

Dear Editor,

Thank you for the constructive comments to our manuscript. We revised the manuscript according to all the issues raised by the Reviewers and we provide below a reply to all their comments in order to improve the paper for publication. Changes are highlighted in yellow in the revised manuscript. We sincerely hope that our manuscript is now suitable for publication in *World Journal of Gastroenterology*.

Reviewer #1: In the present manuscript, Dr. Elena De Mattia et al. reviewed and discussed the pharmacogenetic literature evidence of target therapy drugs. The identification of biomarkers for therapeutic effect prediction is helpful for the choice of clinical treatment. The present manuscript could be accepted on World Journal of Gastroenterology. Comments are as follows:

1. The abstract should be more concise.
2. Tivantinib is c-Met inhibitor, rather than mesenchymal–epithelial transcription factor inhibitor.
3. There were some results described in the article without references, such as chemoembolization clinical trials.
4. Wrong reference cited in reference 54 and 55, please revise it.

We thank the Reviewer for the helpful comments that permit us to improve our manuscript. We have shortened the abstract, changed the Tivantinib definition, added the missing references and corrected the wrong reference.

Reviewer #2:

1. The abstract was a bit longer. Please shorten it.
2. There were up to 10 keywords, which was too many.

We thank the Reviewer for the valuable suggestions; the manuscript was revised accordingly. We have shortened the abstract and reduced the number of keywords.

Reviewer #3: This review study summarized and discussed the pharmacogenetic literature evidence for targeted agents in the systemic treatment of advanced HCC. No comments.

We thank the Reviewer for the positive comments.

Reviewer #4: This review is by far the most comprehensive introduction to the topic of pharmacogenetics in the treatment of advanced liver cancer. I suggest that priority be given to the publication of this review article.

We thank the Reviewer for the positive comments.

Reviewer #5: The paper had carefully read by us. This paper summarized and critically discussed the pharmacogenetic literature evidence, with particular attention to sorafenib and regorafenib, which have been used longer than the others in HCC treatment and introduced the the previous research progress of approved drugs. It is a well written manuscript with a large quantity of data and detailed description.

We thank the Reviewer for the positive comments.

Reviewer #6: I appreciate the thoroughness and completeness of the review paper. However, there are many areas for improvement. Overall, the review paper is very long, unfocused, and does not provide a higher-level synthesis of the data (i.e. much of the manuscript simply restates conclusions from other studies without providing the authors interpretation of what the results really mean, how do they impact current pharmacogenomics research, will it impact clinical practice, what are the next steps needed in research to validate findings, etc.). Further, the authors review many different trials, but did not include any numbers or statistics for most of the trials (see attachment). There is a lot of information that is not pertinent to the aim or title of the manuscript (see attachment).

We thank the Reviewer for the helpful suggestions that we have integrated throughout the revised manuscript. Moreover, we have shortened and/or divided into sub-paragraphs some text sections that were too long (i.e. sections 2 and 3 have been merged) based on Reviewer suggestions, we have eliminated the information that resulted not pertinent to the aim of the manuscript and we have moved the paragraphs that looked like 'discussion paragraphs' in the 'conclusion and future directions' section. Some details regarding the study population (e.g., sample size, ethnicity) and therapy (dose and schedule) characteristics as well as the main findings (e.g. statistical results) of the studies are shown only in the Tables. To avoid the duplication of information in the Tables and in the text, we have now specified what study details are reported only in the Tables and not in the text.