Author’s response to reviews

Title: Study protocol of a phase II clinical trial (KSCC1501A) examining oxaliplatin+S-1 for treatment of HER2-negative advanced/recurrent gastric cancer previously untreated with chemotherapy

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Version: 2 Date: 16 Mar 2017

Author’s response to reviews:

March 16, 2017

Dafne Solera
Executive Editor
BMC Cancer

Dear Dr. Solera:

Thank you for sending us the reviewers’ comments on our manuscript titled, "A phase II clinical trial (KSCC1501A) examining oxaliplatin+S-1 for treatment of HER2-negative advanced/recurrent gastric cancer previously untreated with chemotherapy," by Saeki, et al. We
have revised our manuscript based on these comments, and wish to re-submit it for publication in BMC cancer.

Thank you for your consideration. We look forward to hearing from you.

Sincerely,

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REPLY FORM (1)

MS entitled "A phase II clinical trial (KSCC1501A) examining oxaliplatin+S-1 for treatment of HER2-negative advanced/recurrent gastric cancer previously untreated with chemotherapy" by Saeki et al.
To the Editor:

Thank you for your constructive comments and for your time in reviewing our manuscript. We have addressed each of your concerns here, and revised our manuscript accordingly, based on your comments.

Editor(s)' Comments to Author:

Reviewer 1: The paper focuses on explaining the rationale, aim, inclusion and exclusion criteria of a soon-to-start Phase II not-randomised clinical trial using the combination of S-1 and Oxaliplatin in advanced gastric cancer patients.

This subject, even if somewhat limited in real-life use in Western countries (due to low use of S-1 in these countries due to the disappointing results of trials like the FLAGS trial), is of primary relevance in Asia where combinations of S-1 and platinum-based antineoplastic drugs are considered the gold standard of treatment.

This trial also approaches the relevant issue of dose-limiting toxicities due to Oxaliplatin use, something that is well-known in the everyday clinical practice and that represents a matter of major debate, owing to the difficulties in being able to manage correctly patients who receive Oxaliplatin 130 mg/mq once every 3 weeks (as in the XELOX regimen).

With these pre-stated considerations, I would like to see some points corrected before the article can be considered acceptable for publication:

1. It would be better to further define the population of patients who are going to be enrolled. In particular, authors state that patients who have measurable target lesions accordingly to RECIST 1.1 criteria will be eligible for enrollment. It would be best to clarify if patients eligible for enrollment are advanced gastric cancer patients or the enrollment is limited to metastatic patients (like the keywords would seem to suggest). Even though it could be a minor issue, particularly if response rate is the primary endpoint, it is crucial for other end-points like survival.
2. The trial focuses on the use of Oxaliplatin at the dose of 130 mg/mq once every 3 weeks. The aim of the trial is to demonstrate that a higher dose of Oxaliplatin might be more effective compared with the disappointing results of G-SOX trial where SOX (with Oxaliplatin at 100 mg/mq) was failed to demonstrate not-inferiority compared to SP. In case of relevant toxicities the author stated that they will reduce Oxaliplatin but I could not find in the article at which lower dose level. It would be best to state which new level of dose of Oxaliplatin you are going to use, on the basis of the fact that this trial is mainly focused on the matter of Oxaliplatin dose-intensity.

3. Are gastroesophageal junction (GEJ) tumours excluded from enrollment? It would be best to clarify this matter.

4. Finally, I would like to see some comment by the authors on the published results of the Phase II trial of Hironaka et al. (S-1 plus leucovorin versus S-1 plus leucovorin and oxaliplatin versus S-1 plus cisplatin in patients with advanced gastric cancer: a randomised, multicentre, open-label, phase 2 trial. Lancet Oncol. 2016 Jan;17(1):99-108. doi: 10.1016/S1470-2045(15)00410-6. Epub 2015 Nov 28.). In this trial, SOX (with Oxaliplatin dose of 85 mg/mq once every 2 weeks) was used and response rates that were achieved were particularly relevant (66%) in this group (even though limited, as by Phase II standards, in terms of number of patients treated). In this trial SOX seemingly performed better than SP, with a seemingly more favourable toxicity profile. On this basis I would like to see some comment, in the background or in the discussion area of the paper, on these results and how they might be relevant for this paper.

Reply:

1. Thank you for your comment. The patients with advanced/recurrent gastric cancers who are not amenable to curative surgery are eligible for enrollment, as listed in Table 1, Eligibility Criteria 7).

We have added a sentence clarifying this in our manuscript (page 8, line 20 to page 9, line 1).
2. If the patients exhibit toxicities that meet the reduction criteria, the oxaliplatin dose of 130 mg/m2 will be gradually reduced to 100 mg/m2, 75 mg/m2, and 50 mg/m2. If further reductions are required, the administration of oxaliplatin will be stopped.

We have added this information on page 9, lines 12–14 in the manuscript.

3. Patients in whom the center of the primary tumor is located above the gastroesophageal junction are excluded from enrollment in this study.

We have added this sentence on page 9, lines 1–2 in the manuscript.

