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LUNG CANCER

AURA3 magic reveals new standard

> a key finding is that even patients with CNS metastasis can benefit from osimertinib

Tyrosine kinase inhibitor (TKI) therapy is the standard first-line therapy for patients with *EGFR*-mutated advanced-stage non-small-cell lung cancer (NSCLC). Despite high response rates to TKI therapy, most patients succumb to disease progression within a year of treatment. More than half of patients with disease progression have the T790M 'gatekeeper' *EGFR* mutation, which reduces binding of first and second-generation EGFR TKIs to the target. The irreversible EGFR–TKI osimertinib is selective for the EGFR activating and T790M resistance mutations. Moreover, in the phase I AURA trial, the objective response rate to osimertinib in patients with T790M-positive advanced-stage NSCLC was 61%. Two subsequent phase II trials confirmed this result in more than 400 patients with NSCLC, which prompted the FDA to approve osimertinib under the 'breakthrough therapy' designation.

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Now, findings of the phase III AURA3 trial have been published in the *New England Journal of Medicine*, and the results do not disappoint. Tony Mok, lead author of this latest study, comments on the premise for this trial: "osimertinib was shown to be a highly effective agent against T790M-positive NSCLC in the AURA and AURA2 studies. In fact, the FDA has granted fast-track approval on the basis of these initial trial data. However, a comparative randomized phase III study against the current standard — that is, pemetrexed–platinum combination chemotherapy remains the best way to establish a new standard of treatment ." In this open-label, randomized trial, 419 patients with T790M-positive advanced-stage NSCLC who had disease progression following first-line EGFR TKI therapy were randomly assigned in a 2:1 ratio to receive 80 mg oral osimertinib once daily, or intravenous pemetrexed plus carboplatin or cisplatin for up to six cycles. Maintenance pemetrexed was permitted and a crossover design allowed patients to switch to osimertinib following disease progression on chemotherapy. The trial primary end point was progression-free survival (PFS).

The median duration of PFS was significantly longer for patients receiving osimertinib compared with platinum therapy plus pemetrexed (10.1 months versus 4.4 months, hazard ratio (HR) 0.30, P <0.001). The objective response rate was also significantly better with osimertinib (71%) than with platinum and pemetrexed-based chemotherapy (31%). Furthermore, the duration of response in patients receiving osimertinib was longer than that of those treated in the standard-care arm (9.7 months versus 4.1 months). Among the 144 patients who had metastases in the central nervous system (CNS), the median PFS was longer in patients treated with osimertinib than with platinum-based pemetrexed chemotherapy (8.5 months versus 4.2 months).

As Mok highlights: "a key finding is that even patients with CNS metastasis can benefit from osimertinib. The performance of osimertinib was similar to that noted in the earlier studies, and the treatment outcome of chemotherapy in this trial was also in line with previous studies. What is crucial is the randomized direct comparison."

The proportion of patients with grade 3 or higher adverse events was lower with osimertinib than with platinum plus pemetrexed therapy (23% versus 47%). Among the patients with a response at the time of data cutoff, disease progression or death was reported in 45% of patients in the osimertinib arm and 82% in the platinum–pemetrexed arm.

Mok puts these study findings into the context of future research and trial directions: "with osimertinib being the new standard, we are obligated to test for the EGFR T790M mutation in all patients with resistance to EGFR–TKI therapy. Either a rebiopsy or plasma-based circulating cell-free DNA test will become part of standard patient management. Importantly, osimertinib will be the standard control for any future comparative study assessing third-generation TKIs."

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