Reviewer's report

Title: Hot flashes are not predictive for serum concentrations of tamoxifen and its metabolites

Version: 1 Date: 18 July 2013

Reviewer: N. Lynn Henry

Reviewer's report:

The authors report their findings from a cohort of 115 tamoxifen-treated patients evaluating associations between hot flashes, tamoxifen and metabolite levels, and CYP2D6. The identification of a surrogate biomarker for predicting tamoxifen benefit would be clinically useful. The authors evaluated hot flashes as a potential biomarker and were unable to identify it as a useful surrogate in this small patient cohort.

Major Compulsory Revisions:
1. It is difficult to understand the trial design. On page 4 lines 106-108 the authors report that they do not have to obtain Ethics Board approval for studies that involve a simple single questionnaire. They also mention that they have a cross-sectional design with retrospective collection of hot flash information, and that enrolled subjects had serum concentrations of tamoxifen and metabolites determined as part of routine care. However, this seems to be contradicted by their statements on page 5 lines 111-113 about analyzing the serum samples after a period of storage, which would suggest that the samples were not analyzed for routine care. In addition, it is unclear whether the genetics evaluation was done as part of routine care. Finally, page 6 lines 167-169 refer to 132 returned questionnaires, with 13 patients declining further participation. What additional activities were the patients requested to do (other than complete that single questionnaire)? Therefore, it is not obvious why this protocol did not have to undergo IRB approval and why patients didn’t have to provide informed consent. Even if the patients did have tamoxifen metabolites and genotyping run as part of routine clinical care, a considerable amount of information was collected from these patients other than just having them complete a single questionnaire.

2. It is a significant design flaw to not have information about whether or not patients are receiving treatment for their hot flashes. This impacts the primary endpoint of the trial (hot flash frequency and severity) as well as the CYP2D6 phenotype.

3. The final statement in the Conclusion is quite strong, given the limited data to support use of tamoxifen metabolites as predictors of tamoxifen benefit.

Minor Essential Revisions:
1. In the abstract the authors state “patients with higher estradiol levels reported
more severe hot flashes”. This should be lower estradiol levels.

2. What quality assurance methods were used to verify the genotyping data? There is a very high reported rate of poor DNA quality (18%).

3. In Table 2, what is the difference between median estradiol concentration (whole cohort) and median estradiol concentration (within detection limits), and how many were in the second group.

Discretionary Revisions:
Why was a single questionnaire used to collect hot flash data rather than having subjects complete a diary over a week or so?

**Level of interest:** An article whose findings are important to those with closely related research interests

**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'