Author’s response to reviews

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

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Dear Editor:

Thank you for the opportunity to re-submit our revised version of manuscript BMED-D-18-01234: “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 ” We have addressed all the reviewer’s comments, with all the comments followed by our responses.

We believe the manuscript has improved substantially and we hope that you now find this manuscript acceptable for publication.

Thank you for your time and consideration,

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Reviewer #2: A nice manuscript and a few suggestions for improvement.
1) "objective" and "endpoints" & "outcomes" used interchangeably and conversely - the objective of a trial can be achieved by testing a null hypothesis on data collected for specified endpoints - rationalise language accordingly including that a trial can "meet" an objective not "meet an endpoint".

We thank the reviewer for this comment. We agree and have changed the terms “endpoint”, “objective” and “outcomes” accordingly.

2) Abstract defines Type A and Type B cardiac events - these are not referred to in the main text

We thank the reviewer for this comment. We have included in the “methods section” the definition of cardiac event A and cardiac event B.

3) pCR / ORR etc are activity related endpoints not efficacy (this is not a comparative trial with PFS type endpoint)

Thank you. We have changed the term efficacy for activity.

4) Further justification for the statistical design would be reasonable - the absolute rate of cardiac events will be heavily influenced by age and other demographic factors and thus where there is no control group consideration should be given as to whether the "control" rates observed in other trial is applicable to this patient population - who were generally quite young. Furthermore given the relatively small sample size the number of observed events results in a lack of precision of the estimated rate. this should be acknowledged.

We thank the reviewer for this comment. Unfortunately, the patients included in the trial had few baseline cardiovascular risk factors, which we have described in the results section, and there was an age limit of 75 years to participate in the trial. The majority of HER2-positive breast cancer trials that combine dual anti-HER2 therapy and anthracycline therapies have similar inclusion criteria. We have specified these limitations in the discussion section.
In the PDF you can find this letter with a table that summarizes the neoadjuvant clinical trials with anthracyclines concurrent with trastuzumab and pertuzumab.

5) Results - please include n cases when reporting results not just the %.

We thank the reviewer for this comment. We have included the number of patients accompanying each percentage.

Reviewer #3: 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.

We apologize if it was not clear. We decided to use liposomal doxorubicin, despite not being standard in this setting, due to its lower risk of cardiotoxicity (van Dalen EC el al. Cochrane Database Syst Rev 2010). We have now better explained this in the background section.
2. Please specify the route of drug administration in the Methods section (Procedures) - page 5.

We thank the reviewer for this comment. We have now specified the route of administration of each drug.

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

We thank the reviewer for this comment. We have now indicated the clinical trials under each corresponding treatment.