Editorial

The role of osimertinib in *epidermal growth factor receptor* (*EGFR*)-mutant non-small cell lung cancer

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Activating mutations in the *epidermal growth factor receptor* (*EGFR*) gene is the most common driver oncogene in non-small cell lung cancer (NSCLC), being present in up to 60% of Asian patients and up to 20% in Caucasian patients with advanced NSCLC. First- and second-generation EGFR-tyrosine kinase inhibitors (TKIs) including gefitinib, erlotinib and afatinib are recommended for first-line treatment of patients with advanced *EGFR*-mutant NSCLC (1,2). However, after a median duration of nine to 11 months from treatment initiation, acquired resistance to these EGFR-TKIs invariably develops. The most frequent acquired resistance mechanism, seen in 50% to 60% of cases, is *EGFR* T790M, the gatekeeper mutation in which threonine at amino acid position 790 in exon 20 of the *EGFR* gene is substituted by methionine that interferes with the binding of first- and second-generation EGFR-TKIs to the adenosine triphosphate (ATP)-binding site of the intracellular kinase domain of *EGFR* (3).

Third-generation EGFR-TKIs are specifically designed to selectively inhibit the *T790M* mutation by covalent binding to the C797 residue and possess the ability to also inhibit *EGFR* activating mutations while sparing wild-type *EGFR* and therefore expected to have less adverse effects from wild-type *EGFR* blockade in the skin and gastrointestinal tract. Osimertinib, a third-generation central nervous system (CNS)-active EGFR-TKI, selectively and potently inhibits *EGFR* sensitizing mutations as well as *EGFR T790M* mutations (4).

Based on its impressive clinical activity data and favorable safety profile from the pooled analysis of two AURA phase II single-arm studies, AURA extension and AURA2, involving a total of 411 patients with advanced *EGFR T790M* mutation-positive NSCLC whose disease had progressed after treatment with a first- or second-generation EGFR-TKI, osimertinib received accelerated approval by the US Food and Drug Administration (FDA) in November 2015 and conditional approval by the European Medicines Agency in February 2016 for the second-line treatment of patients with progressive *EGFR*-mutant NSCLC due to acquired *T790M* mutation (5). The pooled analysis showed an objective response rate (ORR) of 66% and median progression-free survival (PFS) of 11.0 months. Osimertinib is now approved in many countries worldwide for the second-line treatment of *EGFR*-mutant NSCLC following treatment failure with first- or second-generation EGFR-TKIs as a result of *T790M* secondary mutation (1,2) based on results of the phase III AURA3 study in which 419 patients were randomized in a 2:1 ratio to receive osimertinib 80 mg once daily or pemetrexed plus cisplatin or carboplatin doublet chemotherapy up to six cycles with an option of pemetrexed maintenance (6). Osimertinib treatment resulted in superior median PFS (10.1 *vs.* 4.4 months) and ORR (71% *vs.* 31%) compared to platinum-pemetrexed chemotherapy. For the 144 patients with CNS metastases in the second-line AURA3 study, significantly longer median PFS was observed with osimertinib treatment compared to chemotherapy (8.5 *vs.* 4.2 months) (6). More recently, the superior efficacy of osimertinib 80 mg once daily compared to standard of care (SOC) with the first-generation

EGFR-TKIs, gefitinib or erlotinib, in the first-line setting has been shown in a total of 556 patients NSCLC patients with activating *EGFR* mutations in the phase III FLAURA trial (median PFS, 18.9 *vs.* 10.2 months) [hazard ratio (HR) 0.46] (7). A strong trend toward improved overall survival (OS) in the osimertinib arm with a HR of 0.63 was observed but did not reach statistical significance at the interim OS analysis at 25% maturity. With its improved PFS, ORR and CNS efficacy, and tolerability based on the FLAURA trial findings, osimertinib has been approved in the first-line treatment of *EGFR*-mutant NSCLC (1). The recent publication of a consensus on the role of osimertinib in the treatment of advanced NSCLC by the AME Lung Cancer Collaborative Group in the *Journal of Thoracic Disease* is timely to review the results of the AURA and FLAURA studies and to discuss the current role of osimertinib and the future directions in the management of *EGFR*-mutant NSCLC (8).

