Author’s response to reviews

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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Version: 3
Date: 26 March 2015

Author’s response to reviews: see over
We wished to examine the activity and role of chemotherapy ‘per se’ and not compare it to chemoradiation. As no treatment arm can be considered standard for rectal cancer, we used a randomized selection design that was based on the approach proposed by Simon9 to allow early termination of any ineffective arm early in the study. The study is not powered for a direct comparison between the two arms.

EDITORIAL REQUEST:

1). Line numbering: Please revise your manuscript to include line and page numbers. Authors are asked to ensure that line numbering is included in the main text file of their manuscript at the time of submission to facilitate peer-review. Once a manuscript has been accepted, line numbering should be removed from the manuscript before publication. For authors submitting their manuscript in Microsoft Word please do not insert page breaks in your manuscript to ensure page numbering is consistent between your text file and the PDF generated from your submission and used in the review process.

Will do As requested

2). Please moved Acknowledgement section after Authors contribution section.

We don’t understand this recommendation

3). Please include the ethics information in the Methods section

This has been done under a section –Ethics and informed consent

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
Date: 5 December 2014
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.

Reply 1:
This study is now recruiting with 15 patients enrolled, as this paper was submitted in July 2014.

The main aim is to improve survival by reduction of distant metastases. Survival is mainly affected by distant metastases rather than local failure, and, therefore, efforts should be directed towards the prevention of systemic disease. However, we also acknowledge that Valentini’s nomograms (Valentini 2011) using individual patient data pooled from five randomised trials showed that adjuvant chemotherapy significantly contributed to local control. So our hopes are that NACT will contribute to both local control and reduction of distant metastases.

But we need to convince Clinicians that routine use of RT may not be the best way forward in patients with LARC if the CRM is clear on imaging and that preoperative systemic chemotherapy may be more effective with less long term complications. That is the rationale for pCR which is an absolute measure of treatment efficacy. We accept that in the postoperative adjuvant setting BEV and CPT-11 have failed to show benefit in survival, but the neoadjuvant setting has the primary in situ. There may be biological differences between micrometastatic disease (adjuvant studies have been negative) and macroscopic disease (most advanced disease studies are positive) in terms of response to biological agents.

We do not think it is a problem that bevacizumab has not been shown to be effective in the postoperative adjuvant setting. The large phase III randomised trial of neoadjuvant chemotherapy in colon cancer (FOXTROT) is currently running in the UK and recruiting (more than 800 patients already). FOXTROT uses cetuximab in one arm, which also has not been shown to be effective in the postoperative adjuvant setting. The point is that in this setting we are not dealing just with microscopic disease as the primary and any involved nodes is in situ.

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.

Reply 2:
The reviewer says

Many reports showed that a 6 to 8 week 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.

True and we acknowledge this in the paper, but this is not a study of liver surgery. There are reports of surgical morbidity with bevacizumab and we have concerns that there could be a potential for anastomotic leakage/ poor healing (cf Borg 2014). That is why we have extended the
interval to surgery to 8-12 weeks in BACCHUS. The Japanese study by Uehara had tumors located at a median distance of 4.7 cm from the anal verge and therefore includes patients with lateral pelvic lymph node dissection – which might be associated with more surgical morbidity. LPLND is not performed in the UK – so this issue has less relevance to BACCHUS, where only patients with tumors above 4cm are included. Anastomotic leakage will be documented and stoma rates at 12 months reported.


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.

Reply 3: In the paper by Hasegawa (Cancer Chemother Pharmacol 2014, 73: 1079), 25 patients with T4 or lymph node-positive rectal cancer underwent three cycles of XELOX plus bevacizumab and an additional cycle of XELOX alone. TME was performed 3-8 weeks after the last chemotherapy session.

A higher dose of Bevacizumab was administered ie 7.5 mg/kg in contrast to BACCHUS where the dose of is 5mg/Kg. In the paper by Uehara TME was also 3 - 8 weeks after the completion of chemotherapy. With a half life of approximately 21 days, we think the BACCHUS schedule is likely to be safer in terms of surgical morbidity.

So we have inserted a paragraph into the discussion

Two small Japanese NACT studies have also demonstrated the feasibilty of this NACT approach (Uehara 2013, Hasegawa 2014), although there is a suggestion of increased surgical morbidity. A higher dose of Bevacizumab was administered ie 7.5 mg/kg in these studies- in contrast to BACCHUS where the dose is 5mg/Kg.

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.

Reply 4: This is a feasibility study. The purpose of the PET is to give an early indication of response in order to avoid 12 full weeks of ineffective chemotherapy and to allow clinicians to resort to short course radiotherapy (5X5Gy), chemoradiation or immediate surgery.
In the study by Aiba et al. (Ann Surg Oncol 2014, 21: 1801) surgery and presumably the PET was performed at a median of 6 weeks after NACT. The reduction rate of the maximum standardized uptake value (ΔSUVmax) was an informative factor (AUC 0.719). We accept that their study showed no added value from PET/CT in addition to MRI where 70% reduction in volume observed when compared to histological appearances, but the aims of the PET in our study are not to predict as accurately as possible the histological regression, just the likelihood of a clinical response. However, others have shown that PET is helpful after CRT.


[18F]-FDG PET and SUV use for early tailoring of treatment in the neoadjuvant setting needs standardisation. Preparation procedures and instrumental factors can introduce slight differences in the measurement of SUV. In any given patient, the two PET examinations must be done at the same centre with the same equipment and methods. In BACCHUS, uptake and reconstruction parameters are kept identical on the sequential PET-CT scans.

Minor Essential Revisions
1. Ahead of Page 7, paragraph is incomplete.
   Reply 5: Thank you for pointing out we have completed this

2. Authors permit both open and laparoscopic surgery. How is robotic surgery?
   Reply 6: There are current trials ongoing in the UK (ROLARR) Robotic surgery would be included as eligible under laparoscopic.

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.
   Reply 7: We wished to examine the role of chemotherapy in the neoadjuvant setting. Radiotherapy alone is still sometimes used preoperatively, although commonly CRT is used. We wished to see what systemic chemotherapy could achieve. In studies comparing RT with CRT the pCR for RT alone is 3-4%. So if we wish to exclude the influence of chemotherapy that is the figure we have taken. Even the low dose 5FU increases pCR to 13-15% in these studies.

4. Authors consider that 14.8% of pCR rate in FOLFOX+BEV and FOLFOXIRI+BEV regimens is satisfactory. However, FOLFIXIRI+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.
   Reply 8: Schrag 2014 achieved a pCR without CRT of 23%. We have excluded patients where the CRM is breached or threatened so we think this figure is reasonable.


Level of interest: An article of importance in its field
Reviewer 2: Ji Zhu

**Reviewer's report:**
This is a phase II, multi-centre, open-label, randomized study of neoadjuvant chemotherapy alone in patients with high-risk cancer of rectum. The primary aim is to evaluate whether these two intensive NACT regimens can achieve an encouraging pCR rate to warrant further investigation.

The study's design is reasonable and good evidence-based, however, several major compulsory revisions will be needed to clarified to make the protocol more sound.

I would again point out that this study is now recruiting with 15 patients enrolled as this paper was submitted in July 2014.

1. In page 9, “patients who do not respond will come off all trial treatment”. What is the scheduled sequence treatment for these cases? Receiving CRT, surgery or some others?

**Reply 9:** Coming off all trial treatment allows the investigator to proceed to whatever treatment id felt most appropraite surgery or SCPRT/ CRT followed by surgery. We have inserted a sentence to clarify this

Patients who do not respond will come off all trial treatment (allowing the investigator to proceed to whatever treatment is felt most appropraite ie surgery or SCPRT/ CRT followed by surgery).

2. In page 11, the section of sample size calculation, the authors anticipate a pCR rate of 20% for intensive NACT, compared to 5% pCR rate for RT alone. However, after the studies of EORTC22921 and FFCD9203, neoadjuvant CRT became the standard care for locally advanced rectal cancer. So, the pCR rate of neoadjuvant CRT should be the control, instead of neoadjuvant RT alone.

**Reply 10:**
There is no control –this is a feasibility study. The study is not powered for a direct comparison between the two arms.

We wished to examine the activity and role of chemotherapy 'per se' and not compare it to chemoradiation. As no treatment arm can be considered standard for resectable rectal cancer (chemoradiation or short course radiotherapy alone (5X5Gy), we used a randomized selection design that was based on the approach proposed by Simon9 to allow early termination of any ineffective arm early in the study.

We acknowledge that CRT achieves a pCR rate of 10-14% (depending on eligibility/clinical stage). This study has carefully controlled entry criteria according to MRI. BACCHUS will not include early T2 cancers so it needs to be demonstrated that a pCR of at least 15-20% can be achieved before
surgeons will consider NACT as a potential alternative to surgery – although we believe pCR could be higher.

3. In the same paragraph, “A regimen will be considered successful if at least 4/27 pCRs are observed”. According to statistical calculation, if less than 3 pCRs are observed, we have more than 80% power to reject the null hypothesis that the actual pCR rate is more than 20%. But in opposite, we can’t draw a conclusion that the pCR rate more than 20% if at least 4/27 pCRs occur. Please clarify.

Reply 11: BACCHUS is a phase II randomised feasibility study. The confidence limits will be wide.

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer’s report:
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”?

Reply 12: The reviewer is absolutely right that there is no common language to define “locally advanced” or “high risk” rectal cancer. The definition for eligibility to BACCHUS is not the same as the GEMCAD study, because it excludes a threatened CRM and low rectal cancers within 4cm of the anal margin - as many surgeons in UK believe such patients should always be treated with preoperative CRT.
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.

