Author's response to reviews

Title: Capecitabine and oxaliplatin combined with bevacizumab are feasible for treating selected Japanese patients at least 75 years of age with metastatic colorectal cancer

Authors:

Yoshinori Munemoto (Y-MUNEMOTO@fukui.saiseikai.or.jp)
Mitsuro Kanda (m-kanda@med.nagoya-u.ac.jp)
Keiichiro Ishibashi (k_ishi@saitama-med.ac.jp)
Taishi Hata (thata@gesurg.med.osaka-u.ac.jp)
Michiya Kobayashi (kobayasm@kochi-u.ac.jp)
Junichi Hasegawa (j-hasegawa@orh.go.jp)
Mutsumi Fukunaga (fukunaga1404@hp.pref.hyogo.jp)
Akinori Takagane (takagane@gobyou.com)
Toshio Otsuji (hxgcd792@yahoo.co.jp)
Yasuhiro Miyake (hotymiyake@hotmail.com)
Michitaka Nagase (mnagase@nagoya-1st.jrc.or.jp)
Junichi Sakamoto (sakamjun@med.nagoya-u.ac.jp)
Masaki Matsuoka (masa2722@mac.com)
Koji Oba (oba@epistat.m.u-tokyo.ac.jp)
Hideyuki Mishima (hmishima@aichi-med-u.ac.jp)

Version: 4
Date: 27 June 2015

Author's response to reviews: see over
June 27, 2015

Dafne Solera, PhD
Executive Editor,
BMC Cancer

Dear Dr. Solera,

We greatly appreciate your thoughtful comments and kind invitation to resubmit our manuscript (ID: 1037706307157790) titled “Capecitabine and oxaliplatin combined with bevacizumab are feasible for treating Japanese patients at least 75 years of age with metastatic colorectal cancer.” We revised the manuscript again according to the comments. Our point-by-point responses to the comments offered by you and the referees are listed below.

We hope that the revised manuscript is now acceptable for publication in BMC Cancer

Best regards,

Mitsuro Kanda, MD, PhD
Department of Gastroenterological Surgery (Surgery II)
Nagoya University Graduate School of Medicine
65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
Tel: +81-52-744-2249
Fax: +81-52-744-2252
E-mail: m-kanda@med.nagoya-u.ac.jp
Dear Authors, at first we would like to thank you for giving us the opportunity to review the revised version of your work. The revised version is clearly an improved version of your study, but a number of points need to be better clarified. So we ask you to revise again the manuscript, on the basis of new reviewers' concerns. In addition, we ask you to improve the quality of the language, i.e.: by the help of experts in the field.

Response: We did our best to use the great opportunity given to us to work towards reconsideration of our manuscript. The manuscript was revised according to reviewers' comments and the English editing was checked again throughout the text.

The authors responded well to most of the concerns raised by the reviewers. In review of the revised manuscript the following issues were identified:

Response: Thank you for your favorable comments. We revised the manuscript in accordance with your suggestions as stated below.

Major:

1. Introduction: the introduction is very lengthy. It emphasizes the data on tx of mCRC in general, the PK information of capecitabine, and data on XELOX. However the main point of the paper is the use of this regimen in older patient. There is no review of the literature in this regard. As noted in the earlier comments there should be some reference to the recent data from large clinical trials among older mCRC patients.

Response: The Introduction section has now been shortened and the recent data from large clinical trials among older mCRC patients were introduced in the text (page 7, line 9-12) and summarized in Table 4. In addition, repetitions between the Introduction and Discussion section were avoided.

2. Methods: page 10 lines 9-12 – the authors added description of how neuropathy was graded. It is not clear from this that there was any dose reduction allowed for oxaliplatin. If no dose reduction was allowed that would be odd and should be clarified.

Response:

The detailed information of dose reduction or stopping criteria was provided in the Methods section (page 10, line 9-16). The dose reduction or stopping criteria of drugs due to adverse events is defined based on the haematological toxicity (Grade 4 neutropenia, Grade 3 febrile neutropenia or Grade 3 or more decrease in platelets) and Grade 3 non-haematological toxicity. Dose reduction due to adverse events was performed for each drug as specified in the study protocol, which provided detailed algorithms to manage drug-specific toxicities such as oxaliplatin-related neuropathy as follows: G1 continue administration, G2/3 until recovery to G1 or less and resume oxaliplatin with the reduction dose (for the first time 100 mg/m², for the second time 85 mg/m²), G4 discontinuation of oxaliplatin.
3. Methods: Page 9 line 5 – The sentence: “no prior chemotherapy or treatment of recurrent lesions with only 5-FU without adjuvant chemotherapy”. This is listed as inclusion criteria – this is confusing and not clear what this means… patients could get 5FU only for metastatic disease? and then enroll on the study? patient’s were not allowed to have adjuvant therapy? Please clarify.
Response: We are sorry for this confusing sentence. It has been corrected as follows: no prior chemotherapy (adjuvant chemotherapy included fluorouracil and/or oxaliplatin was allowed, but the last course of adjuvant chemotherapy must have concluded more than six months prior to colorectal cancer recurrence) (page 9, line 3-5).

4. Results: Page 14, line 7-8: With regards to evaluation of other factors related to older patients. The authors responded that the following factors were evaluated: CCR, ASA score, ASA-PS score, age, BMI, and gender. Although the association with CCR was reported the text does not address the other factors. If no association was seen, that should clearly be state.
Response: No association was found between evaluated factors other than CCR (ASA score, ASA-PS score, age, BMI, and gender) and incidence of AEs ≥G3. This result was stated in the revised manuscript (page 14, line 14-16).

