Author's response to reviews

Title: Customized chemotherapy based on epidermal growth factor receptor mutation status for elderly patients with advanced non-small-cell lung cancer: a phase II trial

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Author's response to reviews: see over
Dear Dr. Ruzzo,

We are uploading the revised manuscript entitled, “Customized chemotherapy based on epidermal growth factor receptor mutation status for elderly patients with advanced non-small-cell lung cancer: A phase II trial <MS: 1703931964617943>”, which we wish to submit for publication in the *BMC Cancer*.

This manuscript contains results of the phase II multicenter study, assessed the efficacy and safety of customized treatment for elderly patients with advanced NSCLC, based on EGFR mutation status. If EGFR mutation is found, patients are assigned to gefitinib. If EGFR wild type is found, patients are assigned to chemotherapy (VNR or GEM). The primary efficacy parameter of this study was the response rate (partial plus complete response). Clinically favorable results are shown in this manuscript. The trial is registered at University hospital Medical Information Network-clinical trial registration (www.umin.ac.jp/ctr/index/htm), registration identification number C000000436.

We are most grateful to you and the reviewers for the helpful comments on the original version of our manuscript. We have taken all these comments into account and submit a revised version of our paper. We have addressed all the comments by reviewers, as indicated below, and we hope that our explanations and revisions are satisfactory.

We hope that the revised version of our paper is now suitable for publication in the *BMC Cancer* and we look forward to hearing from you at your earliest convenience.

Yours sincerely,

Shiro Fujita, M.D., Ph.D.

We are grateful for your critical comments and useful suggestions that have helped us to improve our paper. As indicated in the responses that follow, we have taken all these comments and suggestions into account in the revised version of the manuscript.

-----For Dr. Garassino (referee 1)

Comment #1
-- It should be interesting to point out the reduction doses of both treatment for each patient and in particular for what kind of toxicity.

<Thank you for your comment. We add the description with underline formatting in page 5 and 9.>

Comments #2
Finally numbers are unable to draw any conclusions.

<We agree with your opinion. We changed the conclusion; decisive description was omitted in the revised manuscript (with underline formatting in the Conclusions).>

-----For Dr. Favaretto (referee 2)

Comment #1 (Major Compulsory Revisions)
-- This is a phase II study, so unable to answer the question of the better treatment in elderly patients. The patients were allocated to the different treatment based on the presence of mutation in EGFR exons.
-- The datum of a better disease control with TKI rather than chemotherapy in EGFR positive patients is well known, as well as the better prognosis; elderly patients are not different in this. Moreover TKIs are better tolerated than chemotherapy. So it is nothing new that TKIs are the winners in the competition with chemotherapy as the best treatment in elderly patients with EGFR positive NSCLC.

<As you are fully aware, result of the Japanese phase 3 trial that compared gefitinib with platinum-doublet chemotherapy in patients with an EGFR mutation was first reported at the 2009 ASCO annual meeting. The fact that gefitinib is more active than chemotherapy in EGFR-mutated NSCLC was not known at the time this study was developed. Moreover, there were few trials specifically designed for the elderly population in the issue, as we mentioned in the section “Discussion”. We think that our report of this prospective elderly-specific trial deserves publication, although several limitations exist.>

Comment #2 (Minor Essential Revisions)
-- Patient population is not so large for a study in NSCLC.

<The trial was designed to have adequate power, as we described in the section “Methods”.

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--Moreover the choice of response rate as primary objective of the study about “comparison” of TKI and chemotherapy does not seem the best: TKIs are able to modify the PFS or OS despite minor results in response rate.

<We agree with you regarding to the various effects of EGFR-TKIs; they are able to modify the PFS or OS despite minor results in response rate. We modify the description in the section “Introduction” (page 3). In NSCLC patients with wild-type EGFR, EGFR-TKIs work modestly. However, for tumors of patients with NSCLC and EGFR mutation, these agents often show the “Lazarus response”, as Dr. Langer stated in JCO 2009 (March 20, pp1350-1354). We focused on the particular nature of the agents and did
Comment #3 (Minor Essential Revisions)
- Some interest can derive from toxicity analysis and deserves to be better discussed:
  - Gefitinib overall optimal tolerance in Elderly patients, and in particular the lack of ILD toxicity (that in the past caused concern, especially in Asian people).
  <Thank you for your comments. As you mentioned above, no ILD was observed in the study and this deserves description (with underline formatting in page 9).>

  - Conversely, the high rate of drug discontinuation for AEs, attributed to a supposed “Age-related decreases in organ function “ seems unlikely in a population with such restricted entry criteria (see: no prior chemotherapy; ECOG PS 0-1; adequate bone marrow, renal, and hepatic function; and a life expectancy of at least 3 months. Exclusion criteria included symptomatic brain metastasis, any evidence of interstitial lung disease on chest CT examination, other co-existing malignancies or malignancies diagnosed within the last 5 years other than carcinoma in situ, history of congestive heart failure, unstable angina pectoris or recent history (within 6 months) of acute myocardial infarction, uncontrolled cardiac arrhythmia, severe psychiatric illness, or concurrent disease or condition that would have made the patient inappropriate for study participation).
  <Some of the factors are related to the robustness of informed consent (e.g. severe psychiatric illness; and concurrent disease or condition that would have made the patient inappropriate for study participation) and others are commonly seen in the protocol of a cancer clinical trial (e.g. no prior chemotherapy; adequate bone marrow, renal, and hepatic function; and a life expectancy of at least 3 months). In addition, there were no limitations with regard to organ functions, such as renal (CCr) or cardiac function (estimated by echocardiogram). These eligibility criteria are unable to exclude patients with age-related decreases in organ function. Considering that many recent clinical trial of cancer therapy adopted the functional limitations for enrollment, we do not think that the eligibility criteria were strict.>

Comments #4 (Discretionary Revisions)
In the “background”:
- why the Authors define EGFR as a “presumptive” target of gefitinib?
  <Thank you for your comments. Indeed, this word is misleading. We omitted the word “presumptive” in the revised manuscript.>

Comments #5 (Discretionary Revisions)
- the statement “Responsiveness to gefitinib is a characteristic of distinct subgroups of
patients” is not correct: responses are not restricted to women, non-smokers, adenocarcinoma, Asians.

<We agree with your opinion. We changed the indicated part of the manuscript (page 3).>

-----For Dr. Rocchi (referee 3)

Comment 1
-- 1. because of the nature of the study (i.e. a phase II), I suggest to underline that the comparison of the two arms has only explorative meaning. Although the presence of a control group is admitted, a phase II study is a non-controlled one. In fact, as the Authors correctly did, the sample size is calculated separately for each arm, and not in order to compare results.
So, I suggest to strongly remark the results of single arms separately, and to underline that, from an explorative point of view, some useful information can be obtained from the explorative comparison between groups’ results.
<We followed your advice and describe separately in the revised manuscript (shown by underline formatting in page 7 to 8).>

Comment 2
-- 2. Please, indicate the statistical tests used for comparisons, both of characteristics at baseline and of results (only Kaplan Meier and logrank rest are indicated).
<In the revised manuscript (page 7, with underline formatting) we add the description and we hope this helps the readers’ understanding.>

Comment 3
-- 3. Please, indicate the statistical software (I suppose it is SPSS, as I deduce from graphics) and its release.
<We add the description with underline formatting in page 7, thank you. To explain the software more precisely, we describe the version of the software instead of its release time.>

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Editorial Requirements:

**We would like to ask for name of ethics committee.
**Copyediting**

<We describe the name of ethics committee in detail on page 4. This manuscript was checked by a native-English speaker.>