Reviewer's report

Title: Differential survival following trastuzumab treatment based on quantitative HER2 expression and HER2 homodimers in a clinic-based cohort of patients with metastatic breast cancer.

Version: 1 Date: 24 June 2009

Reviewer: shaheenah dawood

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This is an interesting article the primary objective of which was to look at association of levels of HER2 expression and survival in a cohort of patients who received trastuzumab treatment. This article follows closely to the recent publication by Desmedt and colleagues from the Jules Bordet Institute. My comments to the authors are below.

Minor Essential Revisions

1. The abstract and the main text seem to be written by two different people. The abstract is extremely difficult to read in its present form in that grammar needs to be corrected and objectives and results should be concise and clear.

2. Overall survival is defined by the author as the time from the start of trastuzumab treatment to cancer associated death or the end of the follow up period”. This definition is more accurately breast cancer specific survival rather than overall survival. I would recommend changing the terminology.

3. In the abstract the author mentions in the background that the objective was to look at the association of HER2 expression levels with that of overall survival, time to progression and objective response. The author makes no mention of time to progression and objective response in the main text. The results of this if analyzed should be presented even if no association was found. In the metastatic setting these end points are important.

4. P values, hazard ratios and confidence intervals should be inserted in the results section to make the results clearer.

5. In Figure 2 the author should insert p values and number at risk.

6. In table 1 the author should insert the number of lines of chemotherapy patients received in the metastatic setting before trastuzumab was initiated.

7. Median duration of trastuzumab treatment and median follow up of the cohort should be mentioned.

8. Median and two year survival estimates of the cohort as a whole and stratified by HER2 expression level should be mentioned and discussed.

9. For table 1 it will be interesting to know the number of patients who had recurrent disease vs. those who had stage IV denovo disease.

10. In table 1 9.5% of patients had brain metastases. Did this occur before or
after trastuzumab treatment. Was there any correlation with any specific level of HER2 expression.

11. In table 1 the author should mention the number specimens that had HERR2 2+ and the number with HER2 3+

Major Compulsory Revisions

1. It is important for the author to mention how homogenous the population was in terms of trastuzumab treatment. i.e did all patients receive it as first line treatment for metastatic disease or did the start time differ. If the start time differs this would be a very important limitation of the study survival of patients would differ depending on how early or late patients received trastuzumab.

2. The author mentions that up to one third of patients in the cohort had tumor specimens that were scored as HER2 0 or 1+ when repeated. These patients were included in the final analysis. It is important that the analyses be repeated excluding these patients.

3. It appears for the cox model in table 2 the author looked at estrogen and progesterone receptor separately. With such a small sample size I would recommend looking at this variable as hormone receptor positive vs. negative.

4. In the results section the author needs to do the following:
   a. The results section is hard to follow and author should consider revising
   b. Although the no significant association between OS and H2D and H2D/H2T the p values should be inserted.
   c. The number of patients in the high and low HER2 expression groups should be stated.

5. In the discussion section the author needs to discuss the study by Desmedt and colleagues in more detail comparing and contrasting the two studies.

6. In the discussion section a paragraph on limitations should be inserted.

7. In table 1 upto 16% of patients received single agent trastuzumab. Did the absence of chemotherapy in this group affect survival? Was there any correlation with HER2 expression in terms of response in this group?

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: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.