Author's response to reviews

Title: Multicenter Phase II Study of Apatinib in Non-triple-negative Metastatic Breast Cancer

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

Thanks to your reviewers for their constructive comments. The comments have helped us to make the manuscript more scientific and clear. We have made some changes to the manuscript after carefully checking the data. The answers to the questions and explanations for the changes are listed below. Thank you very much for your time and further consideration.

Sincerely yours,

Xichun Hu

Questions by Claus Hanusch:

Q1. In the Abstract part: please be consistent in using term CBR and DCR... DCR is not explained as disease control rate.

In the Abstract part, CBR has been substituted by DCR (disease control rate). DCR was defined in the “Study Design and Assessments” part.

Q2. Results: "... company’s new policy": what does this mean? What was the original planned sample size? Any recruitment problems, concerns?

The original planned sample size was 60. The study started in December, 2011 and closed in September, 2012. 38 patients were enrolled in 9 months, so it’s not for any recruitment concerns. The trial closure is due to apatinib which has proven effective in metastatic gastric cancer* after the accrual of 38 eligible patients. * Li J et al. Apatinib for
The company decided to focus on indications of gastric cancer and stopped other studies in breast cancer and lung cancer.

**Q3. Statistical Analysis: how is the statistical power affected by the earlier recruitment stop?**

Yes, you are right. The statistical power was weakened for the earlier recruitment stop. The median PFS and OS were 3.3 and 10.6 months, respectively in another phase II study of apatinib in metastatic triple negative breast cancer (TNBC)*, which were similar to those of this study in non-TNBC (4.0 and 10.3 months, respectively). Therefore, we hypothesized that apatinib might be effective in breast cancer with high angiogenesis dependency and the molecular subtypes of breast cancer such as TNBC or non-TNBC was not a potential efficacy predictor.


**Q4. Patients Characteristics: you stated: "...23 (33,9%) patients were heavily pretreated..."- 23 patients would not be 33,9%? Is this really correct?** Table 1: hormone receptor status: 6 unknown: any reason why?
“23 (33.9%)” has been corrected as “13 (34.2%)”. 6 patients were with unknown HER2 status (not hormone receptor status) because they received resection of the primary breast cancer more than 10 years ago (HER2 status was not routinely detected in some hospitals in China before the 21st century) and re-biopsy was impossible for them. However, of the 6 patients with unknown HER2 status, no one was with ER/PR negative, which meant that none of the 6 patients was triple-negative breast cancer (TNBC).

Q5. Efficacy: you stated: ".. 1 was trastuzumab pretreated..." according to the inclusion criteria every Her2 positive patient at least should have received 1 prior line of anti-her2 treatment... can you specify on that? It has been mentioned that any rational reason for no use of anti-HER2 therapy is acceptable on lines 15, page 6. The rational reason included economic reasons for expensive anti-HER2 treatment.

Q6. Discussion: please clarify on your statement: 2 of 6 her2 pos. patients and in the Efficacy Chapter you stated 2 of 9 her2 pos. patients; you mentioned once again that 1 patient had received her2 targeted therapy- could you make this point more clear, why you find that worth mentioned?

We would like to indicate that single-agent apatinib may be effective
against HER2 positive MBC with or without prior exposure to anti-HER2 treatments.

Q7. Conclusions: "...and it might be better to be tested in breast cancer with high angiogenesis dependency." - could you make a short comment on which cancer subtype or patient population you would like to see the compound to be tested in the future.

The median PFS and OS were 3.3 and 10.6 months, respectively in another phase II study of apatinib in metastatic triple negative breast cancer (TNBC)*, which were similar to those of this study in non-TNBC (4.0 and 10.3 months, respectively). Therefore, we hypothesized that apatinib might be effective in breast cancer with high angiogenesis dependency and the molecular subtypes of breast cancer such as TNBC or non-TNBC was not a potential efficacy predictor. Further exploration of the biomarkers is being carried out in our research team.


Minor Compulsory Revisions:

Q1. Patients and Methods: Patients: "... had prior therapy with prior treatment with a..." better: "... had prior treatment with a...

This has been corrected.
Questions by Sara Hurvitz:

Q1. Table 1: Patients with ER negative (31) vs positive (8) tumors adds up to 39. Should only add up to 38.

"30 ER positive, 8 ER negative" and "21 PR positive, 17 PR" negative has been corrected in Table 1.

