Author's response to reviews

Title: Effect and safety of dual anti-human epidermal growth factor receptor 2 therapy compared to monotherapy in patients with human epidermal growth factor receptor 2-positive breast cancer: A systematic review

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Author's response to reviews: see over
Dear editor,

Thanks for your kind reply, and thanks for the reviewers’ beneficial comments. We had revised the manuscript according to the reviewers’ comments and the point by point response is enclosed to this file. The reply was noted in blue. We also had done much work in English language editing. The English revision was provided by the Editage Company.

**Response to the Reviewers’ comments:**

**Reviewer 1: Guillermo Rodrigo**

**Reviewer’s report:**

Q1: The authors were engaged with an interesting and important theme. The Title “Review and Meta-analysis” is misunderstanding. This manuscript is an overview about present published or unpublished studies. In this manuscript data is not consistent enough in the different groups and appear too inhomogeneous to call it a meta analysis.

R1: We appreciate the positive feedback. And we had followed your advice and changed “Systematic Review and Meta-analysis” into “Systematic review” in the title.

Q2: Overall methods are well described, but it is written too extensive.

R2: We have refined the section of method and resorted to an English native speaker to polish the full manuscript.

Q3: Figure 1 shows selection process very well, but it should be commented more clearly in the text.

R3: We have further described the process of the literature selection in the text as following:

“The remaining 52 studies were retrieved for detailed assessment. 44 articles were excluded for the reasons of no combination of anti-agents, Phase II trials without control arms, not phase 2 or phase 3 study. One additional articles was included by searching 2012 ASCO Annual Meeting Abstracts[21]. Furthermore, Two trials were duplicated[22,23]and only the recent ones was included[15,24]. Therefore, a total of 7[15,21,24-28]randomized controlled trials were included in our final analysis, which consisted of 2,609 individual patients (Figure1).”.

Q4: Endpoints in the text included adverse events. It is not mentioned in the Abstract.

R4: According to your suggestions, adverse events have been described in the abstract: “Outcomes included pathologic complete response (pCR), overall survival (OS), progression-free survival
Q5: In line 75 anti-Her2-therapy is described as a standard therapy in the adjuvant setting. However I missed studies with anti-Her2-therapy in the adjuvant setting in your references.
R5: It is a typographical error; we have corrected “adjuvant setting” to “neoadjuvant setting”.
Q6: Line 165 chapter pCR: A comment to the chemotherapy regimens in these 5 neoadjuvant trials would be meaningful.
R6: We totally agree with the reviewers on this point, and we have revised the manuscript accordingly [page 7, line 154].

Original sentence: Five trials [24-28] were reported the data of pCR and all of them were in the neoadjuvant settings.
Revised sentence: Five trials [21,25-28] were reported the data of pCR and all of them were in the neoadjuvant settings. In these trials, anti-HER2 agents were combined with chemotherapy: paclitaxel in three trials [21,26,27], FEC in one trial [28], docetaxel in the remaining one [25]. Additionally, there was one arm without chemotherapy in the Neo-Sphere trial [25], and this arm was excluded in the pooled analysis.

Q7: Line 179 chapter PFS/OS: One study was with and one without chemotherapy. Please mention that in the text and describe different patient population. There are also 2 completely different settings (one first line, the other after progression after trastuzumab).
R7: We have carefully considered this issue. We deleted the pooled results; instead we describe the results of the two trials in detail as following:

