Author's response to reviews

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

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Author's response to reviews: see over
Dear Editor in Chief.

We really appreciate the reviewers’ excellent comments. We tried our best to meet their requests for the revision. For the reasonable comment about the more optimal cutoff for HER2 ECD, we presented our opinions (“changing the cutoff from 15.2 to 7.7 would not be appropriate”) along with the detailed recalculated analysis. We moved all tables and figures from the separate supplemental PDF to the ’tables and figure section’ of the main paper. The additional explanation follows the this paper. I’m afraid there could be persistent stand-off between the reviewer#1 and us about this issue. If so, additional commentary or a letter by the reviewer#1 and our thorough reply to it could be an alternative to solve this problem. And we added the explanation about low use of trastuzumab in the study population into the discussion session.

It would be greatly appreciated if the editor in Chief positively considers this potential disagreement.

Sincerely yours

Jong Won Lee

<Answers to the comments>

1. Reviewer #1

(1) Major compulsory revisions -
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).

We totally agree to the reviewer’s opinion. Frankly speaking, we have already analyzed our data with various cutoffs including 7.7 ng/ml and 10.2 ng/ml, and admit there were difficulties regarding the optimal cutoff value for the aims of this study. However, we concluded that the cutoff of 15.2 ng/ml is acceptable considering following reasons:

(1) In terms of survival outcomes, our initial analysis showed that this cutoff (log rank p<0.001, Figure 4-(A) ; and Cox proportional-hazards regression, adjusted hazard ratio=3.788 , p<0.001, Table 4) was more significant compared with other cutoffs such as 10.2 ng/ml (log rank p<0.001, Figure 4-1-(E) ; and Cox proportional-hazards regression adjusted hazard ratio=3.079 , p=0.003, Table 4-3) and 7.7 ng/ml (log rank p=0.109, Figure 4-1-(G) ; and Cox proportional-hazards regression, adjusted hazard ratio=3.273 ,
As the reviewer commented, we recalculated to find the same results in patients with stage I-II breast cancer (Figure 4-1(A), (B), (C), and (D); Table 4-1, and 4-2). All the detailed results (Table 3-1, 3-2, 4-1, 4-2, 4-3, 4-4, and Figure 4-1) recalculated as you’ve requested are attached.

(2) In terms of the concordance between serum and tissue HER2 status, as we mentioned in the discussion section, a standard test is tissue HER2 and serum HER2 ECD is adjunctive. So, we did not want to increase false positivity inherently caused by lowering a cutoff. As you can see in Table, ROC re-analysis using not only stage I-III patients (Table 3-1-(3)) but also stage I-II patients (Table 3-2-(3)) did not show any superior performance compared with the initial analysis (Figure 3-(1) and (2)).

(3) We also believe that HER2 ECD values in patients with stage I-II and stage III are significantly different (Table 1). We partly agree your comment “it’s like mixing apples and orange”, but breast cancer is a heterogeneous disease, as you know. As you can see in table 1, mean HER2 ECD levels vary according to a lot of anatomical (lymph node metastasis) / biological (grade, hormone receptor, HER2) factors. We would like to say that the aims of this study did not include “which cutoff value is more optimal for early breast cancer vs. advanced breast cancer, high grade vs. low grade, HR+ vs. -, or HER2+ vs. -". Please take into account that we aimed to investigate the clinical utility of HER2 ECD in real practice settings. We hope to be able to determine the controversies regarding more precise cutoffs for HER2 ECD in the future.
(2) Minor essential revisions -
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.

Yes, we did as much as we could. Please take into account we have partly mentioned this in the discussion section, too.

(3) Minor essential revisions -
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.

Yes, we did as much as we could. Please take into account we have partly mentioned this in the discussion section, too.
2. Reviewer #2

(1) Minor: median follow-up of the series must be detailed.

Yes, we did. Median follow-up and the method of computing it were added in the result section (Prognostic value of serum HER2 ECD level) and the method section.

(2) Minor: Use or absence of use of trastuzumab must be explained (this is only mentioned in the discussion, and only 700 cases are analyzed in the figure): was this due to slow penetration of trastuzumab in Korea, or was related to the inclusion of patients with small tumors, in which trastuzumab was not indicated?

Yes, we did. The explanation of the low use of trastuzumab was added in the discussion section.