Reviewer's report

Title: Prognostic value of monitoring tumour markers CA 15-3 and CEA during fulvestrant treatment

Version: 1 Date: 13 February 2006

Reviewer: Kwok-Leung L Cheung

Reviewer's report:

General

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

The study showed that an increase in marker level occurred in almost all scenarios. This should not lead to a conclusion that markers are prognostic. Elevation of markers in patients with CB has been described before (spike phenomenon) though it appeared to have occurred more often in this cohort treated by fulvestrant – this is an interesting finding. However it is unclear from the description of the results as to whether change in marker levels was important. One way to distinguish spike phenomenon from genuine biochemical disease progression is to recheck the markers later. It would be useful if the authors could describe the changes of levels of all markers throughout the treatment duration ie from starting treatment till disease progression. Data beyond 6 months were not presented. This would confirm whether there was a difference between the group with CB and then secondary PD, and the group with de novo PD (within 6 months).

Based on previously published data, marker measurements pre-date clinical/radiological assessment. This occurs even in the group with spike phenomenon and the markers would tend to rise and then fall if there was CB. The mechanism of spike phenomenon is uncertain. A possible association with tumour flare (eg with tamoxifen which also possesses oestrogen agonistic activity) might exist but it would be interesting to see whether similar spike phenomenon exists and if so, its incidence and pattern (when and for how long) with treatment by a pure anti-oestrogen (fulvestrant).

Furthermore the authors should admit that the prognostic implication could only be drawn from surrogate parameters (ie CB or not, based on previous studies showing survival benefit in the CB group) since no actual survival analysis was performed.

Without the above clarifications, it would not be possible to draw the conclusion that markers are of prognostic relevance in the context studied.

Page 5 – The description of assessment method appears to be based on UICC rather than RECIST criteria. Either is acceptable but the description needs to be consistent with the method.

Cut-offs of the two markers should be defined. Also the authors need to clarify if their analysis was based on testing of the trend of levels of the markers regardless of the cut-offs. Cut-off based analysis would disregard the significance of marker values which are below the cut-offs until they rise above them or fall from above to below the cut-offs. This is relevant in this study as for instance, the authors could not accept any changes as significant for CEA in the PR group in Table 1, as the values were all below the upper limit of normal. However if the authors were doing an exploratory analysis regardless of this point, they should state it in the methods and its limitations due to reasons mentioned above.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

It would be of interest to inform readers as to what lines of endocrine therapy fulvestrant was used (and in how many patients).

**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

**Statistical review:** No

**Declaration of competing interests:**

I declare that I have no competing interests