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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Author's response to reviews:

Dear Sir

Attached please find the revised version of our manuscript entitled "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]. We believe that we have answered all the comments of the reviewers (see point-by-point response). We also believe that these changes have strengthened our manuscript.

Thank you for your attention to this matter.

With best regards,

Helmut Friess, MD

Reviewer Andrew Ko:

Major Compulsory Revisions:
-Please elaborate on your first sentence in the Statistical Analysis, "The sample size of the trial was determined clinically and was not based on any consideration of statistical power". Was there a statistician who agreed on designing the trial this way? Please justify.

Answer: In the revised version, we tried to let the text read more convenient. It was a pilot- and feasibility
study. Randomisation was not done for comparison between the arms but to decrease bias. In total 4 statisticians were involved in the design and the report.

-The discussion section is too much a re-recitation of the study results, rather than putting the results into some context (e.g. preclinical data that might support this particular therapeutic strategy specifically in pancreatic cancer; ongoing studies using other anti-angiogenic approaches in pancreatic cancer, such as the incorporation of bevacizumab)

Answer: The required changes have been made in the revised version of the manuscript.

Minor Essential Revisions:
-Please clarify the ITT vs. the PP populations. Specifically, the manuscript states that 89 patients were included in the ITT population, and 76 in the PP population; this difference was due primarily to 12 patients who received less than 4 weeks of treatment. However, in "patient characteristics" the authors report at least 4 patients who met exclusion criteria -- one who did not have histologic confirmation of disease, and 3 who received prior tumor-related therapy. Please clarify/comment on whether these patients were included in the ITT analysis, but not the PP analysis?
Answer: The required changes have been made in the revised version of the manuscript.

Answer: The required changes have been made in the revised version of the manuscript.

-Please include a summary of the actual data (either in the text or as a table) for CA19-9 measurements, as well as VEGF and bFGF levels, even if no clear correlations were seen (e.g. median, ranges).
Answer: The required changes have been made in the revised version of the manuscript for CA 19-9 (really clinically relevant) yet not for VEGF and bFGF (too much text necessary with no relevant information).

-In table 1: include percentages for breakdown of stage and KPS.
Answer: The required changes have been made in the revised version of the manuscript.

Discretionary Revisions:
- In reporting safety data in the text and the tables (6a and 6b), recommend referring to "all grades" and "grade 3 or 4" instead of (or at least in addition to) labelling them simply as adverse events and serious adverse events.
-Consider adding 1-2 sentences in the abstract on specific toxicities seen (e.g. "Slightly higher rates of nausea, dyspepsia, etc. were observed in the gemcitabine and Cilengitide group.")
-Include a sentence in the text specifying that "no treatment-associated deaths were observed on study." Consider including specifics in the "Patients and Methods" section re: entry criteria (e.g. liver/renal/bone marrow parameters, definition of "cardiac/ cardiovascular abnormality"), as well as dose reduction scheme (of particular interest in the Cilengitide arm).

Answer: The required changes have been made in the revised version of the manuscript.

Reviewer Henry Q Xiong:

Major Compulsory Revisions:
1. The major concern is the statistical design. The author stated that the sample size of the trial was determined clinically and was not based on any consideration of statistical power. The author needs to explain why statistical design was not considered (in statistical analysis section or discussion section). Was the sample size (89 patients) predetermined? Were there any early stopping rules?
Answer: In the revised version, we tried to let the text read more convenient. It was a pilot- and feasibility study. Randomisation was not done for comparison between the arms but to decrease bias. In total 4 statisticians were involved in the design and the report.

2. There was confusion in documenting and reporting safety. The author used NCI-CTC Version 2 for monitoring toxicities and reported toxicities based on AE and SAE, grades, and severity (mild, moderate, severe, and life-threatening). There was great redundancy as the author tried to report toxicity or safety based on these classifications. For example, life-threatening events could be either AE or SAE (Table 5). I'd recommend deleting Table 5 and . The readers are interested in toxicities and its grades. Serious adverse events usually include severe and life-threatening events or grade 3 and 4 events. I am not sure same definition applies here. If it doesn't, the author needs to change the title of Table 6b to: serious adverse and life-threatening events possibly related to study treatment.
Answer: The required changes have been made in the revised version of the manuscript.

3. There was discrepancy of toxic events reported between the text (safety) and the table 6a. For example, nausea was 64% vs 50% in the text (page 9, line 6 of second paragraph), but was 36% vs 38%.
Answer: In the text, AEs are reported, in the table "treatment-related" AEs. These clarifications have been
4. The discussion on safety can be deleted or rewritten.
Answer: The required changes have been made in the revised version of the manuscript.

Minor Essential Revisions:
1. The author needs to be more specific in defining eligibility criteria. The criterion, a history of cerebrovascular accident or repeated transient ischemic attacks and cardiac or cardiovascular abnormality (page 4, patients), is not clear.
Answer: The criteria are indeed interpretable, but it is the verbatim text of the exclusion criteria. This has now been emphasized.

2. Why the author uses different starting date for calculation of overall survival (from the start of study drug administration to death) and PFS (the time between the date of randomization and the date of disease progression)?
Answer: Indeed this could have been harmonized, but as it is specified in the SAP and both dates differ in maximum few days, the way it was done should also remain in the paper.

3. Define "condition reduced"(Table 6b) since it is not commonly reported as serious adverse event.
Answer: It means: symptomatic deterioration. This has now been stated in the revised version.

