EDITORIAL

Osimertinib as First-Line Treatment in *EGFR*-Mutated Non–Small-Cell Lung Cancer

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Genetic analysis is now routine in metastatic non–small-cell lung cancer (NSCLC) to identify somatic sensitizing mutations in *EGFR*, typically L858R and exon 19 deletion (Ex19del). Patients with these genotypes are treated with first- or second-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) (e.g., erlotinib, gefitinib, and afatinib) preferentially over chemotherapy owing to their marked superiority in tumor response, progression-free survival, and quality of life. Such molecular selection has seen median overall survival increase among patients with such genetic variants, from a median of 7.9 months in 2002[1] to 27.3 months in 2015.[2]

However, despite rapid and durable responses, acquired resistance is inevitable and occurs through a number of well-characterized biologic mechanisms. Of most concern is the chance of central nervous system (CNS) relapse due to poor drug penetration and acquisition of the somatic *EGFR* T790M gatekeeper mutation; this variant mediates resistance by increasing the affinity of the ATP binding site of the receptor for ATP, thus preventing binding of the inhibitor. The gatekeeper variant is identified in approximately 60% of treated patients, usually on the same chromosome as the original sensitizing mutation. The T790M mutation is more common with the Ex19del genotype than with the L858R genotype, although it is also rarely identified as a germline or somatic mutation de novo.

Osimertinib (Tagrisso, AstraZeneca) is a third-generation EGFR-TKI, rationally designed to potently and irreversibly inhibit mutated *EGFR* alleles, including T790M, L858R, and Ex19del, with minimal activity against wild-type *EGFR*.[3] The care of patients with acquired resistance to first-line EGFR-TKI therapy that is mediated through T790M is now well established, with the AURA3 phase 3 trial confirming the superiority of osimertinib over standard platinum–pemetrexed chemotherapy with respect to response rate (71% vs. 31%), progression-free survival (10.1 months vs. 4.4 months), and quality of life.[4] Moreover, in preclinical models, the CNS penetration of osimertinib is superior to that of afatinib or gefitinib, with AURA3 subgroup analyses confirming superior CNS responses and intracranial progression-free survival over chemotherapy (including in patients with leptomeningeal involvement), alongside a neuroprotective effect.[5] As a result, osimertinib has been rapidly adopted as the standard of care for T790M-mediated acquired EGFR-TKI resistance.

Nevertheless, T790M identification can be challenging in routine care[6]: coexisting conditions may preclude biopsies, progressive sites may not be easily amenable to rebiopsy, low tumor content in tissue obtained during rebiopsy may beget false negative results, and progression may occur in the CNS alone. For these reasons, *EGFR* genotyping from cell-free samples (e.g., plasma circulating tumor DNA) has come to replace tissue genotyping as the preferred initial approach. However, technology sensitivity may bias test performance, as may disease site and bulk, so false negative results are still a risk.

It is against this backdrop that Soria et al.

report eagerly anticipated findings from the FLAURA trial in this issue of the *Journal*.[7] This randomized, double-blind, phase 3 trial aimed to identify whether first-line osimertinib in advanced NSCLC with L858R or Ex19del *EGFR* genotypes is superior to first-generation TKIs (erlotinib or gefitinib) with respect to progression-free survival. Indeed, osimertinib was markedly superior (median progression-free survival, 18.9 months vs. 10.2 months; hazard ratio for disease progression or death, 0.46), with a longer duration of response and no new safety concerns. Efficacy was superior in both those with CNS disease at enrollment and those without it. Although data on overall survival remain immature, analyses at 12- and 18-month landmarks currently favor osimertinib despite crossover (i.e., patients receiving osimertinib after disease progression in the other group), but these results are probably still unstable.

So, is first-line osimertinib the new standard for NSCLC with *EGFR* L858R or Ex19del mutation? Or should it be considered a second-line treatment, used on relapse if T790M-mediated acquired resistance to erlotinib or gefitinib is identified? Several issues should be considered. The FLAURA trial cannot yet evaluate overall survival, an important end point for NSCLC driven by these variants, when survival is now routinely measured in years. Mature data on survival from the AURA3 trial are yet to be reported and will set an important benchmark for second-line osimertinib that the FLAURA trial must beat. Because most patients in the AURA3 trial initially received erlotinib or gefitinib, using osimertinib after first-line afatinib or dacomitinib instead may improve overall survival further, given the superiority of afatinib or dacomitinib over gefitinib with respect to progression-free survival,[8,9] but at the cost of greater toxicity. In addition, further data on the activity of osimertinib in CNS disease from the FLAURA trial are awaited, although the lack of routine CNS evaluation will bias interpretation. Finally, resistance mechanisms to first-line osimertinib and their effect on overall survival currently remain poorly determined. At this point, known osimertinib resistance variants have been identified; the limited phase 1 data from the use of osimertinib as first-line treatment suggest similar findings, but more data are needed to determine whether these mechanisms would limit the use of osimertinib as first-line treatment.[10]

Despite these limitations, the near doubling in median progression-free survival with first-line osimertinib is profoundly impressive. It has activity in CNS disease that is superior to that of the other available TKIs, and it is less toxic. Osimertinib also makes detection of the T790M mutation unimportant. We cannot robustly predict in which patients T790M-mediated acquired resistance to first- or second-generation EGFR-TKIs will develop. Moreover, T790M is irrelevant to the 40% of patients who have disease progression by other mechanisms. These factors and the predictable and durable efficacy of first-line osimertinib make it the ideal first-line choice for *EGFR*-mutated NSCLC.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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