Editorial

Osimertinib for advanced non-small cell lung cancer harboring EGFR mutation exon 20 T790M, acquired resistant mutation for first- or second-generation EGFR-TKI

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Since the results of IDEAL-1 (1) and the approval of gefitinib, a first-class epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), 15 years have passed. The efficacy of first-line EGFR-TKI, gefitinib (2,3), erlotinib (4), icotinib (5), and second-line EGFR-TKI, afatinib (6), is 6.3–11.0 months for median progression-free survival (PFS), 19.4–28.2 months for median overall survival (OS), and 44.1–73.7% for the response rates, respectively.

Osimertinib mesylate (AZD9291, Tagrisso^{TM}) is an oral mono-anilino-pyrimidine small molecule that is promising for the treatment of mutant-selective EGFR-TKI. In particular, osimertinib is anticipated to exhibit potent activity against advanced non-small cell lung cancer (NSCLC) harboring the EGFR mutation, T790M, indicating resistance to EGFR-TKI as the breakthrough therapy (7). Half of the resistance to EGFR-TKI occurs via acquired resistance associated with exon 20 T790M. In the standard of care, cytotoxic chemotherapy has been applied with a response rate of 30–40% and median PFS of four to seven months as a first-line cytotoxic chemotherapy or response rate of 10–20% and median PFS of two months as second-line (8) treatment until the advent of osimertinib. Medical oncologists have been anticipated to respond by following later lines of chemotherapy as a re-challenge of EGFR-TKI with response rates of 4.9–8.2% (9) or the second-generation EGFR-TKI, afatinib, following the failure of first-generation EGFR-TKIs (10). In a second-line setting after the failure of EGFR-TKI harboring exon 20 T790M, osimertinib was confirmatory improved PFS compared to the platinum-pemetrexed combination administered in the phase III trial (AURA3 trial) conducted by Mok *et al.* (11). In the AURA3, 419 patients with T790M-positive NSCLC were randomized to receive either 80 mg osimertinib once daily, or chemotherapy [pemetrexed 500 mg/m^2 every three weeks plus platinum (carboplatin targeting an area under the curve 5 or 75 mg/m^2 of cisplatin)]. The median PFS as the primary endpoint was successfully completed at 10.1 months for the osimertinib arm and over 4.4 months for the chemotherapy arm [hazard ratio (HR): 0.30; 95% confidence interval (CI): 0.23–0.41; P<0.001]. The objective response rate (ORR) was 71% *vs.* 31% for osimertinib and chemotherapy, respectively (odds ratio: 5.39; 95% CI: 3.47–8.4; P<0.001). In this trial, the patients exhibited CNS metastasis at 8.5 months for the PFS of osimertinib compared to 4.2 months for those receiving chemotherapy (HR: 0.32; 95% CI: 0.21–0.49). Among the patients without central nervous system (CNS) metastasis, the PFS was 10.8 months for osimertinib and 5.6 months for chemotherapy (HR: 0.40; 95% CI: 0.29–0.55). In addition, there is promising data indicating that osimertinib is preferable to the penetration of the CNS over other EGFR-TKIs using an animal

model (12). In the BLOOM study (NCT02228369), 20 patients with leptomeningeal metastasis exhibiting an EGFR mutation were treated with 160 mg osimertinib once daily, and demonstrated radiological improvement in 7 patients (13). For CNS lesions, osimertinib was associated with clinically promising activity.

The safety profile of osimertinib was more favorable than chemotherapy as only 6% and 3% of patients receiving osimertinib developed grade ≥3 adverse events (AEs) and severe adverse events (SAEs), respectively, compared to 34% in AEs and 13% in SAEs among those that received chemotherapy. The most frequent AEs associated with osimertinib was diarrhea (41% for all grades) and rash (34% for all grades) adverse, both SAEs were 1%. Grade ≥3 of QTc prolongation on the electrocardiograph for the patients treated with osimertinib was less than 1%. Pneumonitis, one of the most life-threating AEs, occurred in 4% of grades 1 or 2, and one patient died in the osimertinib-treated group. As with other EGFR-TKIs, follow-up is required to assess lung toxicity.

In clinical practice, a re-biopsy following acquired resistance is clinically crucial, but very difficult. In a clinical setting, 38% of retrospective investigations demonstrated the inability to access (14). However, liquid biopsies will be significant for cases in which a re-biopsy of a lung cancer specimen is inaccessible. The sensitivity of a plasma biopsy to detect T790M is 70%, of which the frequency of false negatives is 30%. Therefore, a tumor re-biopsy should be required if the plasma examination detecting T790M is negative (15). The site for the re-biopsy should be performed in accordance with the Jackman criteria (16).

The resistance for osimertinib has already reported as C797S mutation (17). Previously reported resistance, including HER2 gene amplification and transformation to small cell histology may also occur (18). To overcome such resistance will be unmet medical needs at the present issue.

These results influence the following impacts of clinical practice: (I) detecting exon 20 T790M mutation with a tumor or plasma sample should be possible; (II) first-line EGFR-TKI should be considered to gain acquisition to T790M. Fortunately, T790M is acquired in 50% of patients receiving gefitinib, erlotinib, or afatinib. However, no data has been presented for icotinib. Clinically, the best sequence of EGFR-TKI should be the primary concern. Moreover, the treatment strategy for patients exhibiting advanced NSCLC harboring the EGFR mutation will be more complex; four choices of singlet EGFR-TKI, concurrent (19), or intercalated strategies, including cytotoxic chemotherapy (20,21) or add-on bevacizumab (22). Additionally, the FLAURA trial (NCT02296125), an ongoing phase III trial to confirm the superiority of first-line osimertinib to first-generation EGFR-TKI will change the current treatment. Following an acquired resistance for osimertinib, C797S (23), and the targeted agent EAI045.3 (24) should be administered. Therefore, oncologists must confirm the optimal sequential strategy with or without other cytotoxic and molecular targeted agents.

Immune checkpoint inhibitor is not well respond; however, there is possibility to response. Currently, the KEYNOTE-024 trial is a phase III trial to confirm the superiority pembrolizumab (Keytruda™) to chemotherapy for the high expression of PD-L1 (tumor proportion score; TPS ≥50). In the first-line treatment setting, patients were excluded if they possessed driver mutants (25). Therefore, the treatment strategy for advanced NSCLC patients is to first confirm driver mutations; if they are negative, the expression of PD-L1 22C3 should be confirmed via immunohistochemistry.

A multi-arm strategy for patients with EGFR mutations that ensures long-term survival requires a large sample size and optimal design for a successful clinical trial. Therefore, international cooperation is needed, of which East-Asian countries play a crucial role as the population exhibiting the highest frequency of EGFR-mutated NSCLC cases.

The results of randomized trials have confirmed osimertinib to be superior to platinum doublet chemotherapy as a second-line therapy for advanced NSCLC harboring exon T790M following the failure of first or second-generation EGFR-TKI, and establishing a new standard of care. However, the OS must be confirmed to establish a strategy for advanced NSCLC patients harboring the EGFR mutation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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