Reviewer's report

Title: Adjuvant Trastuzumab in the Treatment of HER-2-Positive Early Breast Cancer: A meta-analyses with 9117 patients.

Version: 2 Date: 16 April 2007

Reviewer: Andrew Roddam

Reviewer's report:

General

This paper represents a meta analysis of 5 trials of trastuzumab for HER2 +ve early breast cancer. Whilst meta-analyses and reviews of the literature are to be encouraged as presenting the balanced view of the available evidence I find the motivation for the current one rather weak. Looking at the various figures, of the 5 studies that are included in the analysis all are consistent in their findings for all endpoints except cardiac toxicity (see comments below). Therefore the only benefit of the current manuscript is to provide a summary of the evidence with greater statistical precision than previously.

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

1. The authors find clear evidence of heterogeneity between studies for the assessment of cardiac toxicity but it appears that they have simply ignored this and used a fixed effects model and presented the results. It would be more appropriate to consider either a random effects model and see whether or not that can control the heterogeneity adequately or to consider not showing an overall result for this outcome.
2. There is no investigation or discussion of whether or not the methodological differences in patient population (including the inclusion/exclusion criteria), treatment regimen, etc could explain the differences in cardiac toxicity.
3. Following on from these comments, given the degree of caution highlighted in the discussion on the issue of cardiac endpoints and the validity of any pooled analysis I would suggest that the overall results are not presented but that the phrasing of a suggestion of increased cardiac toxicity is used instead.

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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. Table 1 is very hard to follow for anyone without a clinical background – there are so many abbreviations used that you virtually cannot understand the information. This should be re-presented in a simple way using English and not abbreviations.
2. Given the information presented in Table 1 do the authors really need to describe in such detail each of the trails. Similarly why aren’t the endpoints also described in Table 1 so that it is an overall summary of all the studies included in the analysis. Please expand Table 1 to cover all major aspects of study design, including major inclusion/exclusion criteria, endpoints measured, method of assessing HER2 status, etc, i.e. key differences between trials which might explain differences/heterogeneities in results.
3. At points in the text abbreviations are used without explanation – for example middle page 5 – LVEF.
4. It is stated in the text that the quality scores are summarised in the table of characteristics – I could not see them.
5. Parts of the results section should be re-worded as at present the sentences do not make sense and I cannot tell what the authors are trying to say – specifically the last sentence of the first results para, the last sentence of the overall mortality results.
6. When describing the metastases rate the authors say “Only five studies,...” but that is actually all studies – please change the text.
7. When presenting the results for second cancers other than breast cancer the authors say that the “likelihood of brain metastases was 0.33-fold”, surely this is second tumours?
8. The discussion starts rather oddly – normally one expects a brief summary of the results of the study followed by more in-depth comments.
9. It was unclear to me what the motivation for discussing costs of treatment in the discussion was given that no other costs and no economic data are presented.
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:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests