



Osimertinib a new weapon in epidermal growth factor receptor-mutated non-small cell lung cancer patients

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Non-small cell lung cancer (NSCLC) accounts for about 85% of all new lung cancer diagnoses every year worldwide (1). Unfortunately, in most cases the diagnosis is made when the disease is already in a metastatic stage with the systemic therapy being the standard-of-care. In approximately 20% of Caucasian NSCLC patients (2), and in about 50% of Eastern Asian ones (3), an oncogene-addicted NSCLC is diagnosed, due to the presence of epidermal growth factor receptor (*EGFR*) activating mutations or anaplastic lymphoma kinase (*ALK*) and proto-oncogene tyrosine-protein kinase ROS (*ROS1*) rearrangements. These gene alterations identify patients who benefit from the use of correspondent inhibitors (4,5).

First- and second-generation *EGFR*-tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib, icotinib, and afatinib are the standard-of-care for first-line therapy of NSCLC harboring activating *EGFR* mutations demonstrating high sensitivity in this subgroup of patients (6-13). After an initial activity of an average 9–13 months of first-line *EGFR*-TKIs treatment, a disease progression has been reported in the majority of patients. The onset of the Thr790Met point mutation (T790M) in the gene encoding *EGFR* was responsible for the disease progression in about 50–60% of patients. Osimertinib, a third-generation *EGFR*-TKI, targets selectively the *EGFR* T790M mutation while sparing wild-type *EGFR* (14). The AURA phase I study showed clinical activity of osimertinib administered across oral doses of 20 to 240 mg/day in 253 *EGFR*-mutated

NSCLC patients progressing to first- or second-generation *EGFR*-TKI (15). The AURA phase I study showed that osimertinib treatment was active in both T790M-positive and T790M not detected NSCLC patients although with a different benefit in term of objective response rate (ORR, 61% and 21%, respectively). Despite no dose limiting toxicity was reported also at the higher dose of 240 mg/day, the optimal dose chosen for further phase II evaluation was 80 mg once daily (15).

In April 2017, in the *Journal of Clinical Oncology*, James Chih-Hsin Yang and colleagues (16) presented the results of the AURA extension phase II study. A total of 201 (out of 401 screened patients) advanced NSCLC patients, who had progressed after therapy with an *EGFR*-TKI agent (with or without additional anticancer regimens) and positive for the T790M mutation, received once-daily osimertinib 80 mg. The T790M status was detected by central testing from a tumor sample taken after the disease progression on the most recent treatment regimen (*EGFR*-TKI or chemotherapy). The T790M detection rate was the same regardless of the last prior *EGFR*-TKI treatment (gefitinib, 69%; erlotinib, 68%; afatinib, 68%). A total of 74 patients enrolled in the study had asymptomatic, stable central nervous system (CNS) metastases not requiring corticosteroids. The primary end point was ORR by independent radiology assessment. Secondary end points were disease control rate, duration of response, progression-free survival (PFS), and safety. The ORR was 62% (122

out of 198 evaluable patients) with the median duration of response of 15.2 months. The disease control rate was 90%. ORRs were similar across all presented predefined subgroups (second- and third-line, type of sensitizing EGFR mutation, type of previous EGFR-TKI). Median PFS was 12.3 months, consistent across all subgroups analyzed. Median PFS was shorter in patients with CNS metastases than in those without (7.1 and 13.7 months, respectively). The CNS ORR was 64% (16 out of 25 evaluable patients) with 4 complete and 12 partial responses. The median overall survival (OS) was not reached with a 1-year survival rate of 79%. Patient-reported outcomes, an exploratory end point, were measured by the European Organization for Research and Treatment of Cancer (EORTC) questionnaires QLQ-LC13 and QLQ-C30. Lung cancer symptoms, such as dyspnea, cough, pain and the global health status and physical functioning domains improved during osimertinib treatment. Osimertinib was well tolerated reporting grade ≥ 3 diarrhea and rash in $<1\%$ of cases. Any-grade interstitial lung disease was reported in 8 patients (4%). Nine patients (3%) discontinued osimertinib due to adverse events (16).

