Reviewer's report

Title: Multicenter Phase II Study of Apatinib in Non-triple-negative Metastatic Breast Cancer

Version: 2 Date: 2 May 2014

Reviewer: Sara Hurvitz

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Major Compulsory Revisions:

1) Table 1: Patients with ER negative (31) vs positive (8) tumors adds up to 39. Should only add up to 38.

2) Table 1: This study excluded patients with triple negative disease. However, there were only 9 patients with HER2+ disease, 17 with PR+ disease and 8 with ER+ disease. So it seems that of the 38 patients enrolled, there must have been some that were triple negative? Authors need to change table so that we can see actual tumor characteristics of patients enrolled: how many patients had ER and/or ER+ HER2+ disease, ER/PR-HER2+ disease, ER+and/or PR+ HER2 negative disease?

3) Statistical section speaks of sample size calculation and states the study was designed with two-sided, #=0.05, 80% power to detect a null median PFS of 2 months and experimental median PFS of 4.5 months however does not give what the calculated sample size is (was it 38?) and does not address the fact that the PFS this study detected (4.0 mos) was less than their goal of 4.5 months. This should be acknowledged/discussed in the discussion section rather than only focusing on the response rate.

4) Eligibility requirements include prior capecitabine and (if HER2+) prior trastuzumab but then states that "any rational reason for no use of capecitabine/trastuzumab is acceptable." Authors should define what defines a "rational reason." In fact, it seems quite questionable that of the 9 patients with HER2 positive disease that there would be a rational reason that 6 of them never received trastuzumab.

5) Both the Abstract and the Conclusions indicate that apatinib has "substantial efficacy." While the efficacy seen in this small single arm study may be promising, it is an overstatement to say it is substantial. Many studies of angiogenic inhibitors have shown similar response rates without ever demonstrating an improvement in overall survival. Thus the enthusiasm for angiogenic inhibitors has naturally waned in recent years. The claims regarding apatinib's early activity should thus be more modest.

6) In Abstract and Conclusions, authors state that this drug might be better tested in breast cancer with high angiogenesis dependence. The problem is, no one to date has defined what breast tumor types are highly dependent on angiogenesis. The authors should consider discussing whether any biomarker studies are being
planned or have been done to try to better understand if there is a molecular subtype of breast cancer that would be more sensitive to apatinib. To date, no marker has been discovered/validated that predicts response to angiogenic inhibitors.

7) The authors should acknowledge in the discussion that no angiogenic inhibitor (including bevacizumab, which has been most thoroughly explored with a series of phase III studies) has been shown to improve survival in breast cancer. Why might apatinib be different? Why should we continue to evaluate angiogenic inhibitors like apatinib in patients when no study has shown it helps save lives?

Minor essential revisions:
1) reference numbers throughout text are normal size font (rather than in parentheses or superscript). This is very distracting/confusing.
2) polishing of grammar and syntax is needed

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

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

Roche has paid for travel for me to speak at symposia.
Roche/Genentech has paid my institution research/grant funding on my behalf.