Author’s response to reviews

Title: Predicting for activity of second-line trastuzumab-based therapy in Her2-positive advanced breast cancer

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Dear Sir or Madam,

On behalf of all co-authors, we submit a new version of our manuscript (“Predicting for activity of second-line trastuzumab-based therapy in Her2-positive advanced breast cancer”) for consideration by your journal. We have thoroughly revised the manuscript, have tried to improve the quality of written English and have tried to address all issues raised by the reviewers.

Please find below a point to point response to the reviewers’ comments.
Reviewer 2:

Major revisions:

1. Odds ratio, standard error, and confidence interval are now being provided in the respective tables.

2. According to the reviewer’s suggestion we have included further variables into the statistical analysis of TTP, OS and response: Number of metastatic sites (1 versus 2; 2 versus more than 2); trastuzumab from diagnosis of metastatic disease; progression at the same sites of disease as identified at baseline versus development of new metastatic sites upon progression; lack of response (stable disease or progressive disease) versus response to first-line trastuzumab-based therapy.

We have now used a stepwise approach, thereby including those new variables as well as all others into a univariate model (Kaplan Maier estimation and log-rank test). Only variables exhibiting significance (p<0.05) or near significance (p<0.08) at univariate analysis were now included into the multivariate models of TTP and OS.

3. See point 2.

Minor revisions:

1. The reviewer is right of course. We have clarified the different designs of the cited studies and have included further publications in the reference list.

2. As suggested, we have rephrased the term “median TTP on second-line” throughout the manuscript in order to enhance clarity.

3. In Table 1, we have replaced the term “further trastuzumab-based therapy” with “trastuzumab beyond second-line”.

Reviewer 2:

Major revisions:

1. A number of variables are known to confer better outcome in patients with metastatic breast cancer. Patients usually considered to be at relatively low risk for rapid disease progression or death are those without prior treatment, with non-visceral disease only, long disease-free interval, response to prior treatment, and endocrine responsive disease. Her2-positivity is obviously the most important factor for prediction of activity of trastuzumab-based first-line therapy.

In this retrospective study, we have not conducted an analysis of variables predicting for response to first-line trastuzumab therapy. Patients in this study received a minimum of two lines of trastuzumab for metastatic disease. When trying to identify clinical or histopathological factors predicting for activity of first-line treatment, the inclusion of patients who received only one trastuzumab-based treatment line would have been necessary.
2. Disease-free interval and metastatic sites (visceral versus non-visceral disease) are included in the statistical analysis.

3. As suggested, all results from the univariate analysis are now provided, as well as the odds ratio, standard error and confidence interval.

4. Combination of trastuzumab with endocrine therapy for metastatic disease was not considered a standard option at our centre. Patients receiving trastuzumab in the adjuvant setting however had concurrent endocrine therapy when diagnosed with ER- and/or PgR-positive positive tumours. Treatment consisted of anastrozole for five years in postmenopausal patients; premenopausal patients received three years of goserelin in combination with five years of tamoxifen.

5. By using the term “endocrine receptor”, we intended to summarize ER- and/or PgR-positive tumours. We have now changed that term to “hormone receptor”.

6. Nine patients received adjuvant trastuzumab and were re-challenged upon disease recurrence. In those patients, response was as follows: Four patients (44.4%) PR; three patients (33.3%) SD > 6 months; two patients PD.

We hope that we were able to meet all concerns and improved the quality of manuscript substantially enough to make it acceptable for publication in BMC Cancer.

Sincerely,

Guenther G. Steger R. Bartsch