Two studies[15,24] investigated the dual anti-HER2 therapy in metastatic setting. The CLEOPATRA study was a phase 3 study, which included 808 patients with HER2-positive MBC[15]. The patients were randomized to pertuzumab plus trastuzumab plus docetaxel (dual anti-HER2 therapy group) or trastuzumab plus docetaxel plus placebo (control group) as first-line treatment. The median PFS was 18.7 months in the dual anti-HER2 therapy group and 12.4 months in the control group. The difference in PFS was significant (HR 0.69; 95 % CI, 0.58–0.81; P<0.001). Furthermore, a significant benefit of overall survival was also observed for patients allocated treatment in the dual anti-HER2 therapy group compared with individuals assigned to the control group (hazard ratio 0.66, 95% CI 0.52–0.84; p<0.001). Median OS was 37.6 months for patients allocated to the control group but had not been reached in the dual anti-HER2 therapy group. Another phase 3 study (EGF104900) enrolled patients with HER2-positive MBC whose
disease had progressed during prior trastuzumab therapy. 296 patients were randomly assigned to receive either lapatinib in combination with trastuzumab (dual anti-HER2 therapy group) or lapatinib monotherapy (control group). The median PFS was 11.1 and 8.1 weeks in the dual anti-HER2 therapy group and control group, respectively. Median OS was 14 months for the dual anti-HER2 therapy and 9.5 months for lapatinib alone. The dual anti-HER2 therapy showed significant benefit in PFS (HR, 0.74; 95% CI, 0.58 -0.94; P =0.011) and OS (HR, 0.74; 95% CI, 0.57 - 0.97; P=0.026). Although the two trials were with different patient population and settings, the results of both showed a significant improvement in OS and PFS with dual anti-HER2 therapy.

Q8: Line 193 Chapter subgroup analysis: The sentence “However, no significant difference of pCR was detected between the two groups in the case of chemotherapy-free therapy”.

It is not clear what you would like to say. Please rephrase.

R8: The purpose of this subgroup analyses was to explore whether the type of chemotherapy had influence on the efficacy of dual anti-HER2 therapy. After considering comments from another reviewer, arm without chemotherapy in the Neo-Sphere trial [24] was excluded in the pooled analysis. Therefore, the subgroup analysis of dual anti-HER2 therapy without chemotherapy has been deleted from table 2 and manuscript. The manuscript has rephrased as following:

Original sentence: “Subgroup analyses were performed to explore whether adding chemotherapy would improve the efficacy of dual anti-HER2 therapy. In the neoadjuvant settings, dual anti-HER2 therapy with chemotherapy was associated with a clinically and statistically significant 56% improvement in RR of pCR as compared with monotherapy (RR, 1.56; 95% CI, 1.23-1.97). However, no significant difference of pCR was detected between the two groups in the case of chemotherapy-free therapy (RR, 0.63; 95% CI, 0.39-1.02).”

Revised sentence: “Subgroup analyses were performed to explore whether the type of chemotherapy had influence on the efficacy of dual anti-HER2 therapy. We found the benefit of dual anti-HER2 therapy in pCR was similar when combined with different chemotherapies.”

Q9: Line 195 Chapter Subgroup analysis: There are only two studies (with or without chemotherapy). So subgroup analysis of one study is not possible.

R9: The subgroup analysis of PFS and OS has been removed in table 2 and text.

Q10: Line 215 Chapter AEs: The second sentence is not clear. What does combination therapy means (dual anti-Her2-therapy or anti-Her2 with chemotherapy)?
R10: “Combination therapy” means dual anti-HER2 therapy in our study. In order to avoid ambiguity, we had revised “combination therapy” as “dual anti-HER2 therapy” throughout the manuscript.


R11: Relative risk (RR) is the ratio of the probability of an event occurring (in our study, pathologic complete response (pCR)) in an exposed group (in our study, dual anti-HER2 therapy group) to the probability of the event occurring in a comparison group.

\[
RR = \frac{P_{\text{event when exposed}}}{P_{\text{event when non-exposed}}}
\]

The RR of pCR was 1.56 (95% CI, 1.23–1.97) means the probability of pathologic complete response occurring of the dual anti-HER2 therapy is 156% if that of control is 100% (equal to 56% improvement). In order to help the reader to understand this article, we have revised the manuscript as follows. [Page 7, line 161]

Original sentence: “By pooling the included trials, we demonstrated a 56% improvement in RR of pCR when the dual anti-HER2 therapy was used in the neoadjuvant settings.”

Revised sentence: “The difference in pCR between dual agents and single anti-HER2 agents was significant (RR, 1.56; 95% CI, 1.23–1.97; p < 0.001)”.

