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:** 2  **Date:** 31 May 2006

**Reviewer:** Michele Reni

**Reviewer's report:**

General
The manuscript by H. Friess et al. has been incompletely and somewhere unsatisfactorily reviewed. Further work is necessary before it can be published.

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

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MINOR ESSENTIAL REVISIONS

1) The rational for anti-angiogenesis agents use ...... The statement "Antiangiogenic therapy offers a number of potential benefits including ... and lack of significant toxicity compared with conventional agents" is wrong as e.g. bevacizumab was responsible for toxic deaths in several tumor types including pancreatic cancer.

2) The rational for combining cilengitide .... OK

3) In material and methods section, authors correctly acknowledge ....... OK

4) Material & methods; page 4, line 1: the definition of 'advanced unresectable pancreatic cancer' is subjective and ambiguous. ...... This remains a weakness of the trial: the lack of predefined objective resection criteria and the inclusion of stage III patients introduces a subjective selection bias which hampers interpretation and generalization of results.

5) Statistical analysis, page 7: ....... The lack of a predetermined sample size is another irretrievable weakness of the trial. The meaning of 'clinical determination' of sample size is unclear. In the last paragraph of introduction the sentence 'The primary objective of the study was to investigate overall survival' is incoherent with the statements reported in the section 'statistical design'.

6) Safety: ...... Inconsistency between text (page 10, lines 29-31) and table 6b has not been corrected.

7) Discussion; page 10, line 6: in the 1997 TNM classification used by authors, stage III B does not exist. ...... The mistake in table 1 has not been corrected.

8) Efficacy, page 11, line 8: the sentence 'response rates also compare favorably ....... These results does not 'compare favorably' but are in the previously reported range.

9) Pharmacokinetics, page 12, line 5: the sentence 'the short half-life of Cilengitide ...... In the manuscript quoted by authors' as reference #1 the following sentence is reported : "due to the short terminal plasma half-life, a twice-weekly treatment schedule might not be optimal to yield continuous drug exposure, and different treatment schemes resulting in continuous drug exposure should therefore be explored". This is obviously a speculative argument. However, 'speculation' allows to generate hypotheses on how to improve drug use. It is disappointing that authors did not take into account the previous pharmacokinetic data and the above mentioned 'speculation' when they designed the current trial and then raised the same 'speculative' hypothesis about the lack of benefit of cilengitide in the discussion of their negative results.

10) Discussion: recently, a phase II ...... OK

11) Discussion: while gemcitabine is considered as a standard ..... OK

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

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

DISCRETIONARY REVISIONS

1) When did the trial begin and finish? OK
Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No