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: 1 Date: 14 April 2006

Reviewer: Michele Reni

Reviewer's report:

General
The manuscript by H. Friess et al. reports the negative results of a randomized phase II trial of the addition of the angiogenesis inhibitor cilengitide to gemcitabine in patients with advanced pancreatic cancer. The use of integrin inhibitors in pancreatic cancer is new and their assessment is of interest. The trial was well conducted and well described. The manuscript appears clear, complete, balanced and well written.
The authors should be commended for the choice of a randomized phase II trial design. Single arm phase II trials of pancreatic cancer have to date failed to adequately select candidate treatments for further assessment leading to the negative results which have been observed in manifold resource-wasting phase III trials.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
In my opinion, no major compulsory revisions are necessary.

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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)
1) The rationale for the use of anti-angiogenesis agents in pancreatic cancer should be more thoroughly described.
2) The rationale for combining cilengitide to gemcitabine should be provided as well.
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.
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?
5) Statistical analysis, page 7: sample size calculation is lacking. The authors may wish to justify their unusual choice.
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).

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?

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.

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.

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.

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?

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

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

Discretionary Revisions (which the author can choose to ignore)

1) When did the trial begin and finish?

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.