Editorial

Current role and future direction of osimertinib in epidermal growth factor receptor-mutant non-small cell lung cancer

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Osimertinib (Tagrisso, AstraZeneca) is a third-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) that potently and irreversibly inhibits EGFR-TKI sensitizing mutations and the T790M mutation; the drug exhibits lower-level activity against wild-type EGFR (1). Recently, the AME Lung Cancer Collaborative Group summarized the current role of osimertinib and made recommendations as to how osimertinib could, in future, be employed in various clinical situations (2). Osimertinib is a category 1 drug of both the first-line and the T790M-positive second-line settings of the National Comprehensive Cancer Network (NCCN) guidelines (3). However, the AME Lung Cancer Collaborative Group carefully graded their recommendations based on the quality and consistency of published studies.

Over the past decade, an increased understanding of the molecular pathogenesis of lung cancer and the development of targeted therapies have improved the outcomes of patients with advanced, EGFR-mutant, non-small cell lung cancer (NSCLC). The first-generation EGFR-TKIs, gefitinib and erlotinib, prolonged the median progression-free survival (PFS) by 4–5 months compared to that of standard cytotoxic chemotherapy (9–11 *vs.* 5–6 months) and increased the response rate (RR) 2–3-fold (58–74% *vs.* 15–32%) (4-6). However, cure is near-impossible; disease progression after 1–2 years of treatment is inevitable in most cases. The acquired EGFR T790M mutation in exon 20 and brain metastasis because of poor drug penetration into the central nervous system (CNS) are associated with unfavorable clinical outcomes during the first-generation EGFR-TKI treatment (7,8). Although a second-generation EGFR-TKI (afatinib) has an irreversible and potent activity against the T790M mutation, dose-limiting toxicities compromise the clinical benefits (9-11). After the failure of first-generation EGFR-TKIs, the afatinib-plus-paclitaxel combination modestly prolongs the median PFS by 2–3 months (5.6 *vs.* 2.8 months) and also modestly increases the probability of RR (32% *vs.* 13%) compared to single-agent chemotherapy (10).

In the AURA trial series, osimertinib exhibited remarkable activity in patients with acquired EGFR T790M mutations caused by prior EGFR-TKI treatments (12). AURA3, a randomized phase III trial enrolling EGFR T790M-mutant patients, showed that osimertinib afforded a longer PFS (10.1 *vs.* 4.4 months) than did standard chemotherapy (pemetrexed-plus-platinum) (13). Even in patients with CNS metastases, the PFS was longer in the osimertinib group than the chemotherapy group (8.5 *vs.* 4.2 months). In addition, osimertinib was associated with a lower rate of grade ≥3 adverse events compared to standard chemotherapy (23% *vs.* 47%). Based on such encouraging results in second- or subsequent-line settings, the AME Lung Cancer Collaborative Group assigned osimertinib a Grade A (based on clinical studies of good quality and consistency with at least one randomized trial) for patients with acquired EGFR T790M mutations after disease progression on previous EGFR-TKIs, and a Grade B (based on well-designed studies but without good randomized trials) in those with CNS metastases (2).

Based on the preclinical activity of osimertinib in those with EGFR-sensitizing mutations, and the favorable safety profile of the drug, interest is increasing in how effective the drug might be as a first-line treatment for EGFR-mutant NSCLC patients. Ramalingam *et al.* analyzed the response to first-line osimertinib in two cohorts; this was a secondary objective of the AURA trials (14). The median PFSs were 22.1 and 19.3 months in those receiving 80 and 160 mg osimertinib daily, respectively, suggesting that osimertinib was better than gefitinib or erlotinib for patients with EGFR-mutant, treatment-naïve, advanced NSCLC. Later, the FLAURA trial featured a head-to-head comparison of osimertinib *vs.* first-generation EGFR-TKIs (gefitinib or erlotinib) (15). The median PFS of the osimertinib group was significantly longer than that of the first-generation EGFR-TKI group when all data were analyzed (18.9 *vs.* 10.2 months), even in patients with CNS metastases (15.2 *vs.* 9.6 months). In addition, adverse events of grade ≥3 were less frequent in the osimertinib group than the first-generation EGFR-TKI group (34% *vs.* 45%). After considering these results, the AME Lung Cancer Collaborative Group assigned osimertinib a Grade A– (based on clinical studies of good quality but did not confirmed by another one) for patients with EGFR-activating mutations and Grade B for those with CNS metastases in the first-line setting (2).

