

Peer Review File

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Reviewer A

Comment 1: Background page 6 lines 89-91: please use generic names not brand names for the 3 drugs mentioned

Reply 1: We have changed Cyramza to “ramucirumab,” Zaltrap to “ziv-aflibercept,” and Avastatin to “bevacizumab.”

Changes in the text: We have modified our text as advised (see Page 5, lines 95–97).

Comment 2: Background page 7 lines 93-97: this is unclear, do the authors mean these are candidates for conversion surgery? If so they should clearly mention this and modify manuscript to reflect this

Reply 2: Thank you for highlighting the lack of clarity of this section of the background. As the original text was unclear, we have modified the text to improve clarity as follows: “However, chemotherapy regimens that enable conversion surgery have numerous restricting conditions regarding metastatic lesions, and very few reports exist that present a comprehensive understanding as well as a unified approach.”

Changes in the text: We have modified our text as advised (see Page 5, lines 99–102).

Comment 3: Methods page 7 line 108: followed by imaging for how long?

Reply 3: Patients were followed for 5 years after surgery. We have added this information to the text: “Patients were followed with ultrasound (US) / CT imaging evaluation every 3–4 months for 5 years after surgery.”

Changes in the text: We have modified our text as advised (see Page 6, line 117).

Comment 4: Methods page 8 line 125: define CRT as chemoradiation

Reply 4: Thank you for pointing this out. We have added “Chemoradiotherapy; CRT” to the Abbreviations list and defined CRT in the manuscript.

Changes in the text: We have modified our text as advised (see Page 9, line 177).

Comment 5: Methods page 9 line 129: what is the frequency?

Reply 5: A previous study on the original B-mab XELOX regimen showed that the incidence of hand-foot syndrome was 17% for Grade 3 and 1.7% for Grade 4. We have added the following reference (No. 13) to the main text.

Sato A, Doi T, Boku N, et al. Phase I/II Study of XELOX plus bevacizumab in Japanese patients with metastatic colorectal cancer (JO19380). *Gan To Kagaku Ryoho* 2011;38:561-9 (in Japanese).

Changes in the text: We have modified our text as advised (see Page 6, lines 124–125).

Comment 6: Statistical analysis page 10 line 156: were CT scans used for all patients? Earlier in the manuscript (methods page 7 line 108) ultrasounds are mentioned. Please clarify the

imaging modality used to follow treatment response

Reply 6: Both ultrasound and CT were used to follow treatment response. We have changed the sentence to read “The event day was defined as the day when stable disease changed to progressive disease (PD) on ultrasound and CT scan as calculated from the first day of the first cycle.”

Changes in the text: We have modified our text as advised (see Page 8, line 155).

Comment 7: Results: as this is a single institution retrospective analysis, it would be nice to see how these results compare to patients who received a doublet therapy, such as XELOX in this case for a comparator arm. Were any patients at your institution treated with such doublet therapy and if so how do the 1Y-PFS, 1Y-OS, 3Y-PFS, and 3Y-OS compare?

Reply 7: Thank you for this interesting comment and question. We currently do not have the data to make this comparison, but we believe a further investigation is warranted on this subject.

Changes in the text: There are no modifications to the text.

Comment 8: Results: how many patients were treated with a triplet cytotoxic chemotherapy regimen (eg FOLFIRINOX: 5-FU/irinotecan/oxaliplatin), and how did their outcomes compare to the XELOX-Bmab cohort?

Reply 8: Thank you for this valuable comment. We currently do not have the data to respond to this comment, but we believe a further investigation is warranted on this subject.

Changes in the text: There are no modifications to the text.

Comment 9: Results page 11 line 178: how many of these patients had pre-existing hypertension?

Reply 9: Out of the 70 cases, 24 patients had pre-existing hypertension and all were receiving treatment. We have added this to the Results so the sentence reads “hypertension in 66 patients (94.3%) [Grade 1 in 27 patients, Grade 2 in 35 patients, and Grade 3 in 4 patients; 21/66patients had pre-existing hypertension that was being treated]”.

Changes in the text: We have modified our text as advised (see Page 9, lines 198–199).

Comment 10: Discussion page 13 lines 212-213: what were the reasons for dose reduction and prolongation of the dosing interval? From the adverse events in the results section on page 11 it appears that most adverse reactions were grade 1, so why such a high percentage of dose reduction/interval prolongation?

