Reviewer's report

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

Version: 1  Date: 20 May 2014

Reviewer: Jennifer A Chan

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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 dacarbazine 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.
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)

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.

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?

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I have received research funding from Novartis and Bayer.