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: Alessandro Comandone

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I read with great interest the article from Sant P. Chawla and Coll " Results of Phase I dose escalation study of eltromopag (E) in patients with advanced soft tissue sarcoma receiving doxorubicin and ifosfamide".

As correctly stated in the Introduction and in the Discussion session, Thrombocytopenia (TCP) is still a main problem for the Oncologist and his Patients.

Between 19 to 64% of the Patients receiving chemotherapy suffer from TCP, and this problem prevents CT administration and decreases dose intensity and dose density. At present no active agent against TCP is available as primary as well as secondary administration. The Introduction and the Rationale of the article are well defined and described.

Eltrombopag (E) is a non peptidic drug which acts against thrombopoietin receptor and showed some activities in TCP in chronic liver disease. In Clinical Oncology only one study was completed in Patients treated with Carboplatin + Paclitaxel. In the present study was chosen a specific, rare disease, with a precise chemotherapy combination: Soft tissue sarcomas and Adriamycin + Ifosfamide and Mesna. The methods of the study are complete and well presented. even a little ambitious: in fact a Phase I study with 2 different schedules of administration ( before CT or 5 days before and 5 days after therapy) and 6 level of doses of (E) is a complex design. Moreover too many End Points (EP) were chosen: 2 primary EP: safety and tolerability, and 4 secondary EP: OBD, Pharmacokinetics, pharmacodynamics, pharmacological interaction with Adriamycin. Unfortunately, because of the scarce recruitment, many of those EP were not met.

Only 18 Patients were enrolled in 4 years, but only 12 were teated with (E). The consequent question is: why so few Patients accepted to be enrolled?

In the Results session some question are not answered: how many days of treatment with (E) did each Patient receive? Safety and tolerability are reported in table 2 but not classified in grade. How many severe toxicities ( grade 3 and 4) were recorded? Reading table 2 we saw a strange result: after the administration of (E) at doses of 100 and 150 mg the Authors report 100% of TCP, while after 75 mg of the same drug the same side effect was recorded only in 71% of the Patients. Paradoxically the higher is the dose of (E) the higher is the thrombocytopenia level. Do we have to think a negative interaction between CT...
and (E)?

In the results session (E) is declared a safe drug, but 67% of Patients withdrew prior to study completion, many for SAEs; 11 SAEs in the first group of 7 patient and 1 over 2 patients in 100 mg group is not a real "safe" profile.

None of the secondary EP were reached or reported: either OBD for insufficient enrollment, or PK "reported elsewhere "( why if PK is a tipical EP in Phase I studies?) or PD. No data on effectiveness are presented, even this is not a principal EP in Phase I studies.

The limits of the study are well identified and exposed by the Autors. On the other, the Conclusions are short and not completely in sound with the Results.

As a matter of fact the final statement is obscure and not supported by the results:

"Available data suggest a potential pre and post CT dosing scheme for (E) when administered with AI chemotherapy and support further investigation." and should be changed.

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

**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