Reviewer's report

**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)

**Version:** 3  **Date:** 29 January 2015

**Reviewer:** Jeremy D Shapiro

**Reviewer's report:**

This well-written paper details a recently opened multi-centre Phase III study in advanced colorectal cancer from a highly respected collaborative clinical trials group with an excellent track record in conducting multi-centre phase III studies in similar patient populations, and indeed this study builds on the past work of this group along with recent advances in the field.

The principal aim of this study - to define the optimal aggressive chemo-biologic therapy for RAS WT and RAS mutated liver only, but unresectable colorectal cancer patients - is a currently unanswered, and clinically important question. The study has been thoughtfully designed, with appropriate inclusion and exclusion criteria, and importantly with initial central review of resectability, a major criticism of recently completed studies.

I do indeed consider this paper to be a coherent and sound addition to scientific levels fully worthy of publication.

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.

**Level of interest:** An exceptional article

**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