Author’s response to reviews

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

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Author’s response to reviews:

Dear editor and reviewers,

We are very grateful for your kind letter dated on July 09, 2019, and the reviewers’ reports. We thank you very much for giving us an opportunity to revise our manuscript, we also appreciate you and reviewers for comments on our manuscript entitled “Efficacy and Safety of HER2 inhibitors in Combination With or Without Pertuzumab for HER2-Positive Breast Cancer: A Systematic Review and Meta-Analysis” (ID: BCAN-D-19-01571).

Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have read reviewer’s comments carefully and have made modification on the original manuscript. Revised portion are marked in green in the paper. We would like to thank the referees for taking the time to review this manuscript and giving us these helpful comments. We hope that we have now produced a more balance and better account of our work and trust that the revised manuscript is acceptable for publication. All questions were answered below.

Responds to the reviewer’s comments:

Reviewer 1:

1. Overall appraisal:

The authors performed a good meta-analysis about the efficacy of the combination of pertuzumab or not in HER2+ breast cancer patients from selected 26 studies. The results indicated that the combination with pertuzumab together with trastuzumab related drugs +/- chemotherapy is better than monotherapy for HER2+ breast cancer patients. I think the results
are important for the decision for the treatment of HER2+ breast cancer patients. However, the authors should consider to perform further comparison by adding another group of pertuzumab monotherapy to let doctors or patients clearly know the benefits/ adverse effects among these three different treatments.

Author response:

I am very grateful to the reviewer for your recognition and support for our research, as well as for these very valuable suggestions. It is really important as reviewer suggested that we should perform a comparison of the three groups (trastuzumab monotherapy, pertuzumab monotherapy and dual anti-HER2 targeted therapy) in our research. Unfortunately, we re-searched the database and just found one clinical trial which included the pertuzumab monotherapy group. Due to the lack of data on pertuzumab monotherapy, we could not perform a meta-analysis of the three treatment groups by forest-plots, but we added some explanations in the discussion section. (discussion section, line 8-14, page 15 and line 8-11, page 17).

2.Comment 1: Only the arrangement of "Favours no pertuzumab" or "Favours combination" was different in Figure 3. For making consistence through whole manuscript, it is suggested to change the arrangement of Figure 3 as those of other figures.

Author response:

Thanks you for taking the time. Although the arrangement of "Favours no pertuzumab" or "Favours combination" was different in Figure 3., we could not change the arrangement of Figure 3. Because hazard ratios (HRs) value belongs to continuous variable and odds ratio (OR) value belongs to binary variable, there are differences between them in statistical methods. If the upper and lower limit of 95% confidence interval (CI) of OR value is greater than 1, the incidence of experimental group is higher than that of control group. The incidence of group HER2 inhibitors + pertuzumab ± chemotherapy (H+P) was higher than that of group HER2 inhibitors ± chemotherapy (H) in our research. If the upper and lower limit of 95% CI of HRs value is less than 1, the mean of PFS and OS in the experimental group is longer than that in the control group, then the efficacy of the experimental group is better than the control group. The efficacy of group H+P was better than group H in our paper. Hence, the arrangement of "Favours no pertuzumab" or "Favours combination" in Figure 3(PFS/OS) was different from those in other figures (pCR/incidence of AEs).

3.Comment 2: The qualities of figures were poor, even the original uploaded files. It should be improved.

Author response:

We are very sorry for our negligence of the qualities of figures, and we have readjusted the resolution of our figures.
4. Comment 3: The p value of pCR, PFS, OS, or cardiac toxicity should be provided in abstract section as it was provided for myalgia.

Author response:

Thanks for your professional advice. We agree with this suggestion, and the p value of pCR, PFS, OS, or cardiac toxicity have provided in abstract section. (abstract section, line 1-4 and 8-9, page 3).

Reviewer 2:

1. Overall appraisal:

The authors of this manuscript performed very extensive meta-analysis of published or presented clinical trials that tested trastuzumab or ado-trastuzumab emtansine containing regimen with those who combine these agents with pertuzumab. 1) The meta-analysis has impressive amount of data that was analyzed but suffers from high heterogeneity of studies included. 2) Some of the conclusions drawn in the body of the manuscript are not backed up by the meta-analysis (in particular the conclusion that adding pertuzumab is associated with no clinically meaningful increase in the toxicities). 3) This meta-analysis should focus on randomized prospective trials in 1 clinical setting (neo-adjuvant chemotherapy or specific line of therapy in metastatic disease). 4) Finally, the meta-analysis does not add much in terms of novelty.

