Author's response to reviews

Title: FemZone Trial: a randomized phase II trial comparing neoadjuvant letrozole and zoledronic acid with letrozole in primary breast cancer patients

Authors:

Peter A Fasching (peter.fasching@uk-erlangen.de)
Sebastian M Jud (sebastian.jud@uk-erlangen.de)
Maik Hauschild (maik.hauschild@frauenklinik-rheinfelden.de)
Sherko Kuemmel (S.Kuemmel@kliniken-essen-mitte.de)
Martin Schuette (martin.schuette@uk-essen.de)
Matthias Warm (warmm@kliniken-koeln.de)
Volker Hanf (Volker.Hanf@klinikum-fuerth.de)
Dieter Grab (frauenklinik.kh@klinikum-essen-mitte.de)
Jutta Krocker (j.krocker@sana-kl.de)
Elmar Stickeler (elmar.stickeler@uniklinik-freiburg.de)
Rolf Kreienberg (r.kreienberg@t-online.de)
Thomas Mueller (frauenklinik.kh@klinikum-essen-mitte.de)
Thorsten Kuehn (t.kuehn@klinikum-essen-mitte.de)
Christopher Wolf (chrchristopherwolf@arcor.de)
Steffen Kahlert (steffen.kahlert@med.uni-muenchen.de)
Stefan Paepke (stefan.paepke@lrz.tu-muenchen.de)
Michael Berghorn (michael.berghorn@akh-celle.de)
Mathias Muth (mathias.muth@novartis.com)
Monika Baier (monika.baier@novartis.com)
Birgit Wackwitz (birgit.wackwitz@novartis.com)
Ruediger Schulz-Wendtland (Ruediger.Schulz-Wendtland@uk-erlangen.de)
Matthias W Beckmann (fk-direktion@uk-erlangen.de)
Michael P Lux (Michael.lux@uk-erlangen.de)

Version: 3 Date: 26 July 2013

Author's response to reviews: see over
Dear Editor, dear Reviewers,

thank you for the detailed comments concerning our manuscript. We hope, that we could address them satisfactory. Please let us know, in case you have further concerns or comments.

Yours sincerely

Peter Fasching for the authors.

Reviewer 1

<table>
<thead>
<tr>
<th>Comment 1: I would have liked to know the reasons for poor accrual, but the authors do hint at these reasons in their discussion. (Discretionary revision)</th>
<th>This is a good comment. Unfortunately the screening log were not completed in a satisfactory quality. If course we would have loved to draw some conclusions with regard to the reasons for poor recruitment.</th>
</tr>
</thead>
</table>

Reviewer 2:

| Comment 1: The eligibility criteria seem too simple. The patients did not have to be ER and/or PgR positive? How about Her2? Tumor had be measurable by the RECIST criteria? | Absolutely correct. We must have overseen that. **The relevant inclusion/exclusion criteria were added.** |
| Comment 2: Number of per protocol patients (131) seems low compared with that of randomized patients (168). For instance, ‘unsatisfactory treatment effect’ might be PD and those patients might be included in the per protocol group. | We discussed that as well. However, the number of patients in both arms are equal (n=4). And an “unsatisfactory treatment effect” must not necessarily mean progress. Therefore, we decided not to include these patients into the analysis, as we wanted to make sure that the tumor assessment had a high quality (central assessment). |
| Comment 3: Efficacy endpoint is only the clinical (radiological) response. The authors had better show other endpoints such as pathological response or rate of patients with breast-conserving surgery, considering unreliability of the clinical response rate. | We would have liked to have a better endpoint, however there are almost no pathological complete responses after neoadjuvant, antihormonal therapy and a histological correlation of morphology with response is not well established either. Therefore we chose an endpoint similar to other neoadjuvant antihormonal therapy studies. **We added a sentence in the discussion to make aware of that.** |
| Comment 4: The measurement methods for clinical response are not clearly described. In how much of the patients MMG, MRI or ultrasonography were used? And as the authors described, the response rates are too dissociated between local and central assessment, making the | Sorry for not being clear enough. All patients were assessed with mammography. **We added a section about the discordance between the local and the central review in the discussions section.** |
Reviewer 3:

Comment 1: The paper is well-written but it is disappointing that there is no biological data, rather than just clinical endpoints as this would have made the whole paper more interesting.

Comment 2: It is somewhat disappointing that there is no comment as to why patients declined entry to the trial or why clinicians declined to offer them the trial and randomise them.

Comment 3: The final point of the authors is that there is a difficulty in clinical assessment of response and this is correct. In some way, it diminishes the message of the paper.

Comment 4: I would personally expect to see clear detail on the surgical treatment of these patients as part of a revision, in which the eventual surgery and various tumour grades was compared between the core biopsy (on which presumably the diagnosis was made) and the final surgical pathology.

