Editorial Commentary

Subtype of EGFR exon 19 deletion mutations

Nobukazu Fujimoto^

Department of Medical Oncology, Okayama Rosai Hospital, Okayama, Japan

Correspondence to: Nobukazu Fujimoto, MD, PhD. Department of Medical Oncology, Okayama Rosai Hospital, 1-10-25 Chikkomidorimachi, Okayama 7028055, Japan. Email: nobufujimot@gmail.com.

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Epidermal growth factor receptor (*EGFR*) mutations in non-small cell lung cancer (NSCLC) are associated with favorable clinical response to *EGFR* tyrosine kinase inhibitors (TKIs). There are several EGFR-TKIs approved in the US, Japan, and other countries for the treatment of NSCLC with *EGFR* mutation. The first-generation EGFR-TKIs, gefitinib and erlotinib, bind reversibly to the Adenosine tri-phosphate-binding pockets of the receptor, whereas the second-generation TKIs, afatinib and dacomitinib additionally react covalently with the side-chain of cysteine 797 in *EGFR* (1). A third-generation TKI osimertinib has been shown to improve progression-free survival (PFS) (2) and overall survival (OS) (3) compared to the first-generation EGFR-TKIs in the first-line setting, and also been shown to be effective in the second-line treatment for patients with *EGFR* p.T790M mutation (4).

There are two common *EGFR* mutations; one is in-frame deletions in exon 19 (19Del) and the other is a point mutation in exon 21 (p.L858R), which account for approximately 90% of all alterations and are associated with sensitivity to EGFR-TKIs (5). The efficacy of EGFR-TKIs has established for these common mutations, however, few prospective data are available for other uncommon mutations. Uncommon *EGFR* mutations are highly heterogeneous including p.G719X, p.L861Q, p.S768I, and others (6), and vary widely in terms of their sensitivity to EGFR-TKIs. Afatinib has been applied most for these uncommon mutations possibly because of current availability of data in previous clinical studies, in which patients with uncommon mutations were included (6,7). Recent studies indicate that osimertinib might be active also against certain uncommon *EGFR* mutations (8,9). However, the optimal treatment strategy for these uncommon *EGFR* mutations has not been established.

Although it is fully established that NSCLCs with 19Del are sensitive to EGFR-TKIs, recent studies revealed that there are some subtypes among 19Del. The most frequently observed 19Del is the elimination of 5 amino acids (E746-A750) between the third β-strand of the *EGFR* tyrosine kinase domain and its key regulatory αC helix (10). However, several other 19Del mutations have also been demonstrated between amino acids 745 and 753. Many of these deletions are replacement of the deleted amino acids with a non-native residue which start at leucine 747, where proline and serine respectively are introduced, resulted in L747-A750>P and L747-P753>S variants (11). Very little is known about potential differences in sensitivity to EGFR-TKIs among individual 19Dels. The differences in TKI sensitivity among 19Del have begun to emerge from several studies. A recent report of *in vitro* study suggested that L747-A750>P variant was associated with poor inhibition by erlotinib and osimertinib but was strongly inhibited by afatinib, partly due to structural characteristic of the variant (12). Although there were some different results in

^ ORCID: 0000-0002-4516-0433.

different studies, the importance of EGFR-TKI selection specific to each mutation has been highlighted in these studies.

Grant *et al.* recently reported that patients of NSCLC with L747-A750>P variant of 19Del was associated with inferior PFS compared with the main E746-A750 variant when treated with osimertinib as a first-line therapy (13). They performed a multicenter, retrospective cohort study based on an international cancer registry conducted by American Association for Cancer Research that linked next-generation genome sequencing (NGS) data with clinical information of patients treated at 18 contributing institutions (14). In the study, they identified 72 distinct variants of 19Del ranging in frequency from 28.1% of E746-A750 to 0.03% of L747-A750>P, and demonstrated that main E746-A750 was associated with significantly prolonged PFS (median 21.3 months with 95% confidence interval of 17.0–31.7 months) versus L747-A750>P (median 11.7 months with 95% confidence interval of 10.8–29.4, P=0.043) in patients treated with first-line osimertinib. Although there are some limitations in their study, including its retrospective study design and limited number of patients with uncommon 19Del patients, that is the largest study to compare the clinical efficacy of osimertinib between patients with tumors harboring main E746-A750 and other uncommon 19Dels such as L747-A750>P. In fact, this registry contained more than 3,000 patients of *EGFR*-mutated NSCLC including 86 with E746-A750 and 36 with L747-A750>P, and relevant data including demographic information, smoking history, treatment history, and disease control and survival outcomes were extracted from the electronic medical record. Since there are significant differences in the survival outcomes in their report, it seems reasonable that L747-A750>P variant of 19Del would be classified as one of uncommon *EGFR* mutations.

