Author’s response to reviews

Title: Efficacy and safety of afatinib in Chinese patients with EGFR-mutated metastatic non-small-cell lung cancer (NSCLC) previously responsive to first-generation tyrosine-kinase inhibitors (TKI) and chemotherapy: comparison with historical cohort using erlotinib

Authors:

Victor Lee (vhflee@hku.hk)
Dennis Leung (leungkcd@ha.org.hk)
Tim-Shing Choy (ctsz01@ha.org.hk)
Ka-On Lam (lamkaon@hku.hk)
Pui-Mei Lam (lammei411@yahoo.com.hk)
To-Wai Leung (leungtw@ha.org.hk)
Dora Kwong (dlwkwong@hku.hk)

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Author’s response to reviews:

Thank you very much for offering your expert review on our manuscript. We are now providing our detailed point-to-point responses to the comments of the reviewers as follows.

Reviewer reports:

Associate Editor’s comments:

The study was well-conducted to evaluate prospectively the efficacy and safety of afatinib under a compassionate use program.
However there are several comments in this manuscript. Please read carefully all suggestion and either make appropriate changes in the manuscript and provide suitable replies.

When preparing your revised manuscript:

1. Please describe the name and date of clinical trial registry such as ClinicalTrials.gov. Please clarify that reason if authors didn’t’ register this prospective clinical trial.

Our reply: Thank you very much for your kind comment. we have registered this clinical trial at ClincialTrials.gov (NCT02625168) which has been updated in the revised manuscript.

2. Please describe the eligibility criteria, treatment method, and assessment of the efficacy and toxicities of erlotinib cohort in the Methods part.

Our reply:

We have updated this in the Methods part already in the revised manuscript. Though patients in the erlotinib group are a historical cohort, the data on treatment, response evaluation, efficacy and safety issues were collected in a prospective manner which is exactly the same as for the afatinib group. I hope this explanation is acceptable to the editors and the reviewers. Thank you very much indeed.

Reviewer #1

The study is potentially interesting, but there are some limitations that should be resolved. First, the study design has limitations, namely the small sample size and lack of a translational approach. Although this study is exploratory, the authors should address these limitations and emphasize the importance and purpose of their study. Was a pilot study performed to evaluate the feasibility of the approach? Second the retrospective analysis of erlotinib treatment is unclear; how were afatinib – and erlotinib-treated patients compared? Were they matched according to their clinical characteristics or compared consecutively? This needs to be clarified. The registered trial number should also be provided in the manuscript for the prospective clinical trial of afatinib treatment.
To justify publication, the manuscript should discuss recent publications relevant to the topic ([32], [33] and others). The language also requires thorough editing by a native English speaker.

Our reply: Thank you very much for your great comments. We have already addressed the limitations of our study including small sample size. We have also addressed the retrospective comparison with the patients in the erlotinib cohort though their data were prospectively collected.

Indeed all patients in the erlotinib cohort are ALL the patients in our department who received erlotinib after prior disease progression to gefitinib and systemic chemotherapy. Thus they were not specifically matched with the afatinib cohort according to any baseline or treatment characteristics. However the number of patients in both the afatinib group (25 patients) and the erlotinib group (28 patients) was similar. Despite these limitations, our study provided important clinical information on the efficacy and safety of afatinib as 2nd TKI therapy and its comparable anti-tumor activity but with a different toxicity profile compared to erlotinib in this setting.

In addition, we have registered this clinical trial at ClinicalTrials.gov (NCT02625168) which has been update in the revised manuscript. Thank you very much for your comments.

We have also discussed recent publications relevant to T790M specific EGFR TKI and added two new references in the revised manuscript (ref. 34 and 35) as well. The manuscript was further proofread again by a native English speaker before resubmission. Thank you very much for your valuable suggestions.

The following issues should also be addressed:

1) Who evaluated the response to treatment? A central or external review is routinely performed during phase II clinical trials. Please provide details.

Our reply:

Two independent radiologists in our institution who were blinded to study treatment performed radiological evaluation of tumor response. Any discrepancies between the two radiologists on tumor response evaluation were resolved by consensus. Since this is just a prospective study (but
not a phase II clinical trial), a central review is not considered in this study. I hope this is acceptable to the reviewer.

2) Clarify the time period of the clinical trial.

Our reply:
We have clarified the time period of the clinical trial. Thank you very much for your nice suggestion.

3) Please provide the ethical approval number of the institutional review board.

Our reply:
We have provided the approval number (UW 13-396) of our local institutional review board namely Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster) in “Study design” under “Methods” the revised manuscript. Thank you for your nice suggestion.

