Author's response to reviews

Title: A phase II open label trial evaluating safety and efficacy of a telomerase peptide vaccination in patients with advanced hepatocellular carcinoma

Authors:

Tim F Greten (greten.tim@mh-hannover.de)
Alejandro Forner (aforner@clinic.ub.es)
Firouzeh Korangy (korangy.firouzeh@mh-hannover.de)
Gisele N'Kontchou (gisele.nkontchou@jvr.aphp.fr)
Nathalie Barget (Nathalie.barget@jvr.aphp.fr)
Carmen Ayuso (cayuso@clinic.ub.es)
Lars A Ormandy (ormandy@o2online.de)
Michel Beaugrand (michel.beaugrand@jvr.ap-hop-paris.fr)
Jordi Bruix (jbruix@clinic.ub.es)

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Author's response to reviews: see over
Point-by-point reply

Comments from Reviewer #1:
We thank reviewer 1 for helpful comments and suggestions and hope to have addressed all the points below and in the revised manuscript.

1) The results of GV1001 specific T cell responses analyzed by cytokine secretion and/or proliferation analysis should be fully presented in "Results" section using Figures or Tables even though the responses are negative.

Response:
We have added the data as suggested (Figure 4).

2) The treatment dose of GM-CSF and GV1001 should be clearly mentioned in "Patients and methods" section.

Response:
We have added the information to the revised version of the manuscript.

3) The authors demonstrated that a few patients respond to the DTH test or decrease of regulatory T cells by GM-CSF+GV1001 vaccinations. Are there any relationships between these immune responses and the clinical efficacy against advanced HCC of GM-CSF and GV1001 vaccinations?

Response:
We could not observe any correlations as described in the manuscript.

Comments from Reviewer #2:
We thank reviewer 2 for helpful comments and suggestions and hope to have addressed all the points below and in the revised manuscript.

Discretionary Revisions:
1) Many acronyms have been found throughout the manuscript such as GM-CSF, TTP, TTSP, PFS, OS. For a general reader it should be better to explain in extenso before the use of an acronym.

Response:
All abbreviations are written out throughout the text.

2) The Authors described in the Results sections the patients characteristics. However all of the data presented might be introduced in the Materials and Methods section, more specifically into the Characteristics of patients.
Response:
Patient characteristics are often placed in the result sections. Please see our previous manuscript published in the New England Journal of Medicine (2008; volume 359, page 378).

3) The criteria adopted by the Authors to define the state of “progressive disease” and that of “Stable disease” should be indicated.

Response:
A reference (Llovet et. Al. JNCI 2008) discussing endpoints for clinical trials in HCC has been added.

4) Because the Authors include patients with HCC and underlying a viral (HBV and HCV) and non viral cause (alcohol) of disease it should be interesting to known whether differences in the frequency of CD4+CD25+Foxp3+ regulatory T cells.

Response:
The number of patients are too small to draw any definite conclusions. However, analysis of the data available does not reveal any differences between patients with HCV, HBV and no viral hepatitis.

5) The Authors stated that all of the patients were evaluable for safety analysis and efficacy evaluation. However, they report that efficacy was not assessed in three patients due to clinical progression or death before treatment was initiated.

Response:
This point has been corrected.

6) Additionally, the Authors stated that patients were not eligible if they had received any type of anti-tumour treatment or corticosteroids within the 4 weeks of pre-treatment with cyclophosphamide. However, in Table 1 it is not clear whether 65% of patients had prior received therapy and what kind of therapy or not. This point should better clarified

Response:
The information has been added to table 1.

7.) References should be formatted on the basis of the Journal Instruction for Authors.

Response:
The formatting has been corrected.
Comments from Reviewer #3:
We thank reviewer 3 for helpful comments and suggestions and hope to have addressed all the points below and in the revised manuscript.

1) At what time points were T-cell responses performed?

Response:
T cell responses were performed before and 3, 6 and 12 weeks after treatment was initiated.

2) The conclusion that lack of tumor response may be due to the fact that no clear immune responses were observed needs to be clarified. If I understand the time points correctly, T-cell responses were performed shortly after cyclophosphamide infusion, or were they taken at regular intervals after? In our experience, T-cell responses are to be expected from 6 weeks or later, which means that timing is essential.

Regarding the lack of T-cell responses, less than a third of the patients (11/40) patients have been included in this important part of the study.

Response:
As mentioned above T cell responses were not only analyzed right after vaccination, but also at later time points (i.e. after 12 weeks).

3) Tumor response was the primary end-point at 6 months. Median TTP was 57 days and PFS also 57 days, the time-points of planned CT scans in the study would be interesting.

Response:
CT scans were performed every 8 weeks. The information is given in the revised version of this manuscript.