Author's response to reviews

Title: Bifractionated CPT-11 with LV5FU2 infusion (FOLFIRI-3) in combination with bevacizumab: clinical outcomes in first-line metastatic colorectal cancers according to plasma angiopoitin-2 levels.

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Author's response to reviews: see over
Dear Editorial Committee,

We are very pleased to submit our revised manuscript written by KIM S. et al. entitled “Bifractionated CPT-11 with LV5FU2 infusion (FOLFIRI-3) in combination with bevacizumab: clinical outcomes in first-line metastatic colorectal cancers according to plasma angiopoietin-2 levels.” to BMC Cancer.

Please, find included the point by point response to reviewers. Corrections are highlighted in red in the revised manuscript.

We believe that the data provided by this study might have obvious clinical implementations for colorectal cancer treatment and future clinical trial development.

We certify that these data have not been submitted elsewhere and that all co-authors are in agreement with its submission to BMC Cancer and have no conflict of interest to declare.

Thank you for considering our work. Should you need any further assistance, please do not hesitate to contact me.

Best regards,

Christophe Borg M.D., PhD
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Response to reviewer 1 comment:

Reviewer's report: Generally well written phase II study, which is largely suitable for publication. There should be some discussion of the rationale for using bifractionated irinotecan as opposed to the standard folfiri regimen.

According to reviewer 1 comment, a paragraph was added to the discussion section page 11 line 1-13:

“Irinotecan inhibits DNA replication by interfering with topoisomerase I. Topoisomerase enzymes display an helicase activity involved in DNA repair. Then, it might be possible that topoisomerase blockage following DNA damage could prevent DNA repair and enhance apoptosis induced by chemotherapy. Indeed, preclinical evidence suggested that the anti-proliferative activity of 5FU and irinotecan combination is schedule dependent (reference 1-3 of the revision letter). In line with the above hypothesis, several studies showed that a delayed administration of irinotecan increases FOLFIRI cytotoxicity. FOLFIRI2 regimen (irinotecan delivery at the end of a modified LV5FU2 chemotherapy) in heavily pretreated CRC patients induced promising objective responses but also a limiting hematologic toxicity (reference 4 of the revision letter). As reported here and in previous studies, FOLFIRI3 has a more appropriate toxicity profile (Ref). In addition, FOLFIRI3 was shown to be active in mCRC resistant to FOLFIRI (reference 5 of the revision letter).”

Note that 5 references [reference 15-19 of the revised manuscript] were added in the discussion section.
Response to reviewer 2 comment:

**Major comment 1:** It cannot conclude from your study whether Ang-2 is a prognostic or predictive factor- should make that clear. Reference any data in the literature that addresses this.

As stated by reviewer 2, the results presented in our phase II clinical trial might not allow any conclusion regarding a predictive value for angiopoietin 2 regarding bevacizumab efficacy, since there is no control cohort not exposed to bevacizumab. To our knowledge, angiopoietin 2 monitoring was not reported in randomized clinical trials. However, our results are in agreement with the previous report of Goede et al (reference 6 of the revised letter), where high levels of angiopoietin 2 correlated with a decreased survival in a cohort of 34 colorectal cancer patients treated by chemotherapy and bevacizumab. In our phase II trial Ang-2 above 5ng/mL was confirmed as an independent prognostic factor for progression free survival (HR=0.357; 95%CI: 0.168-0.76, p=0.005) and overall survival (HR=0.226; 95%CI: 0.098-0.53, p=0.0002).

Several evidences support the direct role of angiopoietin 2 in cancer prognosis. First, angiopoietin 2 expression was shown to be correlated with colorectal cancer stages and progression (reference 7 of the revision letter). In addition, angiopoietin 2 was identified as an independent prognosis biomarker in myeloid leukemia and melanoma patients not treated with anti-angiogenic therapies (reference 8 and 9 of the revision letter). Altogether, these results suggest a prognosis value of Angiopoietin 2.

Then, page 10 line 1, “High levels of plasma angiopoietin-2 at baseline predict poor clinical outcomes in patients treated with FOLFIRI3-b” was replaced by “High levels of plasma angiopoietin-2 at baseline correlate with poor clinical outcomes in patients treated with FOLFIRI3-b”

The discussion section was extended to discuss the prognostic value of angiopoietin 2 (line12-29 page 13 of the revised manuscript) and 3 references were added (reference 31-33 of the revised manuscript).
Major comment 2: Comment on impact of bifractionated irinotecan on resources and QOL (extended time in chemo centre)

FOLFIRI3 regimen requires the administration of irinotecan twice per cycle (before and at the end of continuous 5FU), extending both length of hospitalization and medical transportation costs. Then, even if not directly assessed in our study, FOLFIRI3 might interfere with quality of life. However, our results suggest that FOFLIRI3 might be of interest to achieve an objective response and tumor shrinkage in patients previously exposed to oxaliplatin or if FOLFOXIRI is not appropriate.

These comments were included page 12 line 20 of the revised manuscript.

Major comment 3: Inappropriately long discussion of maintenance therapy in the discussion should be culled as not aim of study and conclusions are overdrawn, particularly with no quality of life measures.

The paragraph on the interest of chemotherapy maintenance in first line mCRC was removed as requested by reviewer 2.

Minor Revisions:
-Include comment on timing of metastasectomy (as enrolled patients with resectable disease)-was it stipulated in the protocol or at discretion of individuals?
This was clarified page 5, line 25 of the revised manuscript: “Surgery of metastases was allowed after 6 cycles of FOLFIRI3-b and the precise timing left at the discretion of investigators. “

-Figure 1 and 2 – only 1 of them should be shown as again not a feature of the study to analyse by surgery or not.
As requested by reviewer 2, we decided to remove the Figure 2 from the manuscript.

-Intro end of line 2: “with a metastatic disease”- remove ‘a’: This was performed according to reviewer 2 request.
-Perfusion is used instead of infusion in the intro: this was also modified.
References of the revision letter


