Author's response to reviews

Title: A Phase II Study of Pulse Dose Imatinib Mesylate and Weekly Paclitaxel in Patients Aged 70 and Over with Advanced Non-Small Cell Lung Cancer

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Version: 4 Date: 18 September 2012

Author's response to reviews: see over
September 7, 2012

Dear Professor McKeage and the editorial staff at BMC Cancer:

We appreciate the attentive peer review of our manuscript entitled, “A Phase II Study of Pulse Dose Imatinib Mesylate and Weekly Paclitaxel in Patients Aged 70 and Over with Advanced Non-Small Cell Lung Cancer.” We have revised the manuscript in accordance with the excellent suggestions. What follows is a point-by-point response to reviewers’ stated concerns:

**Reviewer 1:** No major or minor revisions were recommended. Recommendation was made for discretionary shortening of the manuscript’s discussion section.

Thank you for this recommendation. We have made the discussion section more concise to enhance impact.

**Reviewer 2:**

1. “Abstract: I suggest changing the conclusion. Needs clear statement about the inactivity of the regimen, since pre-planned RR considered worthy of further study (35%) not met and limited PFS and OS benefit when historically compared to the existing data on single agent weekly paclitaxel.”

Authors’ Response: The *a priori* decision rule for rejecting the null hypothesis is articulated in the methods section as follows: “A sample size of 35, with 33 eligible patients had 87% power to detect a true RR of 35%, and a 5% chance of falsely rejecting the null rate of 15%. The decision rule rejected the null hypothesis if ≥ 9 of 33 patients responded.”

While the RR of 32% did not numerically meet the value of 35% used to define p1, the confidence interval excluded the null value of 15% and the decision rule was triggered. This was in fact a positive study by the pre-defined primary endpoint and on that basis encouraging. Nonetheless, the regimen was inactive when considered on the basis of PFS and OS and we do not recommend it for further study.

We respectfully propose the following change (italicized) to the abstract which acknowledges that the study met the primary endpoint but makes clear that further study is not recommended:

**Conclusions:** While the combination of imatinib and paclitaxel had encouraging activity as measured by the primary endpoint of RR, PFS and OS were typical for elderly patients treated with single agent chemotherapy and the regimen is not recommended for further study. Adjunct imatinib did not overcome the established association of tumoral PDGF-B expression with inferior PFS. VES-13 was a powerful predictor of poor survival outcomes. Frailty should be further studied as a predictor of non-benefit from chemotherapy.

2. “Methods: Exploratory analysis of correlation between PDGF-B and outcomes not described in the methods?”
Authors’ Response: We draw the reviewer’s attention to the sentence, “Maximum likelihood estimates were conducted to describe the relationship of tumoral PDGF-B expression to RR, PFS and OS” included in the paragraph starting, “Exploratory objectives...”

3. Results: Tabulation error (fatigue) in Table 2. Data about frequency of rash not presented in Table 2. mPFS and mOS not numerically shown on the axis (Figure 1). Would be worthwhile showing the PFS curve (according to VES-13) in Figure 3 as well, since the strongest conclusion about the use of VES-13 frailty scores in future studies.

Authors’ Response: Thank you for these helpful corrections and suggestions.

1) The tabulation error appears to be the result of a formatting issue which has been corrected.
2) The mPFS and mOS figure now includes labels describing median PFS and OS
3) Figure 3 now includes both PFS and OS according to VES-13 frailty score

4. “Discussion: Well conducted. Happy with the conclusions, although not sure whether I would use the word "promising" if the regimen is not recommended for further studying.”

Authors’ Response: This is certainly a reasonable point. While a similar point might be made about the word, “encouraging,” we have changed the word promising to encouraging in both the abstract and discussion. More important, we have carefully applied this description only to the primary endpoint of RR, because it was fulfilled, however we now couple this description to the clear statement that further study is not recommended due to typical PFS and OS in both the abstract and the discussion.

Thank you once again for conducting this detailed review,

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