Author's response to reviews

Title: WSG ADAPT - Adjuvant Dynamic marker-Adjusted Personalized Therapy trial optimizing risk assessment and therapy response prediction in early breast cancer: Study protocol for a prospective, multi-center, controlled, non-blinded, randomized, investigator initiated phase II/III trial.

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Author's response to reviews: see over
Dear Professor Altman,

please, find attached our revised manuscript "WSG ADAPT - Adjuvant Dynamic marker-Adjusted Personalized Therapy trial optimizing risk assessment and therapy response prediction in early breast cancer: study protocol for a prospective, multi-center, controlled, non-blinded, randomized, investigator initiated phase II/III trial", which we would like to re-submit for publication as a study protocol article in the “Trials” journal according to the reviewer’s report.

Regarding the reviewer’s specific comments, please find below our point-by-point response to the concerns:

1. Randomization (chemotherapy vs. no chemotherapy) of patients identified to be intermediate risk with low response cannot be justified. Nevertheless, these patients will be analyzed regarding their response to endocrine therapy. Additionally, a pooled analysis between intermediate risk patients (N0-1, RS 12-25; all treated by chemotherapy) from our previous planB trial and patients at intermediate risk/no response from ADAPT will be performed to evaluate, whether effects of chemotherapy can be addressed to the group predicted to be low responders.

2. The allocation to the respective sub-trials is dependent on the local pathologist’s result for hormone and HER2 receptors. Only within the HER2+ and Triple Negative sub-trials the receptor status has to be confirmed by central pathology for inclusion, because of high discordance rates for HER2 assessment between local and central pathology. HR+/HER2- patients will not be dependent on central pathologic confirmation, but will be included based on the local result. This is due to the fact that in our previous planB trial the concordance between local and central pathology for hormone receptors was good.

3. Patients will be assessed for tolerability of chemotherapy at baseline (within 14 days prior to randomization) based on physical examination, laboratory values and performance status. Only patients who are fit to receive chemotherapy within routine clinical setting should be included into the study. Blood evaluation can be done per protocol after registration, e.g. while genomic signature and central pathology are assessed. If the patient will show abnormal blood values, she will be excluded as drop out. Patients with abnormal blood values, not receiving chemotherapy (low risk or intermediate risk and response) can remain within the trial. In order to clarify this concern “patients receiving chemotherapy…” was removed.

4. EFS will be a primary endpoint of the ADAPT umbrella for comparison involving all four sub-studies. Patients with HR+/HER2- breast cancer and low risk (N0-1 and RS 0-11) are defined to be the “gold” population (94% EFS), showing the best outcome. For clarification we added the EFS value (p. 14).

5. Since so far there are no data available to compare a HR+/HER2- low risk group with either HR+/HER2- high risk, HER2+/HR-, HER2+/HR- or Triple Negative groups the comparison for event-free survival is exploratory, i.e. it is no formal hypothesis, but the purpose of the trial is to explore this assumption more thoroughly in order to develop some specific hypothesis or prediction that can be tested in future research. The term
“hypothesis” was replaced by “analysis” and the character of the analysis is now described (p. 18).

6. The effect of late introduction in poor responders will be evaluated as a secondary objective of the HR+/HER2- sub-trial by a pooled analysis from our previous planB trial, where all patients at intermediate risk (N0-1, RS 12-25) received chemotherapy. These intermediate risk patients from planB will be compared to both the intermediate risk responders and intermediate risk non-responders from ADAPT HR+/HER2-.

7. If EFS >90% will be shown in these patients administration of chemotherapy cannot be justified, irrespective of the risk/benefit ratio.

8. As in clinical routine, all patients with progress/insufficient response after 3-6 weeks of therapy will go off the applied therapy and change treatment. This of course leads to a drop out of the patient from the study.

Numbers from the Neosphere trial show that most of the patients responded well (93.5%) to dual blockade, yet without chemotherapy (Gianni, et al., "Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial." Lancet Oncol. 2012 Jan;13(1):25-32). Recent results from the TBCRC 006 trial confirm these response rates (97%) (Rimawi, et al., "Multicenter phase II study of neoadjuvant lapatinib and trastuzumab with hormonal therapy and without chemotherapy in patients with human epidermal growth factor receptor 2-overexpressing breast cancer: TBCRC 006." J Clin Oncol. 2013 May 10;31(14):1726-31).

We hope to have answered your comments to your satisfaction and will consider our umbrella protocol design for publication in “Trials”.

Yours sincerely,

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Project Manager