In the FLAURA trial, osimertinib has a more tolerable toxicity profile than first-generation EGFR-TKIs. The incidence of grade 3 or higher adverse events (AEs) was lower for osimertinib at 34% compared to SOC EGFR-TKIs at 45% even though the patients were on osimertinib treatment for a longer period. The most common AEs associated with osimertinib treatment were diarrhea (58%) and dry skin (32%) while diarrhea (57%) and dermatitis acneiform (48%) were the most common AEs associated with SOC first-generation EGFR-TKIs (7). The risk of grade 3 skin rash, paronychia and stomatitis was less than 1% with osimertinib treatment (9). Dose reduction and discontinuation rates in the osimertinib arm of the FLAURA trial were 5.4% and 13%, respectively which were less compared to first-generation EGFR-TKIs (7). In LUX-LUNG 7, afatinib treatment was associated with an incidence of grade 3 or higher skin rash, diarrhea and stomatitis of 13%, 9% and almost 5%, respectively and a dose reduction rate of 42.6% (10). Although infrequent, prolonged QTc, cardiomyopathy, keratitis, and interstitial lung disease are important AEs associated osimertinib therapy.

The brain is an important site of disease progression with EGFR-TKI treatment because of poor blood brain barrier (BBB) penetration due to unfavorable molecular weight, pharmacokinetics and drug efflux mechanisms. Preclinical data has shown higher CNS tissue concentration, higher BBB penetration, and lower influence of efflux transporters with osimertinib compared to gefitinib and afatinib (11). The BLOOM study demonstrated improved BBB penetration by osimertinib with cerebrospinal fluid concentration supporting activity in patients with leptomeningeal metastasis (12). Superior median PFS (15.2 *vs.* 9.6 months) with osimertinib compared to SOC first-generation EGFR-TKIs observed in 116 patients with CNS metastasis in the FLAURA study with a HR of 0.47 similar to the HR for systemic disease control supports the preclinical data of good BBB penetration by osimertinib (7). In the FLAURA study, the CNS ORR was 66% versus 43% favoring osimertinib compared to SOC treatment with gefitinib or erlotinib (osimertinib, n=61; SOC EGFR-TKIs, n=67; P=0.011) with a faster time to response of 6.2 versus 11.9 months. Of patients with at least one measurable CNS lesion at baseline, the CNS ORR was 91% (of 22 patients on osimertinib) versus 68% (of 19 patients on SOC EGFR-TKIs) (P=0.066) (13). Of 22 evaluable patients on osimertinib, complete response was observed in five patients compared with none of the patients in the SOC arm. Probability of CNS progression was lower with osimertinib compared to SOC EGFR-TKIs (13).

Despite the superior efficacy of osimertinib in patients with NSCLC harboring both sensitizing and *T790M EGFR* mutations, acquired drug resistance invariably occurs. *EGFR*-mutant NSCLC tumors are highly heterogeneous and undergo clonal evolution and eventually evolve to become genetically more complex during treatment accounting for primary and acquired resistance to successive lines of therapy. In contrast to the dominance of *T790M* mutation as a resistance mechanism to first- and second-generation EGFR-TKIs, resistance to osimertinib is more heterogeneous and include: (I) acquired mutations (such as *EGFR C797S* mutation which interferes with the covalent binding of osimertinib to the cysteine residue at position 797 of *EGFR*) or wildtype *EGFR* gene amplification; (II) alternative pathway activation (such as amplifications of *MET*, *PIK3CA* and fibroblast growth factor receptor-1); and (III) transformation to small cell histology (14,15). Second-line data show that early progression on osimertinib is more likely to be related to the development of alternate resistance mechanisms such as *MET* amplification and histological transformation to small cell lung cancer. Patients who respond to osimertinib longer and develop resistance later are more likely to remain addicted to *EGFR* with the subsequent development of tertiary *EGFR C797S* mutation (15). Diverse resistance mechanisms which included *C797S* mutation, *MET* amplification, *MEK1* mutation and *KRAS* mutation were revealed by analysis of plasma samples from patients who progressed on osimertinib first-line treatment (16). While the resistance to treatment with gefitinib, erlotinib and afatinib is due the slow growing *EGFR T790M* mutant clones in 50% to 60% of the patients (3) which are responsive to second-line osimertinib as evidenced by the high ORR and disease control rate in the AURA studies (5,6), slow growing *C797S* clone constitutes only 15–25% of the resistance mechanism to osimertinib (14-16).

The current standard treatment option for patients who progress on osimertinib is cytotoxic chemotherapy. The results of the Phase III IMpower150 study look promising with the PFS among the subset of patients with *EGFR* mutations or *ALK* translocations being longer with the addition of atezolizumab, a programed death-ligand 1 (PD-L1) inhibitor, to the combination of carboplatin, paclitaxel and bevacizumab compared to the combination of platinum doublet and bevacizumab (17). This observed benefit in patients with *EGFR* or *ALK* genetic alterations is notable, given that monotherapy with PD-L1 or programmed death-1 (PD-1) checkpoint inhibitors after failure of TKI therapy has not been shown by clinical trials to be more effective than standard second-line chemotherapy in these patients.

