Editorial

Unarranged territory in uncommon *EGFR* mutations

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A pooled analysis of the Nordic two phase II studies of osimertinib on non-small cell lung cancer (NSCLC) patients harboring uncommon mutations in epidermal growth factor receptor (*EGFR*) by Eide *et al.* (1) is reported in a previous issue.

Common *EGFR* mutations occur in 30–35% of East Asian and 10–15% of Caucasian NSCLC patients (2). Because of its high frequency as an oncogenic alteration in NSCLC and dramatic response by tyrosine kinase inhibitors (TKI) in *EGFR* mutation, third-generation EGFR-TKI has been developed as the standard of care, and diverse and different strategies by combining them with other agents have been verified in phase III studies. Recent investigations have identified personalized strategies for mutations occurring within *EGFR* exons 18 to 21 that encode a portion of the EGFR kinase domain. Approximately 90% of patients with NSCLC harboring *EGFR* mutations have either deletion in exon 19 (del 19) or a substitution of leucine by arginine (L858R) in exon 21, which are known as common mutations. Other mutations are called "uncommon mutations", and exon 20 insertion comprise half of the uncommon *EGFR* mutations, followed by G719X, S768I, and L861Q substitutions. These uncommon mutations account for approximately 5.8%, 3.1%, 1.1%, and 0.9% of all *EGFR* mutations in NSCLC, respectively (3). Approximately 14% of uncommon positive *EGFR* mutations coexist with other *EGFR* mutations, which are termed "compound mutations" (4). *EGFR* mutations cause a conformational change within the ATP-binding site of EGFR tyrosine kinase, which leads to its constant activation without ligand stimulation. EGFR-TKIs competitively inhibit ATP binding in the EGFR tyrosine kinase domain and suppress dimerization and autophosphorylation of EGFR. Therefore, EGFR-TKIs block proliferation signaling and exhibit antitumor effects (5).

Therefore, molecular differences in the structural and functional changes in EGFR tyrosine kinase domains are essential for determining the efficacy of EGFR-TKIs. A recent study by Robichaux *et al.* classified *EGFR* mutations based on differences in molecular structures and propounded four subgroups: classical-like mutations that are distant from the ATP-binding pocket, T790M-like mutations in the hydrophobic core, insertions in the loop at the C-terminus of the αC-helix in exon 20, and mutations on the interior surface of the ATP-binding pocket or C-terminus of the αC-helix, leading to P-loop and αC-helix compression (PACC) (6). Compared to the traditional exon-based classification, the structure-function-based type can identify drugs that may be effective for each group of mutations, reflecting the fact that mutations in different regions of the gene may induce similar changes in the protein structure.

Classical-like *EGFR* mutations are generally represented by del 19 and L858R and also include the uncommon mutation L861Q. They are sensitive to all generations of EGFR-TKIs, particularly third-generation EGFR-TKIs (6). Regarding the molecular differences between common mutations, the L858R mutant requires asymmetric dimerization to activate oncogenic transformation in

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the absence of ligand whereas, exon del 19 mutants are not required dimerization for activation in the absence of ligand (7). The del 19 mutation deletes three to eight bases from the ATP-binding loop, while the L858R conversion is located away from the ATP-binding pocket (8). Accordingly, del 19 mutations are strongly dependent on EGFR and consequently, their sensitivity for EGFR-TKIs will be better than that of L858R. Subgroup analysis of the FLAURA study revealed that osimertinib, compared with first-generation EGFR-TKIs, improved progression-free survival (PFS) in patients with common *EGFR* mutations; however, the improvement was less noticeable for those with L858R mutation than for those with del 19 (9). Alike L858R mutation, the L861Q mutation has no effect on the structure of ATP-binding pocket; however, it increases the heterodimerization tendency of EGFR, resulting in its aberrant activation (10). Afatinib or osimertinib may be effective for the L861Q mutation *in vitro*, but cells with L861Q are less sensitive than cells expressing common mutations to EGFR-TKIs, which may be owing to the prominent activation of ERBB2 by L861Q mutation, resulting in decreased efficacy of EGFR-specific inhibitors (11). Regarding the second group of Robichaux's classification, T790M-like mutations in the hydrophobic core, the benefit of using osimertinib has been demonstrated in an international phase III trial, AURA3 (12). *EGFR* exon 20 insertion present a heterogeneous response to EGFR-TKIs; insertions in the αC-helix are sensitive to EGFR TKIs, whereas those in the loop following the αC-helix are insensitive (6).

The Food and Drug Administration (FDA) has provided accelerated approvals to amivantamab and mobocertinib for patients with NSCLC harboring *EGFR* exon 20 insertion, after progression with platinum-based chemotherapy. In the fourth group of Robichaux's classification, PACC mutations comprise mutations spanning exons 18–21, representing uncommon *EGFR* mutations, such as G719X, L747X, S768I, L792X, and T854I. For instance, G719X, one of the most well-known and uncommon *EGFR* mutations followed by exon 20 insertion, is located in the phosphate-binding P-loop, which participates in the coordination of ATP and contributes to a set of hydrophobic interactions that hold the αC-helix in an inactive conformation. G719X mutation reduces flexibility of the P-loop and weakens hydrophobic interactions with the αC-helix in the inactive conformation. As a result, structural changes induced by altering the orientation of the P-loop or αC-helix increase the propensity for heterodimerization and subsequent activation of EGFR in a fashion similar to that by L858R mutation (10). A preclinical model of EGFR-TKI susceptibility testing for PACC mutations *in vivo* suggested that second-generation EGFR-TKIs are significantly more active than other TKI classes, including third-generation EGFR-TKIs (6).

