Osimertinib, the winner, but cannot yet take it all

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Osimertinib is a potent, irreversible EGFR-TKI, selective for EGFR T790M mutation as well as EGFR sensitizing mutations (1). In series of AURA trials, osimertinib has shown significant activity for T790M mutation positive patients who had shown disease progression in previous EGFR-TKI treatment (2). The randomized phase III AURA3 trial comparing osimertinib to standard pemetrexed-platinum-doublet chemotherapy in T790M mutation positive patients demonstrated that osimertinib had superior progression-free survival (PFS) of 10.1 months compared to chemotherapy with PFS of 4.4 months [hazard ratio (HR) 0.30; 95% confidence interval (CI), 0.23–0.41; P<0.001]. Of note, the superior PFS was observed even in patients with central nervous system (CNS) metastasis (8.5 *vs.* 4.2 months; HR 0.32; 95% CI, 0.21–0.49). The AURA3 also reported higher objective response rate (ORR) (71% *vs.* 31%, P<0.001) and better safety profile in the osimertinib group (occurrence of grade 3 or 4, 23% *vs.* 47%) (3). Given that osimertinib has preclinical activity in EGFR sensitizing mutations as well as favorable safety profile seen in AURA trials, osimertinib became more attractive as first line therapy. Recently, Ramalingam *et al.* reported the outcomes of osimertinib in treatment-naïve patients participating AURA trials. The median PFS was reportedly 20.5 months (95% CI, 15.0–26.1 months) across doses (80- and 160-mg group) (4), suggesting the meaningful role of osimertinib for not only T790M mutation but also EGFR sensitizing mutations. The notable activity was confirmed immediately by the following randomized phase FLAURA trial comparing osimertinib with the standard first-generation EGFR-TKI therapy, gefitinib or erlotinib (5). Following FLAURA trial showed that a median PFS of 18.9 months in the osimertinib group was significantly longer than that of 10.2 months in the first-generation EGFR-TKI group (HR 0.46; 95% CI, 0.37–0.57; P<0.001).

However, the results in the two studies of osimertinib as first-line therapy raise some issues. First of all, we are wondering which one is the standard of therapy for EGFR sensitizing mutation positive patients. The median PFS of first-line osimertinib in the FLAURA is 18.9 months while the numerical sum of PFS's of first-generation EGFR-TKI followed by osimertinib is 20.3 months, when considering that the first-generation EGFR TKI in the FLAURA gave a PFS of 10.2 months and osimertinib in the AURA3 gave that of 10.1 months. The PFS of 10.2 months in the FLAURA trials is comparable in the literature (6). At a glance, there might be no difference between the two approaches in terms of PFS. However, I would like to point out that the study populations of the studies were different. Actually, in the AURA3 trial, only 419 patients out of 1,036 patients screened (40%) could be randomized, which was mainly due to central confirmation of T790M mutation. Much more patients can be of benefit from osimertinib when used as first-line therapy than as second-line therapy. However, it might be a kind of double-edged sword since it is definitely a happy news to the pharmaceutical company

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but it might be a bad one to healthcare payers as well as patients and family. Therefore, we need final overall survival results of the FLAURA. Fortunately, in the FLAURA the HR for the death in the osimertinib group at the time of 25% maturity was 0.63 (95% CI, 0.45–0.88; P=0.0068), reducing the risk of death by 37% although a P value of 0.0015 was needed to reach statistical significant at that time.

Secondly, from a practical point of view, in order to use osimertinib as second-line therapy we have to identify T790M, meaning that we should get tumor tissue again or draw blood. Tumor biopsies for detecting T790M mutation are invasive, costly and not always feasible at high risk of complications. Plasma circulating tumor DNA often faces a meaningful risk of false-negative results. Therefore, some might not get a chance to use osimertinib due to the reasons even though their tumors harbor T790M mutation. With this regard, use of osimertinib as first-line therapy is more practical, avoiding the problems of re-biopsy or repeated plasma sampling.

Thirdly, CNS metastases are more problematic in patients treated with first-generation EGFR-TKI therapy since CNS is a common site of relapse at 12-month risk of CNS progression of 6% (7).The FLAURA trial reported that osimertinib group had longer PFS regardless of presence of CNS metastases (HR for PFS with CNS metastasis 0.47 *vs.* without CNS metastasis 0.46) and lower rate of CNS progression (6% *vs.* 15%) compared to first-generation EGFR-TKIs. Of note, we already have preclinical data with EGFR mutant xenograft mouse model, which have observed that osimertinib distribution across blood-brain barrier (BBB) was 10-fold higher compared with gefitinib (8). In the BLOOM study assessing the efficacy of osimertinib in EGFR mutation-positive patients with leptomeningeal disease regardless of T790M status, out of 32 patients, 10 had radiological improvement and 13 patients stable disease with a median treatment of duration of 6 months at a higher dose of 160 mg (9). Given the good activity for CNS metastasis including leptomeningeal disease, osimertinib as first-line therapy is more attractive.

Lastly, resistance mechanisms to osimertinib need to be elucidated to establish subsequent treatment strategy. The C797S mutation in exon 20 of EGFR was known to be the most common mechanism for resistance to osimertinib (10). HER2, MET amplification and so on were also identified as well (11). Actually, the resistance mechanisms to osimertinib might affect differently the prognosis compared to those to other EGFR-TKIs.

In conclusion, frontline osimertinib is beneficial to much more patients. It might be more practical and more attractive in various reasons. Osimertinib is the winner of "EGFR mutation-positive NSCLC" but cannot yet take it all "EGFR mutation-positive patients." Final overall survival results and its cost-effective analysis data is needed, which might be more important for healthcare payers than any other stakeholders.

Acknowledgements

Footnote

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