Reply 13: The reviewer is again right that this is not a validated method of correlating histological response, but it is an accepted method of evaluating clinical response. The SUV is to some extent arbitrary, but has been used in the MUNICON studies in oesophageal cancer. This is a feasibility study. The purpose of the PET is to give an early indication of response in order to avoid 12 full weeks of ineffective chemotherapy and to allow clinicians to resort to short course radiotherapy (5X5Gy), chemoradiation or immediate surgery.

3. (Discretionary Revisions) The treatment for patients who come off the trial should be mentioned in the protocol.
Reply 14: please see reply 9 above.

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.

Reply 15: We acknowledge that there is a possibility that the tumour could regrow after chemotherapy if the interval is extended to 12 weeks or more. This interval of 8-12 weeks in BACCHUS has been selected as a balance between ensuring at least 2 half lives of bevacizumab (ie 6 weeks) which gives a chemotherapy free interval of at least 4 weeks. However, in the UK surgeons are now almost invariably waiting 8-12 weeks after the completion of chemoradiation before embarking on surgery. The optimum interval to surgery following chemoradiation is an unanswered question. We think the origin of this approach is based on the literature. Following completion of CRT, both individual series, population studies and a meta-analysis (Petrelli 2013) all show that longer intervals up to a maximum of 12 -15 weeks appear associated with an increased chance of achieving a pathologic complete response at surgical resection, and counter-intuitively outcomes may also improve in terms of a significant reduction in 3-year local recurrence rate (1.2% vs. 10.5%, p = 0.04) (de Campos-Lobato 2011). However, further extensions of this interval do not appear to benefit the patient (Sloothak 2013, Kalady 2009).

The optimum interval following chemotherapy alone is also under debate and there is even less evidence. In the EORTC 40983 study surgery was intended to be performed a minimum of 2-5 weeks after chemotherapy, but in practice surgery was performed at a median of 4-1 (2.0–16.4) weeks after the last administration of preoperative chemotherapy. With this schedule, only 3.8% of patients developed extrahepatic disease while they were receiving neoadjuvant chemotherapy, preventing resection of liver disease. In the NEW EPOC Surgery was intended to be performed a minimum of 4 weeks after chemotherapy – actual timing was not reported.
In the Olivia trial (Gruenberger 2014), using FOLFOXIRI and bevacizumab, patients deemed resectable were offered surgery 5–7 weeks after their last bevacizumab dose and 3–5 weeks after their last chemotherapy cycle. This is little different from the earliest timing of 8 weeks in BACCHUS.

Is there a risk of tumour regrowth with longer intervals? The COIN trial was designed to assess whether intermittent chemotherapy was as effective as continuous chemotherapy and whether the addition of cetuximab to continuous chemotherapy was associated with additional benefit.

In the COIN-B trial (Wasan 2014) we sought to examine different strategies in non-curable advanced colorectal cancer to improve the combinations and sequences of cytotoxic chemotherapy with cetuximab, planned maintenance, and planned interruptions.

The COIN trial recruited patients with a poor outcome (>40% still had the primary in situ and were not considered potentially resectable). This explains the poor survival. Median survival in the ITT population (n=815 in both groups) was 15.8 months (IQR 9.4–26.1) in arm A and 14.4 months (8.0–24.7) in arm C (hazard ratio [HR] 1.084, 80% CI 1.008–1.165).

Data from COIN and COIN-B suggested that attrition before 12 weeks was 16% because of toxic effects or absence of benefit.

After 12 weeks of chemotherapy patients with stable or responding disease started a chemotherapy-free interval (ie, no FOLFOX). Median progression-free survival from week 12 was 12.9 weeks in COIN and 13.1 weeks in COIN B in the intermittent groups respectively. These results are similar to results of the SAKK study with Bevacizumab (SAKK 41/06).

BACCHUS selects a group of patients who have completed 12 weeks of treatment and had a functional response according to PET/CT without progression, death, or leaving the trial. Hence, this should be a selected group with favourable outcomes.

In BACCHUS this timing should be much longer as we are expecting higher response rates from chemotherapy with only the primary site and we are selecting out only patients who respond (and excluding stable disease).

We have added a paragraph in the discussion

In the Olivia trial (Gruenberger 2014), using FOLFOXIRI and bevacizumab, patients with mCRC deemed resectable were offered surgery 5–7 weeks after their last bevacizumab dose and 3–5 weeks after their last chemotherapy cycle. This interval is little different from the earliest timing of 8 weeks in BACCHUS. After 12 weeks of chemotherapy patients with stable or responding disease started a chemotherapy-free interval (ie, no FOLFOX). Median progression-free survival from week 12 was 12.9 weeks in COIN and 13.1 weeks in COIN B in the intermittent groups respectively. These results are similar to results of the SAKK study with Bevacizumab (SAKK 41/06). BACCHUS selects a group of patients who have completed 12 weeks of treatment and had a functional response according to PET/CT without progression, death, or leaving the trial (and excludes stable disease). Hence, this should be a selected group with favourable outcomes.
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.

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

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With best wishes,

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