Clinical efficacy with the combination of first- and third-generation EGFR-TKIs has been reported when *T790M* and *C797S* mutations are in the *trans* conformation (i.e., on different alleles) which exists in about 8% of cases from cell-free plasma DNA surveillance (18). However, no clinical responses have been noted with EGFR-TKIs or combinations when *EGFR T790M* and *C797S* are in the *cis* conformation (i.e., on the same allele) (18,19). Knowledge of whether *C797S* mutation is in *cis* or *trans* conformation following osimertinib therapy is important to guide subsequent treatment. Response to osimertinib and erlotinib in combination to target concomitant *EGFR T790M* and *C797S* in *trans* may be short-lived followed by a change in *C797S* from *trans* to *cis* (20). A rapid decline in the *C797S* mutation measured by circulating tumor DNA (ctDNA) assay within 2 weeks of starting a combination of osimertinib and gefitinib in a patient with *T790M* and *C797S* mutation in *trans* has been reported (21).

The role of liquid biopsy for *EGFR T790M* detection and dynamic monitoring is discussed in the consensus (8). The clinical utility of detecting *EGFR T790M* mutation in plasma ctDNA samples is supported by data from the post-hoc analysis of the AURA study which showed that ORR and median PFS were similar in patients with *T790M*-positive plasma or *T790M*-positive tumor (ORR: 63% *vs.* 62%; PFS: 9.7 *vs.* 9.7 months) (22). Based on these results, the FDA has approved plasma Cobas testing for *EGFR* mutations for osimertinib therapy. However, patients tested negative for *T790M* by plasma ctDNA require a tumor rebiopsy to test for the presence of *T790M* because the sensitivity for detecting *EGFR T790M* by plasma ctDNA is about 60%, which is lower than that for detecting sensitizing *EGFR* mutations, exon 19 deletion and exon 21 *L858R* mutations, which is 70% to 80%) (22). Tissue rebiopsy is also needed to confirm histological transformation to small cell lung cancer. Plasma ctDNA can be used for dynamic monitoring of the therapeutic effect of osimertinib and identifying possible acquired resistance mechanisms.

Osimertinib is the most effective EGFR-TKI in patients with *EGFR* sensitizing mutations with or without *EGFR T790M* mutation (6,7). The superior PFS, ORR, CNS activity and toxicity profile are compelling reasons for osimertinib to be a front-line treatment option for metastatic *EGFR* mutated NSCLC. Compared to first-generation generation EGFR-TKIs, osimertinib is a preferred option for patients with CNS disease and for the prevention of CNS metastasis. It is not clear if the resistance mechanisms after first-line osimertinib are different from that after second-line osimertinib, and active research is ongoing in this area. A significant percentage of patients with *EGFR*-mutant advanced NSCLC do not make it to second-line therapy, so these patients should be offered the safest and most effective therapy upfront. It remains controversial as regard the optimal sequence of EGFR-TKIs of different generations in managing patients with *EGFR*-mutant NSCLC in the long-term. Unresolved issues on osimertinib that need further investigation include characterization of the acquired resistance mechanisms associated with its first-line use, the utility of plasma ctDNA for detecting *EGFR T790M* mutation, its combination with other therapeutic agents and its possible role as an adjuvant therapy. It has been shown that the median duration of treatment can be long at 31.5 months among patients who received sequential treatment with first-line afatinib followed by second-line osimertinib (23). A real-world retrospective study, GioTag, showed that the median time on treatment for sequential first-line afatinib in patients with sensitizing *EGFR* mutations followed by second-line osimertinib because of acquired *T790M* mutation was 27.6 months (24).

Although investigating the best EGFR-TKI sequence should be carried out to determine the therapy that results in the longest duration of clinical response offered by

EGFR-TKIs which might contribute to longer survival, first-line osimertinib is an attractive option currently based on the results of the FLAURA trial. The best strategy for sequencing gefitinib and osimertinib is being explored in the phase II APPLE trial in which first-line osimertinib is compared with osimertinib after gefitinib when *T790M* is detected by plasma ctDNA (25). The activity of osimertinib compared to gefitinib to prevent CNS metastases will also be assessed in this trial. Laboratory studies have shown that combining the EGFR-TKIs, gefitinib and osimertinib may help prevent the development of drug resistance because of the inhibition of major secondary mutations, *C797S* and *T790M*, respectively. A phase 1 study (NCT03122717) in which two different methods of combining gefitinib and osimertinib in patients with newly diagnosed advanced *EGFR*-mutant lung cancer, either with both drugs taken together on the same day or an alternating schedule where participants will alternate taking one drug at a time every 4 weeks, aims to determine the optimal dosing strategy when these two EGFR-TKIs are used in combination. In the study, the clinical response of the participants treated with the drug combination will be monitored to evaluate how well and how long the disease is controlled by the two strategies.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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