Q12: Line 278 Discussion: In your study you included neoadjuvant and metastatic patients. So it is not clear why you mentioned the APHINITY study, which analyzes patients in the adjuvant setting.

R12: At the planning stage of study, we intend to analyze the role of dual anti-HER2 therapy without restriction of setting. However, few study of dual anti-HER2 therapy in the adjuvant setting has been reported and the APHINITY study was ongoing. Therefore, our study did not include study that analyzed patients in the adjuvant setting. We have revised the manuscript accordingly.

Original sentence: Firstly, ongoing trials APHINITY, ALTTO and MARIANNE[1] are still unavailable; however, it is unlikely that would change the conclusions of our study.

Revised sentence: Firstly, ongoing trials ALTTO and MARIANNE[1] are still unavailable.

Q13: Figure 2 and 3 are the other way round than in the text and the legends.
R13: The original figure 3 (legends: Meta-analysis of pathologic complete response (pCR) between dual anti-HER2 therapy and monotherapy) had been deleted in our study according to the reviews’ comments. The revised figure legends were as following:

Figure 1. Flow diagram of the trials search and selection process
Figure 2. Meta-analysis of pathologic complete response (pCR) between dual anti-HER2 therapy and monotherapy
Figure 3. Meta-analysis of adverse events (AEs) between dual anti-HER2 therapy and monotherapy
Figure 4. Meta-analysis of Cardic toxicity between dual anti-HER2 therapy and monotherapy

Reviewer 2: Thomas Ruhstaller

Reviewer's report:

Q14: 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.

R14: Thanks for your suggestions. We had followed your advice and changed “Systematic Review and Meta-analysis” into “Systematic review” in the full text. Furthermore, we also describe in detail the results of PFS and OS in individual trial instead of pooling analysis (Page 8, line 171).

Q15: 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?

R15: Thanks for your suggestions. The design and treatment of Cortes’ study did not conform to our inclusion criterion. Firstly, it was a nonrandomized study but our study only included RCTs. Secondly, in Cortes’s study, dual anti-HER2 therapy was received by 17 of 29 patients who progressed after pertuzumab based treatment. The remaining 12 patients discontinued this study and cannot be considered as appropriate control. Based on the two reasons, we excluded this trial from our study.

Q16: 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.
R16: Your suggestions are very suggestive and consistent with those from the first reviewer. We have revised this section accordingly. Please see our response at comment 3 above for the details of revisions in this regard.

Q17: Change the subtitle: “meta-analysis of pCR” to “pCR in neoadjuvant studies”.

R17: According to your advice, we had changed the subtitle “meta-analysis of pCR” to “pCR in neoadjuvant studies”.

Q18: 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.

R18: This issue has been addressed at the comment 5 of the first reviewer above by clarifying the types of chemotherapy in the manuscript.

Q19: Figure 2 and 3 are not matching in the text and the legends. Please correct it.

R19: This issue has been addressed at comment 13. The original figure 3 had been deleted.

Q20: Change the subtitle: “Meta-analysis of PFS and OS” to “PFS and OS in metastatic studies or setting”

R20: Thanks for your suggestive advice which will help the reader to understand this article. We have changed the subtitle “meta-analysis of PFS and OS” to “PFS and OS in metastatic studies or setting”.

Q21: 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.

R21: We have described in detail the results of PFS and OS in individual trial instead of pooling analysis. Please see our response at comment 6 of the first reviewer above for the details of revisions in this regard.

Subgroup analyses:

Q22: 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.

R22: It is recognized that subgroup analysis should include the arms used in the overall analysis of pCR, and arm without chemotherapy in the Neo-Sphere trial [25] was excluded in the subgroup analysis. Therefore, the subgroup analysis of dual anti-HER2 therapy without chemotherapy has been deleted from table 2 and manuscript and this issue has been addressed. At present, the purpose of this subgroup analyses is to explore whether the types of chemotherapy had influence on the efficacy of dual anti-HER2 therapy. Please see our rejoinder for comment 7 of the first reviewer.

Q23: 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?

R23: This issue has been addressed at comment 21. The arm without chemotherapy has been deleted in this study.

Q24: 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.

R24: Your suggestions are consistent with those from the first reviewer (Q8). This issue has been addressed by deleting the part in table 2 and manuscript.

Q25: 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.

R25: The subgroup analysis of dual anti-HER2 therapy without chemotherapy has been deleted from table 2 and manuscript. So does the subgroup analysis for PFS and OS.

Risk of AE:

Q26: 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.

R26: “Combination therapy” means dual anti-dual anti-HER2 therapy in our study. In order to avoid ambiguity, we had revised “combination therapy” as “dual anti-HER2 therapy” in the whole manuscript.

Q27: 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.

R27: We had deleted the last sentence “the number of patients experiencing those toxicities was more frequent in the combination therapy arm” in the part of “Relative Risk of AEs”.

Discussion:

Q28: 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 too few data).

R28: We agree with the reviewers on this point, and we have revised the manuscript accordingly:

Original sentence: “Combining data from all of the current trials gives greater statistical reliability and reduces the risk of random errors caused by the play of chance, thereby providing a reliable assessment of the role of dual anti-HER2 therapy in this disease.”

Revised sentence: “Combining data from all of the current trials, this systematic review confirms the benefit of dual HER2-directed therapy compared to monotherapy for HER-2 positive breast cancer”

Q29: Whether the chemotherapy could be avoided at the beginning in some cases in the first line setting in MBC should be further evaluated.

R29: In the section of results, the subgroup analysis of dual anti-HER2 therapy without chemotherapy has been deleted (see Q21 above). Hence, the corresponding part in the discussion is also deleted. Instead, we discuss the influence of the chemotherapy type and the anti-HER-2 agents on the efficacy of dual HER2-directed therapy.

Q30: 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.

R30: Thanks for your helpful advice. We have deleted this issue in the manuscript.

Q31: Limitations: several ongoing trials (delete the sentence “it is unlikely that would change anything”, you cannot say that).

R31: We had deleted the sentence “however, it is unlikely that would change the conclusions of our study”.

Q32: 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….

R32: Thanks for your suggestive advice. We had followed your advice and revised the conclusion as “This systematic review 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 underpin the need for further evaluation on the role of dual anti-HER2 treatment. However, it is justifiable to believe that the shift toward a dual therapeutic approach will yield clinically meaningful improvements for patients with HER2-positive breast cancer. In addition, given the increased risk of AEs associated with dual anti-HER2 therapy, it is important for health care practitioners to be aware of the risks and to provide close monitoring to improve patient outcome.”

Q33: Table 1: metastatic and neoadjuvant together

R33: Thanks for your suggestions. We had relisted the five neoadjuvant trials in the front of table 1 and listed the two metastatic trials at the back of table 1.

Reviewer 3: Yu-Hao Zhou

Reviewer's report:

Minor Essential Revisions:

Q34: The manuscript needs deep language corrections before being published.

R34: We have revised this manuscript carefully. All of the spelling, grammatical, bibliographical, typographical errors we found have been revised. And the English presentation has also been improved.
Q35: The following sentence was not suitable: “The search was limited to randomised clinical trials but without publication status (published, unpublished, in press, and in progress) and language restrictions” (line 6-7, “Material and Methods” part). In my review, a meta-analysis cannot be carried out with works in progress. How do you get them?

R35: We cannot get the data from the ongoing trials. Hence, we revised this sentence as following: “The search was limited to randomized clinical trials but without language restrictions”.

Q36: It will be much better if the author could explain the heterogeneity of NSABP B-41 study induced. I was confused why this study could lead to so much heterogeneity.

R36: We understand the importance of considering heterogeneity and have found NSABP B-41 study is the source of heterogeneity. However, there was no obvious reason for this discrepancy, and chance may be a factor. Another possible reason is that, as the authors of NSABP B-41 study pointed out, important heterogeneity in HER2-positive breast cancers may be exist. However, we cannot prove this.

Q37: The author should add the reference of included studies in table 1.

R37: Thanks for your suggestions. We had added the reference of included trials in table 1.