Reviewer's report

Title: Effect and safety of dual anti-HER2 therapy compared to monotherapy in patients with HER2-positive breast cancer: A Systematic Review and Meta-analysis

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Reviewer: Thomas Ruhstaller

Reviewer's report:

The authors are focussing on an important aspect of treatment in patients with HER2-positive breast cancer. However, a lot of aspects have to be improved in this manuscript that it is worth to be published.

Design: This is a systematic overview of results of published and not yet published but presented studies. The term “meta-analysis” is not appropriate to this kind of study, because the observed data are not homogenous enough. From my point of view the search strategies were valid and comprehensive.

Data extraction: well described. However, I missed the data about Pertuzumab +/- Trast. (JCO 2012, Cortes, 1594). Is there an explanation why this study was excluded?

Results: It is not completely clear reading the text, how you have reduced the 52 studies to 7. In Figure 1 this is well explained, however, it should also be mentioned in the text to avoid unclarity by reading the text.

Change the subtitle: “meta-analysis of pCR” to “pCR in neoadjuvant studies”.

In the chapter pCR the impact of the chemotherapy and the type of the chemotherapy has to be clarified. Additionally, there was one arm without chemotherapy in the Neo-Sphere trial, was this arm included in the analysis? Please clarify in the text.

Figure 2 and 3 are not matching in the text and the legends. Please correct it.

Change the subtitle: “Meta-analisis of PFS and OS” to “Analysis of PFS and OS in metastatic studies or setting”

In the chapter PFS/OS one study was with chemotherapy, one without. Please, describe that in detail in the results. All statistical comparisons with two studies only and in completely different patient population are not appropriate. Please delete them, instead you can describe the two studies.

Subgroup analyses:
The first chapter remains unclear. Comparing the RR with chemotherapy mentioned in this chapter and in the chapter “pCR” showed me, that in the overall
pCR results only arms with chemotherapy were compared. However, the text is not self-explaining whether the arm without chemotherapy was included or not.

The sentence “however, no significant difference of pCR was detected……” is unclear. Which arms were here compared? There was only one arm in all neoadjuvant studies without chemotherapy, wasn’t it?

The “subgroup analysis” in the metastastic setting is not a subgroup analysis, because there is no “group”, there is only one study for each possibility (with and without chemotherapy). I suggest deleting this part completely. You may discuss that in the chapter “discussion”. Also the statistical analysis is not appropriate, because there are two studies in completely different settings, one was a first line study in MBC, the other after several lines of chemotherapy and trastuzumab. You can describe this two trials and their outcome in the chapter “results”, but no comparison or statistical analysis is allowed. This part should also be deleted in table 2.

The comparison between different components can only be done in the neoadjuvant setting with the chemotherapy arms. And also that should be done only in a descriptive manner. The comparison between the two metastastic trials is not valid, and should be deleted. In my notes there was no table 3.

Risk of AE:

The first sentence is unclear, I assume you meant dual HER2-targeted therapy was associated with an increase in SAE. The term “combination therapy” is misunderstood, also trastuzumab and chemotherapy is a combination therapy. Please change that over the whole manuscript.

The last part of the last sentence has to be deleted (…, the number of patients experiencing these toxicities….), because it was neither significant nor a trend.

Cardiac toxicity: well done and interesting

Discussion:

This analysis summarize……..

The last sentence in the first chapter is too ambitious. This overview gives only some idea about the role of the dual HER2-directed therapy compared to monotherapy. (the statistical analysis has some value in the neoadjuvant setting, where you have 4 trials in the same setting. For all other statistical analyses you have to few data).

Despite these advantages….

1) Whether the chemotherapy could be avoided at the beginning in some cases in the first line setting in MBC should be further evaluated.

2) This point is not correct. Only the relative difference of dual versus monotherapy in metastatic disease was similar, the absolute difference of their benefit was 4 weeks and 6 months, respectively……and that in completely
different patient population. These kind of comparisons are not appropriate. Please, delete this issue.

3) Toxicity is well discussed.

4) Limitations: several ongoing trials (delete the sentence “it is unlikely that would change anything”, you cannot say that).

Conclusion: this overview shows that according to the present available data dual anti-HER2 therapy seems to be more effective than the monotherapy in the neoadjuvant setting. In the metastatic setting limited data so far..... However, it is justifiable to believe....

Table 1: metastatic and neoadjuvant together

A lot of statistical comparisons in this manuscript are not appropriate, this manuscript needs a complete revision under this aspect. Additionally it should be edited by an English-speaking person.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'