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Reviewer A

The authors retrospectively analyzed clinical efficacies of EGFR-TKIs using Zhejiang Cancer Hospital data. The study showed clinical benefits of afatinib for NSCLC patients with uncommon EGFR mutations in real-world setting. The data appear sound and generally clearly presented; however, the following issues should be addressed.

1. To compare clinical efficacies of EGFR-TKIs for patients with uncommon EGFR mutations, patient's characteristics table based on each EGFR-TKIs treatment are missing. Reviewer recommends to indicate them including uncommon EGFR mutation status.

Reply 1: Thanks for your helpful suggestion. Patient's characteristics (including uncommon mutation types) based on different EGFR-TKIs were shown in Table 4, we hope the added table could clearly show the characteristics between different EGFR-TKIs and meet your expectations (see chart file named Table, Table 4).
Changes in the text: Chart file named Table added Table 4.

2. It would be useful to show overall response rate of each EGFR-TKIs in patients with uncommon EGFR mutations.

Reply 2: Thank you for your comments. We further reviewed the medical records system and updated our database, the ORR of uncommon EGFR mutation was 13.2% (12/91). In addition, the ORR of first-generation EGFR-TKI, second-generation EGFR-TKI and third-generation EGFR-TKI was 9.7% (7/72), 26.7% (4/15) and 25% (1/4) respectively. It was obvious that the second-generation EGFR-TKI had higher ORR. We further compared the ORR among single uncommon mutation (11.3%, 8/71), compound mutation (20%, 2/10) and double uncommon mutation (20%, 2/10) and we found compound mutation and double uncommon mutation had higher ORR (see Page 9, line 194-195; Page 10, line 199-201; Page 11, line 219-220; Page 11, line 238-240).
Changes in the text: We added the data of ORR in Page 9, line 194-195; Page 10, line 199-201; Page 11, line 219-220; Page 11, line 238-240.

3. Some papers already showed that 1st generation-TKIs have weak efficacies against uncommon EGFR mutation, while 2nd generation TKI, afatinib, showed significantly superiority over 1st generation-TKIs. (Lung Cancer. 2019 Jan;127:169-171. Clin Lung Cancer. 2019 Sep;20(5):e576-e583.) The reviewer highly recommends to refer these papers and discuss the therapeutic strategy for NSCLC patients with uncommon EGFR mutations.

Reply 3: Thanks for your careful review, we have cited relevant literature in this study (see Page 13-14, line 282-287).
Changes in the text: We added the relevant literature in Page 13-14, line 282-287.

Reviewer B

In this paper, we believe that it is significant to submit large-scale data that NGS was performed on 2680 samples of non-small cell lung cancer and 132 uncommon EGFR mutations were detected.

Major problem

1.Line 102 says "written informed concents", but it was a retrospective observational study, and I think it was an opt-out. Or if it is part of a prospective observational study with comprehensive consent, the research style will be different.

Reply 1: We sincerely appreciate your kind suggestion. This study was a retrospective study and was compliance with Ethical Standards of the Zhejiang Cancer Hospital, so the written informed consents were waived (see Page 6, line 115-117).
Changes in the text: We have modified our text as advised in Page 6, line 115-117.

2.Mutations detected by NGS on Line 114-117 should include T790M.

Reply 2: Thanks for your careful review. We have modified the text as follows according to your advice (see Page 7, line 132).
Changes in the text: We have added the “primary T790M mutation” in Page 7, line 132.

3.You should describe when the tissue sample that underwent the NGS test was collected. From the description of Line 126-127, it can be read that the examination of the tissue collected after using EGFR-TKI is also included.

Reply 3: Thank you for your comment. I'm sorry about the unclear statement and the part of the emphasized contents are that uncommon mutation patients in our study have accomplished the NGS test before they received EGFR-TKI. We aim to emphasize the fact that the T790M mutation is a kind of primary mutation in this study and acquired T790M mutation has not been enrolled in. (see Page 7, line 135-136,142-144).
Changes in the text: We have added the statement of "We detected 132 uncommon mutation patients through NGS before they received EGFR-TKI" and deleted the last sentence in the part of "Gene mutation detecting" in Page 7, line 135-136,142-144.

4.Abstract and Line 101 state that the test was performed on a patient with 2680 adenocarcinoma, but inferring from the contents described below, isn't it a patient with 2680 EGFR mutation-positive adenocarcinoma?

Reply 4: Thank you for your recognition of our work. We collected 2680 EGFR mutation-positive adenocarcinoma patients, there were 2548 lung adenocarcinoma patients with common EGFR mutation and 132 lung adenocarcinoma patients with uncommon EGFR mutation. We have modified our text as advised (see Page 2, line 28-29; Page 6, line 114).
Changes in the text: We added the "EGFR mutation-positive" in Page 2, line 28-29; Page 6, line 114.

5.Patients with uncommon mutations were divided into 4 groups and 3 were excluded, but the EGFR gene mutation detected in these 3 patients may not be a driver mutation and should be excluded.

Reply 5: Thank you for your comment. There were 3 patients harboring exon 19 T751P mutation, exon 22 uncommon mutation and exon 1 uncommon mutation included as uncommon mutation when compared the treatment efficacy between common mutation and uncommon mutation. The differences between EGFR-TKI and mutation types were excluded when analyzed the treatment efficacy. We reanalyzed the survival data of the treatment efficacy of different EGFR-TKI and changed the survival data, P value, figure 2-3 and table 3 (see Page 2, line 36-37; Page 10, line 204,208;Fig 2-3).
Changes in the text: We have modified our text as advised in Page 2, line 36-37; Page 10, line 204,208;Fig 2-3.

