Reviewer’s report

**Title:** Anthracycline-free neoadjuvant therapy induces pathological complete responses by exploiting immune proficiency in HER2+ breast cancer patients

**Version:** 3  
**Date:** 18 September 2014

**Reviewer:** Anita Wolfer

**Reviewer’s report:**

1. In the methods section, I would like to know what exactly a cycle of weekly paclitaxel is. Patients received 3 cycles of weekly paclitaxel, is that 3 weekly treatments, or is a cycle equal to 3 or 4 weekly treatments or is there a fourth week without treatment? Need to be more precise.

2. It seems to me that the hypothesis of 20% improvement of pCR compared to chemotherapy WITHOUT trastuzumab is not necessarily relevant. The stated objective is to show efficacy of a non-anthracycline containing regimen plus trastuzumab. Therefore, it seems to me that the objective should be to show similar results of this regimen compared to anthracyclin containing regimens.

3. In the discussion, the authors write that their study provides evidence that an anthracycline-free regimen can be used safely PROVIDED that trastuzumab is started early. While I agree that probably this regimen is safe, there is no evidence that the early start of trastuzumab is the essential ingredient. With the data at hand, it cannot be concluded that it is BECAUSE of early trastuzumab that it is effective. I am not suggesting that trastuzumab should be started later but the case must be stated properly.

4. Regarding the cardiac toxicity I think the authors need to be careful not to overstate their case. They are looking at 46 patients. With an expected cardiac toxicity of 10-20% in patients treated with trastuzumab alone depending on the study, one would expect to see at least a few patients with decreased LVEF. While it is true that this regimen is most likely not specifically cardiotoxic I still think it needs to be stated that there were actually fewer events than might have been suspected and that this is most likely linked to the small number of patients treated.

5. I am a little bit surprised not to see a larger difference in pCR between the HR negative and positive HER2 pos tumors. According to other studies, usually HR negative patients have significantly higher pCR rates. The authors should comment about this fact (again most like due to number, and there is a numerical difference).

6. The immune response studies are interesting and confirm the effect of the V/F genotype of the FcgRIII. The cytokine studies are equally interesting and should certainly inspire further studies to further investigate and validate the findings. I find that the authors should be careful about comparing the HER2 neg patients
with the HER2 pos patients since the biology of these two tumor types is likely very different and therefore it seems difficult to compare the immune reaction to them. In addition, the treatment regimen is also completely different, since the HER2 neg tumors are not treated with paclitaxel, therefore it is not only trastuzumab that distinguishes the two groups.

Overall, this is an interesting study. In my opinion the manuscript needs to be re-worked to some extent to attenuate certain statements that are too strong and not entirely supported by the data. I would also recommend to have a statistician look at the statistics section (I am not fluent enough to comment).

All of the above should be addressed as minor essential revisions.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**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.