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

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Reviewer: Pei-Rong Ding

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Since neoadjuvant CRT only reduces risk of local recurrence but not distant metastases, and inevitably results in short-term and long-term toxicities, more and more investigators question the strategy of routine application of neoadjuvant CRT to all patients with locally advanced rectal cancer. Meanwhile, several phase 2 clinical trials demonstrates that neoadjuvant chemotherapy is promising for low and intermediate risk locally advanced rectal cancer. Now the question is whether more intensified neoadjuvant chemotherapy is feasible for higher risk of locally advance rectal cancer. BACCHUS trials aim to answer this questions. Overall this is a well-designed trial with excellent scientific problem, appropriate study population, sound statistics, experienced organization, and serious quality assurance. I do have several comments.

1. (Discretionary Revisions) The definition of “high-risk cancer of the rectum” need to be elaborated further. The term, high risk rectal cancer, was used in several studies. However, the definition of “high risk” varies from one another. Is the study population different from that of the GEMCAD 0801 trial which uses the term “Intermediate-Risk Rectal Adenocarcinoma”?

2. (Discretionary Revisions) Is it appropriate to use PET/CT as the method of evaluation of early response? There are still no sufficient data to support the use of PET/CT as the method of evaluation of early response.

3. (Discretionary Revisions) The treatment for patients who come off the trial should be mentioned in the protocol.

4. (Discretionary Revisions) In the protocol, surgery should be performed 8-12 weeks after termination of chemotherapy. I would doubt that the interval between chemotherapy and surgery might be too long. My concern is that the late effect of neoadjuvant chemotherapy might not work ask long as chemoradiotherapy. Twelve weeks of waiting might increase of risk of tumor regrow. Meanwhile, the edema and inflammation after neoadjuvant chemotherapy is less severe, which weakens the necessity of long term waiting. The study from the Memorial Sloan-Kettering Cancer Center use 3 to 6 weeks from completion of the final cycle of FOLFOX/bevacizumab, which is much shorter from the current trial, which seems more appropriate to my view.

5. (Discretionary Revisions) How to deal with the patients who do not response in final pathology? Theoretically, patients who do not response to neoadjuvant
chemotherapy might not benefit from adjuvant chemotherapy.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests.