Reviewer's report

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]

Version: Date: 29 March 2006

Reviewer: Andrew Ko

Reviewer's report:

General. In this multicenter randomized phase II study, the investigators compared gemcitabine alone to gemcitabine plus cilengitide, a cyclic peptide inhibitor of two integrins expressed on the surface of endothelial cells, in patients with previously untreated advanced pancreatic cancer. No improvement in clinical outcomes were observed in the combination arm. Overall, the manuscript is clearly written.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

- 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.

- 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)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

- 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?

- 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).

- In table 1: include percentages for breakdown of stage and KPS.

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Discretionary Revisions (which the author can choose to ignore)

- 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)

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes

**Declaration of competing interests:**

I declare that I have no competing interests.