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: 25 May 2006

Reviewer: Andrew R Willan

Reviewer's report:

General
I believe that the data should undergo a proper statistical analysis. That fact that it may be underpowered does not mean the analysis is invalid; the analyst sets the type I error. However the type II error may be quite large and the authors need to address this issue. The calculation of the sample size appears to have been governed by convenience and feasibility issues, however this does not mean that a statistical analysis is inappropriate.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
I have concerns with what appears to be an incompatibility between the primary objective of the study and the presentation of the data and conclusions. The authors need to state what the objectives really were. It cannot be to compare two treatment groups; that is part of the methods. Since the conclusion is the combination... is not recommended for phase III evaluation in patients with pancreatic cancer, the real objective must have been to determine if the combination should undergo phase III evaluation. If this is the case, then the authors need to state want observed outcome with respect to feasibility, safety and efficacy would have lead to the conclusion that combination should undergo phase III evaluation. Another important issue is, given that the combination is feasible and safe, what is the probability of reaching the conclusion that combination should undergo phase III evaluation if, in fact, the combination was efficacious enough to justify phase III evaluation. This, of course, is the power (1 - type II error), an issue which the authors feel (incorrectly, I believe) justified in totally ignoring. There is no reason why a randomize phase II trial cannot undergo a standard statistical analysis. It may lack power, perhaps, but the randomization ensures that the statistical tests of hypotheses are valid (i.e. have the correct level). Conclusions come from making inference (proper statistical analysis) on observations. The authors have gone from the observations to conclusions, completely omitting the inferential step. Just using terms such as pilot, phase II and feasibility cannot justify this omission, regardless of the number of times other authors might have done so. The authors have to stop at the observations or conduct the proper statistical analysis in order to reach conclusion with a complete discussion of the issues of power and type II error.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
The Background section of the Abstract needs to be renamed. As it is now, it is a statement of the objective.
The first and third sentences in the Conclusion section in the Abstract and in the manuscript should be removed. They are observations, not conclusions.

Discretionary Revisions (which the author can choose to ignore)

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

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes
Declaration of competing interests:

I declare that I have no competing interests.