Author response:

Thank you for your affirmation of our research and efforts, thank you also for giving us many valuable suggestions to make our paper more and more perfect. We have carefully read and corrected all the problems.

1) Our original intention was to enable readers to obtain comprehensive, reliable, and valuable information from our paper. Therefore, we collected a large amount of data related to our research to avoid insufficient evidence to affect our results. Regarding high heterogeneity, it was only found in the pathologic complete response (pCR)/adverse events (AEs) analysis of single arm trials. The pCR/AEs analysis of single arm trials is to assess the efficacy and safety by aggregation event rates and to determine the range of the rates of pCR/AEs. Moreover, data with high heterogeneity were removed and the remaining data were re-analyzed by conducting forest-plots in sensitivity analysis.

2) We did not classify common and typical AEs as sever toxicity but classified cardiototoxicity as sever toxicity when we analyzed AEs. So our conclusions was different from those of reviewer. All authors of this paper are agree with the suggestions by the reviewer, and we checked throughout the paper and made corrections where needed.
3) We are very appreciated with these important suggestions by the reviewer and agree with this. There were two randomized prospective trials which focus on neo-adjuvant and metastatic settings in our meta-analysis. We analyzed the effectiveness of the randomized prospective trial of neoadjuvant therapy, whereas prospective trials of metastatic therapy were performed safety analysis.

4) In fact, our article is different from other reported meta-analysis about pertuzumab-based therapies for breast cancer.

i. We performed firstly a systematic review and meta-analysis to investigate the benefit from pertuzumab-based dual anti-HER2 therapies versus monotherapies, and to report the results of subgroup analysis conducted with respect to hormone receptor (HR). However, most of the other articles were network meta-analysis which included a small number of clinical trials involving pertuzumab based therapies and meta-analysis of security of pertuzumab.

ii. In our study, sufficient samples have been collected, which increases the statistical power to evaluate the effect of combination treatment. Three new public RCTs of T-DM1 (ClinicalTrials.gov number: NCT01120184, NCT00951665 and NCT00934856), two pertuzumab based therapies (ClinicalTrials.gov number was NCT01491737 and a retrospective study) and fourteen single-arm studies were included in this article, while there were not available in other articles.

iii. In the neoadjuvant phase, we found that pertuzumab-based dual anti-HER2 therapies were associated with a significantly increased rate of pathologic complete response (OR = 1.33; 95% CI, 1.08-1.63), and the highest increase in pCR were found in HER2+ and HR- patients.

iv. In the metastatic setting, we found that pertuzumab-based dual anti-HER2 therapies was beneficial in overall survival (HRs = 0.81; 95% CI, 0.64-1.03) and progression-free survival (HRs = 0.75; 95% CI, 0.68-0.84), indicating pertuzumab in combination with HER2 inhibitors stabilized diseases and prolonged the survival of breast cancer patients.

v. Our article is different from other reported meta-analysis in safety. Rash, diarrhea, epistaxis, mucosal inflammation, and anemia were significantly more frequent with pertuzumab-based dual anti-HER2 therapies than with monotherapies, while myalgia was less frequent (OR = 0.91; 95% CI, 0.82-1.01; p = 0.072), and cardiac toxicity showed no significant difference (OR = 1.26; 95% CI, 0.81-1.95).

2. Comment 1: The results section in the abstract only describe analysis of pCR and do not discuss PFS and OS in metastatic breast cancer.

Author response:
Perhaps our analysis of PFS and OS lied between the analysis of pCR and subgroup of pCR, making you believe that we did not describe PFS and OS in metastatic breast cancer. Actually, we have described these results in the abstract, the discussion of pCR, PFS and OS are listed below.

“In the neoadjuvant setting, H+P significantly improved pCR [odds ratio (OR) = 1.33; 95% confidence interval (CI), 1.08-1.63; p = 0.006]. In the metastatic setting, H+P significantly improved both PFS [hazard ratios (HRs) = 0.75; 95% CI, 0.68-0.84; p < 0.001] and OS [HRs = 0.81; 95% CI, 0.64-1.03; p = 0.082].” (abstract section, line 3-4, page 3)

3. Comment 2: Toxicity data showed significant differences in the rates of rash, diarrhea, epistaxis and mucosal inflammation as well as grade 3 diarrhea and anemia, yet the conclusions are that there are no significant differences in toxicities between H+P and H regimens. This needs to be corrected.

