Author’s response to reviews

Title: Gemcitabine and docetaxel combination chemotherapy for advanced bone and soft tissue sarcomas: protocol for an open-label, non-randomised, Phase 2 study

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Author’s response to reviews:

Dear reviewers and editors

Enclosed please find a manuscript entitled "Gemcitabine and docetaxel combination chemotherapy for advanced bone and soft tissue sarcomas: protocol for an open-label, non-randomised, Phase 2 study ".

Thank you for providing your insightful comments.
We have revised our manuscript in response to all such comments. We look forward to publication of our manuscript in BMC Cancer. Thank you very much.

Sincerely yours,

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Editor Comments:

1. Please have the text edited by a professional language editing service or a native English speaking colleague. There are many issues with grammar, wording, spelling, and/or punctuation that need to be addressed.

   This also includes the Declarations and the Supplementary Materials.

   Response: We have had all material edited by a native English speaker.

2. Please include the Japan Registry of Clinical Trials registry details if the trial has now been registered.

   Response: We have added the registry details on page 3, lines 41-43.
3. Consent for publication refers to consent for the publication of identifying images or other personal or clinical details of participants that compromise anonymity. Seeing as this is not applicable to your manuscript please state “Not Applicable” in this section.

Response: We have revised this section as requested.

4. We note that this trial will include minors (those under the age of 16), please clarify in the Ethics approval and consent to participate section who will consent on behalf of these patients, and whether this will be verbal or written consent. If verbal, why was this method chosen and was this approved by the ethics committee?

Response: We have added the requested details about consent on page 12, lines 245–247. We had already provided the details in additional file 1, so we also have revised the relevant section on pages 5-6, lines 83–91 in additional file 1.

Reviewer reports:

Scott Okuno (Reviewer 1):

1. Phase II study of bone and STS with gemcitabine and Docetaxel with only 20 pts planned study.

2. This manuscript is a proposed study, not a completed study.

3. Primary endpoint is PFS and for combined bone and STS. The endpoints for STS and bone are different. So would not combine in one study 4. Sample size of 20 is too small for any meaningful conclusions.

Response: We agree that the sample size of 20 is too small and that the inclusion of different sarcoma types such as STS and bone tumour is a limitation of this study. We mentioned these limitations study in the Discussion (page 11, lines 224–227). However, a multi-institutional study would be required to achieve a larger sample size because the target diseases of this study are very rare. Thus, we have included the points you have made above as considerations for future studies. Thank you for these suggestions.
5. There are published completed phase II and phase III studies for subsets of sarcomas already with gemcitabine and docetaxel.

Response: We agree that this is true; however, GD therapy for sarcoma has not yet been approved for insurance cover in Japan. In this study, we therefore chose to focus on the efficacy and safety of GD therapy in Japanese patients with advanced sarcomas in the hope that GD therapy would be approved for later therapy of sarcomas.

6. Target sample size is based on response rate, but the primary endpoint is PFS. Not clear what PFS you are looking at, but it looks like PFS at 1 year. Typically the PFS is not at 1 year, but at 16 weeks for STS and different for bone.

Response: Thank you for pointing out this contradiction. We selected PFS as the primary endpoint because prolonging time to disease progression would be important even if the response rate is less than expected. We have included this justification in the text (page 5, lines 92–94). The primary analysis of PFS will be performed one year after the end of the enrolment period; however, we will be able to modify the timing of analysis.

8. Because of the great variations of PFS for the various bone sarcomas, would need to be clear on which bone sarcoma you include and exclude. Need to be clear what STS are included and excluded as the PFS and response to chemo is different.

Response: We agree that it would be ideal to specify the histological subtypes of sarcoma, but we chose to include various sarcomas of soft tissue and bone because the sample number would otherwise be too small.

10. Why the dose of 70 mg of docetaxel. Most use different dosing of 75 or 100 mg/m2?

Response: Thank you for pointing this out. As you say, most clinical studies in Europe and the US have used a dose of 100 mg/m2 of docetaxel. However, even with preventive administration of G-CSF, doses of 100 mg/m2 have reportedly needed to be reduced by 25%. Thus, the difficulty of continuing therapy at a dose of 100 mg/m2 in Europe and the USA has resulted in this dose being regarded as excessive. Moreover, in Japan, preventive administration of G-CSF has not yet been approved; thus, a dose of 100mg/m2 is not realistic.

11. For sarcomas, the dosing of gemcitabine is typically a fix rate infusion, so need to be specific of rate in the protocol.
12. For patients with prior pelvic radiation, the dose of gemcitabine is typically decreased from 900 mg/m² to 675 mg/m².

Response: Thank you for pointing out these matters. It has been reported in Europe and the USA that a fixed-dose infusion of gemcitabine causes considerable toxicity. Combination therapy with gemcitabine and radiation to the chest is currently not recommended; however, prior pelvic radiotherapy does not generally require reducing the dose of gemcitabine.

13. Some would use neulasta on day 9 or on-body on day 8. Please specify if can be used growth factors.

Response: We also agree with using G-CSF on Day 8 or 9. As mentioned above, preventive administration of G-CSF has not yet been approved in Japan, the recommendation being to use G-CSF from the day after anticancer drug administration; we have requested administration of G-CSF on Day 10.

Sandro Pasquali (Reviewer 2): This is the presentation of a protocol. There are some methodological issues that authors should clarify and improve.

Major comments:

The most controversial issue with this study is the main endpoint. The authors stated that their primary endpoint is PFS but then the sample size calculation is based on response rate. This is confusing. Also, this is a phase II study which electively looks at response rather than survival. The authors should clarify their study design and select their main endpoint to perform sample size calculation consistently.

Response: Thank you for your suggestion. As mentioned above, we selected PFS as the primary endpoint because prolonging time to disease progression would be important even if the response rate is less than expected. We have included this justification in the text (page 5, lines 92-94). The primary analysis of PFS will be performed one year after the end of the enrolment period; however, we will be able to modify the timing of analysis..
It would be appropriate to have histological confirmation of metastasis with a biopsy.

Response: We agree. However, we consider a biopsy unnecessary if metastases can be definitely diagnosed clinically. We have added a brief explanation of this approach (page 6, lines 108-110).

The study should be registered in clinicaltrial.gov

Response: We have added the registry details on page 3, lines 41–43.

The title should mention that patients were pretreated.

Response: Thank you for this suggestion; however, our study will also include patients who are unable to undergo standard therapy such as older individuals with advanced osteosarcoma.

The Background section results quite awkward as it started with two type of sarcoma rather than giving the reader a general idea of treatment of metastatic sarcoma. Authors should report median survival of metastatic STS and offered also example of survival variations according to hystoyypes. Then they should reported common chemotherapy regimens which are usually based on anthracycline. Then, they should mention that the different spectrum of sarcomas are sensitive to different chemotherapy regimens. At this point it is worth reporting on osteo and Ewing as well as some soft tissue sarcomas such as leiomyosarcoma. Their study is about both bone and soft tissue sarcoma rather than single histologies.

Line 52 to 69 have no references which need to be added.

Response: Thank you for your suggestions, in response to which we have revised the relevant sections (pages 4-5, lines 66-71 and lines 82–85).
Minor comments


Response: Thank you for pointing out that, we have revised the relevant sentence (page 4, line 49).

References for RECIST and CTCAE should be added.

Response: Thank you. We have added the required two references.