Author's response to reviews

Title: Activity ex vivo of cytotoxic drugs in patient samples of peri-toneal carcinomatosis with special focus on colorectal cancer

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Author's response to reviews: see over
Dear Editorial Office of BMC Cancer

We are happy to see that our manuscript: "Activity ex vivo of cytotoxic drugs in patient samples of peritoneal carcinomatosis with special focus on colorectal cancer" (MS: 3341849728396762) might be accepted for publication in BMC Cancer pending minor revision. The comments from one reviewer are given a point-by-point response below. The resulting changes to the manuscript are highlighted by the track-changes mode in MS Word in the revised manuscript.

It is our hope that the responses and resulting changes to the manuscript now make it acceptable for publication in BMC Cancer.

Sincerely and on behalf of the authors,

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Reviewer's report
Title: Activity ex vivo of cytotoxic drugs in patient samples of peri-toneal carcinomatosis with special focus on colorectal cancer
Version: 3 Date: 12 May 2013
Reviewer: Melissa Teo

Reviewer's report:
Minor revisions:
1. It would be preferable if the authors included a table showing how many samples were analyzable for the various histological subtypes, for example, although they treated 52 colorectal cancer patients, they were only to analyse the results for 23 patients. What about the rest of the histological subtypes? Are the conclusions for the non-colorectal cancer cases made based on only a few patients in each group who were analyzable?

   ◦ All 174 patients included in the study were planned for cytoreductive surgery. All of these patients had successful FMCA results. Thus, all preclinical analyses relating to the whole study include all of these patients. Table 1 gives a clear breakdown according to diagnosis. As such, all of these samples were analyzable for all histological subtypes. Conclusions regarding the whole study set are founded on all the cases. Therefore, we find it unnecessary to add another table detailing the samples included.

   ◦ There might be a slight misunderstanding concerning the colorectal subgroup analysis giving rise to this comment. This may be due to the fact that treatments given in this subgroup analysis were detailed in the general part of the methods section. The treatment description for the colorectal subgroup has now been moved into the colorectal subgroup part of the methods section for clarification (see the methods section revision).

   ◦ In summary, all 52 colorectal cancer patients had analyzable FMCA results and are included in the whole study analysis (as are all other patient samples from the other histological subtypes). The 23 patients referred to in the comment above concern only those included for in-vivo/ex-vivo correlation in the colorectal subgroup analysis. The reason for only including these patients for this analysis were to allow for a reasonably proper analysis, requiring macroscopically radical surgery, leaving us with a total of 23 patients. This is, we think, appropriately described in the methods section and limits the ex-vivo in-vivo evaluation of the colorectal subgroup, which is thoroughly discussed in the article.

2. Why did the authors pick a significantly longer dwell time compared to the actual duration of hipec? This was mentioned in the discussion but no explanation was given on the results with real time.

   ◦ The FMCA method is a thoroughly validated method of chemotherapy resistance evaluation (developed before IPC was in use at this institution). The method was not specifically developed for IPC or HIPEC. Thus, the FMCA dwell time has not been related to IPC dwell time. Furthermore, when it comes to HIPEC, there are several dwell times in use depending on the diagnosis being treated (from between 30min to 2 hours). Therefore, we
chose to continue with the validated method and not do any changes to the method's dwell time. As the FMCA is described and discussed in the manuscript, we think the issue of the difference between the in vivo and ex vivo situation are sufficiently clear. No change made to this point.

3. The information on whether the patients had received prior chemotherapy was available. The drug used in the previous chemotherapy would have been important and of interest, as a tolerance to the drug could have developed, explaining the decreased sensitivity to that particular drug.

- This is a very relevant point in light of the concept of acquired drug resistance, most evident from continuous exposure to low concentrations of cytotoxic drugs in cell lines in vitro. Whether this applies in vivo is less obvious. To comprehensively study this phenomenon there is need for repeated sampling of tumour cells from patients over several treatment lines. As we found no signs at all of a systematic difference in drug sensitivity between samples from patients previously treated and those untreated (detailed in Table 4) and due the problem of patient selection, as discussed, we find it less relevant to provide details on the exact drugs previously given to the patients in this manuscript. We find this point sufficiently covered by the details in Table 4 and the comments in the discussion section.

Level of interest: An article of importance 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: No