Author's response to reviews

Title: A prospective, non-randomized phase-II trial of Trastuzumab and Capecitabine in patients with HER2 expressing advanced pancreatic cancer

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To whom it may concern to,
Dear Natalie

Thank you for the favourable review process. As indicated by the reviewer this is a study protocol and therefore, does not contain results of this study. Please find below a point by point response to the reviewer’s remarks:

1. The reviewer’s comments are correct. The only established indication for Tastuzumab is breast cancer. In pancreatic cancer little is known. Before the study was initiated there was a large screening and grading of pancreatic cancer specimens for HER2 using immunohistochemistry and FISH. The analysis was done at the Department of Pathology at the University of Kiel (German reference pathology for pancreatic cancer). Unfortunately the results of this investigation were not published so far. Based on this finding ROCHE agreed on supporting an investigator driven study (Michael Geissler) with Herceptin in pancreatic cancer. Only HER2/neu grade 2 samples were analysed by FISH. HER grade 3 staining specimens were considered sufficient to be included in the study without additional FISH analysis. We have modified the text (page 11 lanes 9-13) in the manuscript accordingly to clarify this point. Moreover, we modified Figure 1 accordingly. We did not analyse for polysomy 17 in this study, but the reviewers concerns are correct with regard to polysomy 17.

2. The reviewer correctly stated that “it is unclear whether or not the patient recruitment will be limited to patients with HER2 amplification”. We have modified Figure 1 as suggested by
the reviewer and clarified that only patients with HER 3 graded specimens are included and in addition patients with HER2 graded specimens in which gene amplification has been proven by FISH amplification.

3. The reviewer is absolutely correct. As with any phase II study the conclusions to be drawn are limited. Nevertheless, this kind of studies is necessary to show the therapeutic effect of the compound in human pancreatic cancer. Clearly the straightest forward would be a phase III trial, but these are very expensive clinical trials and can only be done as a sponsored study. Because of a lack of evidence with regard to the general efficiency of Trastuzumab in pancreatic cancer we performed a larger phase II study fully aware that a phase III study would better with regard to the level of evidence based medicine.

Regarding the recommendations of the reviewer

In a separate histological study the results of IHC and FISH on all samples will be reported independent of this study with a much higher number of pancreatic cancer samples.

The reviewer is correct that a randomized phase 2 trials with stratification for prognostic factors and for HER2 would be superior but the sample size would increase dramatically. Therefore, we decided to include only patients with HER2 overexpression (grade 3 or grade 2 plus amplification of HER2 in FISH)

We have modified the eligibility criteria and Figure 1

We have further condensed the text as suggested by the reviewer.

Kind Regards

Peter Büchler, M.D.