The results reported in this study are similar to those reported by the phase II AURA2 trial, in which 210 T790M-positive pretreated NSCLC patients received osimertinib 80 mg/day orally (17). In fact, in the AURA2 trial, the ORR in the 199 evaluable patients was 70%, median PFS was 9.9 months, 1-year OS was 81% with 12% of possibly treatment-related grade ≥ 3 adverse events and 1 toxic death due to interstitial lung disease (17). These two single-arm AURA trials confirmed the activity and efficacy of osimertinib in these oncogene-addicted NSCLC patients. The following step was the phase III AURA3 trial in which osimertinib was compared with platinum/pemetrexed regimen in second-line treatment of EGFR-TKI previously treated T790M-positive NSCLC patients. Again, osimertinib confirmed superiority in terms of PFS (10.1 versus 4.0 months), primary end point, ORR (71% versus 31%) and safety (grade ≥ 3 adverse events: 23% versus 47%) versus chemotherapy (18).

Due to these results, osimertinib is now available almost worldwide for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR-TKI therapy.

The T790M mutation is a predictive biomarker for osimertinib therapy in EGFR-mutated NSCLC patients progressing to first- and second-generation EGFR-TKIs. This means that repeated biopsy sample at disease progression is needed to select patients who can benefit

by osimertinib therapy. However, this approach might be challenging in the clinic practice due to 20–40% of patients being unavailable for re-biopsy due to medical or technical issues. Furthermore, the insufficient tumor cellularity taken from tumor re-biopsy is responsible for another 11–21% of patients in which genomic results could not be obtained. Overall, the post-progression tumor genotyping is possible in 48–70% of patients with a high percentage of cases in which the potential presence of T790M mutation is at risk of missing (19,20). For this reason, the circulating DNA genotyping methods have emerged as a further way to overcome this problem. Several data confirmed equivalent outcomes with osimertinib therapy between patients T790M-positive in plasma and those T790M-positive on tissue-based assay results (21,22). These led to the approval of plasma-based T790M testing for osimertinib prescription. Unfortunately, the estimated sensitivity of plasma genotyping is in the range of 70%. Thus, this method might be used to screen T790M-negative patients who should be considered for invasive biopsy sampling. However, a high false-negative rate with plasma testing was reported, and so the analysis of a biopsy sample is recommended for patients also because it is possible to detect the onset of other mechanisms of resistance such as the diagnosis of small cell lung cancer.

The intrinsic mechanism of action of osimertinib is responsible of its high tolerability. In fact, osimertinib binds irreversibly, via the C797 amino acid covalent bond to L858R, exon 19 deletion, and double mutants containing T790M, mutant forms of EGFR at approximately nine-fold lower concentrations than to wild-type EGFR. Thus, osimertinib targeting selectively the EGFR T790M mutation while sparing wild-type EGFR, is characterized by low incidence of severe toxicities (14).

Osimertinib demonstrated greater penetration of the mouse blood-brain barrier than other EGFR-TKI (i.e., gefitinib, rociletinib, afatinib). Moreover, at clinically relevant doses, osimertinib induced sustained tumor regression in an EGFR^{wt} PC9 mouse brain metastases model (23). These preclinical data were confirmed by the encouraging clinical results reported also for CNS metastases with an ORR of 64% in patients with measurable CNS lesions (16). These results are confirmed also by other AURA trials (17,18) and by the BLOOM study in which 20 patients with leptomeningeal metastases from EGFR mutation-positive NSCLC were treated with osimertinib (at the double dose of 160 mg once daily) reporting radiologic improvement in 7 patients (24). This aspect is of paramount

importance given the long-term complications of brain radiation.

Osimertinib demonstrated activity also as first-line therapy in EGFR activating mutations NSCLC patients. In fact, preliminary findings from a cohort of patients treated as part of the phase I AURA trial showed an ORR of 77% with a median PFS of 19.3 months (25). The randomized phase III FLAURA trial, comparing osimertinib versus gefitinib or erlotinib in EGFR-TKI-naïve patients affected by advanced NSCLC harboring EGFR activating mutations, completed the accrual and the results are still expected (NCT02296125). This trial should help to define the best first-line approach in this subgroup of oncogene-addicted NSCLC patients, that is whether the development of T790M can be prevented and whether this approach is associated with a longer PFS than observed with first- or second-generation EGFR-TKIs.

Overall, osimertinib is a further weapon for fighting EGFR mutated NSCLC patients with the goal of chronicizing this disease thus increasing the OS with the due respect of patients' quality of life.

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Footnote

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Ethical Statement: The authors is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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