Author's response to reviews

Title: A phase I study of imatinib, dacarbazine, and capecitabine in advanced endocrine cancers

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Author's response to reviews: see over
To the Editor:

We would like to resubmit the enclosed revised and reformatted article, entitled “A phase I study of imatinib, dacarbazine, and capecitabine in advanced endocrine cancers,” for consideration for publication in *BMC Cancer*. We appreciate the opportunity to respond to the constructive and insightful comments from the reviewers, and agree that each of the recommended revisions strengthens and clarifies the expression of our findings. We hope that this revised version is acceptable for publication. Please find itemized responses to the reviewers’ comments, beginning on the next page.

This article has not been and will not be submitted for consideration by another journal until the editorial board of *BMC Cancer* has decided whether to publish this article.

Sincerely,

Daniel M. Halperin, MD
For the authors
Reviewer: Jennifer A Chan
Reviewer’s report:
In their manuscript “A phase I study of imatinib, dacarbazine, and capecitabine in advanced endocrine
tumors,” Dr. Halperin and colleagues have nicely summarized their findings of a standard 3+3 dose-
escalation study of imatinib, dacarbazine, and capecitabine. Although the study population included
patients with any solid tumor, it was enriched in patients with medullary thyroid carcinoma and adrenal
cortical carcinoma.
Table 1 and pages 7-8 of the manuscript summarize the dosing and observed DLT for each dose level. In
addition to other DLTs, dose-limiting fatigue and dyspnea were noted. Other common toxicities included
edema, fatigue, and nausea.
Radiographic responses were seen in 2 patients with adrenal cortical carcinoma.
This is an interesting observation given the limited treatment options in this patient population.
Although no responses to treatment were seen in patients with medullary thyroid carcinoma, 4/5
patients experienced stable disease.

Major Compulsory Revisions
1. Typically, the MTD or recommended phase II dose is defined as the dose level just below a toxic dose
level in which at least 2 patients among a cohort of 3-6 patients experiences DLT.
The authors note that the recommended phase II dose for this regimen is
dacarbazone 250 mg/m2 on days 1-3, capecitabine 500 mg/m2 BID on days 1-14, and imatinib 400
mg/m2 on days 1-21 of a 21 day cycle (ie, dose level 1).
However, the manuscript indicates that 6 patients were treated at dose level 1 and that all of the last 3
patients treated at this dose level experienced grade 3 toxicity. Table 1 also indicates 9 DLTs at dose
level 1.
At dose level -1, only 1 of 6 patients experienced DLT. Thus, it would seem that dose level -1 should be
the MTD or recommended phase II dose.
Could the authors clarify how dose level 1 rather than dose level -1 was identified as the MTD? Did the
noted grade 3 toxicities experienced by patients treated at dose level 1 occur outside the DLT
observation period? If so, it would be helpful to clarify this.
This point identifies a critical typographical error in the original manuscript. We have reviewed the
original documentation of toxicities occurring during cycle 1, and have confirmed that 3 of the
patients enrolled at dose level 1 experienced grade 3 toxicities during the first cycle, leading to the
enrollment of patients at dose level -1. Dose level -1 is the MTD, and this correction has been made in
the manuscript.

Discretionary Revisions
It is interesting to note that radiographic responses were seen in 2 patients with adrenal cortical
carcinoma, both of whom had prior chemotherapy. Although the information about prior therapy is
included in table 4, this could be highlighted in the manuscript text also (p.8)
Agreed. We have highlighted the prior therapy in the results and discussion sections accordingly, as
they do make the encouraging results in the adrenal cortical carcinoma patients even more
remarkable.

Although no responses to treatment were seen in patients with medullary thyroid carcinoma, 4/5
patients experienced stable disease. It would be interesting to know whether these patients were
experiencing disease progression prior to starting protocol therapy.
None of the patients with stable disease were progressing at the time of study entry. We appreciate that this is a vital detail in light of recent advances in the therapy of MTC, and have made a note in the text, as well as included data on progressive disease at enrollment in table 4.

Table 1 has a column indicating “Dose Reductions.” Although several DLTs are noted for patients treated at dose level 1, no dose reductions were required. Could you clarify how grade 3 toxicity was managed in a manner that did not require dose reduction? Several patients were taken off of the study at the time of the DLT, resulting in the lack of concordance between patients experiencing DLTs and the number of dose reductions. However, on review of the source documentation, two patients did have their doses reduced as a result of grade 3 toxicity, and table 1 has been amended to reflect this change.
Reviewer: Michele Kim
Reviewer’s report:
The authors report their experience in a Phase 1 study of imatinib, dacarbazine, and capecitabine in patients with advanced endocrine cancers. A 3+3 standard dose-escalation design was used. The paper is well-written and clear. This study provides data for consideration of a Phase II study.

Major Essential Revisions
None

Minor Essential Revisions
1. It is worth saying that the patients in this study had heterogeneous pathology i.e., not only ACC and MTC, but also NET, TCC, and melanoma. This is nicely delineated in Table 4, but not in the text.
   Agreed. We have now noted the included tumor types in our description of the patient characteristics.

2. Did all patients have progressive disease at time of inclusion? In addition, if imaging was obtained within a certain time period of study inclusion, please include.
   An excellent question raised by both reviewers. While it was not formally assessed as an entry criterion at the time of the study, the presence of progressive disease on entry has now been included in Table 4. We have also included the baseline imaging requirements in our methods section.

3. Please define extent/stage of disease for included patients. Similarly, if you have data on tumor grade, degree of differentiation, etc, please provide.
   All patients were metastatic at time of entry, and we have updated the text to reflect this fact. Unfortunately, consistent pathological reporting is not available for all patients, so we have refrained from presenting incomplete data.

4. Please give median followup and survival.
   We had originally refrained from including this data given the heterogeneity of the patient population and lack of a comparable referent, instead including the patient-level data in Table 4. However, we are happy to include the medians in our text to lend more clarity to the manuscript.

5. In Table 2, please provide total number (n=20) with baseline patient characteristics. In addition, combine the Number and % columns. For example, gender (male) would read "12 (60%)". Also, no need to include female; male alone suffices.
   This revision significantly improves the visual appearance and clarity of the table. We appreciate the recommendation and have revised the table accordingly.