Reviewer's report

**Title:** Bevacizumab And Combination CHemotherapy in rectal cancer Until Surgery (BACCHUS): A phase II, multicentre, open-label, randomised study of neoadjuvant chemotherapy alone in Patients with high-risk cancer of the rectum

**Version:** 2  
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**Reviewer:** Keisuke Uehara

**Reviewer's report:**

This is an interesting clinical trial to investigate the efficacy and feasibility of neoadjuvant chemotherapy for high-risk locally advanced rectal cancer (LARC). FOLFOXIRI+BEV in neoadjuvant settings for LARC is novel strategy and we are waiting for the favorable results. This clinical trial note shows important information but there are some problems.

**Major Compulsory Revisions**

1. The primary endpoint of this is pCR rate. Authors mentioned that postoperative distant metastasis is now the most important issue to resolve for improving survival. Authors should declare what is the most important purpose of this neoadjuvant treatment. Because we know that preoperative FU/RT has favorable local effect but does not improve survival, so we how introduce aggressive systemic chemotherapy in the treatment strategy. If you seek systemic effect of this treatment, why do you select these regimens? Any study including BEV has been failed to show the improving survival in adjuvant setting, and CPT-11 is same situation. Additionally, there are no reports to show the survival benefit of BEV for resectable disease.

2. In “Discussion” part, authors discussed about BEV-use. Many reports showed that 6 to 8-interval between BEV administration and elective liver surgery did not affect rate of postoperative complications. Moreover, use of BEV could prevent liver injury during chemotherapy. However, there are a few studies which showed the risk of BEV before rectal surgery. (Surgery Today 2014, 44: 1300) showed neoadjuvant BEV was a risk factor of anastomotic leakage. (Jpn J Clin Oncol 2013, 43: 964) indicated that anastomotic leakage was serious issue after rectal surgery after neoadjuvant BEV. Based on these results, authors should discuss about the delayed wound healing of BEV.

3. In “Discussion” part, authors summarized the results of neoadjuvant chemotherapy for locally advanced rectal cancer. They took up a result in presentation about neoadjuvant XELOX+BEV for rectal cancer. However, these results already reported for 2 Japanese clinical trial groups; (Jpn J Clin Oncol 2013, 43: 964) and (Cancer Chemother Pharmacol 2014, 73: 1079). Authors should quote and compare with these results.

4. Another problem is how to evaluate the clinical response. In this study, 30%
decrease of SUVmax is adopted. Although this is still debatable point what is the most optimal method, authors should discuss more about this issues. Because SUVmax is used to decide treatment continuation or stopping, this is a novel strategy. (Ann Surg Oncol 2014, 21: 1801) showed 50% decrease of SUVmax was certainly a potential modality that can quantify the functional activity of cancer cells after neoadjuvant therapy. But they reported that the addition of FDG-PET/CT to MRI did not improve performance of evaluation.

Minor Essential Revisions

1. Ahead of Page 7, paragraph is incomplete.
2. Authors permit both open and laparoscopic surgery. How is robotic surgery?
3. Authors adopted 5% of pCR rate in RT alone. Although current standard is FU/RT, why do you select the data in FU/RT? Please clarify this point.
4. Authors consider that 14.8% of pCR rate in FOLFOX+BEV and FOLFOXIRI+BEV regimens is satisfactory. However, FOLFIRI+BEV is a quite toxic treatment and pCR reta around 15% in XELOX+BEV has been reported. I think this estimation is quite lax. Please discuss about this point more.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: 

No, I do not have any interests.