Peer Review File

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Reviewer A

Major comments:

Although the manuscript is written in clear understandable language, some attention should be paid to correct English. For example methods line 150, discussion line 316, 346, 357.

Reply: According to this comment, we have corrected the English by Enago

Abstract:

Number of patients and distribution over the cohorts should be stated in the abstract.

Reply: Thank you for your constructive comments. We agree with your opinion. We added the number of patients and distribution over the cohorts in the abstract.

Changes in the text: (Page 4, Lines 75–80) A total of 737 EGFR mutation-positive (EGFR M+) NSCLC patients receiving first-line afatinib treatment were categorized by second-line treatment: T790M+ sequentially treated with osimertinib (cohort A, n=116); T790M− given chemotherapy or others (cohort B, n=143); patients with unknown T790M status (cohort C, n=111); and patients who were undergoing afatinib treatment at the time of data collection, were dead, had discontinued afatinib treatment due to serious adverse events, or were lost to follow-up (cohort D, n=367).

Introduction:

Aim: retrospective study should be stated here.

First line EGFR TKI should be first line afatinib

Line 144: options should be sequences.

Reply: As per your comment, we modified description of our study.

Changes in the text: (Page 6, Line 133-135) Therefore, in this retrospective study, we investigated the total TOT along with four treatment options starting from first-line afatinib treatment to various

subsequent treatments, including osimertinib and cytotoxic chemotherapy.

Methods:

The distribution of patients to group A and B is clear. However, group C is different because it does include patients without second line treatment in stead of all T790M unknown patients with second line therapy only.

Also, the inclusion of dead patients in group D is confusing, or do the authors mean that these patients died when on first line afatinib? If patients lost to follow up should be included in this group can be argued (also discussion line 376-7)

Reply: Thank you for your insightful comment. We agree with your opinion. However, we have some limitations. When a patient is transferred to another hospital, it is difficult to find data on subsequent chemotherapy. Cohort C included patients who have not undergone re-biopsy at the time of data cut-off and received chemotherapy or others, supportive care, or delayed chemotherapy. Since not all patients are followed up until death in tertiary hospitals, we had difficulties dividing cohort C into a chemotherapy group and a supportive care group.

Patients who died when on first-line afatinib were included in cohort D. Even if the patients moved to another hospital or were lost to follow-up, we could still obtain survival data from the National Cancer Registry. However, patients who were still alive at the time of data cut-off were included in cohort C.

The cohorts are not fully described in figure S1.

Reply: In accordance with your comment, we have modified the description of Figure S1.

Changes in the text: Figure S1

Results:

A lot of data is presented, some of the results (for example, dose reduction) could be skipped to supplementary data.

Reply: Thank you for constructive comment. As per your suggestion, we have deleted some of the

results including the dose reduction in the Results session.

Changes in the text: (Page 13, Line 293-300)

Conclusion:

Results should not be mentioned again.

The results do not show that afatinib followed by osimertinib is feasible for EGFR M+ NSCLC, but only in patients developing the T790M mutation.

Reply: Thank you for your insightful comment. We have modified the text as advised.

Changes in the text: (Page 17, Lines 412–417) In conclusion, this study demonstrates the efficacy of first-line afatinib and subsequent treatment for advanced EGFR M+ NSCLC. A sequential approach of first-line afatinib followed by various subsequent treatments is a feasible and appropriate treatment option for patients with EGFR M+ NSCLC.

Minor comment:

Figure 1: caption c, should be ©

Introduction line 140 It ◊ it

Reply: Thank you for pointing these out; we have modified the typos.

Reviewer B

The study by Jung et al. is a multicenter retrospective study investigating the effectiveness of 1st line afatinib therapy and 2nd line treatment in EGFR-mutated NSCLC patients. Although similar studies have been published elsewhere, as the authors stated, this is the largest study evaluating this sequential treatment of afatinib followed by 2nd line therapy.

Previous studies have showed only the efficacy of afatinib followed by osimertinib in patients with T790M (Gio-Tag and UpSwinG studies). The current study also demonstrated the effectiveness of afatinib followed by systemic chemotherapy or BSC.

The authors should mention

At the data cutoff, about 50% of patients were still on afatinib treatment (Cohort D). Because these patients whose tumors were controlled by afatinib for a long time were excluded from Cohort A, TOT in Cohort A could be shorter in this study period. It would be better to extend the follow-up time and conduct the final analysis in the future.

Reply: Thank you for your constructive comments. We agree with your opinion. We have added comments about the limitations of our findings.