From now on, new therapeutic options might be applied for patients with such uncommon 19Del variant as L747-A750>P because of significant inferior survival outcomes. A simple approach would be the first or second-generation TKIs. In above mentioned basic research, Truini *et al.* investigated *in vitro* TKI sensitivity of human lung adenocarcinoma cell lines that carried 19Del variants. They generated cell lines transfected with L747-A750>P constructs and demonstrated that those cells exhibited increased sensitivity to afatinib compared to erlotinib or osimertinib (12). These findings strongly suggest that afatinib would be a key for the treatment of these uncommon 19Dels.

There are other possible treatment strategies for *EGFR*-mutated NSCLC. One is the combination of EGFR-TKIs and anti-angiogenetic agent. Preclinical studies have demonstrated that the vascular endothelial growth factor (*VEGF*) and *EGFR* pathways are interrelated (15). Previous clinical trials in Japan have suggested that the combination of erlotinib and an anti-VEGF antibody bevacizumab would be beneficial concerning the PFS (16,17). More recently, an anti-VEGF receptor antibody ramucirumab plus erlotinib showed a significant improvement in PFS in patients with *EGFR*-mutated NSCLC (18). Limited data are available for second-generation EGFR-TKIs in combination with anti-angiogenetic agents. Afatinib was examined in a randomized, phase II trial combined with bevacizumab as first-line treatment for patients with *EGFR*-mutated NSCLC, but the study failed to prolong PFS (19). More recently, osimertinib also failed to improve PFS in combination with bevacizumab among patients with nonsquamous NSCLC harboring *EGFR* mutations as first-line treatment (20). The activities of EGFR-TKIs and anti-angiogenic agents for patients with minor *EGFR*-mutations have not been examined, so some combinations should be examined for patients with 19Del variants such as L747-A750>P.Another strategy for *EGFR*-mutated NSCLC is a combination of EGFR-TKI and cytotoxic chemotherapy with the hope of synergistical effect to induce apoptosis and/or to suppress signal-regulated kinase phosphorylation (21). Combination of gefitinib and carboplatin plus pemetrexed improved PFS in patients with untreated advanced NSCLC with *EGFR* mutations compared with gefitinib alone with acceptable toxicities (22). In another study with similar setting, adding pemetrexed and carboplatin chemotherapy to gefitinib significantly prolonged PFS and OS (23). Furthermore, in a recent study, a combination of osimertinib and platinum-based chemotherapy demonstrated prolonged PFS compared to osimertinib monotherapy as a first-line treatment for advanced NSCLC with *EGFR* mutations (24). Detailed description of minor 19Del cannot be found in these studies, so combination of TKIs and platinum-based chemotherapy also should be examined for those populations in the future.

Recently, genomic concomitant alterations that may accompany *EGFR* mutations have been considered to affect the response to EGFR-TKIs. Though the incidence of concomitant alterations in patients with 19Dels were reported to be lesser than in patients with p.L858R (25), further research is warranted to reveal the impact of such concomitant alterations on sensitivity or resistance to

EGFR-TKIs.

In conclusion, given the rapid progression of sensitive mutation detection methodologies, such as NGS and circulating cell-free DNA techniques, physicians will be more likely to encounter cases of NSCLC with uncommon mutations in clinical practice. Based on a report of Grant *et al.*, it seems reasonable to classify subtypes of 19Del such as L747-A750>P as uncommon *EGFR* mutation. Suitable treatment strategies for patients with these mutations should be tailored for each subtype.

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