Author's response to reviews

Title: A Phase II Experience with Neoadjuvant Irinotecan (CPT-11), 5-Fluorouracil (5-FU) and Leucovorin (LV) for Colorectal Liver Metastases

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Author's response to reviews: see over
Dear Editor,

Thank you very much for the opportunity to address the concerns raised by the reviewers, and to make appropriate revisions. The referees have each made constructive comments, which we believe have prompted an improvement in the manuscript.

We will address the concerns of each reviewer separately.

Reviewer #1 (Dr. L. Capussotti)

1. Dr. Capussotti was concerned about the time of accrual. Admittedly, it took a long time to accrue only 35 patients. However, unlike in Europe, at the time that this trial began, very few surgeons in Canada were willing to administer neoadjuvant chemotherapy to patients with resectable liver metastases. We do not believe that this has invalidated our observations. The median time of follow-up is comparable to (or longer than) most series.

2. As Dr. Capussotti mentioned, there has been a published phase III trial in which toxicity and response rates were compared between those patients with FOLFOXIRI and FOLFIRI (Falcone et al., JCO 2007; 25: 13). We do not believe that observations made in groups of patients with unresectable disease (as in the Falcone trial) can be translated to groups of patients with resectable disease (as in our trial). Rather, there are likely to be unanticipated results when multiple treatment modalities (eg: surgery and chemotherapy) are combined. This is the case in patients with resectable liver metastases, who are known to develop hepatotoxicity related to preoperative chemotherapy and in whom any thromboembolic complications have a significant impact. For this reason, we consider it important to describe the toxicities in our trial, which involves a patient population that is distinct from the one evaluated in the Falcone trial.

3. We did not intend to suggest by our title that chemotherapy improves outcomes. Rather, we are suggesting that administering chemotherapy to patients with resectable liver metastases has some selective advantage. That is, the responders have excellent outcomes, whereas the non-responders fare poorly. This was demonstrated quite clearly by our data. Others have observed this as well (Allen et al., J Gastrointest Surg 2003; Adam et al., Ann Surg 2004; and Alberts, J Clin Oncol 2005). Regardless, we have taken Dr. Capussotti’s suggestion to change the title to a more neutral, conservative title: “A Phase II Experience with Neoadjuvant Irinotecan (CPT-11), 5-Fluorouracil (5-FU) and Leucovorin (LV) for Colorectal Liver Metastases”.

4. The patients who had progressive disease and developed unresectable disease each received second line FOLFOX, which was the standard second line chemotherapy at that time. Of those who underwent resection, none received postoperative chemotherapy. We have described that in the manuscript.
5. We disagree that there is no need to analyze the data in an intent-to-treat fashion. One of the weaknesses of previous studies is that outcomes were measured only in patients who actually underwent resection after preoperative chemotherapy. All of our patients had resectable disease at the time of accrual. The outcomes of such patients who undergo resection alone is known from many previous surgical series. It was recognized, when designing the trial, that some patients would likely develop unresectable disease during the preoperative chemotherapy phase. Therefore, to make any conclusions on the potential benefits of administering chemotherapy first, all patients had to be considered in measuring survival outcomes. For this reason, our *a priori* analysis plan involved an intent-to-treat method of analysis. This was discussed in the original trial description (Bathe et al. BMC Cancer 2004; 4: 32). We have commented on that rationale in the Data Analysis section of the present manuscript. We have also put this into context in the last sentence of the RESULTS section (Survival subsection), as well as in the DISCUSSION section.

6. One patient stopped chemotherapy before response could be evaluated because of a personal choice (related to anxiety); the other stopped because of refusal to continue chemotherapy following a thromboembolic complication. This was specified in the revised manuscript.

7. Dr. Capussotti makes a good point on how length of survival should be measured. We have followed the original analysis plan (Bathe et al. BMC Cancer 2004; 4: 32) in reporting survival. The median time from diagnosis to the start of treatment was 40 days. Because this may inflate survivals, as suggested by Dr. Capussotti, we have also reported key overall survivals from time of treatment start.

8. In the “treatment pathway” section, patients with PR are 13 and not 14, as Dr. Capussotti suggested. We have rechecked all outcomes related to the treatment pathway.

9. Disease free survival was previously defined in the original description of the trial design (Bathe et al. BMC Cancer 2004; 4: 32), and was redefined in the RESULTS section (Survival subsection) of the present manuscript. To address any additional problems related to definitions of outcomes, we have referred to the previous manuscript describing the trial.

10. We have specified the incidence of steatosis (*Treatment-related Toxicities* section, in RESULTS). This is an interesting outcome given the known hepatotoxicity related to irinotecan-based chemotherapy regimens. We have not graded steatosis, nor have we related it to BMI, as suggested by Dr. Capussotti. We believe that this is outside of the scope of this report. Moreover, this has been described in detail by other investigators.

**Reviewer #2 (Dr. L. Aldrighetti)**

1. Dr. Aldrighetti suggested that 35 patients is a small group to assess the real role of neoadjuvant chemotherapy in prolonging survivals. Generally, we would agree. Indeed, the trial was originally designed to accrue 70 patients (see Bathe et al. BMC
Cancer 2004; 4: 32), which was described in the manuscript. Importantly, the trial was stopped prematurely because of safety concerns. We believe that any trial that is stopped for such reasons should be reported, as it provides important cautionary information to the oncology community. We also believe that, despite the premature cessation of the trial, some useful information on long-term outcomes has been obtained. We do not profess that the observations related to survival are definitive. On the other hand, the outcomes can be (and have been) interpreted in the context of other data from similar (small) trials. We have attempted to be conservative in any statements regarding the survival benefits that may be secondary to administration of chemotherapy in patients with resectable liver metastases.

2. We agree with Dr. Aldrighetti that the best way of determining the usefulness of chemotherapy would be to compare patients who have and have not received chemotherapy. It would be particularly important to control for known prognostic factors, as Dr. Aldrighetti suggested. In the DISCUSSION section, we have commented on the only valid comparison of that type that is so far in existence (Nordlinger, Lancet 2008; 371:1007). We have also described that the outcomes in our cohort are encouraging when compared to the many surgical series reported in which patients only underwent resection. The outcomes for the purely surgical series are described in the Introduction section.

Reviewer #3 (Dr. C. Pozzo)

1. Dr. Pozzo has pointed out that several other groups (including Dr. Pozzo’s group) have not observed the high rate of thromboembolic (TE) complications that we have observed. Having said that, we are not the only ones to have observed a high rate of TE complications with irinotecan-based regimens (see Rothenberg et al, JCO 2001; 19: 3801 and Pan et al., Oncology 2005; 69:63). To facilitate the reader’s interpretation of the significance of the TE events, we have attached the details related to each of the thromboembolic events in a supplementary file (referred to in the Treatment-related Toxicities section).

2. The statistical design was a source of criticism, but we interpret Dr. Pozzo’s criticism to stem from the fact that only 35 patients were ultimately accrued. The original data analysis plan was based on a DFS outcome, which is appropriate in a phase II setting and is certainly not unique to our study. We have attempted to stay true to our initial data analysis plan, which was defined at the beginning of the trial and reflects good trial conduct. We have acknowledged that the conclusions based on the DFS and OS were significantly weakened because of the truncated trial enrollment.

Additional Revisions

1. We have added a competing interests section

2. A section describing authors’ contributions has been added.

3. We have specified that informed consent was obtained from trial participants.
4. We have included the trial registration number in the X section.

We hope that the revisions that have been made have been found to be acceptable to the reviewers and to the editorial board.

Sincerely,

Oliver F. Bathe, MD, FRCSC, FACS