Author's response to reviews

Title: Phase II Assessment of Talabostat and Cisplatin in Second-Line Stage IV Melanoma

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Author's response to reviews: see over
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Rikki Graham, Ph.D.
Senior Assistant Editor
BMC-Series Journals

RE:  MS #1428665872245752 – Phase II Assessment of Talabostat and Cisplatin in Second-Line Stage IV Melanoma

Dear Dr. Graham:

We appreciate the thorough review of our submitted manuscript entitled, “Phase II Assessment of Talabostat and Cisplatin in Second-Line Stage IV Melanoma” by the two reviewers. In response to the reviewers’ comments we have edited the manuscript to address each of the concerns. A response to their comments and the associated edits to the manuscript are described below. A revised manuscript is submitted for further review.

**Reviewer #1: Hong-Suk Song**

*(The reviewer outlined 36 specific “Minor Essential Revisions” that were required.)*

**Response:** The revised manuscript incorporates the changes requested.

**Reviewer #2: Kevin Kim**

1. In the abstract, the dose of talabostat should be described as 300 to 400 mcg, and the dose of cisplatin should be described as 75 to 100 mg/m2, as a significant portion of the patients had different doses of cisplatin and/or talabostat. The description of the doses of 300 mcg of talabostat and 75 mg/m2 of cisplatin in the abstract can be misleading.

**Response:** Modifications to the manuscript were made as suggested.

2. This study utilized RECIST for response evaluation. The RECIST doesn’t recognize plain X-Ray as a method of tumor evaluation, yet this study used plain X-Rays for tumor evaluation (Paragraph under Methods section “Patient Population” and “Study Objectives”. Please clarify.

**Response:** Corrected – only spinal CTs or MRI’s were utilized for RECIST determination.
3. One of the major flaws in this study is not counting patients with early disease progression prior to the first CT/MRI evaluation after the first 2 cycles as "evaluable patients". It appears that quite a number of patients had early disease progression of which led to early death. To most readers, these patients should be counted as PD. Although the authors stated that the response rate is 8.1% among ITT populations, they should also explain in the discussion (or methods) section the reasons those early progressors are not counted as evaluable patients.

Response: Actually the ITT population includes all patients who received a single dose of Talabostat. Patients with early disease indeed were included in the ITT population so the 8.1% response rate for the ITT population does include early progressions. I clarified this in the discussion.

4. In the 3rd paragraph of Efficacy section of the Results and the 3rd paragraph of Discussion section, the authors stated that certain subsets of patients had a longer estimated median PFS. The statistical analysis (i.e. p-value) was not provided, and the CIs of these values are quite large. I think the authors should delete the suggestions of PFS advantage in certain subgroups (i.e. pts without prior chemo, those who started at the lower cisplatin dose, etc.)

Response: Modification was made as suggested.

5. A number of early death (before reaching 6 cycles) in this study is much higher than anticipated. Especially deaths during the first 2 cycles (nearly 33% of all patients) are very concerning. The authors should explain the high incidence of early deaths in the discussion section. Did most of these patients have brain mets? Since the eligibility criteria include the expected survival of 12 weeks, I have a concern that talabostat in combination to cisplatin is possibly detrimental to patients, possibly due to accelerating tumor progression.

Response: Added to Discussion, 5th paragraph, issues regarding early deaths to PD.

6. In the 4th paragraph of the Discussion section, it is stated that most patients entered the one-year follow-up period (58/74....). In the Table 6, 22 patients were described as death during the first 2 cycles. The numbers do not match. Please clarify the inconsistency or correct the numbers.

Response: This did not indicate 1 year survival. It was reflective of a follow up protocol entry timepoint and is confusing. This was removed. Table 6 is correct.
7. As cytotoxic chemotherapeutic drugs, such as cisplatin, have a significant myelosuppression, it will be important to describe grade 3 or 4 hematologic toxicities. How many patients had grade 3 / grade 4 neutropenia and thrombocytopenia?

**Response:** 18.9% of patients had neutropenia and 24.3% had thrombocytopenia at ≥ grade 3. This was clarified in the manuscript.

8. A number of patients with PR or PD is not easy to understand in Table 2. The number of PRs decrease as a number of cycles increases. However, also the number of PDs decreases. Shouldn’t a number of PDs at Cycle 5 higher than that at Cycle 3 as a number of SD goes down from Cycle 3 to Cycle 5? I think it will be simpler and sufficient to give an overall number of best responses rather than breaking down into assessment at the different time points.

**Response:** The title of Table 2 was modified to reflect response rate that was achieved at cycle 3 and maintained or achieved at cycle 5 and end of treatment. It was to reflect the time period over which responses were occurring. This was clarified in the manuscript.

In addition, all “Minor Essential Revisions” suggested by this reviewer were made, and the last sentence of the Abstract was deleted, as per the suggestion under “Discretionary Revisions”.

Furthermore, Competing Interests and Authors’ Contributions sections have been added to the manuscript, per your request.

Sincerely,

John Nemunaitis, M.D.