Changes in the text: (Page 14, Lines 325–329)

Minor comments

1. Page 5, data presented in the text and Supplementary Fig. 1 are not consistent. Please correct the number of patients in cohort A, cohort D. In supple Fig. 1, n=727 need to be corrected to 737.

Reply: There was typo. We have modified Supplementary Figure 1.

Changes in the text: Supplementary Figure 1.

2. Please provide the start date of patient enrollment. Was that after osimertinib was approved for patients with T790M?

Reply: As per your comment, we have added data on the start date of patient enrollment.

Changes in the text: (Page 7, Line 141–142) **between October 1, 2013 and April 30, 2019**. **Osimertinib was approved for patients with T790M since May 19, 2016.**

3. The authors should mention that CNS-PFS was only assessed in patients with brain metastases at afatinib initiation in the Methods section.

Reply: We clarified that CNS-PFS was only assessed in patients with brain metastases at afatinib initiation in the Methods and Results.

Changes in the text: (Page 8, Lines 190–195) CNS-PFS was only assessed in patients with brain metastases at afatinib initiation.

(Page 12, Lines 281–282) The median CNS-PFS in 287 patients with brain metastases at afatinib initiation was 24.7 months (95% CI: 19.84–33.15 months).

4. How did the authors perform the significance test for survival?

Reply: As per your comments, we have described the statistical method for survival analysis.

Changes in the text: (Page, Lines 179–180) The overall survival rate was estimated using the Kaplan–Meier method.

5. The authors should explain the meaning of Non-CNS in Figure 3B.

Reply: Thank you for your comment. We have added comments about the competing risk analysis estimating the cumulative incidence for CNS failure. The event time was defined as either the occurrence of the earliest of the three events (CNS progression, non-CNS progression, and death) or the patients were censored at the time of their last assessment.

Changes in the text: (Page 8, Line 192-195) A competing risk analysis estimating the cumulative incidence for CNS failure in the presence of two competing risk events (non-CNS progression and death) was performed using a semiparametric Fine–Gray regression model. Event time was defined as either occurrence of the earliest of the three events or patients were censored at the time of their last assessment.

6. Could the authors add the number at risk to figures?

Reply: Thank you for your comment. We have added the number at risk to the figures.

Changes in the text: Figure 1 and Figure 2

7. Please discuss the results of the UpSwinG study investigating sequential afatinib and osimertinib like the Gio-Tag study.

Reply: As per your comment, we have added the result of the UpSwinG study to the Discussion session.

Changes in the text: (Page 15, Line 361–363) In the UpSwinG study, the median time to treatment failure was 27.7 months and the median OS was 36.5 months (31).

8. Only 117 out of 370 patients (32%) received osimertinib after afatinib failure. The authors should mention and discuss about this finding.

Reply: Thank you for your constructive comments. We agree with your opinion. We added these findings to the Discussion session.

Changes in the text: (Page 14, Lines 325–329) In this study, only 117 out of 370 patients (32%) received osimertinib after afatinib failure. At the data cutoff, about 50% of patients were still on afatinib treatment. Because these patients whose tumors were controlled by afatinib for a long time were excluded from cohort A, the TOT in cohort A could be shorter in this study. The follow-up time to conduct the final analysis should be extended in the future.

Reviewer C

This is the retrospective study regarding the efficacy of the sequential therapy afatinib followed by osimertinib. The favorable efficacy of this treatment strategy was reproducibly demonstrate other retrospective study, such as GioTag and UpSwinG. The strong point of this study was the data regarding populations who could not perform the sequential osimertinib. In South Korea, osimertinib cannot choice as the initial EGFR-TKI for chemo-naïve EGFR- mutation positive NSCLC because of reimbursement. However, osimertinib is selected as the first-line treatment in many countries based on FLAURA results.

Please consider additional data and discussion regarding first-line afatinib to compare with first-line treatment osimertinib (e.g. time on treatment of TKI therapy including overall population A-D)

Reply: Thank you for your insightful comment. As mentioned in your comment, we have included additional data and discussion about first-line afatinib compared to first-line osimertinib in the Discussion session.

Changes in the text: (Page 16, Lines 370–378) In the FLAURA study, the median PFS was 18.9 months in the osimertinib group and the median OS was 38.6 months. In that study, 61.6% of patients received subsequent therapy, and 28.2% of patients died without subsequent therapy after

discontinuation of osimertinib. Our study showed 23.4 months of TOT, and the median OS was not reached during the study period.