Uncommon *EGFR* mutations are rare and heterogeneous; therefore, the accumulation of patients with individual gene mutations is complicated, and cases are much lower than common *EGFR* mutations. Appropriate therapeutic intervention for uncommon *EGFR* mutations, excluding T790M and exon 20 insertions, remains controversial. In a *post hoc* analysis of the LUX-Lung series, afatinib was found to be active against uncommon *EGFR* mutations (13). In a subgroup analysis of 38 patients with uncommon point or compound mutations in exons 18-21, such as G719X, S768I, L861Q, and/or G719X, the objective response rate was 71.1%, and the median PFS and overall response (OS) were 10.7 and 19.4 months, respectively. Based on this result, the FDA approved afatinib as a pan-HER inhibitor for previously untreated NSCLC patients harboring uncommon *EGFR* mutations in January 2018. Among the third-generation EGFR-TKIs, osimertinib showed the superiority in efficacy in treating patients with common *EGFR* mutations over the first-generation EGFR-TKIs, with mild toxicities (9); however, its efficacy against uncommon *EGFR* mutations is still limited. In the AURA study, only seven patients harboring *EGFR* compound mutations concomitant with T790M and G719X or S768I mutations previously treated with EGFR-TKIs were included, which was insufficient to evaluate the efficacy of osimertinib against uncommon *EGFR* mutations (14). In a phase II study in Republic of Korea on 37 patients harboring uncommon *EGFR* mutations excluding exon 20 insertions, the overall response rate was 50%, median PFS was 8.2 months, and median OS was not reached in 36 patients (15). Although this trial was the first and only prospective study to demonstrate the efficacy of osimertinib against uncommon *EGFR* mutations, patients previously treated with other EGFR-TKIs were excluded. In this context, the article presented in *Translational Lung Cancer Research* from Norway provides valuable information (1). Eide *et al.* reported a post hoc subgroup analysis of patients harboring uncommon *EGFR* mutations with pooled data from two northern European phase II clinical trials using osimertinib (NCT02504346 and NCT03804580). Of the 298 enrolled patients in these two trials, 21 had uncommon mutations: 11 were untreated and

10 were previously treated with at least one EGFR-TKI. In the first-line cohort, the objective response rate (ORR) and disease control rate (DCR) were 63.6% and 100%, respectively, and the median PFS and OS were 5.5 and 17.5 months, respectively. In the pretreated cohort, the ORR and DCR were 30.0% and 70.0%, respectively, and the median PFS and OS were 5.5 and 11.9 months, respectively. Overall, ORR and DCR were 47.6% and 85.7% for the whole population, respectively, and the median PFS and OS were 5.5 and 11.9 months, respectively. These results are consistent with those of a previous study (15). The valuable points of the study by Eide et al can be summarized as follows: First, they demonstrated the efficacy of osimertinib in patients harboring uncommon *EGFR* mutations, which had previously been shown only in an Asian population, in a Caucasian population in Northern Europe. The response rate was approximately similar to that reported in the Korean study, but the PFS was comparatively modest. Second, they analyzed compound mutations and indicated that osimertinib was more effective for patients with G719X compound mutations than for patients with other mutations. The ORR and DCR were 62.5% and 100%, respectively, in the group with G719X compound mutation, and 38.5% and 76.9%, respectively, in the group with other mutations. The median OS was longer in the compound mutations group with a median of 29.3 *vs.* 7.5 months in the group with other mutations. Patients harboring uncommon *EGFR* mutations are a highly heterogeneous population, and some patients may strongly respond to osimertinib. Based on their report, G719X compound mutation may be considered as a surrogate marker for selecting a patient group that benefits from osimertinib. However, considering the small sample size and the fact that the previous Korean study did not mention this point, we need careful and further consideration. Third, they sequenced circulating tumor DNA (ctDNA) during osimertinib treatment and showed that most patients had a decrease in the mean number of mutant molecules. This decrease reflects an early response to osimertinib, and this perspective encourages new attempts to demonstrate the efficacy of osimertinib at radiological and molecular level.

Although the efficacy of osimertinib for uncommon *EGFR* mutants is gradually being revealed, the positioning of osimertinib for patients harboring uncommon *EGFR* mutations in NSCLC remains unclear. No statistically significant differences in PFS or OS between the first-line and pretreated cohorts have been observed. However, the sample size was too small for comparison with historical control. We cannot conclude whether osimertinib should be used as a first-line drug or in sequence for treatment. The suitability of optimally using osimertinib or afatinib as a first-line therapy is unclear, and a confirmatory trial is necessary for conclusion. However, conducting a clinical trial for uncommon *EGFR* mutations in NSCLC is difficult, and an observational study will be helpful. The nature of rare cancers is an important practical issue. Therefore, accumulating a series of studies even with a small number of cases is essential. We hope that our ongoing UNICORN study (jRCTs071200002), a prospective phase II study of osimertinib for previously untreated patients with uncommon *EGFR*-mutant NSCLC, will contribute to solving this issue (16).

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