Q2. Table 1: This study excluded patients with triple negative disease. However, there were only 9 patients with HER2+ disease, 17 with PR+ disease and 8 with ER+ disease. So it seems that of the 38 patients enrolled, there must have been some that were triple negative? Authors need to change table so that we can see actual tumor characteristics of patients enrolled: how many patients had ER and/or ER+ HER2+ disease, ER/PR-HER2+ disease, ER+and/or PR+ HER2 negative disease?

It was an unforgivable mistake that we listed just the opposite data of ER/PR status in Table 1 in our submitted manuscript. It has been corrected as was listed in the answer of Q1.

Q3. Statistical section speaks of sample size calculation and states the study was designed with two-sided, #=0.05, 80% power to detect a null
median PFS of 2 months and experimental median PFS of 4.5 months however does not give what the calculated sample size is (was it 38?) and does not address the fact that the PFS this study detected (4.0 mos) was less than their goal of 4.5 months. This should be acknowledged/discussed in the discussion section rather than only focusing on the response rate.

The calculated sample size was 50. Assuming a 20% dropout rate, the original planned sample size was 60 (This sentence has been added in the part of “Statistical Analysis”). The statistical power was weakened for the earlier recruitment stop. However, the median PFS and OS of this study (4.0 and 10.3 months, respectively) were similar to those of another phase II study* of apatinib in metastatic triple negative breast cancer (TNBC) (3.3 and 10.6 months, respectively). Therefore, we hypothesized that apatinib might be effective in breast cancer with high angiogenesis dependency and the molecular subtypes of breast cancer such as TNBC or non-TNBC was not a potential efficacy predictor.


Q4. Eligibility requirements include prior capecitabine and (if HER2+) prior trastuzumab but then states that "any rational reason for no use of capecitabine/trastuzumab is acceptable." Authors should define
what defines a "rational reason." In fact, it seems quite questionable that of the 9 patients with HER2 positive disease that there would be a rational reason that 6 of them never received trastuzumab.

The main "rational reason" referred to economic reason because China is a developing country and its economic development is imbalanced among the different regions. Expensive trastuzumab is not covered by medical insurance in China. Although capecitabine is cheaper than trastuzumab, there are patients, especially those coming from neighbouring provinces, who still cannot afford it.

Q5. Both the Abstract and the Conclusions indicate that apatinib has "substantial efficacy." While the efficacy seen in this small single arm study may be promising, it is an overstatement to say it is substantial. Many studies of angiogenic inhibitors have shown similar response rates without ever demonstrating an improvement in overall survival. Thus the enthusiasm for angiogenic inhibitors has naturally waned in recent years. The claims regarding apatinib's early activity should thus be more modest.

Yes, we replace “objective efficacy” for “substantial efficacy”, since apatinib is efficacious for gastric cancer as reported.

Q6. In Abstract and Conclusions, authors state that this drug might be
better tested in breast cancer with high angiogenesis dependence. The problem is, no one to date has defined what breast tumor types are highly dependent on angiogenesis. The authors should consider discussing whether any biomarker studies are being planned or have been done to try to better understand if there is a molecular subtype of breast cancer that would be more sensitive to apatinib. To date, no marker has been discovered/validated that predicts response to angiogenic inhibitors.

You are right and we totally agree with you.


Now, we are actually doing biomarker study, and we would like to confirm our TNBC findings in patients with other molecular subtypes of breast cancer.
Q7. The authors should acknowledge in the discussion that no angiogenic inhibitor (including bevacizumab, which has been most thoroughly explored with a series of phase III studies) has been shown to improve survival in breast cancer. Why might apatinib be different? Why should we continue to evaluate angiogenic inhibitors like apatinib in patients when no study has shown it helps save lives?

Yes, you are right. Apatinib is the second generation of VEGFR2 inhibitors, which is more specific and may have less off-target effects. It has proven that apatinib has good safety profile in this study and other studies. And since apatinib could target to side population cells and ABCB1-overexpressing tumor cells to enhance the efficacy of chemotherapeutic drugs, it may be worth further exploring, not only with single agent but also combined with cytotoxic drugs.


Minor essential revisions:

Q1. reference numbers throughout text are normal size font (rather than in parentheses or superscript). This is very distracting/confusing.

Reference numbers have all been corrected to the superscript form.

Q2. polishing of grammar and syntax is needed

This has been done.

2 additional references of “29. . . .” and “30. . . .” were added in the “references”. 