Author response:

The conclusions of toxicity data were incorrectly stated in the original manuscript. This has been rectified. We are grateful to the referee for pointing out our error. (abstract section, line 10-12, page 3; conclusion section, line 2-5, page 20)

4. Comment 3: Sentence in line 1 of page 6 (introduction section):

In contrast to trastuzumab/T-DM1, pertuzumab showed its novel mechanism by either homodimerizing with another HER2 or heterodimerizing with a different receptor of the HER family to activate certain downstream signaling pathways through the phosphorylation of tyrosine kinases, and pertuzumab and trastuzumab bind to distinct extracellular domains of HER2.

This sentence is incorrect as written and needs to be revised. Pertuzumab does not homodimerize with another HER2. It binds to a separate domain on the extracellular portion of HER2 (domain 2) and by doing so, it prevents formation of homo- and hetero-dimers which are required for activation of HER2 signaling cascade. This may be due to the fact that English language is not the authors' native language. I suggest revising and breaking the sentence down into 2 or 3 sentences.

Author response:

We agree with the suggestions by the reviewer. Perhaps authors of this paper are not native speakers, this sentence has not been accurately expressed. As suggested by the referee, we have corrected it. The revision have been proofread by a professional English language editing team (American Journal Experts) and we are trying to make it clear and consistent. (introduction section, line 2-6, page 5)
5. Comment 4: Were publications in language other than English included? If not, this should be stated in the materials and methods section.

Author response:

We followed this suggestion and added this information in the materials and methods section. (materials and methods section, line 8-9, page 7)

6. Comment 5: Metastatic disease was also evaluated for efficacy of adding pertuzumab to trastuzumab. This is not evident in the abstract and discussion sections. Please include that information.

Author response:

Thanks for your professional advice. We may not understand your opinion well, but we have made explanations of your suggestion based on our understanding. In metastatic settings, we focus on comparing the efficacy of H(trastuzumab or trastuzumab emtansine ± chemotherapy)+P (pertuzumab) group and H group, and the analysis of PFS and OS were regarded as primary results of efficacy. The hazard ratios (HRs) and 95% confidence intervals (CIs) was extracted and pooled for PFS and OS in H+P group and H group. The HRs outcome from controlled trials was evaluated, by means of forest-plots to determine the overall HRs effect between the experimental group and control group. The HRs value belongs to continuous variable. If the upper and lower limit of 95% CI of HRs value is less than 1 and p < 0.05, the mean of PFS and OS in the experimental group is longer than that in the control group and the results were statistically significant, then the efficacy of the experimental group is better than the control group. 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. All the above results were presented in this paper. (abstract section, line 3-4, page 3; discussion section, line 15-24, page 15 and line 1-3, page 16)

7. Comment 6: The manuscript requires edits by an English speaking writer as there are multiple grammar and style errors.

Author response:

Thanks for expertise advice. First of all, we checked throughout the paper and made corrections where needed. Then, we submitted our manuscript to a professional team (American Journal Experts) to modify the language when we have completed self-checking. We confirmed the current version after all modifications have been completed. The editorial certificate is submitted to the supplementary materials named “Language editorial certificate”.
8. Comment 7: Line 17 on page 16 (Discussion):

"In metastatic settings, compared to H, H+P for treating patients with HER2+ demonstrated significant benefits for PFS (HRs = 0.75; 95% CI, 0.68-0.84; p < 0.00001) (Fig. 3) and OS (HRs = 0.81; 95% CI, 0.64-1.03; p = 0.082) (Fig. 3)."

The difference in OS did not reach statistical significance, hence this conclusion is wrong.

Author response:

We are sorry for this mistake, and we checked throughout the manuscript and made changes accordingly. (discussion section, line 17-21, page 15)

9. Comment 8: Figures are not labeled and I do not know when Figure 1 ends and when Figure 2 begins, and so on.

Author response:

We have added the captions and corresponding explanations of the Figures.


"In clinical practice, these adverse reactions are quite common for targeted therapies, and their effects are smaller and more tolerable than those in clinical trials."

I disagree with this statement. Typically toxicities of therapies are lower in clinical trials due to careful selection of patients with good performance status, good organ function and excellent health otherwise. Many times, rates of toxicities seen in clinical trials end up higher in general patient population.

Author response:

We are very appreciated with these important suggestions by the reviewer and agree with them. This statement has been revised in accordance with the reviewer's suggestion. (discussion section, line 22-24, page 17 and line 1-4, page 18)

Finally, thank you for the comments and help again, and giving us the opportunity to revise. I hope that the correction will meet with approval.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,
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