Author’s response to reviews

Title: The Clinical Efficacy of Afatinib 30 mg Daily As Starting Dose May Not Be Inferior to Afatinib 40 mg Daily in Patients with Stage IV Lung Adenocarcinoma Harboring Exon 19 or Exon 21 Mutation

Authors:

chih-jen yang (chjeya@cc.kmu.edu.tw)
Ming-Ju Tsai (960216kmuh@gmail.com)
Jen-Yu Hung (jenyuhung@gmail.com)
Yu-Chen Tsai (poppy_snow@hotmail.com)
Jui-Feng Hsu (940360@mail.kmuh.org.tw)
Ta-Chih Liu (d730093@cc.kmu.edu.tw)
Ming-Shyan Huang (shyang@kmu.edu.tw)
Inn-Wen Chong (chong@kmu.edu.tw)
Ying-Ming Tsai (yingming@kmu.edu.tw)
Mei-Hsuan Lee (mhsuan99@yahoo.com.tw)

Version: 1 Date: 22 May 2017

Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for giving us the opportunity to improve our manuscript. We have revised the manuscript based on the suggestion from the reviewers. We have also answered the questions raised by the reviewers in a point-by-point fashion.

Dereje Nigussie Woldemichael (Reviewer 1)

The manuscript is well written but it has some limitations such as the follow-up time was too short to calculate median OS, which is important part of the study.
Reply: Thanks. We will extend the study period to calculate OS in the future.

Esther Black (Reviewer 2)

The article "The Clinical Efficacy of Afatinib 30 mg Daily As Starting Dose Is Not Inferior to Afatinib 40 mg Daily in Patients with Stage IV Lung Adenocarcinoma Harboring Exon 19 or Exon 21 Mutation" is an interesting retrospective study of the clinical efficacy of 30mg starting dose of afatinib in EGFR mutated patients. While it is true that the numbers are small and that half of the patients were still alive at the end of the study, these data might indicate clinical benefit for patients by beginning at a lower dose. The observations will need to be validated in a separate study. However, reducing ADRs is likely to improve adherence and since the disease control rate was equal, a larger population followed through survival may be demonstrate a difference in response rate. It did seem a bit odd that the regression analysis in Table 3 does not show a significant effect of dose on response rate, given the graphs in Figure 1.

Reply: As shown in Figure 1A, the PFS was similar between the patients receiving 30 mg and 40 mg daily of afatinib (median PFS: 469 vs. 443 days, log-rank p = 0.8418). This findings is compatible with the non-significant effect of dose on PFS shown in Table 3.

In the Discussion, line 31, I'm not sure "dramatic improvement" is an appropriate conclusion from the data shown.

Reply: We delete the word “dramatic”. In fact, the “dramatic improvement” in the manuscript means that when patients who had EGFR mutation and received EGFR TKI, the PFS had significant improvement when compared with chemotherapy in many large-scale clinical trials.

Barbara Wiśniowska (Reviewer 3)

The paper describes study aimed to evaluate efficacy and safety of two different doses of afatinib. This is very interesting research problem as the LUX-Lung trials showed decreased incidence of ADRs and similar PFS in patients that required dose reduction due to the occurrence of ADRs. If the efficacy of afatinib starting dose of 30 mg is proven to be similar to 40 mg, it will offer advantages of both safety and financial costs. My main concerns are:
1. Very small group being evaluated, especially in subgroups and therefore substantial differences in groups' characteristic, including chosen confounding factors; thus the statement on non-inferiority of afatinib 30 mg is not sufficiently supported by the presented results. It is a small observational study without confounding control while groups do differ significantly, thus in my opinion any meaningful conclusion is unjustified.

Reply: Yes, we totally agree with you opinion. The enrolled patients number is too small is indeed the critical problem in this study. Actually, though the enrolled patients numbers were limited, we consider the issue of lower initial dose afatinib is urgent and timely for these poor patients. We will continue to enroll more patient and will design a prospective study to compare the different initial dose of afatinib in the future.

