Reviewer's report

Title: Predicting time to progression and response to second-line trastuzumab-based therapy in Her2-positive advanced breast cancer

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Reviewer: Filippo Montemurro

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Bartsch et al conducted a retrospective analysis in 97 HER2-positive metastatic breast cancer patients receiving continued treatment with trastuzumab beyond progression. The main aim of the analysis was to identify factors that could indicate benefit from the application of this policy. The paper is very well written and provides no evidence that, based on clinical or histopathological indicators, time to progression and response can be predicted in patients receiving second-line trastuzumab-based therapy in these patients. The general outcome results of this paper do not add to what is currently known on this subject. Furthermore, as displayed, the results of the multivariate analyses of factors predicting for TTP, response or overall survival are not informative. There might be, in fact, trends that, although not statistically significant, could be hypothesis generating.

Major compulsory revisions:

1) All the Hazard Ratios, Odds Ratios and their 95% confidence intervals should be included in the tables summarizing the results of the multivariate analysis.

2) The uni and multivariate analysis should include other potential predictors: for example, the number of metastatic sites (i.e. 1 versus 2 versus more than 2), whether the patients had received the first trastuzumab-based regimen as first-line therapy for HER2-positive disease or as further line of treatment. In the results section, in fact, the authors state that 36.8% of the patients had received prior non-trastuzumab containing therapy for metastatic disease.

3) Furthermore, sill on the same subject, another factor that might be included is pattern of progression during first-line trastuzumab based therapy, indicating whether the patient progressed at the same sites of disease identified at the baseline or developed newer sites of metastases. In a recent publication our group identified trends towards better outcomes in patients receiving second-line trastuzumab based therapy if they had developed liver progression during first-line therapy (Montemurro et al, Clinical Breast Cancer 8; 436, 2008). In the same paper we also identified a trend towards a benefit in patients who had stable disease or progressive disease during first line therapy. It might be interesting analyze also these factors and see if the trend is confirmed in an independent population.

Minor revisions
1) Introduction: “...data from phase II trials...” not all the references cited by the authors refer to phase II studies or the single randomized study, which implies a prospective design. The paper by Fountzilas et al was a retrospective analysis, the paper By Tripathy was in fact prospective, but not really a phase II study. It was an evaluation of the safety of trastuzumab beyond progression based on patients enrolled onto the pivotal trial, and not designed as a phase II study.

2) Response and Survival data: “Median TTP on second.-line...”; please, consider rephrasing to increase clarity.

3) Table 1. Further trastuzumab-based therapy I guess indicates further therapy beyond IIInd line. The authors may wish to include a note to specify this point.

Level of interest: An article of limited interest

Quality of written English: Acceptable

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'