Reviewer #1: The article by Marisi G reviews the recent progress in biomarkers for sorafenib therapy in hepatocellular carcinoma. In general, the manuscript was well written. I have a few minor concerns.

1. FDA approved sorafenib for treating advanced unresectable hepatocellular carcinoma in 2007. The article has mentioned a couple of times that sorafenib was used for treating advanced HCC in 2008. Please clarify which year is correct.

Reply: FDA approved sorafenib for treating advanced unresectable hepatocellular carcinoma in 2007, but in Europe is possible to prescribe Sorafenib from 2008. We agree with the reviewer and we change the year in the abstract (page 3, line 3) and in the text (page 5, line 4).

2. Regarding adverse events of sorafenib treatment, a recently published meta-analysis review article can be cited (Hand-foot skin reaction is a beneficial indicator of sorafenib therapy for patients with hepatocellular carcinoma: a systemic review and meta-analysis. Expert Rev Gastroenterol Hepatol. 2017 Sep 3:1-8).

Reply: Thank you for the suggestion. We have inserted a sentence about this paper and cited this meta-analysis review article as reference number 14 (page 7, lines 11-12).

3. Please modify Figure 1. It is well-known that sorafenib inhibits the Raf/MEK/ERK signaling pathway and tyrosine kinase receptors including VEGFR, PDGFR, Flt3 and c-Kit. However, from Figure 1, it seems that sorafenib inhibits the Raf/MEK/ERK signaling pathway through its inhibitory effects on VEGFR, PDGFR, Flt3 and c-Kit.

Reply: We have modified Figure 1. Sorafenib is a multityrosine kinases inhibitor against VEGFR, PDGF-R, Flt3 and c-Kit, and also targets Raf kinases involved in the MAPK/ERK pathway. We have enlarged the symbol of the sorafenib inhibition near the Raf kinases (page 31).

4. The manuscript reviews each biomarker based on single-factor analyses. It would be better by discussing multiple-factor analyses. Please see the reference: Novel biomarker-based model for the prediction of sorafenib response and overall survival in advanced hepatocellular carcinoma: a prospective cohort study. BMC cancer, 2018, 18(1): 307.

Reply: We have added a sentences in the introduction of the biological markers (page 12, lines 12-15) and we have added a paragraph on multiple-factor analyses (page 14, lines 1-9).

5. The manuscript could also be improved by including some markers based on medical imaging examinations. Such as: Advanced Hepatocellular Carcinoma: Pretreatment Contrast-enhanced CT Texture Parameters as Predictive Biomarkers of Survival in Patients Treated with Sorafenib. Radiology, 2018: 171320.

Reply: We have included some markers based on medical imaging examinations inserting a new paragraph (page 11, lines 19-27 and page 12, lines 1-5).

Reviewer #2: This manuscript summarized the research results in recent 10 years for the possibility to find the potential factor(s) or marker(s) to predict the treatment response of sorafenib in advanced unresectable hepatocellular carcinoma (HCC). Although the conclusion is still no validated prognostic or predictive factor or marker, the contents of the manuscript may provide a whole view of sorafenib in HCC treatment. I recommend publishing this manuscript.

Minor comment:

1.All abbreviations should be spelled in full in their first appearances and be applied consistently in whole text. (e.g. PFS should be spelled in full in its first appearance in page 7 rather than in page 8. The hand-foot skin reaction (HFSR) was spelled as HSFR in page 7. It is not necessary to describe "hand-foot skin reaction (HFSR)" again in page 8.)

Reply: We have corrected these abbreviations (page 6, line 19; page 7, line 16; page 8, line 2).

2. The authors need to make sure the following sentences are correct. a. They showed, in a small series of patients treated with sorafenib, that patients with > grade 2 of HSFR had a significantly higher disease control rate with respect to patients without HSFR or HSFR. (page 7) b. Casadei Gardini et al. evaluated for the first time SII, NLR e platelet-lymphocyte ratio (PLR) in a small case series[40], observing that SII and NLR were independent prognostic factors for OS. (page 13)

Reply: We have corrected these sentence and we are sorry for the mistakes (page 7, lines 6-7; page 11, line 13).

Reviewer #3: Although a few markers associated with HCC prognosis have been reviewed, authors should find to more biomarkers to predict its efficacy in patients with advanced HCC.

Reply: Thank you for the suggestion .We have added a paragraph on multiple-factor analyses and a paragraph on markers based on medical imaging examinations (page 14, lines 1-9; page 11, lines 19-27 and page 12, lines 1-5).