4) The discussion contains redundant information and the findings are not adequately summarized; this should be improved.

Our reply:
We have abridged the redundant information while also adding new and relevant issues in the Discussion part and hope this revised manuscript is acceptable to the reviewer. Thank you very much for your great comments.

5) The tables contain redundant information and should be simplified; additional, non-essential information can be presented as supplementary information.
Our reply:

Thank you very much for your suggestion. Though the tables (especially Table 1) may not a little clumsy, we all consider that they are essential to demonstrate the distribution of different subgroups in the afatinib and erlotinib cohort so that the readers understand if there is any uneven distribution in any of the subgroups. We think that the data in Table 2, Table 3 and Table 4 are more succinct and comprehensible to the reviewers and readers. We hope this is acceptable to the reviewers.

6) Figures need some formatting, to make them easier to interpret. Specifically, the number of patients at risk is lacking and the title of the vertical axis is inaccurate; it should read “proportion of patients surviving” rather than progression-free survival”.

Our reply:

Thank you very much once again for your suggestion. We have revised the format of the figures and changed the title of the vertical axes in the Kaplan-Meier curves in the revised manuscript and hope they are acceptable to the reviewers.

Minor essential revisions:

Abstract

Patient and methods

- Clarify the time period of the clinical trial
- Clarify the study design or primary endpoint(s)

Our reply:

We have clarified these in the revised manuscript already. Thank you very much for your nice suggestions.
Results

- I think it is inaccurate to say that the ORR of the afatinib and erlotinib cohorts are “similar” and not significant. I recommend changing this description.

Our reply:

We have modified the phrasing of this sentence already. Thanks very much for your nice suggestion.

Conclusions:

The conclusions of the abstract repeat the result should be modified.

Our reply:

This has been modified already. Thank you very much for your nice suggestion.

Introduction

- The references and data need to be refined in the introduction section to make it suitable for publication in an international journal.

- Line 3:

  the abbreviation “PFS” should be defined in full upon first use.

Our reply: All the above suggestions by the reviewers have been fully adopted and the revised manuscript should be more appropriate and acceptable.

Methods

Study designs

- Please add the ethical approval number of the institutional review board or the registered number of clinical trial in this study.
Our reply:

We have provided the approval number (UW 13-396) of our local institutional review board namely Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster) in “Study design” under “Methods” the revised manuscript. Thank you for your nice suggestion.

Study population patients

- The term “evaluable lesion” is unclear. Please clarify

Our reply:

This has been rephrased and modified already. Thank you very much indeed.

Treatment

- Define the abbreviation “CT” in full.

Our reply:

Computed tomography has been added preceding its short form in the revised manuscript. Thank you very much indeed.

Assessment of efficacy and treatment-related toxicities

- Were the responses sufficient to confirm treatment efficacy? This should be clarified.

- The descriptions of PFS and OS are unusual and should be changed.

- How did the authors confirm that the assessment were the “same”? Was the historical cohort also analyzed in the prospective study? Or during the same time period? The time period of the erlotinib cohort analysis is an important factor as time-to-event endpoints were described in the present clinical trial and selection bias may easily have had an influence.
Our reply:

Thank you very much for your kind comments. We think that “Treatment efficacy” is just a general term to describe the prespecified outcomes including the response rate, disease control rate and the survival endpoints after treatment with afatinib or erlotinib. We are not saying treatment with afatinib/erlotinib is efficacious in this setting of our study but we can use the term efficacy to generally describe our treatment outcomes. I hope this is acceptable to our reviewer. The descriptions of PFS and OS have been further modified in the revised manuscript.

In “Assessment of efficacy and safety profiles” under Methods in our revised manuscript, we clearly stated that all these parameters of all patients in the afatinib group in this study were compared to a historical cohort of all patients who received erlotinib after prior failure to gefitinib and at least one line of systemic chemotherapy in our department from January 2009 to December 2011, with the same inclusion and exclusion criteria as for the patients who received afatinib in this study. All patients in this erlotinib historical cohort received erlotinib at 150 mg once daily, and they were assessed by the same imaging modalities for treatment response evaluation, as well the same departmental protocol for safety profiles and survival outcomes as for those who received afatinib in this study. There is no overlap of the study period for patients in the erlotinib historical cohort (January 2009 to December 2011) and the afatinib group (January 2013 to February 2014) in our study and so there is no issues of selection bias. I hope this further elaboration in the revised manuscript is acceptable to the reviewer.

Statistical analysis

- The statistical methods used to compare each endpoint should be clarified.

- “SPSS” is generally described as: “SPSS version XX (SPSS, INC., Chicago, IL)”. Please change if appropriate.

