Author's response to reviews

**Title:** Trastuzumab with either docetaxel or vinorelbine as first-line treatment for patients with HER2-positive advanced breast cancer: a retrospective comparison

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**Author's response to reviews:** see over
Dear Sir or Madam, thank you very much for giving us the opportunity to submit a revised version of MS # 1525853606286982. We have valued all the concerns raised by the referees and the manuscript has undergone major revisions, which are listed in the present letter. Furthermore, the paper has undergone professional editing. We hope that in its current format the paper will now be suitable for final acceptance.

Referee 1:

Major revisions:
1) The referee raises a very important point as, in the presence of two potentially effective chemotherapy-regimens, the toxicity profile is a major factor influencing therapeutic choices. Unfortunately, the process of data collection for our database did not include a detailed description of treatment-related toxicities. Furthermore, if the context of a retrospective analysis is already potentially biased when one analyzes tumor outcomes, a comparison of toxicities would result even more difficult to interpret. For this reason, honestly, we are not able to provide accurate toxicity data, if not for a small fraction of the patients in this dataset. In order to address at least partially the concern of referee number 1, we have introduced in the discussion a brief paragraph on the expected differences in toxicity between the two regimens as these are reported in well conducted, large phase II trials that are available in the medical literature. We are aware that this does not fulfill the referee’s request but, at least, it will put some focus on the toxicity issue.
2) We have provided a more detailed definition of the populations analyzed for tumor response (only evaluable patients) and for disease free and overall survival (all patients according to an intent-to-treat principle) (see Patients and Methods, Analysis of Tumor Response, Analysis of Disease Free and Overall Survival and Footnote 1 to table 1).
3) The median duration in cycles for docetaxel and in weeks of treatment for vinorelbine has been reported (see Patients and Treatments).

Minor revisions:
1) The text has been changed according to the referee’s suggestion
2) The text has been changed according to the referee’s suggestion
3) A paragraph has been added to the discussion to address the potential confounding factor of prior chemotherapy
4) We agree, at least in part, that due to current patterns of practice, a randomized trials might not be indicated. However, because vinorelbine-trastuzumab is a popular alternative to taxanes-trastuzumab both in Europe and in the USA, we still believe that correct sequencing of chemotherapy in combination with trastuzumab is an issue that is worth of further investigation.

Referee 2

Major revisions:
1) We agree with this criticism. We have gone through the data again and conducted sensitivity analyses keeping patients with stage IV disease at diagnosis separate from the others. In fact, we have not found that these patients carry a more severe prognosis compared with patients with recurring disease after surgery of localized disease. Indeed, the “Stage at first diagnosis” variable does not affect response, time to progression and overall survival neither positively, nor negatively. We have therefore modified the discussion according to the referee’s comments.
2) The possible prognostic impact of prior exposure to taxanes in the adjuvant setting has been addressed in the discussion

Discretionary revisions:
1) We partially agree with this comment, because the vinorelbine/trastuzumab combination was initially developed in the USA (the first study was published in 2001) in the context of a few very influential clinical trials. It is reasonable to assume that this regimen, because of a favorable toxicity profile, high clinical activity and a preclinical rationale of synergism between vinorelbine and trastuzumab, is in fact considered an alternative to taxanes-based combinations. Since 2006, the National Comprehensive Cancer Network guidelines suggest both taxanes and vinorelbine as valid first-line options for HER2-positive metastatic breast cancer (see also NCCN guidelines V 1.2010). In Europe, the scenario is very similar as our analysis shows. Having said this, we still believe that correct sequencing of chemotherapy in combination with trastuzumab is an issue that is worth of further investigation.

Minor revisions:
1) The manuscript has undergone professional linguistic revision
2) “different associations” has been changed into “different combinations” as requested
3) “cytostatic agents” has been changed into “cytotoxic agents as requested”.
4) We have rephrased the whole sentence to improve readability. A.S. stands for Anna Sapino who is the Pathologists carrying on FISH analyses. “A.S.” has been removed in order to avoid confusion.