Reviewer's report

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

Version: 1 Date: 02 Feb 2017

Reviewer: Riccardo Giampieri

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 end-point, 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.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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I am able to assess the statistics

**Quality of written English**

Please indicate the quality of language in the manuscript:

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