Author’s response to reviews

Title: A randomized multi-center phase II trial of the angiogenesis inhibitor Cilengitide (EMD 121974) and gemcitabine compared with gemcitabine alone in advanced unresectable pancreatic cancer [ISRCTN13413322]

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Dear Iratxe Puebla:

Thank you very much for your email regarding our mentioned manuscript and the chance to submit a re-revised version of our manuscript.

After having carefully read all the comments of the reviewers we have to admit that we cannot fully understand your decision to let our article get reviewed by a statistician after the first revision. We wish to point out that the reviewer who suggested letting the paper be reviewed by a statistician was satisfied with our first revision and our point-by-point response.

Now, we are in some kind of dilemma: the previous three clinical reviewers were satisfied with our revised version (there were no <major compulsory revisions>). However, if we would change the paper according to the suggestions of the statistical reviewer, we also would change the clinical content. Thus, a non-clinician would have had the last word on a mostly clinical article.

Nonetheless, we believe that some of the issues raised by the last reviewer were valid, and we have incorporated these changes in the revised version of the manuscript. We wish to point out that some termini used, can either have statistical or empirical meanings, but in the way we use them now, there should not be any misunderstanding.

Since these were general changes, we were not able to include a point-by-point response to the reviewer. We have, however, highlighted all changes in the manuscript.
If this is not acceptable for you, we would have to change nearly everything in the article (as an effect of the requested changes of the statistical reviewer), and this would likely result in a re-review by the other three reviewers.

As the "level of interest" of the article was seen as "important" in various categories by the reviewers in the last version, we would not like to make substantial changes.

Nevertheless, the changes in our paper might also be sufficient to get the biostatistician's approval. In fact, most of the remaining comments by the biostatistician as well as the clinical reviewers (e.g. the comment of the definitions of OS and PFS) are comments on pitfalls, many study teams have gone through in the past and even in the present, especially concerning new "smart" drugs.

These comments are reminders to us and the whole of the scientific community to be better in the future; but as they refer to the study design, they cannot be the base for changes in this trial, because it was already conducted, and so the primary design cannot be changed.

We hope that you and the reviewer can accept our point of view. We appreciate the efforts of the reviewers in helping us to improve our manuscript.

With best regards,

Helmut Friess, MD