The AME Lung Cancer Collaborative Group (2) also addressed several unresolved questions and explored future directions. First, although the early separation of the PFS curve in the FLAURA trial could be interpreted as reflecting a lower frequency of early resistance to osimertinib compared to first-generation EGFR-TKIs used as first-line therapies (15), acquired resistance to osimertinib is still inevitable. The mechanisms include acquired EGFR mutations (e.g., C797S); amplifications of MET, EGFR, HER2, and/or KRAS; activating mutations in PIK3CA and KRAS; and transformation to small-cell lung cancer, all of which were observed when the drug was used as either a first- or second-line treatment (14,16). A better understanding of acquired resistance, and strategies to overcome the problem, are required. Second, the diagnostic sensitivity of the plasma-circulating tumor DNA (ctDNA) test in terms of EGFR T790M mutational status remains suboptimal. Practically, the EGFR T790M mutation must be confirmed by re-biopsy of tumor tissue or plasma ctDNA when osimertinib is to be used as a second-line therapy. Although blood sampling for ctDNA analysis is easy, the sensitivity of the test is only approximately 60% in terms of detecting the EGFR T790M mutation (17). Therefore, almost half of true EGFR T790M-positive-patients may require biopsy, which is invasive and sometimes technically difficult. The NCCN guidelines recommend initial plasma-based testing of T790M mutational status in patients exhibiting progression while on EGFR-TKIs, and subsequent tissue-based testing of re-biopsy material for those who are negative on the plasma test (3). The AME Lung Cancer Collaborative Group assigned the detection of EGFR mutations (including T790M) in tissue a Grade A in terms of reliability and the plasma ctDNA test a Grade B (2). Third, the efficacy of osimertinib in patients with EGFR exon 20 insertion mutations should be explored. Such mutations may account for ~4% of all EGFR mutations, are resistant to first- and second-generation EGFR-TKIs, and are associated with unfavorable outcomes (18). Although some preclinical trials have shown that osimertinib was highly effective in some forms of exon 20 insertion mutations (19), efficacy should be evaluated in a clinical setting. Fourth, brain metastasis is a common problem during the clinical course of advanced NSCLC; any role for upfront osimertinib in this context should be validated in a prospective, multi-institutional randomized trial. In TKI-naïve, EGFR-mutant, NSCLC patients with brain metastases, upfront stereotactic radiosurgery followed by an EGFR-TKI (erlotinib) afforded better outcomes than did upfront EGFR-TKI with deferral of radiotherapy (adjusted hazard ratio 0.39, P<0.001) (20). Although osimertinib has exhibited excellent clinical activity in patients with CNS metastases, as mentioned above, further research is needed to define how best to control CNS metastasis: upfront osimertinib followed by radiotherapy *vs.* upfront radiotherapy followed by osimertinib. Finally, we look forward to the results of ongoing clinical trials evaluating distinct combinational strategies of immune checkpoint inhibitors (NCT02143466), bevacizumab (NCT02803203), dasatinib (NCT02954523), and adjuvant treatments for patients with EGFR-mutant, stage Ib–IIIa NSCLC who have undergone complete tumor resection (NCT02511106).

In conclusion, osimertinib seems to be the best EGFR-TKI for patients with advanced NSCLCs featuring EGFR-TKI sensitizing or T790M mutations. However, problems include the need to overcome acquired resistance, suboptimal diagnostic sensitivity of plasma ctDNA testing for the EGFR T790M mutation, uncertainties surrounding the optimal treatments for patients with CNS metastases or exon 20 insertion mutations, the need to optimize combinations of osimertinib with other promising drugs, and the issue of a role for osimertinib in adjuvant therapy.

These issues must be resolved one-by-one.

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Footnote

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

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