Editorial

Osimertinib for pretreated epidermal growth factor receptor Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study

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Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI), gefitinib, erlotinib, afatinib are effective in patients with advanced non-small cell lung cancer (NSCLC) harboring an EGFR-TKI sensitizing mutation (1). However, most patients have developed disease progression (2-4). *EGFR* Thr790Met mutation is the most common mechanism of acquired resistance (5). Osimertinib is an oral, selective and irreversible EGFR-TKI of both *EGFR*-sensitizing and Thr790Met resistance mutation (6). Two hundred and fifty three patients with locally advanced or metastatic NSCLC, who had radiologically documented disease progression following prior treatment with an EGFR-TKI, received osimertinib in the AURA trial. Thirty one patients were treated with osimertinib 20, 40, 80, 160 or 240 mg once daily in the dose-escalation cohorts. No dose-limiting toxic effects were observed at any dose levels. Two hundred and twenty two patients in five expansion cohorts received osimertinib (20, 40, 80, 160 or 240 mg once daily). The most common adverse events were diarrhea, rash, nausea, decreased appetite and dry skin. Six patients experienced potential pneumonitis-like events. Prolongation of QTc interval was observed in 11 patients. Grade 3–5 adverse events were reported in 32% of the patients. Adverse events led to dose reduction or drug discontinuation in 7% and 6% of patients, respectively. The overall objective tumor response rate (ORR) [confirmed partial response (PR) or complete response (CR)] was 51% [95% confidence interval (CI), 45–58%] and the disease control rate (CR, PR or SD) was 84% (95% CI, 79–88%). Among 127 patients with confirmed *EGFR*-Thr790Met, the ORR was 61% (95% CI, 52–70%), and the disease control rate was 95% (95% CI, 90–98%). Among 61 patients with no detectable *EGFR*-Thr790Met, the ORR was 21% (95% CI, 12–34%), and the disease control rate was 61% (95% CI, 47–73%). In *EGFR*-Thr790Met positive patients, the median progression-free survival (PFS) was 9.6 months (95% CI, 30% maturity). In *EGFR*-Thr790Met negative patients, the median PFS was 2.8 months (71% maturity). The ORRs across all osimertinib dose levels were similar in patients with detectable *EGFR*-Thr790Met. The incidence and the severity of the adverse events increased at the 160 and 240 mg dose levels. Therefore, 80 mg once daily was determined as the recommended dose of osimertinib (7).

In the following AURA2 trial, the efficacy of osimertinib in the recommended dose was validated in a multicenter, open-label, single-arm, phase 2 study. Locally advanced or metastatic NSCLC patients with *EGFR*-Thr790Met mutation positive who progressed after EGFR-TKI were recruited from 44 study centers in eight countries. Rebiopsy to assess *EGFR*-

Thr790Met was required before study entry. Two hundred and ten patients initiated osimertinib between Jun. 13, 2014 and Oct. 27, 2014, of whom 11 patients without measurable disease at baseline were excluded from the evaluable patients for response analysis set (n=199). At data cutoff (Nov. 1, 2015), 122 (58%) patients remained on treatment. The median duration of treatment was 12.9 months [interquartile range (IQR), 7.3–14.0; range, 0.03–16.49). The primary endpoint was the proportion of patients who achieved an objective response. Secondary endpoints were PFS, duration of response, disease control, tumor shrinkage, overall survival, safety, health-related quality of life change from baseline, QTcF interval change after multiple dosing, and pharmacokinetics.

The objective response rate was 70% (95% CI, 64–77%) including 3% CR and 67% PR. The disease control rate was 92% (95% CI, 87–95%). Seventy of 140 patients, who had achieved objective response, had progressed or died at the time of data cutoff. The median duration of response was 11.4 months (95% CI, 9.0–not calculable). Out of the 210 patients, 120 (57%) progressed or died. Median PFS was 9.9 months (95% CI, 8.5–12.3 months). There were no differences in ORR in subgroups regarding treatment line, ethnicity, co-occurring EGFR-TKI sensitizing mutation, duration of most recent previous EGFR-TKI, central nervous system (CNS) metastasis at entry, smoking history, and last treatment before this study. PFS did not differ significantly between subgroups regarding line of therapy, presence of CNS metastasis, ethnicity, and mutation status in post-hoc analysis. About three-quarters of osimertinib-treated patients had significantly better QLQ-LC13 (n=85) and QLQ-C30 (n=90) scores at the week 54. A symptom proving worsening of scores was diarrhea. The common grade 3 and 4 adverse events were pulmonary embolism [seven patients (3%)] prolonged electrocardiogram QT [5 (2%)], decreased neutrophil count [4 (2%)], and anemia, dyspnea, hyponatremia, increased alanine aminotransferase, and thrombocytopenia [3 (1%) for each]. Interstitial lung disease (ILD) occurred in 4 (2%) of 210 patients (grade 1, n=2; grade 3, n=1; grade 5, n=1). Six patients required dose reduction. Osimertinib discontinuation due to an adverse event was reported in ten patients (5%). Possibly treatment-related serious adverse events occurred in 11 patients; ILD [2 (1%)], lung infection, thrombocytopenia, dehydration, cerebral infarction, pleurisy, pneumonitis, pulmonary embolism, drug-induced liver injury, jaundice, and pyrexia [1 patient (<1%) for each]. Seven patients died due to the adverse events; pneumonia (n=2), pneumonia aspiration (n=1), rectal hemorrhage (n=1), dyspnea (n=1), failure to thrive (n=1), and ILD. The possibly treatment-related fatal event was ILD (8). AURA2 showed osimertinib was effective and tolerable for patients with *EGFR*-Thr790Met positive NSCLC who progressed on previous EGFR-TKI therapy.

The AURA3 (NCT02151981) is a randomized, international, open-label phase 3 trial comparing the efficacy and the safety of osimertinib with the platinum-based doublet chemotherapy (pemetrexed/cisplatin or carboplatin) as the second line therapy for locally advanced or metastatic NSCLC with *EGFR*-Thr790Met mutation, which has progressed on previous EGFR-TKI. The duration of PFS was longer with osimertinib than with the platinum-based doublet chemotherapy (median, 10.1 *vs.* 4.4 months; hazard ratio, 0.30; 95% CI, 0.23–0.41; P<0.001). Of 144 patients with the central nervous system metastases, the median duration of PFS was longer with osimertinib than with the platinum-based doublet chemotherapy (8.5 *vs.* 4.2 months; hazard ratio, 0.32; 95% CI, 0.21–0.49). The ORR was greater in the osimerinib group (71%; 95% CI, 65–76%) than in the platinum-based doublet chemotherapy group (31%; 95% CI, 24–40%) (odds ratio for objective response, 5.39; 95% CI, 3.47–8.48%; P<0.001). The median response duration was 9.7 months (95% CI, 8.3–11.6 months) in the patients with osimertinib and 4.1 months (95% CI, 3.0–5.6 months) in the patients with the platinum-based doublet chemotherapy. Of the patients with an objective response at the time of data cutoff, the proportion of patients who had disease progression and died was 88 of 197 patients (45%) in the osimertinib group and 36 of 44 patients (82%) in the platinum-based doublet chemotherapy group. At the time of data cutoff, 61 patients had died, including 35 (13%) of 279 in the osimeritinib group and 26 (19%) of 140 in the platinum-based doublet chemotherapy group. The number of the patients with new lesion of CNS was 13 (5%) in the osimeritinib group and 20 (14%) in the platinum-based doublet chemotherapy group. The number of the patients with new lesion of lung was 24 (9%) in the osimeritinib group and 25 (18%) in the platinum-based doublet chemotherapy group. The incidence of adverse events of grade 3 or more was lower with osimertinib than with the platinum-based doublet chemotherapy [63 (23%) *vs.* 64 (47%)]. The most commonly reported adverse events in the patients with osimertinib were diarrhea [113 patients (41%)], rash [94 (34%)], dry skin [65 (23%)], and paronychia [61 (22%)]. The most commonly reported adverse events in

the patients with the platinum-based doublet chemotherapy were nausea [67 patients (49%)], decreased appetite [49 (36%)], constipation [47 (35%)], and anemia [41 (30%)]. The incidence of ILD-like adverse events was 4% (10 patients) in the osimertinib group (grade 1/2, n=9, one death) and 1% (1 patient) in the platinum-based doublet chemotherapy group (grade 3, n=1) (9).

Currently, several trials of osimertinib are ongoing. The randomized, double-blind multinational phase 3 FLAURA (NCT02296125) trial compares osimertinib with erlotinib/gefitinib as the first line therapy in patients with locally advanced or metastatic *EGFR* mutation-positive NSCLC. The primary endpoint is PFS.

For adjuvant therapy, ADAURA (NCT02511106) is a randomized, double-blind multinational phase 3 trial, comparing the efficacy and the safety of osimertinib with those of placebo in patients with EGFR-mutation positive stage IB-IIIA NSCLC following complete surgical tumor resection. The primary endpoint is a disease-free survival.

In the escalation and expansion cohorts of the phase 1 AURA study, genotyping of cell-free plasma DNA (cfDNA) was performed by using BEAMing. Because of the 30% false-negative rate of plasma genotyping, patients with a plasma Thr790Met-negative result who have disease progression after the first line EGFR-TKI need a tumor biopsy to determine Thr790Met status (10). In AURA3 and FLAURA, cfDNA is assessed.

In the phase Ib TATTON (NCT02143466) trial, the combination of osimertinib with the MEK1.2 inhibitor selumetinib, the MET inhibitor savolitinib and the PD-L1 inhibitor durvalumab (MEDI4736) was investigated. The combination of osimertinib and durvalumab was suspended due to high incidence of ILD (11). We recently reported a high incidence of osimertinib-related ILD in Japanese patients who had been treated with nivolumab immediately before osimertinib. Sequential administration of osimertinib immediately after the nivolumab therapy may increase the risk of developing ILD (12).

The therapeutic strategy for patients with *EGFR* mutation-positive NSCLC differs from those without *EGFR* mutation-positive NSCLC. FLAURA and ADAURA may change the therapeutic strategies of the first line and the adjuvant therapy for *EGFR* mutation-positive NSCLC.

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Footnote

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References

1. Lee CK, Brown C, Gralla RJ, et al, Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. J Natl Cancer Inst 2013;105:595-605.
2. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8.
3. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
4. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.

5. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 2013;19:2240-7.
6. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 2014;4:1046-61.
7. Jänne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med 2015;372:1689-99.
8. Goss G, Tsai CM, Shepherd FA, et al. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small cell lung cancer (AURA2): a multizentre, open-label, single-arm, phase 2 study. Lancet Oncol 2016;17:1643-52.
9. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med 2017;376:629-40.
10. Oxnard GR, Thress KS, Alden RS, et al. Association between plasma genotyping and outcomes of treatment with osimertinib (AZD9291) in advanced non-small-cell lung cancer. J Clin Oncol 2016;34:3375-82.
11. Ahn MJ, Yang J, Yu H, et al. 136O: Osimertinib combined with durvalumab in EGFR-mutant non-small cell lung cancer: Results from the TATTON phase Ib trial. J Thorac Oncol 2016;11:S115.
12. Kotake M, Murakami H, Kenmotsu H, et al. High incidence of interstitial lung disease following practical use of osimertinib in patients who had undergone immediate prior nivolumab therapy. Ann Oncol 2016. [Epub ahead of print].

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