Reviewer's report

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.

Version: 1 Date: 25 July 2013

Reviewer: Daniel Sargent

Reviewer's report:

This is a very ambitious protocol for the treatment of breast cancer. It is reflective of the current emphasis on individualizing therapy using both biologic subtype as well as early response biomarkers. The partnership demonstrated between academia and multiple industry partners is remarkable and provides an example for all clinical trialists, as does (if successful) the ability to conduct pathologic and genomic assessments in real-time. The design, although complex, is presented clearly and logically. As with any attempt to leap forward, certain decisions/assumptions were made; the discussion could elaborate somewhat on the possible repercussions should the results not provide clear support for these decisions. Statistically, while some adjustment is proposed for multiple comparisons, given the large number of total tests being conducted with 80% power, it must be recognized that the experiment-wise likelihood of one or more false positive or negative findings is high. Interestingly, the authors have chosen to perform fixed randomization, as opposed to adaptive randomization such as in the ISPY-2 trial, this decision may warrant discussion. Also, while path CR is a promising endpoint, its clinical utility within each different sub-type requires further validation, so long-term follow-up for all patients will be very important. Additional specific comments follow.

Specific Comments

1. Page 6, first paragraph – It should be acknowledged that the ADAPT design does not really test whether chemotherapy helps those predicted to be low responders.

2. Page 7, first paragraph, seventh sentence – The inclusion status is unclear to me as the last sentence of this paragraph states patients are eligible only if central review confirms the local results.

3. Page 8, second paragraph – It is not known at registration which patients will receive chemotherapy, so must not this criteria (ability to tolerate treatment) apply to all patients?

4. Page 14, Outcome Assessments Section – “… has a comparable outcome to …. ” – This is not clearly defined – on what endpoint is ‘comparability’ assessed?
5. Page 17, last paragraph, first sentence – “As an exploratory hypothesis….” – Please provide a definition for an ‘exploratory hypothesis’.

6. Page 18, ADAPT HR+/HER2 – Sub-trial section, first paragraph – This is a clear aim – that N0-1/RS 12-25 patients who are ‘responders’ based on Ki-67 do as well as N0-1/RS 0-11 patients. However, if clinical practice is to start chemotherapy in all N0-1/RS 12-25 patients, it is clinically useful only if the delayed introduction of chemotherapy can salvage the poor responders, since at the outset you will not know which patients will have a good Ki-67 response.

7. Page 18, ADAPT HR+/HER2 – Sub-trial section, second paragraph – If the outcomes of the N0-1/RS 12-25 responders are intermediate between N0-1/RS 0-11 and the N0-1/RS 12-25 non-responders, it will be unknown whether chemotherapy would have provided a benefit to such patients.

8. Page 20, end of second paragraph – This implicitly assumes that in non-responders, a late introduction of chemotherapy would provide the same benefit as the early introduction, a hypothesis that is not being confirmed here.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests'