Editorial

Osimertinib for EGFR T790M positive non-small cell lung cancer—making it happen, turning good idea into great results

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Epidermal growth factor receptor (EGFR) activating mutations account for approximately 50% of non-small cell lung cancer (NSCLC) in Asian population and about 20% in Caucasians (1-4). Several famous phase III clinical trials have demonstrated the superior efficacy and quality of life of the first or second generation EGFR tyrosine kinase inhibitors (TKIs) including gefitinib, erlotinib, icotinib and afatinib in patients with EGFR-mutant advanced NSCLC when compared to first-line standard platinum-based chemotherapy (5-8). To date, EGFR-TKIs have been extensively accepted for the first choice for patients with untreated advanced NSCLC and EGFR activating mutation. Despite the substantial benefit of EGFR-TKIs, the vast majority of patients would experience disease relapse so called acquired resistance within about 1–2 years (2,3,9). Previously, a large number of studies have revealed the mechanism of acquired resistance against first-generation EGFR-TKIs and they can be summarized into four parts: (I) second mutations in EGFR; (II) histological transformation; (III) bypass signaling pathway activation and (IV) other mechanisms. Among them, the most common mechanism was the gatekeeper mutation involving the substitution of threonine at position 790 with methionine of EGFR exon 20, known as EGFR T790M mutation (10). It can hindrance the binding of first-generation EGFR-TKIs to the ATP-binding site of EGFR and was found in more than 50% of acquired resistance cases (3,11,12).

To overcome the acquired resistance caused by EGFR T790M mutation, third-generation EGFR-TKIs with high selectivity against EGFR T790M as well as EGFR-activating mutations have been evaluated for the treatment of advanced NSCLC with EGFR mutations. Among the numerous third-generation EGFR-TKIs (osimertinib, rociletinib, olmutinib, EGF816, ASP9273, WZ4002 and PF-06747775), osimertinib is the only one to be approved by the US Food and Drug Administration (FDA) and the European Medicines Agency for treatment of patients with EGFR-T790M mutated NSCLC (13). As a novel irreversible covalent EGFR-TKI, osimertinib is a mono-anilino-pyrimidine compound and showed potent inhibitory activity against distinct EGFR mutations (exon 19 deletion, L858R, exon 19 deletion/T790M and L858R/T790M) than wild-type EGFR (14). Osimertinib is structurally and pharmacologically different from other third generation EGFR-TKIs such as rociletinib and WZ4002 and could irreversibly target the cysteine-797 residue in the ATP-binding site through covalent bond formation (14,15). In the preclinical study, osimertinib showed the potent activity

of inhibiting signaling pathways and cellular growth in both EGFR sensitizing mutation and EGFR sensitizing mutation/T790M mutant cell lines *in vitro*, with lower activity against wild-type EGFR lines. *In vivo* study further demonstrated that it can sustain tumor regression in EGFR mutant tumor xenograft and transgenic models (15).

On the basis of the preclinical findings, several clinical trials were designed to investigate the clinical activity and safety of osimertinib in patients with first-generation EGFR-TKIs treated advanced NSCLC and acquired EGFR T790M mutation. The first trial is a phase I/II multicenter study (AURA) with 253 patients with advanced NSCLC and EGFR sensitizing mutations, who had disease progression on prior EGFR-TKIs (16). For 127 patients with confirmed T790M mutation, the objective response rate (ORR) was 61%, and progression-free survival (PFS) was 9.6 months. The most common adverse events (AEs) were rash, diarrhea, nausea, and decreased appetite with only a few serious events. In the subsequent phase II trial (AURA2), 210 NSCLC patients with sensitizing EGFR mutations and confirmed T790M after progression on prior EGFR-TKIs were included (osimertinib: 80 mg qd) and the ORR was 71% (17). In a recent pooled analysis (n=411) that included AURA extension and AURA2 NSCLC patients with centrally confirmed T790M mutation after progression on previous EGFR-TKIs, the ORR was 66% and PFS was 11.0 months. These results prompted the FDA to approve osimertinib under the 'breakthrough therapy' designation (18).

More recently, the phase III clinical trial, AURA3, lets our dream into final reality (19). In this open-label, randomized study, 419 patients with EGFR T790M-mutant advanced NSCLC who had disease progression after first-line EGFR-TKIs were randomly assigned to receive oral osimertinib (at a dose of 80 mg qd), or intravenous pemetrexed plus carboplatin or cisplatin for up to six cycles in a 2:1 ratio. Maintenance pemetrexed and switch to osimertinib following disease progression on chemotherapy were permitted. The primary end point was PFS. As the results published in the *New England Journal of Medicine* shown, the median PFS was dramatically longer for patients treated with osimertinib compared with chemotherapy [10.1 *vs.* 4.4 months, hazard ratio (HR) =0.30, P<0.001]. The ORR was also markedly better with osimertinib (71%) than with platinum and chemotherapy (31%). Furthermore, among 144 patients with the central nervous system (CNS) metastases, the median PFS was also significantly longer among patients receiving osimertinib than among those receiving chemotherapy (8.5 *vs.* 4.2 months; HR =0.32).

With the success of AURA3, there is no doubt that osimertinib would become the standard care for patients with EGFR T790M mutation-positive NSCLC who have progressed on previous EGFR-TKI treatment. Furthermore, there are several future directions of osimertinib that should be addressed. First, AURA3 supported the feasibility of detecting EGFR T790M mutation from plasma circulating tumor DNA (ctDNA) samples, indicating the application of ctDNA will be a reliable alternative to tumor re-biopsy to test for T790M status. Moreover, recent studies also suggested that ctDNA can be used to explore the resistance mechanisms to osimertinib (20). Second, Mok *et al*. highlights, "A key finding is that even patients with CNS metastasis can benefit from osimertinib." As we previously mentioned, lung cancer had a high incidence (about 40%) of CNS metastasis with a dismal prognosis and limited therapeutic strategies (21). If the encouraging result was demonstrated in the future strict-designed, prospective study, it will shift the management of patients with EGFR mutant-NSCLC and CNS metastasis. Third, in AURA first-line cohort, the ORR was 77% and PFS was 19.3 months in treatment-naïve patients with sensitizing EGFR mutations, suggesting its superior efficacy in first-line setting. The phase III First-Line-AURA (FLAURA) trial that directly compared osimertinib with first-generation EGFR-TKIs (gefitinib or erlotinib) in patients with EGFR activating mutation as first-line therapy is ongoing. The result is anticipated. Fourth, to further improve the efficacy of osimertinib, a preliminary study investigated the combination of osimertinib and the anti-PD-LI antibody durvalumab in pretreated EGFR-mutant NSCLC patients with or without T790M mutation. The result showed 52% of evaluable patients obtained partial response. However, the high incidence of interstitial lung disease in combination group remains a challenging issue. Last but not least, despite the splendid efficacy of osimertinib in both sensitizing EGFR mutation and EGFR T790M mutation, resistance is still inevitable. Preclinical studies revealed a tertiary acquired EGFR C797S mutation may be the mainly mechanism (20,22). Two recent studies explored the new approaches to overcome the C797S mutation and found the promising antitumor effect in mouse model (23,24). However, whether these strategies could benefit the patients need the future clinical investigation.

From the development to the final approval, osimertinib took less than 3 years. It represents one of the fastest cancer drug development programs in the case of approval for the

treatment of patients with EGFR T790M-positive NSCLC who had disease progression on previous EGFR-TKIs. As mentioned by Lisa Hutchinson, "With osimertinib being the new standard, we are obligated to test for the EGFR T790M mutation in all patients with resistance to EGFR-TKI therapy. Either a re-biopsy or plasma-based circulating cell-free DNA test will become part of standard patient management. Importantly, osimertinib will be the standard control for any future comparative study assessing third-generation TKIs (18)."

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Footnote

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