2. The character of the analysis is not clear. Patients treated from May 2014 till August 2016 were followed until December 2016, according to the text, but when the study was initiated? Was the data collected prospectively for all of the patients? This also brings another problem, if patients were qualified successively some of them were observed for a much shorter period than others, so how the survival analysis with the time scale of ca. 630 days was done? The drop in the number of cases on Figure 1 can be both due to patient death and termination of the individual observation time.

Reply: This was a retrospective study showing the real-world data. In Taiwan, the Nation Health Insurance Bureau permitted both different doses (30 mg and 40 mg daily) of afatinib as the first line therapy in advanced lung adenocarcinoma with activating EGFR mutation since May 2014. In this retrospective study, we started the study in Dec 2016 and reviewed all patients with lung adenocarcinoma harboring susceptible EGFR mutation who took different initial doses of afatinib as the first-line EGFR TKI in two hospitals since May 2014.

3. The Authors claim that: factors predictive for PFS and OS were identified (pp 8 line 58-63; pp 10 line 38-43; pp 12 line 49-52) and no difference in OS in 2 groups was found (pp 10 line 13) and OS was similar in 30 and 40 mg group (pp 11 line 52). At the same time (pp 12 line 38-39) "in our study, OS is still undefined due to most patients are still alive until Dec 2016."

Reply: We thank the careful review from the reviewer. The K-M curve with log-rank test and COX regression of OS were presented in our study, which might be a preliminary findings. We therefore adjust the statement in the Discussion to “However, since the median OS was not
reached in both groups because most patients were still alive till Dec., 2016 in our study, further follow-up is warranted to confirm our preliminary findings.”

4. Pp 11 line 3-7: Grade 3 skin rash occurred in three patients (16%) using 40 mg daily of afatinib, while no patients using 30 mg daily had grade 3 skin rash - probably there is no statistically significant difference between the groups (3 and 0 cases of rash); data does not allow to draw some statistically significant conclusions. Thus it cannot be seen as a proof of lower skin rash risk in case of afatinib 30 mg.

Reply: Yes, we agreed with your opinion. We should not make a conclusion in such few patients.

5. There are statistically important differences between groups (30 and 40 mg) in age, sex, weight and height. The Authors state that male gender is a predictive factor of PFS, so the similar PFS value in 30 mg group can occur due to more female than male patients in this group. Also, while afatinib concentrations were not monitored and afatinib 30 mg group has lower BW and height, it is possible that effective concentrations do not differ between groups.

Reply: Yes, the effective concentration may be similar between two groups. Actually, based on previous experiences, physicians tended to prescribe lower dose afatinib to treat those with smaller body size.

6. Pp 12 line 10-17: “in a pooled analysis of the LUX-Lung 3 and LUX-Lung 6 trials, afatinib showed a statistically significant PFS benefit when compared with chemotherapy (HR [95% CI]: 0.42 [0.34 -0.53] [9].” I could not find this data and such statement in the referenced publication. Please clarify.

Reply: We appreciate your careful review. The data was from “Greenhalgh J, et al. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. Cochrane Database Syst Rev. 2016;(5):CD010383,” which stated in the “Main Result” section that “Afatinib (n = 709) showed a statistically significant PFS benefit when compared with chemotherapy in a pooled analysis of 2 trials (HR 0.42; 95% CI 0.34 to 0.53).” We have cited the paper as a reference.
7. Pp 12 line 27-32: results were reported with the use of various time units (months and days). It would be easier to compare them if both are given in the same units.

Reply: We appreciate the worthy suggestion from the reviewer. In the Result section, we keep the unit “days” due to the relatively short follow-up period of the current study. As suggested, we unify the unit in the Discussion section as “months” to compare our data with other studies. (“In our study, the median PFS in 30mg and 40mg were 15.6 months and 14.8 months, respectively.”)

8. "Lug-Lung series" - should it be LUX-Lung?

Reply: We thank the careful review from the reviewer. The word is corrected.

9. Keywords are missing.

Reply: We appreciate the warm remind. The keywords are added in the revised manuscript.