Reviewer’s report

Title: Efficacy and Safety of Pharmacological Interventions in Second- or Later-Line Treatment of Patients with Advanced Soft Tissue Sarcoma: A Systematic Review

Version: 1 Date: 5 February 2013

Reviewer: Margaret von Mehren

Reviewer’s report:

Major Compulsory Revisions:

1. The authors list a number of agents they evaluated. However, the rationale for picking the agents is not elucidated nor the reason for limiting the agents they studied.

2. Data presented in this article on pazopanib are those provided by GSK, which they state are different from those published. Given that all the other data included is from the published literature and that GSK funded this manuscript, it is of concern that this difference in extraction of data is biased.

3. Page 13: The authors state that in the majority of phase II studies they reviewed, the primary study endpoint is not reported; in the following paragraph, the authors state that using the Downs and Black checklist, the studies are reported reasonably well. These two statements seem in contradiction to each other.

4. Analysis of Gemcitabine results in particular, but this may apply to other drugs tested: were all the studies using the same dose and schedule of drug? Did you analyze if differences in how a drug was given affected the efficacy?

5. As you were intending to assess the benefit of agents following therapy of doxorubicin, is the inclusion of studies with liposomal doxorubicin appropriate?

6. Page 19- could another reason for greater discontinuation for pazopanib be that it is a chronic therapy where the toxicity is experienced on a daily basis without any reprieve as one has with cytotoxic therapies?

7. Conclusion: further randomized studies in advanced STS are underway and none have included the three therapies you indicated should be the standard comparators. I take issue with the recommendation to consider gemcitabine and dacarbazine as the standard of care based on one randomised phase II study with very limited additional clinical trial data, and I suspect the perspective of a pharmaceutical company trying to license an agent, this would be not accepted. In addition, other regimens that are more universally utilized such as gemcitabine and docetaxel, in which a randomized trial has been completed with additional single arm phase II studies and is for many a de facto standard of care for these patients, was excluded from discussion because the publications did not include data required for your study design. Lastly, the recommendation for trabectedin as a standard arm, fails to recognize that this agent is not available or approved
in some parts of the world.

Minor Essential Revisions:
1. Page 12: last line of Treatment Discontinuation: “Error- reference source not found”
2. Page 13: 3rd line and last line of Efficacy Results: “Error- reference source not found”
3. Page 18: discussion of the trabectedin phase II RTC: discussion is incorrect: the three weekly schedule was not superior the q 3 week schedule. Table 2 is correct, but the verbiage is confusing and appears later in the discussion/conclusion. Would be clearer as the “every 3 week” schedule
4. Page 19, 2nd paragraph, line 2: (Table Results…. Suspect editing is required here

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

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I am a scientific consultant for Pharma Mar, maker of Trabectedin
I serve as a lead investigator for the ongoing randomized trial of Trabectedin versus Dacarbazine and receive compensation from Jansenn for this.
I have served as a consultant to GSK.