Author’s response to reviews

**Title:** Randomized controlled phase I/II study to investigate immune stimulatory effects by low dose radiotherapy in liver metastases of colorectal cancer

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**Version:** 2 **Date:** 14 February 2011

**Author’s response to reviews:** see over
Dear Mrs. C. Chap

Please find enclosed our manuscript entitled “Randomized controlled phase I/II study to investigate immune stimulatory effects by low dose radiotherapy in liver metastases of colorectal cancer” by C. Reissfelder et al., which we submit for review as an article in *BMC Cancer*.

The presented study describes a clinical phase I/II trial in patients with liver metastasis from colorectal cancer with scheduled resection. The liver metastases will be irradiated two days prior to surgery using external beam radiotherapy. As primary endpoints we will determine the active local radiation dose leading to metastasis infiltrating T cells as a surrogate parameter for antitumor activity. Secondary objectives include local tumor control, survival, treatment toxicity as well as quality of life of the patients. Further, frequencies of tumor reactive T cells in blood and bone marrow will be correlated with blood cell transcriptomics and plasma-proteomics.

The final clinical trial protocol, the patient information and informed consent sheets were approved by the independent ethics committee of the University of Heidelberg S081/2008 (http://klinikum.uni-heidelberg.de). Further, the study has been approved by the German Federal Authorities for Radiation Protection (Bundesamt fuer Strahlenschutz, Salzgitter, Trial Number Z5-22461/2-2009-002). Written informed consent is obtained from each patient in oral and written form before inclusion in the study. This study is carried out in accordance to the current Declaration of Helsinki (sixth revision, 2008), the principles of “Good Clinical Practice” (GCP), and the Federal Data Protection Act. It is registered at the Clinical-Trials.gov protocol registration system (www.clinicaltrials.gov) and the assigned identification number is NCT01191632.
To our knowledge this is the first clinical study to validate the influence of external beam radiotherapy on tumor infiltrating T cells in colorectal liver metastasis. We are therefore confident that these findings will be of high interest to the readership of *BMC Cancer*.

All authors have seen and approved the final version of the manuscript. The detailed contributions of each author are:

**Christoph Reissfelder**: study design, patient and data acquisition, data analysis and interpretation, drafting of the manuscript

**Carmen Timke**: study design, data acquisition, data analysis and interpretation, drafting of the manuscript

**Hubertus Schmitz-Winnenthal**: study design, patient and data acquisition, data analysis and interpretation

**Nuh N. Rahbari**: study design, patient and data acquisition, manuscript revision

**Moritz Koch**: study design, patient and data acquisition, manuscript revision

**Felix Klug**: study design, data acquisition, manuscript revision

**Falk Roeder**: study design, data acquisition, manuscript revision

**Jürgen Debus**: study design, data acquisition, manuscript revision

**Markus W. Büchler**: study design, data interpretation, manuscript revision

**Philipp Beckhove**: study design, data interpretation, manuscript revision

**Peter E. Huber**: study design, data acquisition, data analysis and interpretation, manuscript revision

**Jürgen Weitz**: study design, data analysis and interpretation, manuscript revision

Thank you very much for your consideration.

Best personal regards,

Jürgen Weitz