Our reply:

Thank you very much for your great comments. This has been revised in the manuscript and the description of SPSS has also been revised in the new manuscript.

Results

Patient characteristics
- The recruitment period should be provided as this affects the chemotherapy or supportive treatment.

- Define “ECOG” in full.

Our reply:
These have been updated already. Thanks for your suggestions.

Treatment efficacy

- However should be inserted in line X.

- Define “CI” in full upon first use (p8, line 1).

Our reply:
These have been modified and updated already. Thanks for your suggestions.

Discussion

- p9, line 16: “however” should be used.


- p11, line 28: “unfortunately” should be used.

- p11, line 60: “interestingly” should be used.

- p12, line 6: “BR.26” is correct, not “Br.26”.

- p13, line 54: I think the lines are misleading; the present study is a prospective trial of afatinib treatment for EGFR-mutated NSCLC, not erlotinib treatment (the study design is neither randomized nor a parallel phase II trial).

Our reply:
These have been updated already. Thanks for your suggestions.
Authors’ contributions

Authors’ contributions should be provided in more detail.

Our reply:

All authors in our study actively participated in conception and design of this study. They also contributed significantly to patient recruitment, data acquisition, interpretation and analysis. They were also responsible for drafting, revising and final approval of the manuscript before submission. These have been further updated already. Thank you very much for your comments.

Reviewer #2

This study is quite similar as the design of LUX-Lung1 trial but offers some interesting points of view.

1) The erlotinib arm seems to be a historical control in the study. How are these patients selected and how are these side effect recorded?

Please describe more clearly in the Methods part.

Our reply:

Thank you very much for your valid comments. The erlotinib arm is a historical cohort in which all patients received erlotinib as 2nd TKI therapy after failure to prior gefitinib and at least 1 line of systemic chemotherapy. Though they belong to a historical cohort, all the treatment outcomes and toxicity profile after erlotinib were collected prospectively.

Same as the response to Reviewer 1, in “Assessment of efficacy and safety profiles” under Methods in our revised manuscript, we clearly stated that all these parameters of all patients in the afatinib group in this study were compared to a historical cohort of all patients who received erlotinib after prior failure to gefitinib and at least one line of systemic chemotherapy in our department from January 2009 to December 2011, with the same inclusion and exclusion criteria as for the patients who received afatinib in this study. All patients in this erlotinib historical
cohort received erlotinib at 150 mg once daily, and they were assessed by the same imaging modalities for treatment response evaluation, as well the same departmental protocol for safety profiles and survival outcomes as for those who received afatinib in this study. There is no overlap of the study period for patients in the erlotinib historical cohort (January 2009 to December 2011) and the afatinib group (January 2013 to February 2014) in our study and so there is no issues of selection bias. I hope this further elaboration in the revised manuscript is acceptable to the reviewer.

2) A great part of patients in both arms have brain metastasis before treatment with afatinib or erlotinib.

Did these patients receiving brain radiation before study?

Do you evaluate the response of afatinib or erlotinib in brain metastasis? And what’s the response?

Our reply:

Thank you very much for your valuable suggestions. All patients who had brain metastases before starting afatinib or erlotinib received either gross tumor removal or radiation therapy and their brain metastases were all asymptomatic requiring no corticosteroid therapy for at least 14 days before starting afatinib or erlotinib. The objective responses of brain metastases were also reported in the revised manuscript, showing no significance difference between the afatinib group and the erlotinib group. I hope the above elaboration is acceptable to the reviewer.

3) IN the LUX Lung 3/6 combined analysis published in Lancet Oncol, the response and OS in patients with EGFR mutation of exon 19 deletion and L858R different.

How about the response of 2nd line TKI in these 2 different mutations in this study?

Our reply:

We have also performed PFS analysis for those who had exon 19 deletion versus those who had L858R mutation. It showed that no difference in PFS was noted between these 2 types of mutations in both the afatinib group and erlotinib group. This has been updated in the revised manuscript. I hope this is acceptable to the reviewer.
4) Because of small study patient number, I would suggest a table comparing this study result and LUX-Lung1 for better understanding.

Our reply:

Thanks very much indeed. We have added a new table contrasting the results and selected safety profiles of LUX-1 and our current study in the revised manuscript. I hope this is acceptable to the reviewer.

5) IN the Table 1, the number of Erlotinib patients treated with 1st line geftinib is 28 and should be 100%, not 0%.

Our reply:

Thank you very much indeed. This silly typo has been corrected in the revised manuscript.

All the revisions and changes in our revised manuscript were highlighted for your reference.

I am looking forward to your favorable reply very soon.

Thank you very much for your kind consideration.