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: 0 Date: 17 Jun 2019

Reviewer: Robert Wesolowski

Reviewer's report:

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. The meta-analysis has impressive amount of data that was analyzed but suffers from high heterogeneity of studies included. The studies ranged from non-randomized trials in metastatic breast cancer to randomized studies in neo-adjuvant settings. This presents a difficulty in interpreting the results. In addition, 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). This meta-analysis should focus on randomized prospective trials in 1 clinical setting (neo-adjuvant chemotherapy or specific line of therapy in metastatic disease). Finally, the meta-analysis does not add much in terms of novelty. Clinical benefit of adding pertuzumab to trastuzumab containing chemotherapy (albeit at a cost of additional toxicities, in particular diarrhea) has been well established from well designed, prospective randomized trials.

Comment 1:

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

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.

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.

Comment 4:

Were publications in language other than English included? If not, this should be stated in the materials and methods section.

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.

Comment 6:

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

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.

Comment 8:

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

Line 28 on page 18 (discussion):

"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.

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.

Unable to assess

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

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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