Discretionary Revisions:
1. The authors may want to add "randomized phase II trial" as a key word.
2. Typo: Area under the curve (page 6, second to the last line).
Answer: The required changes have been made in the revised version of the manuscript.

Reviewer 3

Minor Essential Revisions:
1) The rationale for the use of anti-angiogenesis agents in pancreatic cancer should be more thoroughly described.
Answer: The required changes have been made in the revised version of the manuscript.

2) The rationale for combining cilengitide to gemcitabine should be provided as well.
Answer: The required changes have been made in the revised version of the manuscript.

3) In the material and methods section, the authors correctly acknowledge that results can be presented only in a descriptive manner. In fact, a randomized phase II trial does not allow a comparison of the outcomes of study groups. However, in the title, the abstract and the results section the terms 'compared with', 'to compare', 'no ... statistically significant difference in survival between the treatment groups' appear. This could be misleading and must be avoided.
Answer: Statistically significant, etc. rewritten or deleted, "compare" partly left in the text, because a descriptive comparison is always possible.

4) Material & methods; page 4, line 1: the definition of 'advanced unresectable pancreatic cancer' is subjective and ambiguous. In table 1, we observe that 7 patients had stage III disease. Stage III patients have a resectable disease and have a more favorable prognosis as compared with stage IVa or IVb patients. The erroneous inclusion of 8-18% patients with stage III (T3N1M0) disease is common in trials of advanced unresectable pancreatic cancer and may confound the interpretation and generalization of results. Their inclusion should be better justified: were they unresectable due to comorbidity or pathological conditions other than pancreatic cancer, or did they refuse surgery?
Answer: The verbatim was "not amenable for surgery"; as stated, this is indeed erroneous, but the same situation in all comparable studies. "respectable" or not is subjectively decided by the investigator.

5) Statistical analysis, page 7: sample size calculation is lacking. The authors may wish to justify their unusual choice.
Answer: The required changes have been made in the revised version of the manuscript.

6) Safety: the description of adverse events and serious adverse events seems a bit confusing. Ten and 9 possibly related serious adverse events in cilengitide and gemcitabine arm and gemcitabine alone arm, respectively, were reported in the text (page 9, lines 19-20). However, in table 5 the numbers are 50 and 64, respectively. If the authors refer to life-threatening serious adverse events, this should be clarified in the
text, but remains inconsistent with table 6b where the values are 12 and 8, respectively. In the title of table 6b 'life-threatening' should be added, or SAE other than life-threatening should be added. Another inconsistency in the number of life-threatening SAE which occurred in the combination arm appears between table 5 (N=10) and table 6b (N=12).

Answer: Text and tables include, according to their headlines, different sets of data.

7) Discussion; page 10, line 6: in the 1997 TNM classification used by the authors, stage III B does not exist. The same applies to table 1, in which 'stage IV' is reported: does this mean stage IVa or IVb? Answer: These mistakes have been corrected.

8) Efficacy, page 11, line 8: the sentence 'response rates also compare favorably with published data where rates of 6% to 11% have been reported...' is wrong, as response rates of 16-26% with single agent gemcitabine were reported in other phase III trials (Bramhall SR, et al. Br J Cancer 2002, 87, 161-167; Bramhall SR, et al. J Clin Oncol 2001, 19, 3477-3455; Louvet C, et al. J Clin Oncol, 2005, 23: 3509-3516). I retain that response rates and the general outcome which have been observed in the current trial are in the range of those previously observed in trials of single-agent gemcitabine.

Answer: The required changes have been made in the revised version of the manuscript.

9) Pharmacokinetics, page 12, line 5: the sentence 'the short half-life of Cilengitide may have contributed to the lack of clinical benefit seen in this study' is surprising, as this was already known from phase I data (authors' reference #1). Thus, the authors may wish to justify why they chose a treatment schedule which was previously indicated as non-optimal to yield continuous drug exposure and why they did not explore different treatment schemes.

Answer: Neither in the previous nor on the current study, this was obviously non-optimal. It is only one speculative argument.

10) Discussion: a phase II trial describing the results obtained with bevacizumab, another angiogenesis inhibitor, has recently been reported (Kindler HL, et al. J Clin Oncol, 2005, 23: 8033-8040). A comment on advantages and disadvantages, similarities and differences between the two agents may be useful.

Answer: The required changes have been made in the revised version of the manuscript.

11) Discussion: while gemcitabine is considered as a standard treatment in advanced pancreatic cancer, this drug achieves a poor outcome and other agents with comparable overall activity and efficacy, such as 5-fluorouracil when administered as protracted venous infusion (Maisey N, et al. J Clin Oncol 2002; 20:3130-3136), are available. In the last decade many targeted therapies have failed to improve survival of pancreatic cancer when used in combination with gemcitabine. Do the authors want to speculate on the hypothesis that gemcitabine may not represent the best candidate agent to combine with cilengitide? Or do they believe that a different sequencing of treatments may achieve better results?

Answer: This would, indeed be a very interesting topic for a review, but the data of the current study do not justify a speculation.

12) Footnote of table 6a is redundant with the title.

Answer: Has been deleted in the revised version.

13) Legend of figure 2: the term 'time to progression' should be substituted with 'progression-free survival'

Answer: The required changes have been made in the revised version of the manuscript.

Discretionary Revisions:
When did the trial begin and finish?
Answer: 1999-2001