Reply 10: The background behind reducing the dose/prolonging the dosing interval is outlined on p.10, lines 214-221 and p.11, lines 231-241.

Changes in the text: There are no modifications to the text.

Comment 11: Conclusion: prior to making comments regarding the efficacy and toxicity, the XELOX-Bmab regimen at your institution needs comparator data against other regimens to support these claims

Reply 11: Thank you for this valuable comment. In order to phrase our conclusion more appropriately, we have changed the text to read “Bevacizumab in combination with XELOX showed promising OS in our study. Given the efficacy and toxicity data obtained in this study,

it is possible that this treatment may become acceptable for Stage IV colorectal cancer patients in Japan.”

Changes in the text: We have modified our text as advised (see Page 13, lines 273–275).

Reviewer B

I read with great interest this original article from Yokoyama and colleagues, reporting efficacy of modified bevacizumab-XELOX therapy in Japanese patients with Stage IV recurrent or non-resectable colorectal cancer. I have several concerns before potential publication. Please consider the following comments.

Major comments

Comment 1: I disagree with the term of neoadjuvant chemotherapy in a metastatic setting. Even if a resection can be obtained, it is not appropriate in a metastatic setting.

Reply 1: We agree that resection of remote metastatic lymph nodes is not appropriate. We have deleted “remote lymph nodes” from our description in the Methods section (Page 6, lines 119–120) and have added “Patients with remote metastatic lymph nodes were also excluded from this study.”

Changes in the text: We have modified our text as advised (see Page 6, lines 119–120 and Page 7, lines 138–139).

Comment 2: Please clarify: “27 patients with advanced recurrent cancer following resection of the primary tumor and 43 patients with non-resectable tumors and remote metastasis”: Your sentence is not clear. Are you talking about metachronous and synchronous metastases?

Reply 2: We have added further information for clarity and modified the text as follows: “Of the 27 patients with recurrent cancer, 19 patients had metachronous metastases (Stage I: 2 patients, Stage II: 5 patients, and Stage III: 12 patients).” to the Results section and modified Table 1 to include data on metachronous metastases.

Changes in the text: We have modified our text as advised (see Page 8, lines 167–169).

Comment 3: Precise in the abstract whether patients are naïve of treatments in the metastatic setting or not, and whether they received adjuvant chemotherapy at time of resection.

Reply 3: We have added “Seventeen patients were receiving chemotherapy at the time of the first resection (Stage II: 1 patient and Stage III: 16 patients).” to the Results section (lines 169–170) and modified Table 1 to include data on adjuvant chemotherapy at the time of the first resection. We have also added a comment regarding this to the abstract.

Changes in the text: We have modified our text as advised (see Page 3, lines 52–53 and Page 8, lines 169–170).

Comment 4: Did you exclude patients that had received less than 3 cycles of chemotherapy? This could induce a bias since these patients could be different, with worse prognosis. Analyses should be performed with all patients including those that received less than 3 cycles.

Reply 4: We did not exclude patients who did not receive the 3 intended cycles of chemotherapy, as the regimen consisted of 1-month cycles and diagnostic imaging was performed every 3–4

months.

Changes in the text: We have modified our text as advised (see Page 7, line 136–138).

Comment 5: Do you also perform curative treatments with interventional radiology procedures (radiofrequency for example), which is appropriate in several cases, especially for lung metastases?

Reply 5: As mentioned on p.6, lines 112-114, at our hospital we preferentially perform surgical resection if R0 resection of the primary or metastatic tumors is macroscopically feasible. Accordingly, we also preferentially resect lung metastases when feasible, although we understand that treatments are available.

Changes in the text: There are no modifications to the text.

Comment 6: This part is already results, and shouldn't be in the methods part: "Since 2009, we have employed various regimens containing bevacizumab (B-mab) as chemotherapy for Stage IV colorectal cancer, conducting a total 110 of 2466 cycles in 190 patients. Since April 2014, B-mab + capecitabine and oxaliplatin (XELOX) have been used systemically, and 82 patients have received a total of 941 cycles." There seems to be a mixing between results and methods part since many parts of the methods are results. Patients characteristics should be in the result part. Please clarify.

Reply 6: Yes, the patient characteristics and description of patient numbers should be in the Results section, and we have moved these parts accordingly.

