Dear Dr. Monjur Ahmed, Rosa M Jimenez Rodriguez and Pathtoon Murtaza Kasi
Editors-in-Chief of World Journal of Gastrointestinal Oncology

January 27, 2021

Manuscript NO: 61387
Manuscript Title: Clinical efficacy and safety of second-line and salvage aflibercept for advanced colorectal cancer in Akita prefecture

We appreciate your helpful comments for improving the quality of our manuscript. We carefully looked into the comments by the reviewer and reconsidered of our study. We attach here our revised manuscript, as well as a point-by-point response to the reviewer's comments.

Thank you very much for your kind consideration.

Sincerely,

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To reviewer

Thank you for your encouraging and warm comments. We respond to each comment. And we rewrote the manuscript like bellow as red color.

Comment 1: In this study, the author mentioned three different angiogenesis inhibitors, but there is currently no evidence to suggest which AIs to choose in combination with FOLFIRI has the best efficacy. This is also a good point with promising clinical value. If possible, the authors could follow up relevant multi-center joint clinical trials.

Response: We also think this point is very important, and again started to search the evidences showing which one is most advantageous drug in these three AIs. However, we can not get any convincing evidences including direct comparison among three AIs in the literature. This issue still stands alone in front of us, medical oncologists, and should be dissolved in the near future.

Comment 2: Only 41 cases were included in this study, sample size was too small to be convincing. It is recommended to expand the sample size and analyze whether the results are consistent.

Response: We thank you for your critical comments. Actually, two thirds of patients bearing wild RAS genes have 4 alternatives, and one thirds of patients bearing mutant RAS genes have 3 alternatives, in their second or latter lines of chemotherapy and we exclude the former irinotecan users. Roughly estimated, five in 36 patients (13.8%) can be enrolled in this study. The efficiency of recruiting is not good. Non the less, your comment is true, and we tried to collect further participants. We sent the letters to the investigators in AAA group, to examine the other patients receiving AFL in the second or more lines of treatment. However, we could not get enough number of data to the dead line of this revision. We are sorry not to expand the information. We are going to collect 2 times or more data from AAA group in a couple of years, and will publish the data elsewhere in the future.

Comment 3: Data showed that AFL has a similar safety and efficacy in the salvage therapy setting as in the second-line setting. Whether other AIs drugs have similar safety and effects in these two groups? Compared with others, what are the advantages of choosing AFL?

Response: We thank you for your good comment. We added the following sentences and table 4 in the last part of discussion. We also added the following five references.

We gathered the data in the literature including rather smaller number of patients as many as 20 patients, where the AIs were applied in the salvage setting (Table 4). There are two ramucirumab papers and three bevacizumab papers, but no AFL papers. We compared the efficacies (PFS and OS) and safety (the rate of the adverse events) with ours. There were no differences in the efficacy with 3 AIs in the salvage lines, but the Bmab was most safety among them, followed by AFL and Rmab in this order.

Table 4 summary of data from recent reports including salvage therapy with three angiogenesis inhibitors plus chemotherapy

Treatmant	**Line**	**No. of patients**	**mTTP mo**	**MST mo**	**AE (grade≥ 3)**
FOLFIRI+Rmab[19]	3rd or later	13	4	6.1	NA
FOLFIRI+Rmab[20]	2nd	22	5.4	17.4	Neutropenia (54%) Hypertension (4%) Proteinuria (8%)
FOLFIRI+Rmab[20]	3rd or later	17	2.8	13	Neutropenia (35%) Hypertension (6%) Proteinuria (24%)
Cx+Bmab[21]	3rd or later	42	5.3	9.5	Neutropenia (43%) Hypertension (5%)
Cx+Bmab[22]	3rd or later	46	8.9	13.8	NA
Cx+Bmab[23]	2nd	154	8.5	19.1	Neutropenia (4%) Hypertension (1%)

Cx+Bmab[23]	3rd or later	62	6.3	14.9	Neutropenia (2%) Hypertension (2%) Proteinuria (2%)
FOLFIRI+AFL[18]	2nd	54	4.4	11.9	Neutropenia (9%) Hypertension (6%) Proteinuria (2%)
FOLFIRI+AFL[18]	3rd	69	4.3	11.1	included in the above
FOLFIRI+AFL[18]	4th	47	3.4	8.1	included in the above
FOLFIRI+AFL*	2nd	22	4.1	22.4	Neutropenia (14%) Hypertension (9%) Proteinuria (5%)
FOLFIRI+AFL*	3rd or later	19	2.4	13.2	Neutropenia (11%) Hypertension (5%) Proteinuria (11%)

*They are our results.

mTTP: median time to progression, MST: median survival time, AE: adverse event, Rmab: ramucirumab, Cx: chemotherapy (FOLFIRI or FOLFOX), Bmab: bevacizumab, AFL: aflibercept

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We again appreciate your suggestion, and we revised our manuscript according to your suggestion. It's our great pleasure if you accept this new manuscript.

very best