefore not include the proposed statement on CD44v9 and HPCAL1, although these mechanisms warrant further investigations.

Editorial comments:

1. An audio core tip is provided as a separate file.
2. Formatting suggestions and reference section were updated according to the editorial comments. There are no repeated references. PMCID was removed.
   No DOI was available for references 6, 45.
   No PMID was available for reference 58.
   PDF title pages of these references are submitted in file 48028-References.
3. All changes are marked in track change mode.