Letter to the Editor

Is there a role for sequential afatinib and osimertinib in patients with EGFR mutation?

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Epidermal growth factor receptor (*EGFR*) mutation is the most common driver mutation in patients with non-small cell lung cancer (NSCLC), and multiple tyrosine kinase inhibitors (TKIs) have been developed targeting EGFR. Accordingly, there are several treatment approaches for this patient population. Recently, Popat *et al.* presented the results of the UpSwingG study, a global observational study of patients with NSCLC and *EGFR* mutation who received sequential afatinib and osimertinib treatment (1). The primary objective of the study was to evaluate time to treatment failure (TTF), i.e., the time from the first dose of afatinib to the last dose of osimertinib or death by any cause, and the key secondary objectives were overall survival (OS) and objective response rate (ORR). The median TTF and OS were 27.7 months [95% confidence interval (CI): 24.0–30.2] and 36.5 months (95% CI: 32.9–41.8), respectively, and the ORR was 74% for afatinib and 45% for osimertinib. The authors concluded that sequential afatinib and osimertinib may be a reasonable treatment option for patients with NSCLC and *EGFR* mutation, and similar results have been reported previously in the GioTag study (2). However, both the UpSwingG and GioTag studies are observational studies that only included T790M mutation-positive patients who most benefit from osimertinib after afatinib failure. As the authors of both studies mentioned, this is the best scenario for *EGFR* mutation-positive NSCLC patients receiving afatinib as their initial treatment.

The current standard first-line treatment for NSCLC patients with *EGFR* mutation is osimertinib. In the FLAURA study, the median OS for osimertinib was 38.6 months (95% CI: 34.5–41.8), which is numerically similar to that found in the UpSwingG and GioTag studies (1-3). However, a subgroup analysis of the FLAURA study revealed that there was no significant OS difference in patients with L858R mutation, while those with ex 19del derived significant OS benefit from osimertinib (3). Considering its significant OS benefit, mild toxicity, and no need for re-biopsy, osimertinib seems to be the best choice for patients with ex 19del. However, more effective treatment is necessary for patients with L858R mutation.

Looking at the efficacy of sequential afatinib and osimertinib treatment based on the mutational subtypes, the median OS was inferior in patients with L858R mutation in both the UpSwingG study (38.0 months for ex 19del *vs.* 33.1 months for L858R mutation) (1) and GioTag study (41.6 months for ex 19del *vs.* 33.0 months for L858R mutation) (2). In addition, patients with L858R mutation are less likely to develop T790M after receiving first- or second-generation EGFR-TKI. According to two Japanese studies, the prevalence of T790M after receiving first- or second-generation EGFR-TKI is 55.6% and 63.4% for patients with ex 19del and 43.0% and 37.5% for patients with L858R mutation, respectively (4,5). In fact, the distributions of ex 19del and L858R mutation were 70.7% and 29.3% in the UpSwingG study and 73.5% and 26.0% in the GioTag study, respectively. To summarize, patients with L858R mutation have less chance to develop T790M after afatinib failure, and, more importantly, the treatment efficacy of sequential afatinib and osimertinib for L858R mutation is inferior to that for ex 19del.

In this respect, combination therapies with EGFR-

TKI and vascular endothelial growth factor (VEGF) or VEGF-receptor (VEGFR) inhibitors are promising. In the RELAY study, although the OS data are still immature, progression-free survival was significantly better for the erlotinib+ramucirumab arm of ex 19del [hazard ratio (HR) 0.65; P=0.0098] and L858R mutation (HR 0.62; P=0.0060) (6). There is growing evidence that compound *EGFR* mutations and concomitant mutations outside of the *EGFR* gene, which are significantly associated with the reduced efficacy of EGFR-TKI, are more prevalent in patients with L858R mutation compared to patients with ex 19del (7). Adding a VEGF(R) inhibitor to EGFR-TKI may improve the outcomes of patients with L858R mutation compared with EGFR-TKI alone. The NEJ026 study failed to demonstrate significant OS improvement with erlotinib+bevacizumab in patients with L858R mutation (HR 0.79: 95% CI: 0.460–1.358); however, the 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 (8).

In conclusion, for patients with ex 19del, osimertinib is currently the best treatment option, though the results of an ongoing comparative study are still awaited (9). On the other hand, more effective treatment is necessary for patients with L858R mutation, and combination with EGFR-TKI and a VEGF(R) inhibitor seems most effective for this patient population. Currently, several phase III studies comparing osimertinib and osimertinib + VEGF(R) inhibitor are ongoing (10,11). The results of these studies might redefine the standard treatment for NSCLC patients with *EGFR* mutation. 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.

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Footnote

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