Reviewer's report

Title: Preoperative serum HER2 extracellular domain levels in primary invasive breast cancer

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Reviewer: Sasha Badzek

Reviewer's report:

First of all, the article is thorough and well-written, emphasizing a very interesting aspect of a two decades old HER2 story. Personally I have enjoyed reading it.

I have a few comments though:

It has already been suggested:

- that HER2ECD is a separate prognostic and predictive factor in metastatic and locally advanced breast cancer (Mehta et al 1998, Sasaghatchian et al 2001)

- that serum HER2 positivity is not a substitute for tissue HER2 positivity because it is the reflection of a different HER2/neu activation process

- that in patients with early breast cancer (stage I-II) a lower cutoff value should be used (i.e. 7.4-7.7 ng/mL - derived from comparison with healthy controls!) in future research (Badzek et al 2011, Ma et al 2012), and

- that prognostic and predictive value of serum HER2 positivity should be established for patients with stage I-II breast cancer, but using a lower cutoff value than one suggested for stage III-IV disease.

Therefore, the article is on the right way establishing a prognostic value of the serum HER2 testing in early breast cancer, but I do not understand why the authors grouped patients with stage I-II disease together with patients with stage III disease, while using a stage III-IV cutoff value, when it is clear that these populations are basically different?

Although (thankfully to the large sample size) prognostic value of serum testing has emerged, forcing of metastatic cutoff value could be misleading in future research utilizing serum HER2 testing in patients with early breast cancer.

It's like mixing apples and oranges, and therefore I think that the analysis should be recalculated to include sample of patients with stage I-II disease only - according to the quality of statistical analysis that clearly should be no problem to the authors.

Therefore,

- major compulsory revisions -
1. recalculate the analysis to include only patients with stage I-II disease, and/or use serum HER2ECD cutoff value of 7.4-7.7 ng/mL (or 10.2 ng/mL as suggested for Korean population).

- minor essential revisions -

1. please clarify in the introduction why there is a discrepancy between tissue and serum HER2 positivity (different activation methods of the HER2/neu). It is not clear from the introduction that the serum HER2 positivity is a separate molecular process, reflecting in a separate prognostic and predictive value in patients with breast cancer.

2. please comment out in the introduction that clinical usage of tissue-only HER2 positivity determination results in (not yet certain) percentage of biologically HER2 positive patients not being treated with anti-HER2 agents, as well as in (not yet certain) percentage of tissue positive patients treated with trastuzumab although they are non-responders.

**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.