4. Hironaka et al. have reported the results of a randomized phase II trial that compared the combinations of S-1 with leucovorin only, with leucovorin and oxaliplatin, and with cisplatin, respectively, in patients with advanced gastric cancers [New Reference 12: Hironaka S, et al. S-1 plus leucovorin versus S-1 plus leucovorin and oxaliplatin versus S-1 plus cisplatin in patients with advanced gastric cancer: a randomised, multicentre, open-label, phase 2 trial. Lancet Oncol. 2016; 17: 99-108.]. The objective response rate in the group that underwent treatment with S-1 plus leucovorin and oxaliplatin (with an oxaliplatin dose of 85 mg/m2, once, every 2 weeks) was 66%, and the authors concluded that an S-1 plus leucovorin and oxaliplatin regimen was more active than other regimens, and had acceptable toxic effects. Although the protocol of this regimen seems promising, an oxaliplatin dose of 85 mg/m2, once, every 2 weeks is not approved by the National Health Insurance. Therefore, this regimen was not included in our study, because our current study was conducted in an investigator-initiated fashion. A phase III trial comparing S-1 plus leucovorin and oxaliplatin with S-1 plus cisplatin as chemotherapy for patients with advanced gastric cancers is currently ongoing (NCT02322593).

We have added these sentences on page 16, lines 6–18 in the manuscript.

**REPLY FORM (2)**

MS entitled "A phase II clinical trial (KSCC1501A) examining oxaliplatin+S-1 for treatment of HER2-negative advanced/recurrent gastric cancer previously untreated with chemotherapy" by Saeki et al.
To the Editor:

Thank you for your constructive comments, and for your time in reviewing our manuscript. We have addressed your concerns here, and have revised our manuscript accordingly, based on your comments.

Editor(s)' Comments to Author:

Reviewer 2: Dear Editor/Authors,

This study has some relevant issues.

1. the study is non-controlled and will therefore not yield definitive data on the value of the SOX 130 mg regimen.

2. the study uses ORR as the primary endpoint. ORR is notoriously poorly correlated with clinical benefit (e.g. OS, PFS), and therefore the primary endpoint will not yield relevant data.

3. the study is powered to show an ORR >45%, while other studies using SP or SOX 100 mg showed ORR rates with confidence intervals encompassing 45 (upper boundaries up to around 60). Therefore, no superiority can be demonstrated in the current study, even if it would be assumed that ORR is a relevant endpoint. Since this is a non-controlled study, no definitive conclusion can be drawn in any case (as mentioned under 1.)

In conclusion, I question whether this study is appropriately design to yield sufficient data to justify the SOX 130 mg regimen in clinical practice. I wonder whether it is ethical to perform a single-arm study that will yield minimal additional information to what is already known on the SOX regimen and which will expose patients to the risk of a higher dose of OX.
My recommendations:

1. First perform a tolerability study (phase 1), to determine the safety of the SOX 130 mg regimen.

2. If tolerability has been sufficiently investigated by the authors or otherwise, I recommend to perform a controlled study comparing safety of SOX 100 with SOX 130.

Alternatively, or even better: the authors should perform a controlled study comparing the efficacy of SOX 130 mg with the approved regimens with a clinically relevant endpoint such as OS (alternatively PFS, but OS should be feasible considering the short life expectancy of gastric cancer patients).

I hope this review helps the authors. Please feel free to contact me otherwise, and please inform me on the process of the review of this article.

Reply:

1. Thank you for your constructive suggestions. Per your recommendation, performing a phase I study to investigate the safety of an oxaliplatin plus S-1 regimen with an oxaliplatin dose of 130 mg/m2 in Japanese patients is ethically reasonable. In a phase I/II study of first-line therapy for patients with metastatic colorectal cancers that was conducted in Japan, oxaliplatin plus S-1 with an oxaliplatin dose of 130 mg/m2 has previously been evaluated, and found to be easily manageable [New Reference 10: Yamada Y, et al. Phase I/II study of oxaliplatin with oral S-1 as first-line therapy for patients with metastatic colorectal cancer. Br J Cancer. 2008; 98(6): 1034-8.]. Based on this evidence, we aimed to conduct a phase II clinical trial that would examine the efficacy and safety of oxaliplatin plus S-1 with an oxaliplatin dose of 130 mg/m2 for advanced/recurrent gastric cancers, without using a phase I study.

We have added these sentences on page 7, lines 4–9 in the manuscript.

2. Per your recommendation, a comparison of the safety or overall survivals (or both) associated with oxaliplatin plus S-1 regimens with oxaliplatin doses of 100 mg/m2 and 130 mg/m2, respectively, is needed if the tolerability of the oxaliplatin dose of 130 mg/m2 is to be
sufficiently investigated. Considering this viewpoint, if this current phase II study meets the defined endpoints, we further plan to perform a prospective controlled study that would compare the safety and efficacies of oxaliplatin plus S-1 regimens with oxaliplatin doses of 100 mg/m² and 130 mg/m², respectively.

We have added this information to the manuscript (page 19, lines 3–6).