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

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Author’s response to reviews: see over
15th April 2013

Dear Editor

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

My colleagues and I are delighted to submit our revisions to our previously submitted manuscript, in accordance with the reviewer comments. We attach a word document summarising the major edits that we made in the manuscript (reproduced below for ease of reference). Also, we confirm that all typographical errors identified by the reviewers have been corrected.

We hope you and the reviewers will find these edits satisfactory and we look forward to proceeding to the next step regarding publication.

We would like to draw your attention to one change in the authorship list, where Stephanie Manson has been added as the corresponding author. Dr. Manson has played an active role in the team in terms of content development and manuscript preparation, and we feel her inclusion is therefore justified, and meets the authorship conditions as set forward by the ICMJE. Dr. Manson will be responsible for managing all future correspondence related to this manuscript, but in the meantime, I remain at your disposal if you have any questions. This authorship change is reflected in the manuscript, and includes a summary of author contribution and a conflict of interest statement.

For future correspondence, please direct this to the details below.

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If you have any questions or need additional information, please don’t hesitate to be in touch. I look forward to hearing from you.

Sincerely,

Sarah Powell

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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. The rationale for choosing the selected agents has been provided within the text. The reason that the agents were limited was according to PRISMA guidelines for systematic reviews, it is important to provide an explicit statement of the questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). Further details about PRISMA criteria are included in Additional File 1 of the submission.

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. The data used for pazopanib are from the analysis that was used for regulatory approval, and has only very minor differences from the published academic analysis (Van Der Graaf 2011/12) due to different (more conservative) rules for patient censoring and data handling. In nearly all cases, the regulatory analysis presented is less favourable towards pazopanib than the academic analysis. A table has been added illustrating these differences in a transparent manner. It was decided not to use the academic analysis for this study because it was not fully published until after the cut-off date for the literature search.

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. We agree that these statements are not coherent and have therefore removed the reference regarding the primary endpoints, as this statement is not particularly informative for these types of studies.

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? We have added dose information to the chart of prospective non-randomized studies. For therapies where multiple doses and schedules were investigated, there does not appear to be a major difference in efficacy linked to dose, possibly due to the typically small sample sizes in such studies, but we have commented on this in more detail in the text.

5. As you were intending to assess the benefit of agents following therapy of doxorubicin, is the inclusion of studies with liposomal doxorubicin appropriate? Given that our inclusion of therapies is based on guidelines, liposomal doxorubicin was included as a matter of completeness, even if this is something that might not be considered in standard clinical practice and the evidence is limited. There were two studies identified testing liposomal doxorubicin that met our criteria (Skubitz 2003, Toma 2000).
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? This could absolutely be an explanation, and has been added to the discussion.

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.

A statement has been added about trabectedin availability. We have also made the language in the conclusion more flexible about treatment choices and comparators in trials, and also included a statement about the need to better understand the efficacy/toxicity ratio of therapies that only have Phase II evidence. We have further elaborated on the TAXOGEM study (gemcitabine plus docetaxel) in the discussion.