Author's response to reviews

**Title:** Combination chemotherapy of intermittent erlotinib with pemetrexed for pretreated patients with advanced non-small cell lung cancer: a phase I dose-finding study.

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**Author's response to reviews:** see over
Dear Christna Chap;

Enclosed please find the revised manuscript (MS: 9224822666015169) entitled “Combination chemotherapy of intermittent erlotinib with pemetrexed for pretreated patients with advanced non-small cell lung cancer: a phase I dose-finding study” by Minami S. et al.

First of all, we are happy to hear that our manuscript is potentially acceptable for publication. In addition, we’d like to thank for the favorable comments of two reviewers on this study.

According to their suggestions, we revised the manuscript providing additional explanation and discussion. We mentioned about treatment process of two cases with activating EGFR mutations in ‘Results’ part. We also added comments about the limitations of this study in ‘Discussion’ part. We believe that the manuscript has been much improved by revision following the reviewers’ suggestion. Point-by-point replies to the comments are enclosed.

To Referee #1; Dr. Lucio Crino

The reviewer made a favorable comment on our study and gave us only a few minor issues.

1. We specified ‘platinum-based’ pre-treatment as first-line chemotherapy in inclusion criteria (1) of ‘Patients Selection’ section in ‘Methods’ part (page 6).
2. More speculation was requested on the fact that the two patients with activating EGFR mutations did not respond.
   - We added treatment process and efficacy assessment of these patients in ‘Antitumor Efficacy’ section in ‘Results’ part (page11).
   - Both of the patients successfully kept long-term SD for longer than 6 months, though they did not meet the definition of PR by RECIST. Therefore, we are not afraid at all that combination therapy of pemetrexed plus erlotinib is antagonistic in activating EGFR mutation-positive patients.
   - Our discussion on efficacy of this combination therapy in activating EGFR mutations was added in 4th paragraph in ‘Discussion’ part (page 12).
3. As suggested, we inadequately compared our only 12 patients with results from several large-scaled phase III trials in ‘Discussion’ part. So, we deleted almost all the discussion on antitumor activity. We’d like to discuss on this issue in our future manuscript of our ongoing phase II study.

To Referee #2; Dr. Atul Sharma

The reviewer made a favorable comment on our study that the study is well defined with satisfactory methods and data, and gave us only a few minor essential and discretionary revisions.

Minor essential revisions
1. As suggested, in ‘Background’ section of ‘Abstract’ part, we replaced the sentence ‘We investigated the safety in combination of erlotinib and pemetrexed in pretreated NSCLC patients’ with ‘We investigated the safety of erlotinib in combination with pemetrexed in pretreated NSCLC patients’ (Page3).

2. As suggested, we corrected the incomplete sentence in ‘Definition of DLT and MTD’ in ‘Methods’ part; ‘Since the purpose of this study was to examine if erlotinib could enhance the antitumor activity of pemetrexed and erlotinib beyond 150 mg was known to increase the incidence of severe AEs that would probably interfere with the administration of pemetrexed.’ to ‘The purpose of this study was to examine if erlotinib could enhance the antitumor activity of pemetrexed. Moreover, erlotinib beyond 150 mg was known to increase the incidence of severe AEs that would probably interfere with the administration of pemetrexed’ (Page8).

3. In ‘Results’ part, spelling of “patients” and “Safety” was corrected. Incomplete sentence in ‘Safety, DLT and RD’ section in ‘Results’ part was corrected from ‘As summarized in Table 2, dermal, gastrointestinal, and hematologic disorders were the frequent categories.’ to ‘As summarized in Table 2, dermal, gastrointestinal, and hematologic disorders were the frequently observed AEs’ (Page9).

Discretionary revisions

1. Incomplete sentence in ‘Patients characteristics’ section in ‘Results’ part was corrected from ‘The clinical data were collected up to May 2011 when the antitumor efficacy and the RD were fixed’ to ‘The antitumor efficacy and RD were fixed at the end of May 2011’ (Page9).

2. Unfortunately, we did not analyze the time line for attainment of best response and cycles needed before achievement of response or progressive disease. We expect additional analysis on the antitumor efficacy in our ongoing phase II trial.

3., 4. and 6. We did not conduct QOL assessment using questionnaire and pharmacokinetic analysis. Therefore, we mentioned these unplanned analyses as study limitations in the 5th paragraph of ‘Discussion’ part (Page12).

5. As suggested, despite of phase I trial, we had put too much emphasis on the response rates and survival aspects. We deleted the paragraph on efficacy and survival benefits in ‘Discussion’ part.

We hope that the revised manuscript is now suitable for publication in ‘BMC cancer’.

All the authors have read and approved the revised manuscript.

We’d like you to take kind considerations of the revised manuscript.

Sincerely yours,

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