Author's response to reviews

Title: Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases, the randomised phase 3 CAIRO5 study of the Dutch Colorectal Cancer Group (DCCG)

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Author's response to reviews: see over
Dear Professor McKeage,

We have revised our manuscript according to the reviewers and editorial request we have received; I hereby give you reply to the reviewers and description of the changes we have made:

Comment reviewer #1:
Whilst I do have some concerns in regards to the choice of primary endpoint and study power, which I shall detail below - I would consider these concerns only a "Discretionary revision" and would acknowledge that the trial management committee would have carefully considered the choice of primary endpoint, and optimal statistical design, and the difficulties of choosing a primary end point in this patient population has been well documented, with quite significant variance in recently completed , and similarly designed phase III studies.

My concern related to the authors stated hypothesis for the RAS WT tumours where they "hypothesize that FOLFOX or FOLFIRI + panitumumab will improve PFS as compared to FOLFOX or FOLFIRI + bevacizumab" ( I have less of a concern for the RAS mutated group - where they "hypothesize that FOLFOXIRI + bevacizumab will improve PFS as compared to FOLFOX or FOLFIRI + bevacizumab" as the authors present data in their introduction that supports this hypothesis).

However for RAS WT tumours, the 2 large phase III studies comparing biologic agents given with doublet chemo failed to show any significant differences in PFS, as the authors nicely detail in their introduction, and hence they do not appear to provide any justification for their hypothesis suggesting a likely benefit for panitumumab. Given this, the choice of the PFS endpoint and the resultant optimistic power calculations suggest that this study is most unlikely to achieve this endpoint.

Furthermore, since the principal aim of aggressive chemo-biologic therapy in this liver-only unresectable patient population is to achieve an R0 resection, and hence increase the chance of cure (as noted by the authors in their introduction) consideration should be given to select R0 resection rate as the primary study endpoint, and power accordingly.

Reply:
We thank the reviewer for his valuable comments, and we fully understand his concerns. Given the fact that combination chemotherapy plus bevacizumab is the current standard in The Netherlands, any deviation from this should be proven more effective in prospective trials. Hence the superiority design. We appreciate that given the results of the FIRE-3 and CALGB 80405 trials, a superiority of panitumumab appears unlikely. However, these trials were conducted in the general population of metastatic CRC patients, and since the unresectable, liver-limited metastatic CRC patients may have a chance of cure (in contrast to the FIRE-3 and CALGB 80405 studies, which had a palliative intent), justifies in our opinion this trial. As outlined in the paper, retrospective (and mostly unplanned) subset analyses of FIRE-3/CALGB80405 will not provide satisfactory answers for the liver-only population, given the large variability of surgical views and approaches.
The trial committee had a long discussion about the choice of primary endpoint, and although R0 resection at first glance appeared most suitable, this was rejected since this would be very much biased by the percentage of patients with initially permanently unresectable liver metastases. On the other hand, to exclude this latter population would also introduce a bias since no objective criteria are available to define this population (which also did not allow to stratify for this item). So we wanted a trial with a population of unresectable liver-only metastases, with as little as selection bias as possible, and prospectively evaluate the currently most effective induction treatments. Our statistician informed us that in this setting a co-primary endpoint was not possible. Therefore we settled for PFS, with R0 resection rate as secondary endpoint.

Comments reviewer #2:
Major Compulsory Revisions
The SPIRIT 2013 Statement which provides guidance for protocols of clinical trials has not been adhered to and therefore there are many items that are missing from this article which prevent carrying out a full review:

1. It is helpful if the title state that it is a study protocol

   Reply:
   In the title, it is mentioned that this concerns a study: the randomised phase 3 CAIRO5 study of the Dutch Colorectal Cancer Group (DCCG)

2. No details of randomisation, either sequence generation (method of randomisation and stratification factors) or allocation concealment

   Reply:
   We have added a sentence on this issue. Line number 151-153.

3. No details of who will be blinded in the trial - from my reading this may be the Central Review Panel, but the make up of this panel is not explicitly stated or whether it is independent or not.

   Reply:
   The panel is blinded for the treatment; we have added this in the text. Line number 187.

4. The sample size is included, but in the methods section it state that cross-over between antibody regimens after treatment failure (still unresectable at 12 weeks). Has this cross-over been taken into account in the sample size calculation. Please make it clear that there are two separate embedded trials for the patients with/without KRAS mutations and therefore the number of events is required for each comparison, not overall. It is not clear how long patients will be followed up for, will this be one year after last patient enters the study?

   Reply:
   Treatment failure (PFS) is not defined as unresectability at 12 weeks, but as RECIST progression or death of disease. Cross-over of antibodies is not a prospective part of this study, but is only recommended. Since PFS is the primary endpoint, any event after PFS will have no impact on sample size calculations. We have changed the text on this issue. Line number 219-225. Given the fact that the median PFS is expected to be comparable in the control group (FOLFOX/FOLFIRI + bevacizumab) of both strata (RAS wildtype and RAS mutant tumors), there is no need for a difference in statistical calculations in these strata. All patients will be followed until death, given the fact that median OS is a secondary endpoint.

5. There is no mention of Data management including data collection methods, and data monitoring.

   Reply:
   All studies in cancer patients in The Netherlands have to comply with standard procedures
concerning data management and monitoring. We considered this information not very relevant for a publication in BMC. However, we’ve added text on this issue. Line number 252-259.

6. There is no description of planned statistical analysis for any of the outcomes. As a minimum details for the primary outcome should be included.

Reply:
We have added text on this issue. Line number 244-250.

7. There is no description on the collection of safety data - some of these treatment combinations are likely to throw up complications.

Reply:
See our reply to item 5, this will be done according to standard practice: toxicity will be recorded at the start of each treatment cycle, and will be recorded in the CRF. Safety is a secondary endpoint of the study, as mentioned in the text. We have added text on this issue. Line number 262-272.

8. There is no description on any trial monitoring committees such as a data monitoring Committee and/or Trial Steering Committee who would usually be in place to monitor safety of the participants and conduct of the trial.

Reply:
See our reply to item 5, this will be done according to standard practice: all trials of this format require an Independent Data Monitoring Committee in The Netherlands. We have added this in the text. Line number 273-278.

Minor essential considerations:
9. The length of a treatment cycle is not specified and whether this is the same for all regimens.

Reply:
All systemic treatment regimens are standard, and all cycles have a length of 2 weeks. We have added text on this issue. Line number 211-212.

10. The current article seems to have 2 copies of Figure 1.

Reply:
We have corrected this.

We thank the reviewers for their valuable comments, and we hope that we have provided satisfactory answers, which allow our paper to be acceptable for publication in BMC.

With kind regards,

Joost Huiskens, Thomas van Gulik and Kees Punt, on behalf of all authors.