Author's response to reviews

Title: Phase I study of OM-174, a lipid A analogue, with assessment of immunological response, in patients with refractory solid tumors.

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Author's response to reviews: see over
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Dr. Angela Marten
Editor BMC Cancer

Dear Dr Marten,

1407545552807984 -
Title : Phase I study of OM-174, a lipid A analogue, with assessment of immunological response, in patients with refractory solid tumors.

Thank you for reviewing our manuscript. We have received the reviewers’ comments and are happy to provide a point-by-point rebuttal below. We are resubmitting a revised version of the manuscript with the changes highlighted.

We thank you for considering our study for publication in your journal and look forward to your decision following our revisions.

Yours sincerely,

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Point by point response to the Reviewers and the Editorial team

Reviewer #1 (Dr Dario Sangiolo) (Reviewer Comments to the Author):

Reviewer's report:
In this work Dr. Isambert et al report results from a phase I clinical trial with OM-174, analogue of lipid A, on 17 patients with various types of solid tumors. They reported the safety and pharmacokinetic profile of the drug; MTD and recommended dose was however not established as no limiting toxicity was observed. Preliminary information on the activity is suggested by temporary disease stabilization in 3 patients. Overall the study is interesting and well designed. The hypothesis of synergism with chemotherapy is interesting and needs to be supported by published preclinical data to support new clinical studies.

1) Page 8. It would be helpful for the reader to reduce the length of the first sentence, and provide a bit more background information about the referenced phase I trials.

Authors’ response
The first sentence was reduced and more information about the referenced phase I trials are provided.

2) Were enrolled patient required to have measurable disease at study entry? This information should be added in the methods or in the table of patients’ characteristics. Similarly it could be informative to add information, either in the text or table, regarding the disease status at study entry (i.e. metastatic sites, minimal disease vs bulky etc.). It would also be interesting to mention the distance by last chemotherapy treatment for each patient.

Authors’ response
This is a very relevant point. We have modified our paper accordingly as follow: in the Patients and Method section, it is specified that patients were eligible if they have a measurable disease. In table 2, information about the disease status (minimal vs bulky) at study entry, the metastatic sites as the distance by last chemotherapy treatment are provided.

3) Among the evaluated cytokines reported in the methods, IL10 is not included while it is afterwards reported in the results.

Authors’ response
This error has been corrected
4) Last sentence of discussion appears too long. It would be useful to reference the preliminary data, even if published just in abstract form, or at least add more details about the mentioned preclinical experiments. Knowledge or publication of such preclinical data would be recommended before a new trial.

Authors’ response
This sentence was modified and shortened. Preliminary data have been reformulated to appear more understandable.
Reviewer #2 (Dr Inge Marie Svane) (Reviewer Comments to the Author):

Reviewer's report:
Manuscript by Isambert et al.
Phase I study of OM-174, a lipid A analogue, with assessment of immunological response, in patients with refractory solid tumors.
The manuscript presents clinical and biological data from a phase I trial testing OM-174 a synthetic lipid A analogue with TLR-2 and -4 activity. In total 17 patients were included on 6 different dose levels over a period of approx. 2½ year.

Major comments.
Trial design including in-and exclusion criteria as well as aims of the study are adequately described.

1) The trial was approved by legal authorities and a trial ID is given, however, a trial identification number from registration in a public trial registry such as www.clinicaltrial.gov is missing.

Authors' response
Identification number from registration in a public trial registry (www.clinicaltrial.gov) was added.

2) The authors have declared that they have no competing interests (page 22) however, further disclosure to clarify the commercial relationship is needed; is OM-174 patented by any of the authors or the manufacturing company? OM Pharma is stated as the drug supplier; according to the website OM Pharma Pharmaceuticals does not exist and have been integrated in Vifor Pharma in 2009, if true, this information should be included. The author Jacques Bauer is affiliated with OM-Pharma this should be stated under competing interests.

Authors' response
Concerning Competing interest, it has now been mentioned that all the authors except Jacques Bauer declare that they have no competing interests and that Jacques Bauer is an employee of OM-Pharma which has been integrated in Vifor Pharma in 2009.

