Reviewer’s report

Title: Phase I Dose-Escalating Study of Docetaxel in Combination with 5-Day Continuous Infusion of 5-Fluorouracil in Patients with Advanced Gastric Cancer

Version: 1 Date: 2 May 2005

Reviewer: Peter C Thuss-Patience

Reviewer’s report:

General
It's a well written, clear report. Because 3 already published phase 1 studies with this combination (Burris 1997, Ando 1998, Van Den Neste, 2000) exist and 2 large phase II studies, published in abstract form (Ajani, ASCO 2003, Hawkins, ASCO 2003) already show the feasibility of the combination 5-FU continuous infusion /5 days and docetaxel) the study is not of very outstanding importance. The scientific value of the results reported is diminished by the fact that the authors have obviously chosen only the first cycle of chemotherapy to be important for the determination of DLT. This design is the correct approach to determine the best doses of a totally new unknown combination. For the combination docet/5-FU it would be more interesting to evaluate the toxicity of several cycles so that cumulative toxicity is not missed.

The limited value of the result achieved by this phase I study is underlined by the fact that even at the recommended dose level 6 of 10 patients experienced grade 3 stomatitis in further cycles (see table 2). This proofs that regarding only toxicity of cycle 1 as DLT is of limited help to predict toxicity of this regimen.

It is totally unclear why the authors have used hematological growth factors (like G-CSF) in further cycles of their regimen. If the authors believe their own data which says that there is no hematological DLT at dose level 2, it is not logical to allow G-CSF in further cycles. If you perform a phase I study to assess the tolerability of a regimen without G-CSF (cycle 1), why should you administer G-CSF in further cycles.

Major work regarding the combination of docetaxel and 5-FU is not discussed nor cited, most importantly Hawkins et al ASCO 2003. The study of Hawkins reported good tolerability and manageable toxicity of docetaxel 85mg/m and 5-FU 750 mg/m d1-5 in 43 patients and 232 cycles! Choosing the dose of docetaxel and 5-FU for future phase II trials the study reported by Hawkins is probably of more value than a phase 1 study considering only the toxicity of cycle one in 16 pts. Nevertheless the study reported by Park et al adds valuable information to the scientific community which might be helpful for future trial designs.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1) At page 8 (treatment plan) it should be clearly stated whether only the 1st cycle is evaluated to determine DLT. The authors should comment on this approach and explain why they think that this design should be preferred rather than choosing a design in which the first three cycles are considered.
2) The authors have to discuss their policy of using hematological growth factors and compare this to ASCO guidelines.
3) Important publications have to be included in the discussion (at least the work of Hawkins et al.)
4) At page 13 the authors state that .."the addition of 5-FU to docetaxel increases the hematological toxicity". It is not clear how this statement can be retrieved from the current study..
5) At page 13 it is stated that febrile neutropenia remains the main DLT of this regimen although of the 3 DLTs reported, two were stomatitis CTC grade 3. This should be clarified.
6) The DCF regimen reported by Ajani is not discussed correctly. a) In the discussion of the report by Ajani, ASCO 2003, the authors cite a 30 day mortality, 30 days of last infusion to show that the Ajani DCF is very toxic. If therapy is administered up to tumor progression 30-day of last infusion mortality does not give any information about the toxicity of the regimen. Usually mortality in the 30 days following the first infusion is reported to evaluate the toxicity of the chemotherapy (Rothenberg et al J Clin Oncol 2001: pp 3801-3807). Ajani reports an any cause mortality within 30 days of first infusion of 2.3%, which compares favorably to standard cisplatin/ 5-FU regimens. b) The authors report a grade 3 and 4 toxicity of 82 % for the Ajani DCF regimen to underline their point of view that DCF is too toxic. In fact looking at Ajanis ASCO presentation he reports grade 3 and 4 adverse events in 68%. Besides, at the recommended dose level 2 in the report by Park et al 60% of patients had grade 3 stomatitis, 40% grade 3 asthenia and 40 % grade 3 neutropenia, a toxicity comparable to that reported for DCF. c) The judgement that the Ajani DCF regimen will never be a standard is a personal point of view of the authors which is not shared by the scientific community.

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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) At table 2 footnote 2 does not give any additional information, as it is not stated at which dose level the toxicity occurred.
2) Eliminate brand name Taxotere (page 5) from a scientific report
3) Page 6: Include citation when describing ..."most previous studies...."
4) Page 8: Include citation about ..."traditional phase I methodology"
5) Page 9: Include citation what the authors consider to be standard dexamethasone and 5-HT3 inhibitor therapy. Besides, it is arguable whether 5-HT3 inhibitors are standard for the low emetic combination docetaxel and 5-FU.
6) Table 1: change .."recurrent" in "locally advanced"
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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: No

Declaration of competing interests:

I declare that I have no competing interests.