Reviewer’s report

Title: Results of a phase I dose escalation study of eltrombopag in patients with advanced soft tissue sarcoma receiving doxorubicin and ifosfamide

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Reviewer: Mark Linch

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In this paper, Chawla et al present a dose finding study for the thrombopoietin receptor agonist, Eltrombopag. They identify the need for improved therapy for soft tissue sarcoma, possible by dose intensification of standard sarcoma chemotherapy along with platelet growth factor support. This study set out to identify the optimal biological dose (OBD) in combination with doxorubicin and ifosfamide chemotherapy.

This dose finding study used a stepwise dose escalation phase and had a planned expansion phase. Due to poor recruitment the study was unable to meet it stated end-points but does report good tolerability of doxorubicin and ifosfamide in combination with Eltrombopag up to a dose of 150mg/d.

The conception and design of this study is clear and the authors should be commended for their attempt to recruit for a sarcoma trial and perseverance of this study (requiring many protocol amendments). It is important that studies of this sort are carried out in rare tumour types such as soft tissue sarcoma.

The work is well presented and takes the reader through the data in a straightforward manner. The data is sound.

The study itself is not novel in an oncology setting as a randomized phase II trial in combination with paclitaxel has been reported. Only one patient was recruited that received a higher dose of Eltrombopag (150mg) than reported elsewhere. Due to the poor recruitment to this study it failed to determine the optimal biological dose or dosing strategy. The investigators were unable to embark on the expansion phase.

At the doses tested Eltrombopag doesn’t seem to add to the toxicity of doxorubicin and ifosfamide. There is a suggestion that 5 days pre and post chemotherapy (Days -5 to -1 and Days 5 to 9) is the preferred dosing strategy to prevent TCP but this is speculative at best.

I feel that it is important to get this patient data presented on a rare tumour type. I only have a few minor corrections. The lack of recruitment and thus conclusions that can be derived from this study, however, is it major weakness and will therefore be of questionable interest to the oncology community. These weaknesses and limitations are well defined in the text. I think this data would be better served if combined with the pharmacokinetic data, however I would still
support its publication in this journal.

**Minor Essential Revisions**

1) Dosing schedules are somewhat confusing in the text. Can you explain the increase in Plt count on D1 cycle 2 of patients 1 and 2. These patients won’t have received Eltombopag at this stage.

**Discretionary Revisions**

1) It would be useful to have the rate of G3/4 TCP in table 2. The reader will then be able to compare with the historical control of 22-63% G3/4 TCP as mentioned in the introduction.

2) Not really necessary to have the double asterisk on Figure 3 – this is self evident.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**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'