3) Table 3 summarize non-haematological adverse events as written on page 14, and no grade 3 or 4 events are reported. However, it seems reasonable to include the grade severe bronchospasm described on page 15 in order to make the table complete.

Authors' response
Occurrence of the bronchospasm was added in table 3.

4) According to the authors 7 patients experienced fever and were treated with antipyretics (page 14). Why was antipyretics used if the patients only experienced grad 1 or 2 fever? Did the authors consider a possible link between fever and treatment activity? Fever has previously
been shown to correlate with objective response and survival after cancer immune therapy with Interleukin-2 (abstract 8569, ASCO 2010), this should be commented on in the discussion.

**Authors’ response**

This is once again a very relevant issue raised by the reviewer. At the time our study was designed and conducted this potentially favourable effect of fever per se was not known. More over treating fever was part of the standard of care for patients included in OM-174 trials as fever and chills are bothersome adverse events, as most of our patients. The following sentence was added in the discussion “It might be argued that giving acetaminophen or NSAIDs to patients with grade 1 or 2 fever might impair antitumoral effect as it has been suggested that response to IL-2 plus interferon-alpha might be altered by acetaminophen in patients with metastatic melanoma. Nevertheless our patients were included prior to this report that has never been published as a full paper and only a trend was suggested. Unfortunately, the number of patients with disease stabilization observed in our study (3) is too small to allow for an appropriate assessment of the influence of acetaminophen or NSAIDs use in tumour response”

A new reference (abstract 8569, ASCO 2010) was added.

5) NK activity is the only cellular immune activity assessed (page 17); a possible increase in NK number and activity is reported in some patients. These data should be shown.

**Authors’ response**

More information about an increase in NK number and activity were reported and a new figure (figure 2) was provided.

6) Three patients are reported to achieve SD during treatment. To make it possible for the reader to appreciate these data more information is needed; e.g. was time from baseline to first evaluation? On page 11 it is only written that tumor measurements were performed at baseline and at the end of the treatment; the 3 patients were treated bi-weekly with 5, 10, and 15 doses respectively were they evaluated at the same time point? And in this regard, how should SD of 1 and 2 months for patient 9 and 17 be interpreted? Please add to discussion.

**Authors’ response**

In materials and methods (page 11), details in relation to the assessment period were provided by the number of injections received by patients. Significance of stable disease for patients is discussed.

7) More information on disease state is needed; include ‘disease burden’ or ‘number of metastatic sites’ in table 2 and 5.

**Authors’ response**

Table 2 has been modified as suggested. Information about the disease status (minimal vs bulby) at study entry and metastatic sites were provided.

8) Figure 1a,b,c; Insert explanation of symbols and number of patients included in the analyses.
Authors' response

The explanation of symbols was inserted.

9) Minor comments.
The last sentence on page 21 (We have shown....) is hard to follow and should be revised.
The last sentence on page 17; 'not trend' should be 'no trend'
Figure legend 1B and 1C; 'The most important peak...' another wording is suggested

Authors' response

These changes were made.
Reviewer #3 (Dr Francesca Pica) (Reviewer Comments to the Author):

**Reviewer’s report:**
Based on the results of previous pre-clinical and clinical studies on the safety profile of the administration of various lipid A analogues in healthy volunteers or cancer patients, the present study is aimed at determining tolerability, toxicities, pharmacokinetic profile and biological response induced by a multidose administration schedule of OM-174. The study is well designed with regard to patients selection, ethic statement, schedule of treatments, and clinical as well as pharmacokinetic and immunological parameters evaluated. The low number of patients examined represents, however, a limitation of the study. The proposed idea to associate OM-174 to other cytostatic drugs for obtaining a higher anti-tumor response is reasonable and correct but doesn’t represent an innovative observation.

**Authors’ response**
*We would like to thank reviewer 3 for her quite favourable assessment of our paper. We agree that the relatively low number of patients represents a limitation of our study. There are several factors that might explain this relatively low numbers of patients, the more relevant being competition with recruitment in other phase 1 or phase 2 trials with very promising molecules.*