Reviewer's report

Title: Impact of neo-adjuvant Sorafenib treatment on liver transplantation in HCC patients - a prospective, randomized, double-blind, phase III trial

Version: 2
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Reviewer: Matteo Cescon

Reviewer’s report:

This study reports the results of a RCT comparing patients with HCC within Milan criteria and undergoing TACE + sorafenib vs. TACE + placebo as neo-adjuvant treatments before liver transplantation. Comparable results were achieved between the 2 study groups as assessed by different tumour-related end-points and survivals, with patients treated with sorafenib showing a higher rate of severe toxicity.

Well-designed prospective comparative trials on the present topic are lacking, while there is a theoretical strong rationale for targeting cancer-related angiogenesis with chemical agents, especially where a potential enhancement of neo-angiogenesis is provoked by incomplete neo-adjuvant treatments. In this view, the study by Hoffmann et al. is to be commended for its appropriate design, end-points, and statistical measures chosen.

Unfortunately, the results are negative as no advantages in terms of efficacy were demonstrated by adding sorafenib to TACE. However, since mostly speculative data are available up to now (ref. # 14, Vitale et al., Hepatology 2010), this kind of study with high-level scientific evidence is necessary. The clinical practice is often different from mathematical models.

In my opinion, in the discussion the Authors should reduce the space reserved to the better results in terms of general safety compared to previous studies with sorafenib in favour of some important concerns: 1) a possible explanation of the mechanisms by which sorafenib was not superior to placebo; and 2) the possibility that other agents used with TACE (i.e. doxorubicin instead of carboplatin) would have led to better results. In addition, it would be worth knowing whether measures like AFP, VEGF or other biological markers of tumour progression were analyzed in this study.

Minor comments
Page 14, line 15: “bile duct insufficiency” is not an appropriate terminology; the Authors should explain what they mean by “insufficiency”.
Page 14, line 6: “tissue” should be changed with “organ” or “graft”.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being
published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.