Report from the World Conference on Lung Cancer

Non-small cell lung cancer

A BRIGHTER FUTURE FOR PATIENTS WITH EGFR-MUTATED NSCLC

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TRIAL SUMMARY: Osimertinib in EGFR TKI-resistant advanced NSCLC

Papadimitrakopoulou V, Wu YL, Ahn MJ, et al. Randomised phase III study of osimertinib vs platinum–pemetrexed for EGFR T790M-positive advanced NSCLC (AURA3); World Conference on Lung Cancer, Vienna, Austria, December 6, 2016, Abstract PL03.03.

AURA3 is a phase 3, open-label, randomized study assessing the efficacy and safety of osimertinib vs platinum-based chemotherapy plus pemetrexed in patients with epidermal growth factor receptor (EGFR) T790M-positive advanced non-small cell lung cancer (NSCLC), whose tumours progressed on first-line EGFR tyrosine kinase inhibitor (TKI) therapy. The trial was carried out in more than 130 locations worldwide, including the USA, Canada, Europe, China, Japan, Korea, Taiwan and Australia. In the study, 419 patients ≥18 years with documented EGFR sensitizing mutation (EGFRm), radiologic disease progression following first-line EGFR TKI and centrally confirmed T790M-positive (by Cobas® EGFR Mutation Test) from a tissue biopsy after disease progression were randomized 2:1 to osimertinib 80 mg orally once daily, or platinum-pemetrexed every 3 weeks for up to 6 cycles; pemetrexed could be continued as maintenance treatment. Primary endpoint was progression-free survival (PFS) by investigator assessment according to RECIST v1.1. Secondary endpoints included overall survival (OS), overall response rate (ORR), duration of response (DoR), disease control rate (DCR), safety and measures of health-related quality of life.

Results: Osimertinib significantly improved PFS compared with platinum-pemetrexed: median 10.1 months vs 4.4 months (HR, 0.30; 95% CI, 0.23–0.41; p<0.001). ORR was significantly improved with osimertinib (71%) vs platinum-pemetrexed (31%); OR 5.39 (95% CI, 3.47–8.48; p<0.001). Median duration of response was 9.7 months (95% CI, 8.3–11.6) with osimertinib and 4.1 months (95% CI, 3.0, 5.6) with platinum-pemetrexed. Among 144 patients with metastases to the central nervous system (CNS), median PFS was longer among patients receiving osimertinib than among those receiving platinum-pemetrexed (8.5 months vs 4.2 months; HR, 0.32; 95% CI, 0.21, 0.49). Grade ≥3 causally-related adverse events (AEs) as assessed by the investigator were reported in 6% of patients treated with osimertinib and 34% of patients treated with platinum-pemetrexed. The most common AEs in the osimertinib group were diarrhea (29% [grade ≥3, 1%]), rash (28% [<1%]), while in the platinum-pemetrexed group nausea (47% [3%]) and decreased appetite (32% [3%]) were most common.

IN BRIEF

Already known

- While tyrosine kinase inhibitors (TKIs) effectively target epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer (NSCLC), they have side effects and progression remains likely within a year.

What this trial showed

- The phase 3 AURA3 trial compared osimertinib to chemotherapy in patients who progress due to T790M mutation following treatment with TKIs.
- Progression-free survival was 10.1 months with osimertinib vs 4.4 with chemotherapy.

Next steps

- Adopt osimertinib as a new standard of care for patients who progress due to T790M mutation following treatment with TKIs.

COMMENTARY: The future for patients with EGFR-mutated tumours just got brighter. When we see a new consult for NSCLC and the patient's tumours has an EGFR driver mutation, we celebrate. We can treat that patient with an oral TKI, which directly targets that abnormal mutation. We can turn off the "drive" in almost all patients. We have choices of both first- and second-line EGFR TKIs. Unfortunately, all have side effects that often require treatment, dose adjustment and monitoring. And although we celebrate, it is still sobering to know that all treatment is palliative, progression is likely within a year and OS is limited to only several years.

Because of limited choices in subsequent therapy that may be effective, we have learned to keep our first treatment going for as long as possible. We ask our radiation oncology colleagues to give local therapy to growing metastases. Brain metastasis upon progression is also common and, if it is the only site of metastasis, we consider local stereotaxic treatment and even surgery. Adding monoclonal antibodies such as cetuximab to first-line therapies such as afatinib has been shown to improve response, but at the cost of significant toxicity. Immunotherapy in these tumours with low mutational load does not work. Moving to chemotherapy is often the only

choice. Early work on determining the mutations that develop upon progression showed that, in over half the cases, a mutation in exon 20 named T790M was the culprit. When this mutation occurs, the binding pocket changes in structure and first- and second-generation EGFR inhibitors no longer fit.

Osimertinib was developed to inhibit the T790M mutation. Most importantly, it spares the wild-type EGFR receptor so toxicity such as rash and diarrhea is only mild. It penetrates the blood-brain barrier so brain metastases and leptomeningeal disease may be controlled. AURA3, a randomized phase 3 trial comparing osimertinib to chemotherapy in patients whose tumours acquire a T790M mutation while on first-line treatment with either first- or second-generation EGFR TKIs confirmed this treatment's superiority and tolerability. PFS in patients on osimertinib was 10.1 months vs 4.4 months with chemotherapy. This is a 5.7-month improvement. In the 34% of patients with brain metastases, PFS was also significantly greater with osimertinib (8.5 months vs 4.2 months). Both reached statistical significance.

What does this mean for our patients? For those whose tumours develop or acquire a T790M mutation, this is a new standard of care. Osimertinib is an oral medication that offers disease control, little toxicity, prolonged survival and hope.