Reviewer’s report

Title: Efficacy and Safety of HER2 Inhibitors in Combination With or Without Pertuzumab for HER2-Positive Breast Cancer: A Systematic Review and Meta-Analysis

Version: 1 Date: 18 Aug 2019

Reviewer: Robert Wesolowski

Reviewer's report:

The reviewers addressed many of my comments and wrote a very detailed rebuttal which is greatly appreciated. The manuscript was edited based on the comments and the English grammar is greatly improved. I have several additional comments.

Comment 1:

Result section in the abstract: Please provide p values for pCR, PFS and OS results (only 95% CIs for respective HRs were provided and some of 95% CI crossed 1 (such as OS in metastatic disease) but the authors commented that the HR was statistically significant). This request has already been made by a reviewer before but the revised abstract still lacks these p-values.

Comment 2:

In the response to reviewer 2's comment 5, the authors state:

"...After statistical analysis, our results showed that H+P significantly improved PFS (HRs = 0.75; 95% CI, 0.68-0.84; p < 0.001). Unfortunately, statistical significance was not observed in the OS analysis (HRs = 0.81; 95% CI, 0.64-1.03; p = 0.082) (Fig. 3). However, we found that the efficacy of group H+P was superior to that of group H by analyzing the OS results. We suspect that the p value of OS may be due to insufficient sample size, further larger scale and well-designed RCTs are needed to identify this trend. Hence, we believe that the efficacy of group H+P was better than group H in our paper."

When overall survival difference does not meet statistical significance, one has to acknowledge that it is unacceptable to definitively conclude that the difference was meaningful. The fact that p value for OS is not statistically significant (0.082) makes any statement implying that H+P is associated with superior survival compared to H not valid (regardless of the number of patients or events that were analyzed). P-values reflect cut off for an acceptable alpha error (i.e. probability that rejection of null hypothesis is incorrect). In other words if one accept <5% chance that your conclusion that H+P has superior OS to H regimens, then one cannot make that conclusion if the calculated alpha error of 8.2%. One could state that there was a trend towards better overall survival but that it did not reach statistical significance. One could also mention
that this could be possibly due to insufficient number of events but it is absolutely incorrect to state that this means that the survival was better.

I strongly suggest that this important point is taken into account and corrections are made in the abstract and manuscript to acknowledge this.

Comment 3:

Highlighted sentence in Line 2-6 on the second page of introduction (page 11):

"...that involves either its homodimerization with another HER2 or heterodimerization with a different receptor of the HER family,..."

Please delete this part of the sentence (which is incorrect mechanism of action of pertuzumab) and keep the second part of the sentence (which is correct).

Comment 4:

Consider changing the last sentence of the introduction to the following:

"The present systematic review aimed to assess the efficacy and safety of H+P versus H in the (neo)adjuvant treatment of OPERABLE HER2+ breast cancer AS WELL AS METASTATIC DISEASE and to stratify the other influencing factors."

Comment 5:

Line 50 in Discussion:

"Unfortunately, statistical significance was not observed in the OS analysis (HRs = 0.81; 95% CI, 0.64-1.03; P = 0.082) (Fig. 3). However, we found that the efficacy of group H + P was superior to that of group H by analyzing the OS results. Further larger scale, well-designed RCTs are needed to identify this trend."

Pls revise to:

Unfortunately, statistical significance was not observed in the OS analysis (HRs = 0.81; 95% CI, 0.64-1.03; P = 0.082) (Fig. 3). However, we found that the efficacy of group H + P was superior to that of group H by analyzing the OS PFS results AND TRENDED TOWARDS BETTER OS WHICH DID NOT REACH STATISTICAL SIGNIFICANCE. Further larger scale, well-designed RCTs are needed to identify this trend.
Comment 6:

I am not clear as to what is the difference between figure 2A and 2B? Figure 2A legend states that it is analysis in single arm trials. What is then the comparator? Is the comparator historic controls? Please clarify in the figure legend.

Comment 7:

Section 3.2.1, line 39: The following sentence needs to be clarified as I am unable to understand what is being said:

"The pooled estimates using a fixed-effects model indicated that H+P significantly increased the pCR of the control group [THE CONTROL GROUP ARE PATIENTS WHO RECEIVED H] compared with the effect of H in HR+ (absolute rate 18 = 0.39 versus 0.30) or HR- (absolute rate = 0.68 versus 0.51) patients. However, no significant difference was found between HER2+ and HR+ breast cancer (OR=1.37; 95% CI, 0.88-2.13; P = 0.162) or HR- (OR=1.37; 95% CI, 0.91-2.07; P = 0.126) (Fig. 2B) patients." [THIS IS BASICALLY CONTRADICTING THE FIRST SENTENCE].

Comment 8:

Section 3.2.2, line 11:

"Regarding OS, the analysis revealed a substantial OS benefit from H+P (HRs = 0.81; 95% CI, 0.64-1.03) (Fig. 3)."

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further
assessment in your comments to the editors.

I recommend additional statistical review

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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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