Author's response to reviews

Title: Design paper: A phase II study of Bevacizumab and Erlotinib in patients with non-Squamous non-small cell lung cancer that is refractory or relapsed after 1-2 previous Treatment (BEST)

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

We revise the enclosed manuscript entitled “Design paper: A phase II study of Bevacizumab and Erlotinib in patients with non-Squamous non-small cell lung cancer that is refractory or relapsed after 1-2 previous Treatment (BEST)” by Shiro Tanaka, Yuichi Sakamori, Miyuki Niimi, Megumi Hazama, Young H Kim and Kazuhiro Yanagihara. The MS number is 1328428054517825. We enclose the manuscript with under lines and highlight in red color indicating the differences from the previous manuscript and our point-by-point response to the comment.

I hope you will give favorable consideration to the manuscript and find it acceptable for publication in your journal.

Sincerely yours,

Shiro Tanaka

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Reviewer: 1

We wish to express our appreciation to the time and effort that the reviewer allocated our manuscript. Overall, we agree with the reviewer’s comments. We indicate the differences by under lines and red color in the manuscript. Our point-by-point response to the comments is as follows.

1. **Use more standard language in the statistics section i.e. a null hypothesis response rate of 20% and an alternative hypothesis of a response rate of 35%**
   
   >>Thank you for the valuable comment. We reviewed the terminology and revised accordingly.

2. **Justify the choice of null response rate. Why would 20% be seen as uninteresting? What are typical response rates in this setting? What are the response rates to single agent Bevacizumab or Erlotinib alone?**
   
   >>We decided the null hypothesis of 20% by the response rate of erlotinib monotherapy which ranged 8.9 to 28.3% in the previous trials. According to the reviewer’s suggestions, we added the following sentences in Sample size determination section:
   
   “In the previous trials, the ORR of erlotinib monotherapy ranged 8.9 to 28.3% [9,10]. Thus we consider that an ORR of 20% indicates no value of further investigation of the combination.”

3. **80 patients is very large for a Phase II. The authors need to justify this.**
   
   >>We agree with this comment. We justified the null hypothesis response rate of 20% as above and we believe that this clarifies the reason for the relatively large sample size.

4. **The lack of an interim analysis is extremely unusual. The authors need to justify why they chose not to use a two stage design (e.g. Simon minimax design).**
   
   >>We really appreciate the reviewer’s insightful suggestion. Given the suggestion, we are considering a plan of interim analysis of futility. We would like to exclude the following sentence in Statistical consideration section:
   
   “Formal interim analysis is not planned.”

   In my calculation, the total sample size of the Simon minimax design is 77 in our setting. Therefore we consider that revision of Sample size determination section is not necessary since the sample size would be similar to the current plan if we decide to use a two-stage design.

5. **The statistical methods to test effect of EGFR on response need to be made**
explicit.

Accordingly, we describe statistical methods for the subset analysis as follows:
“ORRs with 95% confidence intervals are calculated in the subsets of mutant and wild
type, and compared with a null hypothesis of 20% using one-sided testing at a 5%
significance level separately. Multiplicity is not adjusted for since this is a secondary
analysis.”