Reviewer’s report

Title: A study of docetaxel and irinotecan in children and young adults with recurrent or refractory Ewing sarcoma family of tumors

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Reviewer: Aaron Weiss

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Review of Manuscript: A study of docetaxel and irinotecan in children and young adults with recurrent or refractory Ewing sarcoma family of tumors

Due to the extremely dismal outcome for this patient population, the authors should be commended for their efforts to perform a prospective study utilizing a novel salvage therapy combination. The detailed disease and patient characteristics (before, during and after therapy) provided for each enrolled patient was highly valuable in interpreting the feasibility and efficacy of this regimen in such a heterogeneous population particularly when small numbers precluded rigorous statistical application. The provided tables and figures were excellent.

I have provided some comments/suggestions which have been subdivided in requested categories:

Discretionary Revisions:

• In Table 2, it is noted that paclitaxel was administered as prior therapy (alone or in combination). It may be helpful to know how many patients received this and identifying which ones (Table 1) to see if prior exposure of a taxane may have impacted efficacy. Since no prior patients received camptothecans, this is not a confounding issue.

Minor Essential Revisions:

• The reference (13) provided for the following introduction statement (page 3-4): “docetaxel and irinotecan (DI) have demonstrated an additive and synergistic activity in vitro and in vivo” did perform any of these studies. Please provide the appropriate reference.

Major Compulsory Revisions:

• No rationale is given for the much lower than expected enrollment (10 of 34 anticipated) over the 4.5 year study period.

• Rationale for the chosen drug dose and administration schedule was provided within the discussion (page 13-14). However, this seemingly very important aspect of the study design was not given reciprocal serious weighted discussion within the study limitation section (page 15-16). As an example, the selection of docetaxel scheduling being made for cost purposes was briefly mentioned as
potentially have a negative impact on toxicity, however, the potential impact of
these decisions on efficacy was not. This is particularly important since the dose
and schedule chosen for this study differs significantly from the referenced
articles and use of these drugs in various combinations within clinical and in vitro/
in vivo settings.

- Along the lines of above, why was a smaller pilot or phase I study (particularly if
cost and drug supply was an issue) testing various DI doses and schedules
(especially ones based more on scientific than practical reasons) considered. It
would have brought further justification to the chosen phase II design. This study
design makes interpretation of the results, beyond descriptive analysis,
challenging.

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

**Quality of written English:** Needs some language corrections before being
published

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

**Declaration of competing interests:**

I declare that I have no competing interests