Author’s response to reviews

Title: A phase-II trial of combined chemotherapy with S-1, oral leucovorin, and bevacizumab in heavily pre-treated patients with metastatic colorectal cancer

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Author’s response to reviews: see over
Cover Letter

December 25, 2014
Dafne Solera, Executive Editor

BMC cancer
Floor 6, 236 Gray’s Inn Road, London
WC1X, United Kingdom

Dear Dr. Solera

Re: “A phase-II trial of combined chemotherapy with S-1, oral leucovorin, and bevacizumab in heavily pre-treated patients with metastatic colorectal cancer” by Kazuhisa Yamaguchi, Hiroya Taniguchi, Azusa Komori, Yukiya Narita, Sohei Nitta, Motoo Nomura, Shigenori Kadowaki, Daisuke Takahari, Takashi Ura, Masashi Andoh, Kei Muro, Keita Mori and Yoshinori Igarashi; MS. No 1755515626154829.

Please find attached, the revised version of our paper. We are most grateful to you and the reviewers for the helpful comments on the original version of our manuscript. We have taken all these comments into account.

In your letter of April 8 2015, you suggested that we should state the full name of the Ethics committee that approved our study. We have changed as follows “ethics review committee of Aichi Cancer Center Hospital” (page 7, line 18-19). Moreover, as two referees pointed to need statistical review of our paper, we requested it to a statistician, Keita Mori, to improve the reliability of the results. So please accept to add him on author list.

We have addressed all the comments by reviewers Dr. Guy van Hazel and Dr. Prem Sinha, as indicated on the attached pages, and we hope that our explanation and revisions are satisfactory.

We hope that the revised version of our paper is now suitable for publication in the BMC cancer and we look forward to hearing from you at your earliest convenience.

Sincerely,

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We are grateful to reviewer Dr. Guy van Hazel for the special comments and useful suggestions that have helped us to improve our paper. As indicated in the responses that follow, we have taken all these comments and suggestions into account in the revised version of our paper.

**Comment #1**
I believed the conclusion in the abstract is too strong. As the authors admit, their good results could have been due to patient selection and without a control group we cannot be certain that the patients had prolongation of PFS and survival. I believed their conclusion in the main article is better. I have made a suggestion.

**Response**
We agree with the comment and the sentence in the abstract has been changed as suggested (page 4, line 2).

We are grateful to reviewer Dr. Prem Sinha for the critical comments and useful suggestions that have helped us to improve our paper. As indicated in the responses that follow, we have taken all these comments and suggestions into account in the revised version of our paper.

**Comment #1**
1) It will be useful for a general reader who is from a non-medical field to follow the paper if a table is provided listing the existing therapies including the current one at different stage of colorectal cancer and limitations/benefits/progression free survival/overall survival rates etc. of various existing practices.
2, 3) Also, please avoid the use of medical acronyms in the text, if possible; it hinders the flow for a general reader. Explain Eastern Cooperative Oncology Group PS 0-2 and BEBYP studies. Define CEA and CA (page 12, line 9) and include them in the list of abbreviations.

**Response**
1) We newly provided a list of therapies including different stage of colorectal cancer as “additional file 1” and it has been cited in the revised texts (page 5, line 8-9).

2, 3) We cited the reference in the revised text (page 21, line 12-13). About BEBYP studies, we have been revised as below (page 15, line 25 - page16, line2).

“Similar result was also observed in an Italian multicentre study (BEBYP study), which demonstrated a significant improvement in PFS and OS continuing Bev plus second-line chemotherapy [13].”
4) We described CEA and CA as follows (page 11, line 9-11) and cited in the list of abbreviations (page 17, line 23-24).

“The patient’s serum tumor markers including CEA and CA19-9 levels decreased remarkably during the protocol treatment”.

Comment #2
Figure 2 and 3 needs some explanation in the legends. Also, pleas label the x-axes.

Response
We re-wrote in the figure 2 and 3 legends as suggested (page 25, line 8-10 and 12-14). And we labeled x-axes in figure 2 and 3.

Comment #3
In table 2, there are two sub-columns in the sections “all grades and grades 3/4”. Please explain them in the legend and text.

Response
We added explanations in the legend (page 29, line 1-3).

Comment #4 and 5
Page 17, line 6-8, “With this speculation….. to be resistant”: unclear sentence; please re-phrase the sentence
Page 16, line 24, “According to these reports….. are limited”: unclear sentence; please re-phrase the sentence.

Response
As suggested, the paragraphs were unclear. We have been revised as below (Page 15, line 18 – page 16, line 9.).

“Little comparative data are available regarding the activity of Bev after second-line therapy. Bev therapy in the later-line setting has been reported in several phase-II studies and in retrospective series [23-28]. According to these reports, Bev does not show a tendency for reduction in tumour size but results in tumour stabilisation and improved survival. However, studies evaluating its effect in later-line treatment of Bev re-introduction are limited. Recently, international multicentre study (ML18147 study) revealed that continuation of Bev after initial tumour progression significantly improved PFS and OS [12]. Similar result was also observed in an Italian multicentre study (BEBYP study), which demonstrated a significant improvement in PFS and OS continuing Bev plus second-line chemotherapy [13]. These results imply disease may still partially depend on VEGF after disease progression and raises the possibility that the angiogenic signal may continue throughout the tumor lifespan. With this speculation, Bev re-introduction may
still contribute to enhance anti-tumour activity that has already proved to be resistant. Although we must note that prospective and randomized clinical trials are lacking regarding the role of Bev in chemo-refractory mCRC patients, we could speculate that a combination with Bev provides some efficacy in a heavily treated population.”