Changes in the text: We have modified our text as advised (see Pages 8–9, lines 160–177).

Comment 7: Please discuss intrahepatic arterial infusion chemotherapy that can achieve to complete hepatic metastases surgery.

Reply 7: Thank you for this valuable comment. We have added "A previous study showed that hepatic arterial infusion resulted in high response rates, and another reported that resection may be achieved in liver metastases that were previously unresectable [27, 28]. However, recent advances in systemic chemotherapy indicate that the high response rates to hepatic arterial infusion do not affect long-term prognosis [29–31]." to the Discussion section and have included the following new references.

26) Arai Y, Inaba Y, Takeuchi Y, et al. Intermittent hepatic arterial infusion of high-dose 5-FU on a weekly schedule for liver metastases from colorectal cancer. *Cancer Chemother Pharmacol* 1997;40:526-30.

27) Bismuth H, Adam R, Lévi F et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996;224:509-20.

28) Hohn DC, Stagg RJ, Friedman MA, et al. A randomized trial of continuous intravenous versus hepatic intraarterial floxuridine in patients with colorectal cancer metastatic to the liver: The Northern California Oncology Group trial. *J Clin Oncol* 1989;7:1646-54.

29) Martin JK, O'Connell MJ, Wieand HS, et al. Intra-arterial floxuridine vs systemic fluorouracil for hepatic metastases from colorectal cancer. A randomized trial. *Arch Surg* 1990;125:1022-7.

30) Kemeny N, Daly J, Reichman B, et al. Intrahepatic or systemic infusion of fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma. A randomized

trial. *Ann Int Med* 1987;107:459-65.

Changes in the text: We have modified our text as advised (see Page 12, line 254–258).

Comment 8: You state that “Four patients (9.3%) underwent resection of both the primary tumor and a metastatic lesion.” Was this R0/R1 resection? or were there any metastasis left?

Reply 8: The 4 patients underwent R0/R1 resection. Of these 4 patients, 2 patients had peritoneal dissemination, and 1 patient had multiple liver metastases. We have added this to the main text.

Changes in the text: We have modified our text to reflect these changes (see Page 8, lines 174–176).

Comment 9: Please state the number of chemotherapy lines received before. If none, your ORR and clinical benefit rates are very low, please discuss.

Reply 9: Seventeen patients were receiving chemotherapy at the time of the first resection (Stage II: 1 patient, Stage III: 16 patients).

Changes in the text: There are no modifications to the text.

Comment 10: “This NAC-based approach aims to achieve p-CR for breast cancer”: this is not the same, since for breast cancer it is for non-metastatic patients.

Reply 10: Thank you for this valuable comment. We have deleted this sentence.

Changes in the text: We have modified our text as advised.

Comment 11. Table 1 is missing, meaning many important clinical characteristics are not visible.

Reply 11: We have modified Table 1. Please see our responses to Comments 2 and 3.

Changes in the text: Table 1 has been modified.

Minor comments

Comment 12: Please use preferably international name and not brand name for drugs (instead of Cyramza or Zaltrap for example).

Reply 12: We have changed Cyramza to “ramucirumab” and Zaltrap to “ziv-aflibercept” so the text now reads “ramucirumab and ziv-aflibercept.” Avastatin has been modified to bevacizumab.

Changes in the text: We have modified our text as advised (see Page 5, lines 95–97).

Comment 13: Line 93: conversion surgery can sometimes be performed, not always.

Reply 13: Thank you for this valuable comment. To clarify the limitations regarding conversion surgery, we have changed the text to “However, chemotherapy regimens that enable conversion surgery have numerous restricting conditions regarding metastatic lesions, and very few reports exist that present a comprehensive understanding as well as a unified approach.”

Changes in the text: We have modified our text as advised (see Page 5, lines 99–102).

Comment 14: Please add a specific section for results. There may be a title missing.

Reply 14: Thank you for noting this. The missing Results heading has been labeled and the

Results section was modified as per comments above. Subsections have also been added.

Changes in the text: We have modified our text as advised (see Page 8, line 160-).

Comment 15: Line 125 you use CRT abbreviation without its meaning.

Reply 15: Thank you for pointing this out. We have added “Chemoradiotherapy; CRT” to the Abbreviations list and defined CRT in the main text.

Changes in the text: We have modified our text as advised (see Page 9, line 177).