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 Aug 19, 2019. Thank you very much for taking the time to review the manuscript again and giving us an opportunity to publish our paper in BMC cancer, and we appreciate you and reviewers again for these 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-19-01571R1).

Those comments are all professional and valuable. We have modified the manuscript carefully according to the reviewers’ comments. Revised portion are marked in green in this paper. 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:

Overall appraisal:

The authors have done a great improvement of their manuscript and answered all the questions or revised their manuscript according my previous suggestions. I think the manuscript provided an important information for clinical doctors about the use of Herceptin and Pertuzumab in Her2+ breast cancers and should be accepted for publication in your journal.
Author response:

Thank you for taking the time to review the manuscript again, and thank you also for the comments you provided previously. It is precisely your professional and valuable suggestions that the quality of our paper had been improved quickly. We appreciate you again for your recognition and support for our research, it will play an important role in our further research.

Reviewer 2:

Overall appraisal:

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.

Author response:

Thank you for your approval of our revision, the comments you provided last time had greatly improved the quality of our paper. We greatly appreciate for taking the time to review the manuscript again and giving us many professional and helpful comments. We read the comments carefully and specially agree with you. We have made modification on the manuscript, all questions were answered below.

1. 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.

Author response:

We are very sorry for our negligence of lack of p-values, and our misunderstand of the result of OS in metastatic disease. We have provided p values for pCR, PFS and OS results, and the results of OS in metastatic disease are modified. (abstract section, line 1-5, page 3)

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

"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. "

1. 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.

Author response:

We are very sorry for our negligence of lack of p-values, and our misunderstand of the result of OS in metastatic disease. We have provided p values for pCR, PFS and OS results, and the results of OS in metastatic disease are modified. (abstract section, line 1-5, page 3)
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). 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.

Author response:

Thank you very much for your professional comments on my erroneous views and for explaining this problem in detail. I have already realized my mistakes. We checked throughout the manuscript and made changes accordingly. (abstract section, line 4-5, page 3; result section, line 9-10, page 12; discussion section, line 20-24, page 15)

3. Comment 3: "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).

Author response:

We are very appreciated with the important suggestions by the reviewer and agree with them. The incorrect mechanism of action of pertuzumab has been deleted in accordance with the reviewer's suggestion. (introduction section, line 2-4, page 5)

4. 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."

Author response:

Thanks for expertise advice. We followed this suggestion and rectified this sentence in the introduction section. (introduction section, line 3-6, page 6)

5. Comment 5: "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
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.

Author response:

We are grateful to the referee for pointing out our error and giving us detailed comments for modification. We have modified this OS part in discussion section according your comments. (discussion section, line 20-24, page 15)

6. 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.

Author response:

Thank you for taking the time.

First, we have added instructions to the figure legend according your suggestions. (figure 2; graphical abstract section, line 15-19, page 20)

Second, I would like to explain to you the differences between figure 2A and 2B. 1) Figure 2 is the forest plots of the pCR rates, including single-arm studies (only one treatment group: combination of pertuzumab with HER2 inhibitors) and controlled studies(two treatment group: combination of pertuzumab with HER2 inhibitors versus HER2-targeted therapies without pertuzumab) for patients with HER2+ breast cancer. 2) There are some differences of the purposes for the research between single-arm trials and controlled-arm trials: (1) Regarding single-arm studies, we could determine the differences in the efficacy of H+P on HR+/HR-breast cancer patients; we could intuitively analyze whether the effect of H+P for patients with HER2+ breast cancer is significant; we also determined the range of pCR in HR2+ breast cancer patients treated with H+P. (2) In the controlled studies, we could confirm the differences of the efficacy of H+P between HR+ and HR- breast cancer patients, and assess the influence of the efficacy of H+P versus H based on HR status. 3) The literature collection of single-arm studies and controlled studies in our research is different.

Third, all analyses were conducted with STATA 11.0 (State Corporation, Lake Way, Texas, USA). The data of single-arm could be analyzed by STATA, and one need to choose the
"Effect/SE" or "Effect/CI" option in "Type of Data" in STATA. The comparator was not collected in the single-arm studies, nor did we collect historic controls. Hence, the results of single-arm studies were presented in this paper.

7.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].

Author response:

We are sorry for this mistake, because our statement is not clear, the results have not been accurately expressed. We have corrected it, and the revision have been proofread by a professor who is fluent in English. Thank you very much for your criticism and correction. (result section, line 15-23, page 11)

8.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)."

Author response:

Thanks for your valuable advice. We have modified this result according to your previous comments. (result section, line 9-10, page 12)

Please take some of your time to review the revision again. If you have any question about it, please do not hesitate to let me know at your earliest convenience. I hope that the correction will meet with approval.

We greatly appreciate your time and consideration. We look forward to hearing you.

Yours sincerely,
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