Author's response to reviews

Title: Phase I/II study of first-line irinotecan combined with 5-fluorouracil and folinic acid Mayo Clinic schedule in patients with advanced colorectal cancer

Authors:

Prof Thomas Kuehr (thomas.kuehr@khwels.at)
Paul Ruff (ruffp@medicine.wits.ac.za)
Bernardo L Rapoport (brapoport@icon.co.za)
Stephen Falk (stephen.falk@ubht.swest.nhs.uk)
Francis Daniel (danielff@phnt.swest.nhs.uk)
Conrad Jacobs (conrad.jacobs@cancercare.co.za)
Neville Davidson (neville.davidson@meht.nhs.uk)
Josef Thaler (josef.thaler@khwels.at)
Blandine Boussard (blandine.boussard@aventis.com)
James Carmichael (james.carmichael@astrazeneca.com)

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Thomas Kuehr, Paul Ruff, Bernardo L. Rapoport, et al.

Answers to reviewers' comments

Reviewer's report #9133854292996363
Discretionary revisions:
- Two of the early deaths occurred in patients with a WHO performance status of 2 and one patient had a WHO PS of 1. This has been added to the text.
- This median time was referring to the time between cancer diagnosis and metastasis diagnosis. However, as it appeared to be confusing it has been removed from the tables.

Reviewer's report #2110166579307934
Major compulsory revisions:
1 - We agree that two populations from the phase I study should not be combined. However, as the phase I results have not been published previously, we feel it would be interesting to summarize them in this article. In keeping with the reviewer's comments, we have presented only the phase I results from patients receiving 5-FU by the same infusion schedule (15-minute) as in the phase II part of the study. This enables meaningful comparison between the two phases of the study. To this end, the text and Tables 2, 3, and 4 have been amended.

2- We agree: the text has been modified accordingly (page 2).

3- The conclusion of the abstract was modified (page 2-3).

4- The evaluable population was defined as eligible patients with measurable lesions according to the WHO criteria. The maximum time between tumor imaging and inclusion was 3 weeks, and this has been added to the text (see page 5-6).
Ultrasound was indeed allowed as some countries do not always have easy access to more performing assessment techniques.

5- At the time of this trial, the irinotecan labelling indicated that the infusion could last between 30 and 90 minutes. No specific toxicity was found with a shorter infusion duration, so the hospitals were free to choose the infusion duration they found most convenient.

6- As outlined in our answer to point 1, the phase I results have not been published before and we feel it is interesting to present them, but for only those patients receiving the 15-minute 5-FU infusion.

7- The toxicity grades necessary for dose reduction were grade 4 for neutrophils and platelets and grade 3 or 4 for diarrhoea and mucositis. Leucovorin was not reduced. Only one dose reduction was allowed.

8- At the time of this trial, the time to progression (TTP) was calculated from the time of the first infusion to the date of documented progression or death due to malignant disease only.

9- Please see point #1.

10- According to the protocol, confirmation of responses was not a requirement.

11- There are in fact 3 patients censored at about one month, all of whom died as a result of toxicity (reason= neutropenic sepsis, page 12). The patient censored at about three months died of bowel obstruction not related to study treatments. As mentioned in point 8, the TTP in this study was assessed on the basis of deaths due to malignant disease only. Therefore, these four deaths were censored.

12- Please see point #1.

13- As mentioned previously (point 10), there were no confirmed responses in this study.

Minor essential revisions:

1- The overall response for the ITT population was 29%, and the text has been corrected accordingly (page 2).

2- The version of the NCI-CTC used was version 1. This has been added to the text (page 8).

3- Although minor response is not a WHO criterion, it is often used in colorectal cancer and we therefore thought it useful to present this response also (it is defined in the protocol as a decrease by at least 25% but by less that 50% of the size of the lesion). However when we refer to stable patients in the text we count the "minor responses" as well as the "stable diseases".

4- We think the tables and the text can support each other so we would prefer to present both.

5- Same as point #4.

6- The WHO criteria for tumour assessment were applied. Therefore, when a method differed from the one used at baseline the response had to be considered non-evaluable.

7- The text has been modified (page 14-15).
8- We added reference 30 [Sargent et al., N Engl J Med., 2001], which presents deaths occurring with oxaliplatin combinations.

9- We agree with the reviewer that the bolus regimen is not the standard first choice. The text has been changed accordingly (page 15).

10- We cannot provide the breakdown you propose as only the median range was calculated.

Discretionary revisions:

1- We consider that information on irinotecan monotherapy provides interesting background information to this study and would prefer that it were kept in.

2- Long time survival was not an objective in this study, and was therefore not studied.

3- This median time was referring to the time between cancer diagnosis and metastasis diagnosis. However, as it appears to have caused confusion, it has been removed from the results (Table 1).

4- We feel that the results are clearer when presented in 2 different tables.