Reviewer’s report

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

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Reviewer: Kevin Kim

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This manuscript describes a phase II trial of a combination of talabostat and cisplatin in patients with metastatic melanoma who had received up to 1 prior systemic therapy. This study was designed on the bases of the preclinical data of synergistic/additive anti-melanoma activity when both drugs are combined. In this study, 74 patients with ECOG performance status of 0-2 with expected survival of 12 weeks received 75-100 mg/m2 of cisplatin every 21 days and 300-400 mcg of talabostat twice daily. The authors concluded that this combination regimen was generally well tolerated, but it was not better than a single agent drug in this patient population.

The concept of the study was original. This report demonstrated that talbostat with its unique anticancer / immunostimulatory properties did not add much benefit to cisplatin in patients with metastatic melanoma. In this sense, this study makes a contribution to the knowledge regarding the efficacy of cytotoxic chemotherapy in the field of melanoma. Therefore, I believe that the findings from this study deserves to be published.

However, I have several major and minor concerns which need clarification and a revision before this manuscript can be accepted for publication.

• Major Compulsory Revisions

The author must respond to these before a decision on publication can be reached. For example, additional necessary experiments or controls, statistical mistakes, errors in interpretation.

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.

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.

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.

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.)

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.

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.

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?

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.

• Minor Essential Revisions

1. In the Abstract, cisplatin dose is described as 75 mg/mm2, and the dose of talabostat is 300 mg. Please correct mm2 to m2, and mg to mcg, respectively. In addition, it should be clear that dosing schedule for talabostat is from days 2-15, every 21 days.

2. Line 7 of page 3 (the first paragraph of Introduction), please correct the spelling “dicarbazine”

3. Table 5, please correct spelling “NE = non-estimable” in the footnote.

• Discretionary Revisions
1. The last sentence in the abstract does not add much to this manuscript. Unless the authors have a hypothesis which patient subsets may benefit, I’d recommend that they delete this sentence.

2. Since a higher than expected number of patients had early death due to disease progression, I suggest that the authors describe the number of patients with brain metastases at the time of study entry in Table 1.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.