Reviewer's report

Title: Neoadjuvant Trials in Early Breast Cancer: Pathological Response at Surgery and Correlation to Longer Term Outcomes - What does it all mean?

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Reviewer: Lajos Pusztai

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The manuscript is timely but could be made more informative with a few modest changes and clarifications.

1. The investigators discuss at length the different path CR classification schemas but the impact of these is likely to be modest on the overall relationship between pCR and survival since the definition of pCR is very similar in all. I would suggest they include a table that actually shows in one study, maybe their own, how the different path response quantification methods classify the same patient population.

2. A stronger statement is needed at the end of this section that, after all the meandering, now there is a preferred, FDA endorsed definition of pCR and this is what should be used in future studies. They could point out that categorizing the extent of residual cancer is less uniformly agreed upon.

3. In the section on the variable impact of pathologic response on survival by disease subtype, the authors repeat a misleading and incorrect statement that unfortunately common. They state “breast cancers that are low grade….have a week association between pCR and survival outcome”. This is completely contrary to all evidence. pCR has a consistent and strongly significant association with excellent survival in all breast cancer subtypes. However, the extent of residual cancer is less prognostic in low grade ER+ cancers. It is critically important to understand the difference between these two statements: “In ER+ low grade cancers, pathologic response has less prognostic value than in other subtypes” (correct statement). “In ER+ low grade cancers, pathologic complete response has less prognostic value than in other subtypes” (incorrect statement because these patients have just as good survival as cases with pCR in other subtypes.).

4. The statement that “absence of ctDNA after neoadjuvant therapy may provide more robust signal of cure than pCR” is rather naïve. The survival of cases with pCR is already very good so further selecting patients from that group is somewhat of a futile idea. They may want to clarify what they mean. Perhaps, that neoadjuvant therapy clearing up circulating tumor DNA even if there is some modest amount of residual disease would imply excellent survival compared to those with persistent ctDNA.

5. My recollection of the Hatzis at all presentation is that they proposed that what
has a major impact on the relationship between trial arm level survival and improvement in pCR is the baseline prognosis of the accrued patient population. This makes intuitive sense and implies that even large increases in pCR rate will translate into very modest improvement in survival if the baseline prognosis is already good (an extreme example would be developing a drug that induces 100% pCR rate in DCIS, yet it would not improve survival from DCIS). When discussing the BEATRICE and ALTTO trials, they need to point out that in both studies, both trial arms had remarkably and unexpectedly good survival! This is consistent with the Hatzis statistical model.

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests