Osimertinib given as first-line treatment may alter biology of EGFR mutated NSCLC

April 14 2016

The third generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) osimertinib is effective in the first-line treatment of EGFR mutated non-small-cell lung cancer (NSCLC), according to a late-breaking abstract presented at the European Lung Cancer Conference (ELCC) 2016 in Geneva, Switzerland.1 A second late-breaking abstract confirms the drug's effectiveness in patients with the T790M mutation.

EGFR inhibition is the standard of care for NSCLC patients with EGFR activating mutations but nearly 50 to 60% develop resistance by developing a T790M mutation. Osimertinib is a potent inhibitor of the original EGFR mutations (exon 19 and exon 21) and the T790M. The study presented today investigated whether the use of osimertinib as first-line therapy for EGFR mutation positive NSCLC would result in favourable efficacy due to delayed T790M mediated resistance.

The study included 60 patients from two phase I expansion cohorts of the AURA trial that had locally advanced or metastatic EGFR mutated NSCLC. Thirty patients received 80 mg a day and 30 received 160 mg a day in the first-line setting. The median follow-up was 16.6 months.

The overall response rate was 77%. Median progression free survival (PFS) was 19.3 months for the 160 mg dose and has not yet been reached for the 80 mg dose. Median duration of response has not been reached. The drug was well tolerated with few adverse events, particularly at the approved 80 mg dose, where just 10% of patients

required dose reduction to manage toxicities.

Prof Suresh Ramalingam, professor of haematology and medical oncology at Emory School of Medicine and deputy director of Winship Cancer Institute, Atlanta, Georgia, US, study author, said: "The overall response rate was among the best reported for first-line therapy of EGFR mutated NSCLC. The PFS results are exciting, well exceeding the historical control rates of 10 to 13 months with first or second generation drugs. Many of the patients have not had disease progression on the study and are still benefitting from treatment."

Initial data suggests that patients who had disease progression did not have T790M mutation as the mechanism of resistance. "That tells us that we may be changing the biology of the disease with the use of first-line osimertinib," said Ramalingam.

The findings will be further investigated in a phase III clinical trial in more than 500 patients comparing osimertinib to either erlotinib or gefitinib for front-line therapy. Results are expected in up to 18 months.

Commenting on the findings, Dr Enriqueta Felip, a medical oncologist at Vall d`Hebron University Hospital in Barcelona, Spain, not involved in the study, said: "The results with osimertinib in the first-line look promising. The ongoing randomised trial will define the role of osimertinib in the treatment of EGFR mutated patients who are treatment-naive."

A second late-breaking abstract presented today reveals the mature results of two AURA studies that investigated osimertinib at the recommended 80 mg dose in EGFR mutated and T790M positive NSCLC patients who had progressed on previous EGFR TKI therapy. Response rates were 71% in the phase I dose expansion cohort of 63 patients and 66% in pooled results from two phase II studies of 411

patients. PFS was 9.7 and 11 months for the phase I cohort and phase II studies, respectively.

"We found a response rate and PFS that were consistent between the two studies and with earlier reports from the AURA studies," said lead author Prof James Yang, director of the Department of Oncology and Department of Medical Research, National Taiwan University Hospital, Taipei, Taiwan. "Adverse events such as interstitial lung disease and QT prolongation2 were infrequent, with similar rates to our previous analyses."

He concluded: "In this mature pooled analysis for T790M positive EGFR mutant patients who have progressed on prior EGFR TKI, we were able to show a high overall response rate, encouraging duration of response and good tolerability profile. PFS was long compared to the four to five months provided by chemotherapy. This is good news for patients with EGFR mutations who have failed EGFR TKI, for whom osimertinib is now standard of care. Molecular diagnosis for T790M must now be the standard as well."

Commenting on the results, Felip said: "The study confirms the good results with osimertinib in this setting. Nowadays, in patients with EGFR mutation who progress after an EGFR TKI, there is a clear need for T790M testing since we now have a highly active agent, osimertinib, for this situation."

Osimertinib recently received accelerated approval as the first indicated treatment for patients with EGFR T790M mutation positive metastatic NSCLC in the US, EU and Japan.

Provided by European Society for Medical Oncology

Citation: Osimertinib given as first-line treatment may alter biology of EGFR mutated NSCLC (2016, April 14) retrieved 6 May 2024 from https://medicalxpress.com/news/2016-04-osimertinib-first-line-treatment-biology-egfr.html

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