Peer Review File

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Reviewer A

Comment 1: Can the author also discuss whether the addition of chemotherapy to Osimertinib (FLAURA2) could be beneficial in L858R patients? Is there room for liquid biopsy in order to identify the L858R patients who may need extra-therapies besides EGFR-TKI?

Reply 1: Thank you for your valuable comment. We completely agree that combination of EGFR-TKI and chemotherapy is another promising treatment option; however, there has been no data that efficacy of chemotherapy differs among ex19del subtype and L858R subtype. In this letter, we would like to focus on the different sensitivity to EGFR-TKI between ex19del and L858R. Therefore, we decided citing FLAURA2 study in not appropriate in our letter. We appreciate your understanding.

Reviewer B

Comment 1: Afatinib is the only currently approved TKI for advanced NSCLC patients with uncommon EGFR mutations and it remains unanswered whether patients with uncommon EGFR mutations could obtain benefits from osimertinib after progression on afatinib and acquiring EGFR T790M mutation. Therefore, the role for sequential afatinib and osimertinib in patients with EGFR uncommon mutations remains to be defined.

Reply 1: Thank you for your insightful comment. Uncommon mutational subtypes account for approximately 10% of the patients with EGFR mutation, and more effective treatment for this population is critical; however, both the UpSwingG and GioTag studies included only patients with common mutations (ex19del and L858R) and there was no discussion about uncommon EGFR mutation. Therefore, we decided not to discuss uncommon mutation in our letter. We appreciate your understanding.

Reviewer C

Comment 1: This letter is focused on the sequential treatment with Afatinib followed by Osimertinib for patients with EGFR mutation. The document is well written and comprehensive. In terms of combination therapy with EGFR-TKI and VEGF blocker, authors should mention about NEJ026 trial which is a phase III trial comparing erlotinib and bevacizumab with erlotinib alone. In this trial, the combination therapy could not statistically improve OS among patients with L858R mutation.

Reply 1: Following your invaluable comment, we cited the NEJ026 study and discussed it at the end of the fourth paragraph in our letter. There was no significant difference of OS in patients with L858R; however, HR was in favor of erlotinib+bevacizumab. Originally, the NEJ026 study was not designed to detect statistical OS difference in each mutational subtype. Furthermore, effective subsequent treatment might have compromised statistically significant PFS improvement of erlotinib+bevacizumab. Therefore, we believe that further studies are warranted to verify the efficacy of the combination of EGFR-TKI and a VEGF(R) inhibitor in patients with L858R mutation.

Reviewer D

Comment 1: But, authors should consider the cost effectiveness and reimbursement in several countries. Osimertinib and RELEY regimen cannot use due to insurance reimbursement in some counties. In that case, wouldn't sequential use of afatinib to osimertinib be an important treatment option? If possible, please add some considerations from this point.

Reply 1: The reviewer's comment is absolutely to the point. Therefore, we added the following sentence at the end of the fifth paragraph in our letter: Nevertheless, sequential afatinib and osimertinib treatment continues to be an important treatment option in some countries where osimertinib or RELAY regimen are exempt from insurance reimbursement.