Reviewer’s report

Title: Safety, activity and molecular heterogeneity following neoadjuvant non-pegylated liposomal doxorubicin, paclitaxel, trastuzumab and pertuzumab in HER2-positive breast cancer (Opti-HER HEART): an open-label, single-group, multicenter, phase 2 trial

Version: 0 Date: 23 Sep 2018

Reviewer: Renata Duchnowska

Reviewer's report:

Safety, efficacy and molecular heterogeneity following neoadjuvant non-pegylated liposomal doxorubicin, paclitaxel, trastuzumab and pertuzumab in HER2-positive breast cancer (Opti-HER HEART): an open-label, single-group, multicenter, phase 2 trial.

This phase 2 study addresses the safety of neoadjuvant chemotherapy (NAC) in stage II-III HER2-positive breast cancer patients. The article is well written, assumptions and conclusions are clearly formulated. Primary and secondary outcomes i.e. cardiac safety, pCR and ORR were achieved. An original input is gene expression analysis using the nCounter platform (Nanostring Technologies) at baseline and after NAC. The analysis showed the association between the mRNA level of CD8A and PD1, and the likelihood of achieving a pCR.

Minor comments:

1. The use of the non-pegylated liposomal doxorubicin (please correct the name on page 3) within a perioperative chemotherapy in breast cancer is not standard. Please briefly justify the choice of this compound.

2. Please specify the route of drug administration in the Methods section (Procedures) - page 5.

3. Figure 5. The authors might consider specifying the trials below the schemes.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Not applicable

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below

If your reply is yes to any, please give details below.

I have received travel grants and lectures from Roche, Amgen and Teva in the past five years.
**Statement on potential review bias**

Please complete a statement on potential review bias, considering the following questions:

1. Did you co-author any publication with an author of this manuscript in the last 5 years?

2. Are you currently or recently affiliated at the same institution as an author of this manuscript?

If you can answer no to all of the above, write 'I declare that I did not publish with these authors in the last 5 years and also meet the affiliation criteria”. If your reply is yes to any, please give details below.

I declare that I did not publish with these authors in the last 5 years and also meet the affiliation criteria

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal