Reviewer's report

Title: In situ aromatase expression in primary tumor is associated with estrogen receptor expression but is not predictive of response to endocrine therapy in advanced breast cancer

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Reviewer: Ratna K Vadlamudi

Reviewer's report:

In this study, Lykkesfeld et al., examined whether expression of aromatase alone or in combination with PR predicts the response to treat with aromatase inhibitors and or with tamoxifen. Using two different methods of staining of antigens (whole section and tissue micro array), authors demonstrated a lack of association between PR and in situ aromatase expression and showed that aromatase expression alone has no predictive value for determining endocrine therapy. However, they found a strong trend between levels of aromatase, and expression of ER as a good prognostic indicators. Another interesting finding is that aromatase expression in combination with PR may select letrozole treated patients with longer time to progression. Understanding the role of local E2 in the breast tumor progression and predictive value of aromatase expression in breast tumors is clinically important as they allow patient targeted therapy options. This manuscript contains potentially important information regarding expression of local aromatase enzyme and the predictive value of therapy response and should be published. I have few suggestions/concerns and addressing these questions will make this manuscript considerably stronger.

Concerns:

1. The findings that aromatase expression is too heterogeneous and lack predictive value is interesting. Authors have used two different methods to semi quantitative the expression of aromatase and its associated molecules. It is necessary to include representative IHC images from both methods as part of the manuscript and also representative IHC to go with level of expression.

2. The statement that “local estrogen synthesis is not the major source of the for intratumoral estrogen” is only weakly supported by circumstantial data and needs to be revised.

3. Some discussion of about the mechanisms of aromatase induction is important since authors measured COX2 and tried to correlate it with aromatase expression.

4. Inclusion of prognostic importance of ER is important. Correlating PR and aromatase may not mean much because some ER-ve tumors also express PR and ER is the key transcription factor and effector of local synthesized E2.
5. Shorten the paper since most of the findings are confirmatory

**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