5. Results: Page 13 line 7-9: The following sentence is not clear: “Fourteen, 12, and two pt. received the protocol treatment after discontinuation of oxaliplatin, capecitabine and bevacizumab and capcecitabine alone respectfully.” This is not clear, did some patients get oxaliplatin alone? Or bevacizumab alone? Please clarify.
Response: The sentence has been revised (page 13, line 8-10). There were 14 patients who continued to receive the protocol treatment after withdrawal of oxaliplatin (capecitabine with bevacizumab for 12 and capecitabine alone for two patients).

6. Discussion: When discussing the shortcoming of the paper, there should be additional wording regarding the lack of elderly specific evaluation (comprehensive geriatric assessment).
Response: Thank you for your suggestion. The lack of elderly specific evaluation, such as the comprehensive geriatric assessment, has been added in the limitations of this study (page 19, line 15-18).

Minor:
1. Abstract: the rate of male/female and colon/rectal is reported as ration (i.e. 21:15) this is not a typical way to present this data.
Response: The sentence were revised according to your suggestion (page 5, line 3).
2. Introduction: page 6 line 7 – the OS state is 20m; the recent CALGB data should be used with OS closer to 30m.
Response: Survival data was updated with appropriate references (page 6, line 6-7).

3. Methods:
Response: The word “late” has been deleted.

b. Page 10 line 19 – CA19-9 was tested? Is this correct? Not clear why this would be included in a mCRC study.
Response: In Japan, CA19-9 has been commonly test CA19-9 accompanying with CEA in patients with CRC.

c. Page 11 line 10-13 – the authors added a list of factors that were evaluated in this elderly population (CCR, ASA score, age, BMI, etc) in this paragraph it says that the association was tested with discontinuation of therapy. However, in the results section the association is listed with toxicity. This needs to be clarified.
Response: We are sorry for the serious mistake, which has now been corrected.

e. Page 11 line 15-17 - The authors added a definition of TTF. This definition should be included in the section where PFS and OS are described.
Response: Definition of TTF was transferred to the section where PFS and OS are described (Statistical analysis).

4. Results:
a. Page 13, line 1: change the ratio reporting to the typical way of reports.
Response: The text was revised according to your comment.

b. Page 13, line 4 – this line read median of 8 cycles of treatment. However the following line reports a median of 5 cycles, this is not clear.
Response: The sentence “The 36 patients underwent a median of 8 cycles of treatment (range 1–25).” has been deleted to avoid confusion.

c. Page 14, line 14 – when discussing efficacy – should there be ref to table #3?
Response: Table 3 has been referred for descriptions of efficacy (page 15, line 4).

5. Discussion:
a. Page 18 line 16: “studies in general population” – wording should be changed since this is not a
Response: As you pointed out, FIRE-3 and CALGB/SWOG 80405 trials focused on patients with wild-type Kras (not general population). Accordingly, the wording “general” has been changed into “younger” (page 18, line 15).

b. Page 19 line 13-14 – “Oxaliplatin is easier than cisplatin” – This is irrelevant since cisplatin is not used in management of CRC.
Response: We agree with your opinion. This sentence has been deleted.

[Referee 2: 1374640113175998]
your article has improved over the earlier version and questions have been answered. Still, may I ask to revise it for a second time.
Response: Thank you for your encouraging comments. We revised the manuscript in accordance with your suggestions as stated below.

Major Compulsory Revisions:
This is a small series, thus I would stick as much as possible to your data. Please review the text in this sense and phrase conclusions more cautiously. In my view your study shows that Xelox-Bev can be given in a selected population of elderly, fit patients, but maybe toxicity was kind of a concern. I think that no conclusions can be drawn beyond this.
Response: The manuscript was checked careful attention to this point. We rephrase the title and the conclusions in the abstract and text according to your suggestion.

Could you provide data on RAS/BRAF status ?
Response: Unfortunately, data on RAS/BRAF status is unavailable. This point was newly described as a limitation of our study (page 19, line 15).

How many patients received second-line treatment ?
Response: The study protocol had no provisions regarding the second-line treatment. Accordingly, the detailed information of second-line treatment is unavailable. This point has been mentioned in the text as one of limitations of this study (page 19, line 18-19).

Discretionary Revisions:
To me, personally the text seems lengthy now, and some information redundant. Please shorten. E.g., I felt the info on capecitabine pharmacodynamics too lengthy and also general remarks on CRC.
Response: The text has been shortened and focused more on relevant topics. In addition, repetitions between the Introduction and Discussion section were avoided.
My main problem is that you cite a large number of trials, which included different populations (in the past) to discuss many different aspects: Efficacy, toxicity, safety. E.g. page 18: You cite FIRE/CALBG saying that OS was longer, but the info that this is a different population (age, RAS status, surgery/resection rate) is missing. I got lost with this. Could you regroup, delete or rephrase?

My suggestion:
1) Provide a table of all trials you discuss in your paper, to summarize key trial details, e.g. patient age + PS, intervention, RR/PFS/OS, AEs.
2) reorganize your paper: discuss outcome (against PS, age, chemo used), tox etc

Response: We thank the referee for thoughtful suggestion. We made Table 4 to organize relevant references and make our manuscript reader-friendly. With this, the Introduction and Discussion section has been reorganized.

While i had myself asked for recommendations of how to monitor for cerebral vascular events, i feel your suggestions now a bit strong on wording. E.g.: From our experience, we propose to monitor neurological signs on each visit and perform cerebral imaging on low threshold in symptomatic patients. But, this is only a suggestion.

Response: The sentence has now been revised as you suggested (page 18, line 4-5).

I might have overread it, but please state if response rate assessment was done locally, or by central review.

Response: In this study, response rate assessment was done locally. This point was added in the text (page 11, line 6).