Author's response to reviews

Title: Thymostimulin in advanced hepatocellular carcinoma: a phase II trial

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Author's response to reviews:

Dear Dr. Edmunds:

Dear Reviewers:

Thank you for the opportunity to reply to your helpful comments and revise our manuscript accordingly. We have registered the trial with the "International Standard Randomised Controlled Trial Number Register" and responded to all of the questions in the decision letter. In the following, we would like to answer each of the reviewers' comments point by point:

Reviewer 1:

1) A more detailed description of the analysis leading to the selection criteria for best response to thymostimulin was added in the sections "Abstract", "Methods" ("Statistical methods") and "Results" ("Overall survival" and the new Table 3).

2) Details on the clinical course of patients with a complete response or surviving longer than 2 years were added in the section "Results" ("Response and progression-free survival").

3) Unfortunately, Table 4 (now Table 5) could not be omitted since reviewer 2 asked for a more detailed comparison of survival between patients in our trial and patients with other treatments or without treatment.
Reviewer 2:

1) Unfortunately, the description of our data has been capable of being misunderstood, but mortality at 12 months was 50% for all patients and 68% for patients solely treated with thymostimulin, not 90% at 11 months ("Overall survival" and Table 1 in section "Results").

2) We strongly agree with the reviewer and have emphasized in the paper that the benefit of thymostimulin over best supportive care in treating advanced HCC can only be proven in a controlled trial. As suggested, we have added information on survival in patients without treatment and with other treatments in the section "Discussion". Unfortunately, comparisons between trials are difficult due to varying study populations; however, we have discussed our data accordingly.

3) Table 2 now includes information on the cause of death of patients. In HCC, the distinction between liver failure and tumor progress is inherently difficult and depends on the definitions used. We defined liver failure as cause of death in patients without tumor progress on imaging. In contrast, proven tumor progress was defined as cause of death in the patients affected by it.

4) Details on patients with and without concomitant treatment were added to Table 3.

5) In the section "Discussion" further details of other treatment options have been added including data on safety and side-effects. There is currently no standard therapy for advanced HCC with proven effect on survival assessed in a large controlled trial. Sorafenib appears to achieve a survival benefit in selected patients, but has only been published in a meeting abstract, as yet. In contrast to most other treatments employed including sorafenib, thymostimulin does not appear to have any major side-effects. This had been added to the sections "Discussion" and "Conclusion".

6) As described above, mortality in our study was 50% at 12 months. However, thymostimulin will not be an efficient treatment for all patients with advanced HCC. In our opinion, the benefit of our study is the establishment of selection criteria for best response thus providing the basis for further trials, e.g. a larger controlled trial or a trial with thymostimulin as a component of a multimodal therapy concept. Costs of the compound have not been determined by the company for this indication without a phase III trial to prove the efficacy unequivocally.
We hope the revised manuscript meets your requirements and thank you again for your consideration.

Yours sincerely,

Matthias Dollinger MD PhD Professor Wolfgang Fleig MD