Reviewer's report

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

Version: 1 Date: 1 August 2011

Reviewer: Hung Khong

Reviewer's report:

The manuscript is very well written. Patients with advanced lung cancer generally has a poor prognosis and limited options. Therefore, I commend the investigators for initiating this interesting immunotherapy study. Small phase II cancer vaccine studies in recent past have shown promising survival benefit compared to historical controls. However, large phase III trials are essential to confirm the true benefits of immunotherapy in lung cancer.

1. Study design: This is a double blind, placebo-controlled, phase III study. Stratifications: stage, histology (adenocarcinoma vs non-adenocarcinoma), and type of primary chemoradiotherapy.

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.

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?

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?

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


4. Writing: The manuscript is very well written.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

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