First-line osimertinib in patients with EGFR-mutated advanced non-small cell lung cancer

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Epidermal growth factor receptor (EGFR) mutations, including exon 19 deletions and the point mutation L858R in exon 21, are found in 10–35% of non-small cell lung cancers (NSCLCs) and determine the treatment response to EGFR/tyrosine kinase inhibitors (TKIs) (1,2). Compared to standard intravenous chemotherapy with cisplatin-docetaxel, first-generation EGFR/TKIs (gefitinib and erlotinib) show longer median progression-free survival (PFS) (9–11 *vs.* 5–6 months) and higher objective response rates (ORRs) (58–74% *vs.* 15–32%) in patients with stage IIIB/IV disease (3-5). However, most patients develop drug resistance within 1 year of treatment, and 50–60% of such patients harbor a secondary T790M point mutation in exon 20 (6). Other resistance mechanisms include amplification of MET, HER2, and MAPK1; the epithelial to mesenchymal transition; PIK3CA or BRAF mutations; and small cell transformation (7,8). Although second-generation EGFR/TKIs (afatinib) have an irreversible and potent activity against the T790M mutation in preclinical studies, dose-limiting toxicity has hindered clinical success (9). After the failure of first-generation EGFR TKIs, afatinib plus paclitaxel offers a modest benefit with 5.6 months of PFS and a 32.1% ORR, compared with single agent chemotherapy (2.8 months PFS and 13.2% ORR) and rechallenge treatment with gefitinib (2.8 months PFS and 4.9% ORR) (10,11).

Osimertinib mesylate, a third-generation EGFR/TKI, is a mono-anilino-pyrimidine small molecule that selectively inhibits EGFR T790M and EGFR/TKI sensitizing mutations with lower activity against wild-type EGFR (12). Osimertinib was approved in the USA in November 2015 by showing positive results in phase I and phase II clinical trials of patients with the EGFR T790M mutation (13,14). Osimertinib is useful in patients with metastatic EGFR T790M-positive NSCLC after the failure of EGFR/TKI therapy. In a second-line setting after the failure of EGFR/TKIs in patients harboring the EGFR T790M mutation, osimertinib had significantly greater efficacy than platinum-pemetrexed combination therapy in the AURA3 (phase III) trial (15). The median PFS was significantly longer (10.1 *vs.* 4.4 months) and the ORR was significantly higher (71% *vs.* 31%) with osimertinib than with platinum-pemetrexed combination therapy. Moreover, adverse events of grade 3 or higher occurred less frequently in the osimertinib group than in the platinum-pemetrexed combination group (23% *vs.* 47%).

Based on preclinical studies reporting that osimertinib delays the emergence of resistance in EGFR-mutated tumors and sustains the inhibition of tumor growth (16,17), researchers expected that osimertinib would be effective and potentially delay the emergence of resistance as a first-line treatment in patients harboring EGFR/TKI sensitizing mutations. Ramalingam *et al.* (18) analyzed the treatment response of osimertinib as a first-line treatment in two cohorts with a secondary objective of the AURA study to investigate the safety and efficacy of osimertinib in treatment-naïve patients with EGFR-mutated advanced NSCLC. In that study, 60 patients received 80 or 160 mg of osimertinib once daily (30 patients/group) during a median of 19.1 months. The median PFS rates were

22.1 months [95% confidence interval (CI), 13.7–30.2 months] in the 80 mg group, 19.3 months (95% CI, 13.7–26.0 months) in the 160 mg group, and 20.5 months (95% CI, 15.0–26.1 months) across doses. These data suggest that PFS is prolonged when using osimertinib than when using gefitinib or erlotinib as the first-line treatment in patients with EGFR-mutated advanced NSCLC; this is being evaluated in a head-to-head comparison phase III study (osimertinib *vs.* gefitinib or erlotinib; FLAURA study; ClinicalTrials.gov identifier: NCT02296125). Furthermore, PFS seems to be similar when using osimertinib as the first-line treatment (about 20 months) and as the second-line treatment after the failure of first-generation EGFR TKIs (about 10 months PFS for first-generation EGFR TKIs plus about 10 months PFS for second-line osimertinib) in patients with EGFR-mutated advanced NSCLC. Seven (7/60, 12%) patients had the *de novo* T790M mutation. Of the seven, six patients had a partial response (ORR, 86%) with a median 18.0 months (range, 6.9–27.7 months) duration of response (DOR). Considering that the ORR was 77% and the median DOR was 18.0 months in the 60 patients, the treatment response seemed to be unaffected by *de novo* EGFR T790M.

In previous studies, the mechanisms of osimertinib resistance in T790M-positive NSCLC included an acquired mutation in EGFR (C797S), MET or HER2 amplification, and small cell transformation (19-21). In this study, of 38 patients with progression and plasma samples for next-generation sequencing analysis at the data cutoff, 19 patients had detectable circulating tumor DNA (ctDNA) in their post-dose sample. Of these, nine patients had putative genomic resistance mutations, including EGFR C797S; amplification of MET, EGFR, or KRAS; and acquired mutations in PIK3CA and KRAS. In particular, an acquired EGFR C797S mutation without T790M was identified in one patient. Considering that gefitinib has potency to inhibit a tumor harboring EGFR C797S without T790M (22,23), osimertinib could be salvaged by second-line gefitinib. Interestingly, there was no evidence of the acquired T790M mutation in the post-progression plasma ctDNA samples analyzed.

In this study, possibly causally related adverse events (AEs) of grade 3 or higher were observed in 4/30 patients (13%) in the 80 mg group, 7/30 (23%) in the 160 mg group, and 11/60 (18%) across doses. The most common AEs were a rash, diarrhea, and dry skin. Dose reductions due to AEs occurred in 3/30 patients (10%) and 16/30 (53%) in the 80 and 160 mg groups, respectively. In the 80 mg group, dose reduction was determined due to nausea (n=1), neutropenia (n=1), and thrombocytopenia (n=1). These data suggest that the previously approved 80 mg once-daily dosage in a second-line setting is effective and tolerable in the first-line setting.

In conclusion, first-line osimertinib (80 mg) appears to be effective and safe in patients with EGFR-mutated NSCLC without evidence of an acquired T790M mutation. The mechanism of resistance to first-line osimertinib remains to be fully elucidated. The results of FLAURA study, which directly compared osimertinib with erlotinib and gefitinib, will help guide us as to which one should be the first-line treatment and establish a new standard of treatment for patients with EGFR-mutated advanced NSCLC.

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None.

Footnote

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

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