Comment 5: The model appears based on radiological tumour size change rather than final pathological tumour size and for those cases where patients have discordance between the radiological and final pathology size, the final pathology size is more value but appears to be unclear here.

Comment 6: At the very least, a comparison of the final pathology size versus radiological size prior to surgery, should be available. How did the pathology relate in terms of changes in the stroma, which zoledronic acid has been said to affect, compared to those treated with Letrozole alone. It would also be interesting to know whether side-effect profile related to tumour response as there has been considerable data in the literature with other drugs, that patients who have side-effects are more likely to have a tumour response. In short therefore, I have some issues about the methods used to assess response and how they relate to final tumour pathological size.

Comment 1: There are some blood samples available for biomarker assessments and some fresh frozen tumor samples. However this paper should report on the clinical outcomes only. We hope to provide that data in the near future.

Comment 2: See comment 1 of reviewer 1: This is a good comment. Unfortunately the screening log were not completed in a satisfactory quality. If course we would have loved to draw some conclusions with regard to the reasons for poor recruitment.

Comment 3: Unfortunately yes.

Comment 4: We included the surgery type in the results section. However we do not have information about the grading in the final surgery.

Comment 5: This is correct. The advantage of that method is, that you use the same measurement technique for the comparison rather than comparing the pathological tumor size and the size in the mammogram. We did a study in 2005 (Heusinger, K., et al. "Assessment of breast cancer tumor size depends on method, histopathology and tumor size itself*." Breast Cancer Res Treat 94(1): 17-23. The deviance for tumors up to 3 cm appeared to be rather low in average. Unfortunately we do not have the pathological tumor size, so we cannot report on that. We added a section in the discussion.

Comment 6: This comment is well appreciated. I would like to know that as well. Unfortunatly this was not assessed in the study conduct.

Please see the section that was added in the discussion (see your last comment)

With regard to subgroup analyses (side effects vs. no side effects) we felt that with the small sample size, the dataset would not be robust enough to do more statistical tests.
Reviewer 4:

<table>
<thead>
<tr>
<th>Comment 1: The authors explain why they have used clinical response as a primary outcome, however pathological response should be known and are valuable data to report.</th>
<th>Unfortunately pathological assessments from the time of the surgery are not available. Please see comments 5 and 6 of reviewer 3. <strong>We added a sentence in the discussion.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Comment 2: Abstract, methods: define primary endpoint and how this was measured</td>
<td>Done.</td>
</tr>
<tr>
<td>Comment 3: Abstract, results: change 'for the treatment arm' in 'for the experimental arm'</td>
<td>Done.</td>
</tr>
<tr>
<td>Comment 4: Abstract, conclusion: a non-significant increase should be changed in 'no increase' or similar findings etc. Then in second sentence however a trend.</td>
<td>Fair enough. Done.</td>
</tr>
<tr>
<td>Comment 5: Introduction First sentence, 'neoadjuvant therapy has helped improve health care for breast cancer patients' is rather general statement can you be more specific?</td>
<td>Omitting this part of the sentence seemed to make it more specific and informative. <strong>Done.</strong></td>
</tr>
<tr>
<td>Comment 6: Introduction ZOFAST trial was in postmenopausal pts</td>
<td>Sure. Thanks for the correction.</td>
</tr>
<tr>
<td>Comment 7: Introduction: On the basis of clinical evidence from studies of metastasis: as far as I know data from patients with metastasis are discordant, we currently use bisfosfonates for SRE and osteoporosis but not standard for the antitumor effect.</td>
<td>You are right. We simplified the sentence, that the reader is not tempted to think that.</td>
</tr>
<tr>
<td>Comment 8: Methods: 2nd paragraph: first sentence belongs to first paragraph -Please define adequate renal function -Treatment and tumor assessment plan, 2nd paragraph: please define how clinical response was measured (palpation/MRI/ultrasound?)</td>
<td>Renal function was defined. All patients were assessed by measuring the diameter of the tumor in the mammogram. This was commented on by another reviewer as well and was added/changed. (See Comment 4 of reviewer 2)</td>
</tr>
<tr>
<td>Comment 9: Results, Patients: please insert reference to Table 1 -Please add pCR (see before)</td>
<td>Table 1 is referenced in the second paragraph. There is no information about pCR.</td>
</tr>
<tr>
<td>Comment 10: Results: Measurement of FACT-B should also be described in methods -Safety, line 4:please delete 'as expected', please add is differences in toxicity were significant</td>
<td>Done:</td>
</tr>
<tr>
<td>Comment 11: Discussion: Consider to add that in the neoadjuvant setting similar results have been found in two trials with neoadjuvant chemotherapy plus/min zoledronic acid presented at last ASCO [abstract 1028 and 1029].</td>
<td>Done.</td>
</tr>
</tbody>
</table>