Author's response to reviews

Title: INSPIRE: A phase III study of the BLP25 liposome vaccine (L-BLP25) in Asian patients with unresectable stage III non-small cell lung cancer

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To the Editor-in-Chief:

Re: INSPIRE manuscript: response to peer review comments
(reference 9182620125454170)

Thank you for your consideration of our manuscript, “A phase III study of the BLP25 liposome vaccine (L-BLP25) in Asian patients with unresectable stage III non-small cell lung cancer”, submitted to BMC Cancer. A point-by-point response to the reviewer comments is provided below.

1. In my opinion, it is rather difficult to have a true double-blind, placebo controlled study in cancer immunotherapy. The treatment group will receive BLP25 lipopeptide, the carrier lipid matrix, and an immunoadjuvant (monophosphoryl lipid A). In contrast, the control group will receive only the carrier lipid matrix.

As we know, the most common side effect of any immune adjuvant is local reaction (redness and swelling), which can be substantial. Based on this alone, both the treating physician and the patient may be able to predict with a reasonable certainly which group the patient belongs to; therefore, this may defeat the purpose of having a study that is blinded.

The local injection site reactions associated with L-BLP25 in previous studies have, for the most part, been mild. It is true that adjuvants are more likely to be associated with reactions but this is only a subset of patients receiving MPL A. Because many patients do not develop reactions to L-BLP25, many patients believed to be on “placebo” will actually be on L-BLP25. Thus both patients and investigators will often not know which arm of the trial they are on. This will help to support the double-blind.

Response: The following sentence has been added to the end of the second paragraph of the ‘study design and treatments’ section of the manuscript: “L-BLP25 can be associated with local injection site reactions; however, as these reactions tend to be mild and are not universal, patients and physicians cannot definitively determine who receives placebo or vaccine.”

2. Secondly, not giving the control group the immunoadjuvant (monophosphoryl lipid A), may complicate the interpretation of the eventual outcomes. Can the immune adjuvant by itself, without the specific antigen (L-BLP25), activate the host in a nonspecific manner that may result in meaningful prolongation of survival?

The immune adjuvant would be highly unlikely to stimulate a nonspecific immune response that could have any meaningful impact on survival time. This is an interesting question and we are often asked this by participating investigators. There are two responses: first, it is highly unlikely that a non-specific activation of the immune system would lead to an improvement in survival. There are little data to suggest this and certainly no data to suggest MPL A has that effect. Second, the trial is designed to show an improvement in survival compared to the control arm. That is, even if the placebo in this trial had medical efficacy it would be inferior to the L-BLP25 arm and therefore of less medical interest. Of course, it is not known that the placebo has efficacy and showing the placebo has medical efficacy would require a third arm in the trial which is not feasible.

Response: The following sentences have been added to the discussion: “The
control arm of the trial is reflective of the global standard of care received by patients with stage III disease. The placebo used in the control arm has neither the adjuvant nor the BLP25 antigen. The adjuvant was excluded from the placebo, given that even if the adjuvant was capable of eliciting a non-specific immune response in the absence of the BLP25 antigen, it is highly unlikely that any non-specific response would lead to an improvement in survival. As the placebo does not contain the peptide either, the placebo is very unlikely to elicit an immune response or influence overall survival time.

3. Regarding the stratification based on adenocarcinoma versus non-adenocarcinoma, is there a rationale for this stratification? Most chemotherapy or chemoimmunotherapy trials in lung cancer were stratified based on squamous versus non-squamous. Is there any reason why the investigators believe that patients with adenocarcinoma may respond or react differently compared with patients with non-adenocarcinoma?

At the time when the INSPIRE protocol was drafted, the impact of EGFR status on the prognosis of Asian NSCLC patients was not as clear as it is today. It was, however, known that the prognosis of Asian adenocarcinoma patients was better than that of Asian non-adenocarcinoma patients. It was suspected at the time of protocol drafting that this difference was mainly linked with a mutated EGFR status. A stratification for adeno- vs non-adenocarcinoma was expected to address additional important factors like EGFR status.

Response: The following line was added to the first paragraph of ‘study design and treatments’, following the sentence on stratification of treatment groups: “Asian patients with adenocarcinoma have been shown to have a better prognosis than patients with other types of histology.”

4. The INSPIRE study uses the 6th edition of the TNM staging system published in 2002, and not the updated version in 2009. However, since pleural effusion is an exclusion criterion, this will not affect the study.

We agree that this is a valid point, and have highlighted this issue in the discussion section of the manuscript.

Response: No change has been made to the manuscript, as the second-to-last paragraph of the discussion states the following: “The INSPIRE study uses the 6th edition of the staging system published in 2002 by the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). In the 7th edition, published in 2009, malignant pleural effusion now constitutes metastatic disease and as such is stage IV [36]. However, this will not impact on the INSPIRE study as malignant pleural effusion is an exclusion criterion.”

5. Details: The route (IV, ID, or SC) of vaccination should be listed.

We agree that the route of administration of vaccination/placebo is an important omission.

Response: The abstract and the second paragraph of ‘study design and treatments’ have been amended to state that L-BLP25 and placebo will be administered subcutaneously.
6. **Treatments are continued until disease progression. How often are patients scanned to evaluate their disease? Since immunotherapy usually take longer time (than chemotherapy) to work.**

   Again, we agree that it is important to discuss the frequency of scanning in order to evaluate disease progression. This will vary from site to site, as the investigator will determine disease progression according to the standards of the institute. The technique and timing of scans will be determined by hospital practice, so that the patients would receive follow-up as they would in the ‘real world’ setting.

   **Response:** The following sentence has been added to the third paragraph of ‘study design and treatments’: “As the investigators will evaluate disease progression according to institutional standards, the technique and timing of imaging will vary from site to site.”

7. **Will patients be taken off study as soon as disease progression is seen on scans? or will there be a certain criterion where patients will be allowed to continue to receive the vaccine despite some disease progression seen on the first scan?**

   Patients will stop receiving the study treatment upon documentation of progressive disease, which must be evaluated according to RECIST 1.0 criteria. As stated above, the imaging intervals are not specified in the protocol, as they will be determined by institutional standards. However, despite the fact that the trial treatment will no longer be administered, the study investigators will endeavor to observe the patient’s survival since overall survival reflects the primary endpoint of the trial.

   **Response:** The following line has been added to the third paragraph of ‘study design and treatments’: “Although patients with disease progression will no longer receive either the study medication or placebo, where possible they will remain in the trial for the evaluation of the primary endpoint, overall survival time.”

8. **Additional points**

   As requested, we have highlighted in the methods section the fact that the study will be approved by all relevant local ethics committees. As the study will be performed in approximately 40 trial sites, we did not feel that it was feasible to list the names of the bodies which gave approval. We have also highlighted the fact that written informed consent will be provided by all patients.

   We hope these responses and amends address the reviewer comments in a satisfactory manner, and that the revised manuscript is now suitable for publication in *BMC Cancer*. We look forward to hearing from you.

   **Best wishes,**

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