Author's response to reviews

Title: Final results of a phase I/II pilot study of capecitabine with or without vinorelbine after sequential dose-dense epirubicin and paclitaxel in high-risk early breast cancer

Authors:

Volkmar Müller (vmueller@uke.de)
Thomssen Christoph (christoph.thomssen@medizin.uni-halle.de)
Marcus Schmidt (marcus.schmidt@frauen.klinik.uni-mainz.de)
Manfred Glados (praxis.dr.glados@t-online.de)
Christian Jackisch (Christian.Jackisch@klinikum-offenbach.de)
Volker Heilmann (v.heilmann@praxis-dr-heilmann.de)
Axel Hinke (axel.hinke@wisp.de)
Antje Lehnert (antje.lehnert@gmx.de)
Henryk Borowicz (h.borowicz@frauenarzt-borowicz.de)
Volker Moebus (volker.moebus@klinikumfrankfurt.de)

Version: 2 Date: 18 May 2010

Author's response to reviews: see over
16th of May, 2010

Dear Editor,

enclosed we submit our revised manuscript entitled “Final results of a phase I/II pilot study of capecitabine with or without vinorelbine after sequential dose-dense epirubicin and paclitaxel in high-risk early breast cancer” for consideration as a research article in “BMC Cancer”.

Thank you for the careful review of our manuscript and the suggestions that helped to improve our work. The issues raised by the reviewers and the improvements of our manuscript are listed on the two following pages.

We hope that the manuscript seems appropriate for publication in its revised form.

All authors agreed to the submission of the revised manuscript that is not submitted elsewhere for publication.

Yours faithfully, on behalf of the authors,

Volkmar Müller, MD, PhD
Author reply Mueller et al.: „Final results of a phase I/II pilot study of capecitabine with or without vinorelbine after sequential dose-dense epirubicin and paclitaxel in high-risk early breast cancer“

Reviewer 1 (Marc L. Citron):
„I recommend acceptance without revision.“

Reviewer 2 (Simon Van Belle) has suggested the following improvements:

Major compulsory revisions:
- in the section Study treatment (p6) the authors describe the use of darbepoetin: “All patients received darbepoetin alfa from day 1 of chemotherapy until the end of radiotherapy”. In the paper itself it is not described when or how radiotherapy is included in the total protocol. This should be added to this section.

Author reply:
We have added a statement on page 6 describing the recommended radiotherapy (standard at the time of study recruitment for patients with more than 3 included lymph nodes) “Radiation of the supraclavicular, infraclavicular, and parasternal lymph nodes, as well as radiation of the breast in patients with partial mastectomy or to the chest wall in case of mastectomy, was recommended in all patients.“

- it is advisable to include a figure outlining the different parts of the treatment in view of time (otherwise the readers have to compose the therapy puzzle themselves)

Author reply:
We think that this is a very good suggestion and have added a new figure as Figure 1.

- in the Discussion there is only a minimalistic discussion about the use of Erythropoetin Stimulating Agents (ESA’s) (Darbepoetin in this case) in the setting of adjuvant therapy, with reference to the Sankt Gallen conference. Meanwhile there have been several adaptations of the guidelines (EORTC, ASCO…) and warnings about the use of ESA’s. This discussion should be expanded including reference to these warnings.

Author reply:
In the paragraph with discussion of ESA’s, we also mentioned the ASCO and EORTC guidelines by stating “However, since starting this phase I/II study, the general consensus on the role of epoetin-containing drugs in cancer patients has changed substantially [26,27], based on some data suggesting poorer overall survival in non-anaemic patients receiving epoetin compared with placebo [28] and increased risk of thromboembolism [29].”

To make this point even more clear, we have modified this to “Darbepoetin alfa was effective in preventing grade 3/4 anaemia. However, since starting this phase I/II study, the general consensus on the role of epoetin-containing drugs in cancer patients has changed substantially and current guidelines demand a more cautious use of these compounds as in our study [26,27]. This is based on data suggesting poorer overall survival in non-anaemic patients receiving epoetin compared with placebo [28] and increased risk of thromboembolism [29].”

Minor essential revisions:
- p3§2: ref. 3 is followed by the sentence “and accepted for publication in JCO: must be included as a normal reference (= ref 4).

Author reply:
We have added the complete reference of the JCO manuscript (Moebus V, Jackisch C, Lueck HJ, du Bois A, Thomassen C, Kurbacher C, Kuhn W, Nitz U, Schneweiss A, Huober J et al: Intense Dose-Dense Sequential Chemotherapy With Epirubicin, Paclitaxel, and Cyclophosphamide Compared With Conventionally Scheduled Chemotherapy in High-Risk Primary Breast Cancer: Mature Results of an AGO Phase III Study. J Clin Oncol 2010, 28:Online ahead of print on May 10.) which became available online on May 10th 2010 and replaced the reference for the meeting abstract which would be redundant.
Author reply Mueller et al.: „Final results of a phase I/II pilot study of capecitabine with or without vinorelbine after sequential dose-dense epirubicin and paclitaxel in high-risk early breast cancer“

- p7§1: "The planned dose of epirubicin or paclitaxel was reduced in 43 of 300 cycles": add percentage (14.33 %) as was done in the next sentence.
   **Author reply:**
   Good point, we have added the percentage.

- p7§2: describes the dose of darbepoetin: does this mean that all patients received a 100 % in the epirubicin-paclitaxel part of the therapy? This is not clear.
   **Author reply:**
   We have clarified this by changing the statement to “All patients received at least one dose of darbepoetin alfa during the treatment with ET.”

- p8§2: it is stated that the median Hb level was 13.5 g/dL at the last cycle. Which last cycle? The last of epirubicin-paclitaxel or the real final one?
   **Author reply:**
   We have clarified this by changing the sentence to “at the end of chemotherapy”

- p9: Discussion: §2 and 3 discusses the possible value of adding capecitabine to a certain “basic” treatment referring to several published studies, but there is no conclusion about this. We propose to add a tentative conclusion or at least a statement that this is still unclear.
   **Author reply:**
   We thank the reviewers for this suggestion and have added a sentence stating “These results allow no definitive conclusion about the role of capecitabine in the adjuvant setting.”

- p11§1: the statement "The efficacy data from the present study after 35.2 months' median follow-up are very promising“ cannot be made in the setting of a phase I/II study only that is in the expected range.
   **Author reply:**
   We have changed the sentence as proposed by the reviewer to “For a population with a median of nine positive axillary lymph nodes, the 82% 3-year relapse-free survival rate after 35.2 months’ median follow-up is within the range reported for dose-dense anthracycline-taxane-cyclophosphamide regimens [2,3,24,25]. Long-term follow-up is ongoing.”

**Author comment:**
Thank you for the careful review of our manuscript and the suggestions that helped to improve our work.