6.The N numbers should also be listed in the groups treated with 1st and 3rd

generation EGFR-TKIs on Line 174-178, which totals 78 in Figure 2. Adding 15 people treated with 2nd generation EGFR-TKIs does not match the total of 102 in groups 1-3. Please indicate whether these patients did not receive EGFR-TKI treatment or were enrolled in other clinical trials and excluded from the analysis.

Reply 6: Thank you for your comment. We have added the number of patients treated with 1st and 3rd generation EGFR-TKIs (see Page 10, line 203). Of 132 uncommon mutation patients, 115 received EGFR-TKI. And of 115 patients received EGFR-TKI, 72 patients received first-generation EGFR-TKI, 15 patients received second-generation EGFR-TKI and 4 patients received third-generation EGFR-TKI. The remaining 24 patients received EGFR-TKI were in primary T790M mutation group and this part of population were analyzed separately. The total of patients harboring single uncommon mutation, compound mutation and double uncommon mutation was 102 and only 91 patients treated with EGFR-TKI (Fig 2) due to the economic problems. At that time, targeted drugs did not enter medical insurance and a part of uncommon mutation patients received chemotherapy and other palliative care couldn't afford targeted therapy. (see Page 2, line 35; Page 9, line 182-187).
Changes in the text: We have modified our text as advised in Page 10, line 203; Page 2, line 35; Page 9, line 182-187.

7.OS is also considered for the second-generation EGFR-TKI treated group, but the rate of detection of T790M after resistance and the rate of use of osimertinib should also be mentioned.

Reply 7：Thank you for your kind reminder. Our statement was needed to be amended, uncommon mutation patients (including primary T790M mutation patients) collected in this study underwent the NGS test before they received EGFR-TKI. The information of the rate of acquired T790M mutation and use of Osimertinib was not collected in this study. We aim to emphasize the primary T790M mutation and the treatment efficacy of EGFR-TKI towards this mutation.
Changes in the text: No changes.

8.It also contains gene mutations that are sensitive to 3rd generation EGFR-TKIs such as L861Q, but the effect of 3rd generation EGFR-TKIs is very low in this study. Do you have any thoughts on that? Also, what is the percentage of uncommon mutations that have been confirmed to have EGFR mutations by RT-PCR, etc.?

Reply 8：We sincerely appreciate your comments and your recognition of our work.

The reason for the limitation of treatment efficacy on 3rd generation EGFR-TKI was the small sample size of patients received Osimertinib, only 4 uncommon mutation patients (excluding primary T790M mutation) received Osimertinib, so it is necessary to extend the sample size of uncommon mutation patients to validate the clinical efficacy of Osimertinib. Another reason is that there is no evidence-based medical evidence that the Osimertinib is effective at that time. Of 132 uncommon mutation patients, all patients were detected as uncommon EGFR mutation via NGS, this could be made it clear.
Changes in the text: No changes.

9.Exon 20 insertion is also considered to be resistant to second-generation EGFR-TKIs, and all EGFR-TKIs should not be administered at this time. Is it included in the analysis of PFS and OS?

Reply 9: Thank you for your comment. Of 132 uncommon mutation patients, 21 were exon 20 insertion and this part of patients were included in this study. Of 21 exon 20 insertion, 16 received 1st generation EGFR-TKI, 2 received 2nd generation EGFR-TKI and 1 received 3rd generation EGFR-TKI, it will not affect the experimental results to some extent. In addition, there were no effective targeted agents for exon 20 insertion at that time.
Changes in the text: No changes.

Minor
1.~(Line57, 60, 68) are incorrect as an expression.
Reply 1: Thank you for your suggestion. We have modified our text as advised in Page 4, line 69,72,80.
Changes in the text: Page 4, line 69,72,80.

2."19 delition" should be described as "exon 19 deletion". (Line66, 115)
Reply 2: We have modified our text as advised in Page 4, line 78;Page 6, line 131.
Changes in the text: Page 4, line 78;Page 6, line 131.

3.Epidermal growth factor receptor should be abbreviated as EGFR. (Line68-69)
Reply 3: We have modified our text as advised in Page 4, line 81.
Changes in the text: Page 4, line 81.

4.Please write the PR as partial response without abbreviation and correct the appearance of the whole sentence. (Line81)
Reply 4: We have modified our text as advised in Page 5, line 92-93;

Changes in the text: Page 5, line 92-93.

5.Line92 “NGS” should be abbreviated as “next generation sequencing”, and Line115 “next generation sequencing” should be abbreviated as “NGS”.
Reply 5: We have modified our text as advised in Page 5, line 105-106; Page 6, line 131
Changes in the text: Page 5, line 105-106; Page 6, line 131

6.Line133 “Overall survival” should be abbreviated as “OS”.
Reply 6: We have modified our text as advised in Page 7, line 152
Changes in the text: Page 7, line 152

7.The percentage of age items in Table 1 is incorrect.
Reply 7: We have modified our table 1 in chart file named Table as advised
Changes in the text: Chart file named Table, table 1