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
Dear Dr. Manoj Pandey

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 referee for the helpful comments on the original version of our manuscript. We have taken all these comments into account.

We have addressed all the comments by reviewer Dr. Andrea Evangelista, 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.

**Major Revisions**

There are some statistical issues arising, as follows:

- In the first sentence of “Statistical analyses” section, does not appear clear to which group (SL/Bev or historical control) the proportion “of 41%–44% reported in previous large trials” relates. According to the sample size justification described later, it would seem the expected proportion in the experimental group (SL/Bev). In general, however, it would be more clear a more explicit indication of 1) treatment administered in the historical control, 2) proportion of DCR in the historical control 3) expected improvement in the group SL / Bev (e.g. “The objective was to demonstrate a xx% improvement in DCR with the new regimen SL/Bev relative to an expected DCR of xx% with “X” treatment”).

- The authors should give a reference for the 22% DCR (assumed as proportion of DCR in the historical control) that has been used for sample size calculation (null hypothesis). Although some references to prior published data were reported in the “Discussion” section, the authors should cite prior studies also in the “Statistical analyses” section.

- The authors should explain in more detail the type of study design. The sample size proposed seems compatible with a Fleming-A'Hern single-stage design for Phase II trials. Is it correct?

**Response**

We agree with the comment and the sentence in the Statistical Analysis has been changed as suggested (page 9, line 13-18).

“A one sample binomial design (Fleiss JL. Statistical Methods for Rates and Proportions (1981), pp. 13-15.) was used to determine the sample size. The estimates were based on DCR of previous two trials comparing new drugs and best supportive care (BSC). DCR in the trial of regorafenib and TAS102 were 41% and 43.8%, while the DCR of BSC group in these trials were 15% and 10.5%, respectively [15-16]. Therefore, we hypothesized it would be beneficial if DCR was at least 44% with this therapy, while under 22% would be the lower limit of interest.”

- Parameters to establish whether SL/Bev was a success and then to determine its activity should be described in the “Statistical Analysis” section. Generally, in a single-arm phase II trial using a dichotomous primary endpoint (as DCR), the experimental treatment is declared active on reaching of a predetermined number of successes. Or, according to sample size justification, if the lower limit of one-sided 95% confidence interval of DCR exclude the null value (22%). In the “Results” section, the authors state “this study met its primary endpoint” since DCR was higher than the predefined expected hypothesis of 44%. However, according to the specified “null (22%)” and “alternative (44%)” proportion of DCR, the activity of the SL/Bev would arise even with a proportion of DCR less than 44%.

**Response**

We agree with the comment and the sentence in the “Results” has been changed as suggested (page 11, line 20-22).

“The lower limit of one-sided confidence interval of DCR (45%) was higher than the
predefined null value (22%); therefore, this study met its primary endpoint.”

**Minor Revisions**
- the title of the manuscript should specify that this study is a single-arm trial.

**Response**
We change the title to “A single-arm phase II trial of combined chemotherapy with S-1, oral leucovorin, and bevacizumab in heavily pre-treated patients with metastatic colorectal cancer”

- for continuous variables described in the “Results” section (text and tables), include also the 25th and 75th percentile (IQR). The range (min-max) is sensitive to outliers and does not use all the observations (in most cases only 2 observations: the highest and lowest values).

**Response**
We change as follows.

(In the text)
- The median age was 69 years (range 37-86 years, interquartile range 61–73 years)
- The median follow-up period was 11.8 months (range 37-86 years, interquartile range 9.6–18.2 months) as of June 2014.
- The total number of treatment cycles administered was 299 and the median number of cycles administered was 9 (range 1-24, interquartile range 4–13).

(In the tables)
- Median CEA level ng/ml (range, interquartile range) 116 (0-42230, 31–350)
- Median CA19-9 level ng/ml (range, interquartile range) 222 (5-9820, 38–965)

- please add the number of patients at risk beneath the survival curves (Fig 2 and Fig 3).

**Response**
We revise the Figure 2 and 3 added the number of patients at risk.

- if possible, at the end of the discussion, authors may suggest the comparator arm that could be included in a future RCT designed to evaluate the efficacy of SL/Bev.

**Response**
We change the sentence to (page 18, line 13-16)
“To confirm its efficacy, further prospective randomized control trial is necessary to compare SL/Bev with BSC in patient with refractory mCRC.”

**Discretionary Revisions**
- subgroup analyses are generally underpowered also in phase III trials. Thus, the authors may consider removing results of the log-rank test for comparison between wild and mutant KRAS patients, reporting only the estimates of median OS. For the same reason, the authors may consider to remove from the study limitations the fact that “the number of subjects is too small to perform significance subgroup analysis”.

Response

We delete the sentence “These differences were not significant (log-rank test; \( p = 0.84 \) and \( p = 0.29 \), respectively).” (page 12, line 14-15) and “The second limitation is that the number of subjects it too small to perform significance subgroup analysis.” (page 18, line 6-8).