Editorial Commentary

Osimertinib in first line setting: for Asian patients

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The discovery of the epidermal growth factor receptor (*EGFR*) gene as the first driver gene in lung cancer has led to a major paradigm shift in lung cancer treatment. Gefitinib and other EGFR-tyrosine kinase inhibitors (TKIs) have demonstrated excellent antitumor activity against EGFR mutation-positive non-small cell lung cancer (NSCLC). However, resistance to TKI emerged over the course of treatment, and resistance due to T790M mutations was noted in approximately half of the cases (1,2).

Subsequently, the efficacy of treatment with osimertinib was confirmed in T790M mutation-positive cases resistant to EGFR-TKI, and further, FLAURA studies reported the usefulness of primary treatment with osimertinib in untreated EGFR mutation-positive cases (3,4).

The FLAURA trial is a randomized controlled trial of osimertinib compared to standard-of-care (gefitinib or erlotinib) to evaluate the efficacy and safety of osimertinib in patients with advanced-stage EGFR mutation-positive lung cancer. In a study of 556 patients, including 62% Asians, the primary endpoint of median progression-free survival (PFS) was 18.9 months in the osimertinib group (n=279) and 10.2 months in the conventional group (n=277), showing a significantly higher PFS with osimertinib in the initial treatment. Our results further highlighted the efficacy of osimertinib as a first-line treatment for EGFR mutation-positive lung cancer.

This study reports an Asian subset analysis of the FLAURA trial. Of the total 556 patients, 323 Asian patients had PFS of 16.5 months in the osimertinib group and 11 months in the standard-of-care group (HR, 0.54; 95% CI, 0. 41 to 0.72; P<0.0001), indicating a significant beneficial effect of osimertinib in Asian patients. Furthermore, osimertinib was almost as safe as the standard-of-care drug in this study, and serious adverse events of Grade 3 or higher were lower (40% *vs.* 48%) than those in the standard-of-care group. We conducted a prospective clinical study of osimertinib (phase II, recurrent EGFR-positive NSCLC, T790M-positive cases, n=36) in elderly patients (75 years of age or older) in Japan, and found that the disease control rate was 93%. Malaise (38.9%) and diarrhea (36.1%) were the common adverse events, but good results have also been observed with regard to efficacy and tolerability in the elderly (5).

The usefulness of EGFR-TKI in Asians has been reported.

The OPTIMAL trial, a randomized controlled trial of chemotherapy and erlotinib for Exon19-deletion or L858R-positive cases conducted at 22 Chinese institutions, reported a significantly better PFS of 13.1 months (4.6 months in the chemotherapy arm) in the erlotinib arm (6). In addition, the PFS of afatinib was 11.1 months overall and 13.8 months in the Japanese population in the LUX-Lung 3 trial, a randomized controlled trial of chemotherapy and afatinib that included approximately 70% Asians. The non-Asian HR of 0.62 (95% CI, 0.36 to 1.06) also did not differ significantly from the Asian HR of 0.45 (95% CI, 0.33 to 0.62) (P=0.62) in terms of overall survival (OS), suggesting a higher efficacy in Asians (7). Regarding afatinib, in a combined analysis of LUX-Lung 6

examining the usefulness of afatinib in Asian regions and the aforementioned LUX-Lung 3, an examination of the OS following standard chemotherapy revealed a significantly longer OS in patients with del19 mutations, suggesting that EGFR-TKI sensitivity varies not only by ethnicity but also by genetic mutation patterns (8,9).

EGFR mutations are reported in 40–50% of lung adenocarcinomas in East Asians but in as low as 15% of North Americans and Europeans, suggesting regional differences in genetic background. A recent study has strongly suggested the use of may have established osimertinib as a primary treatment for EGFR-positive cases, particularly in Asians (10).

Meanwhile, the effectiveness of osimertinib for cases with brain metastasis has been reported. Ballard *et al.* have reported that osimertinib is efficacious in simian models of brain metastases (11). Given these results, the FLAURA trial included a subset analysis of brain metastases and provided valuable prospective data on the treatment of brain metastasis cases with TKIs. Previously, erlotinib, an EGFR-TKI, was suggested to be marginally effective in patients with brain metastases, but the results were not statistically significant (12). Although current data are premature, osimertinib significantly prolonged PFS in patients with brain metastases compared to standard-of-care. However, the number of patients with brain metastases in this Asian cohort was relatively small, about 20%. Despite its seemingly superior efficacy, the difference between the treatment groups was not statistically significant. Furthermore, although the osimertinib group tended to show improved OS, it should be noted that further follow-up reports are pending. Overall, the low transition rates post treatment in the osimertinib group (63%) and in the standard-of-care group (58%), may reflect medical economy in Asia and should be interpreted with caution.

Given the favorable results of the FLAURA trials, the use of the drugs investigated therein as the first-line therapy in patients with positive EGFR mutations will continue to be discussed. The total PFS was expected to be more than 20 months if first-line treatment was initiated with conventional EGFR-TKI and second-line treatment with osimertinib in T790M positive cases (9,13,14). This figure may be greater than the PFS achieved with osimertinib as first-line therapy. In addition, the efficacy of dacomitinib over gefitinib in ARCHER1050 (OS 34.1 *vs.* 26.8 months) suggests that, except for adverse events and tolerability issues, dacomitinib may be the better choice as first-line treatment (15). It has also been suggested that second-generation TKI such as afatinib and dacomitinib are more efficacious than first-generation TKI for cases with uncommon mutations (9).

It has been reported that the incidence of T790M with the use of conventional EGFR-TKI as first-line treatment is similar to, or marginally lower than, that observed with gefitinib, erlotinib, and afatinib as first-line therapy (16,17). The incidence of T790M after dacomitinib administration is unknown and is expected to be reported in the future. Thus, the incidence of T790M influences the selection of the EGFR-TKI for primary treatment. Future studies will focus on predicting T790M-positive cases.

Moreover, the effectiveness of the combined use of various treatments, except for EGFR-TKI, has recently been demonstrated, and the effectiveness and safety of the combined use of immune checkpoint inhibitors (ICI), radiotherapy, and platinum doublet have also been evaluated. The usefulness of combination therapy with gefitinib and platinum doublet has been shown in Japan, and similar effects may be expected with osimertinib (18).

Although programmed cell death ligand 1 (PD-L1) and tumor mutation burden (TMB) were not measured in this study, the efficacy of EGFR-TKI treatment was found to be significantly worse in cases with EGFR mutation positive and PD-L1-tumor proportion score (TPS) of 1% or more (19). Furthermore, atezolizumab significantly improved PFS when used in combination with chemotherapy after EGFR-TKI treatment in EGFR mutation-positive cases (20). Based on these reports, selection of therapeutic agents other than EGFR-TKI may be crucial in patients with elevated PD-L1 expression. For patients with EGFR mutation positivity and a PD-L1 TPS of 1% or more, treatment strategies may include the use of a combination of atezolizumab and platinum doublet after EGFR-TKI therapy and second-line therapy. Thus, the efficacy of ICI as post-treatment in EGFR mutation-positive cases will be noticed in the future. However, the effectiveness of atezolizumab in EGFR mutation-positive patients has not been demonstrated in the OAK study, and further studies are needed.

I am very pleased that this study confirmed the high efficacy and safety of osimertinib in Asians. In the future, it is expected that individualized treatment will become possible upon the establishment of various biomarkers and advancement in comprehensive gene analysis.

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Footnote

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