Editorial

Management of non-small cell lung cancer harboring epidermal growth factor receptor mutations in the era of first-line osimertinib

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Osimertinib (AZD9291, Tagrisso™), a third-generation irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), has brought about rapid transformative changes to the treatment of EGFR-mutation-positive advanced non-small cell lung cancer (NSCLC). After acquiring resistance to first- or second-generation EGFR-TKIs, osimertinib showed greater efficacy than the combination of pemetrexed and platinum-based chemotherapy in patients with the exon 20 T790M resistance mutation in the AURA3 trial (1). More recently, osimertinib has been found to confer superior progression-free survival (PFS) than first-generation EGFR-TKIs in patients with previously untreated, EGFR-mutation-positive NSCLC in the FLAURA trial (2). In the face of the latest clinical findings of these monumental phase III trials, thoracic oncologists are required to reconsider the positioning of osimertinib and further refine the therapeutic strategies for advanced NSCLC patients harboring EGFR mutations. The point that has received the most attention is the optimization of the therapeutic sequences and the choice of a first-line treatment. In a consensus article, Jiang *et al.* (3), on behalf of the AME Lung Cancer Collaborative Group, reviewed the clinical features of osimertinib and offered a perspective on the future directions of EGFR-TKI treatment.

In the FLAURA trial, 556 patients with previously untreated, activating EGFR-mutation-positive (exon 19 deletion or L858R) NSCLC were randomized to receive either osimertinib (80 mg) or a first-generation EGFR-TKI (250 mg of gefitinib or 150 mg of erlotinib) once daily as the standard of care. The median duration of PFS as the primary endpoint was 18.9 months for the osimertinib arm and 10.2 months for the first-generation EGFR-TKI arm [hazard ratio (HR) =0.46; 95% confidence interval (CI), 0.37–0.57; P<0.001]. As the secondary endpoint of interim analysis (25% maturity), the overall survival (OS) rate at 18 months was 83% (95% CI, 78–87) for the osimertinib arm and 71% (95% CI, 65–76) for the first-generation EGFR-TKI arm (HR =0.63; 95% CI, 0.45–0.88; P=0.007), with an early separation of the Kaplan-Meier curves of OS. Adverse events greater than grade 3 were less frequent with osimertinib than the first generation of EGFR-TKIs (34% *vs.* 45%, respectively). In lieu of these results, the consensus article recommended osimertinib as an appropriate first-line treatment for patients with EGFR activating mutations (recommendation level: grade A–). In regard to safety and tolerability, osimertinib is reportedly superior to first- and second-generation EGFR-TKIs (grade A–). Hence, osimertinib has become the standard of care for patients with previously untreated EGFR-mutation-positive NSCLC. However, whether osimertinib is an "absolute" first-line treatment remains debatable because the OS results are premature. Nonetheless, osimertinib absolutely may be acceptable for patients with a poor performance status and the elderly as PFS was longer than that with first-line EGFR TKIs.

On the basis of current available data from the results of various clinical trials, other first-line treatment options

include monotherapies with second-generation EGFR-TKIs, including afatinib and dacomitinib, and combination therapies with platinum doublets or bevacizumab. In the ARCHER 1050 phase III trial, 452 patients with previously untreated, activating EGFR-mutation-positive NSCLC and no brain metastasis were randomly allocated to receive either 45 mg of dacomitinib or 250 mg of gefitinib once daily. The median PFS duration as the primary endpoint was 14.7 months for the dacomitinib arm and 10.2 months for the gefitinib arm (HR =0.59; 95% CI, 0.47–0.74; P<0.001). As the final OS analysis of the ARCHER 1050 trial, Mok *et al.* (4,5) reported a significant improvement in the median OS as the secondary endpoint (34.1 months for the dacomitinib arm *vs.* 26.8 months for the gefitinib arm; HR =0.76; 95% CI, 0.58–0.99; P<0.0438). At the 2018 American Society of Clinical Oncology Annual Meeting, the results of two other phase III trials testing first-line combination therapies were presented. Nakamura *et al.* (6) presented the results of the NEJ009 trial, which evaluated the efficacy of a combination of gefitinib and platinum doublet chemotherapy in 452 patients with previously untreated, activating EGFR-mutation-positive NSCLC who were randomized to receive either 250 mg of gefitinib once daily or a combination therapy of gefitinib (250 mg once daily), carboplatin (area under the curve =5), and pemetrexed (500 mg/m^2 every 3 weeks; GCP). The median PFS1 as the primary endpoint was 20.9 months for the GCP arm and 11.2 months for the gefitinib arm (HR =0.49; 95% CI, 0.39–0.63; P<0.001), whereas PFS2, as another co-primary endpoint, was 20.9 months for the GCP arm and 20.7 months for the gefitinib arm (HR =0.97; 95% CI, 0.77–1.22; P=0.774). Although the trial had not met the primary endpoint according to the Gatekeeping method, the median OS duration, as determined by explanatory analysis, was 52.2 months for the GCP arm and 38.8 months for the gefitinib arm (HR =0.70; 95% CI, 0.52–0.93; P=0.013). Furuya *et al.* (7) presented the interim PFS results of the NEJ026 trial, which evaluated the efficacy of a combination therapy of erlotinib and bevacizumab in 226 patients with previously untreated, activating EGFR-mutation-positive NSCLC who were randomized to receive either erlotinib (150 mg once daily) or a combination therapy of erlotinib (150 mg once daily) and bevacizumab (15 mg/kg every 3 weeks; EB). The median PFS duration as the primary endpoint was 16.9 months for the EB arm and 13.3 months for the erlotinib arm (HR =0.61; 95% CI, 0.42–0.88; P<0.016). Although OS was not reported, an updated analysis of the preceding phase II JO25567 trial found no prolongation of OS in the EB arm (8,9). Anti-vascular endothelial growth factor antibody combined with an EGFR-TKI may be promising to improve efficacy, and clinical trials of ramucirumab, an anti-VEGFR2 antibody, in combination with EGFR-TKIs are underway.

EGFR-TKIs or the combination regimens described above showed a survival benefit in well-conducted phase III studies; thus, both should be considered as new first-line treatment options for patients with EGFR-mutation-positive NSCLC. However, these results, together with those of the FLAURA trial, should be interpreted with caution when applied in actual clinical practice. First, the effects of these regimens on the metastasis to the central nervous system (CNS) are crucial points, as described in the consensus article. Osimertinib is recommended for patients with CNS metastasis either in first- and subsequent-line settings (grade B). In the FLAURA, NEJ009, and NEJ026 trials, 19% (n=53), 22% (n=38), and 32% (n=36) of patients, respectively, in the experimental arms had baseline CNS involvement, and the ARCHER 1050 trial excluded such patients. In a preplanned exploratory analysis in the FLAURA trial, the efficacy and survival benefit of osimertinib were promising for patients with CNS metastasis, in agreement with previous pooled analysis of the phase II AURA and AURA2 trials, as well as subgroup analysis of the AURA3 trial (10,11). The median PFS duration of patients with measurable and/or non-measurable CNS lesions was not reached with osimertinib (n=61) and 13.9 months with first-generation EGFR-TKIs (n=67; HR =0.48; 95% CI, 0.26–0.86; P=0.014), with a greater CNS response and lower probability of CNS progression in the osimertinib arm. These data suggest that the benefits of osimertinib are superior for patients with CNS metastasis than with conventional EGFR-TKIs in first-line settings. In the NEJ009 and NEJ026 trials, a survival benefit of combination therapy was implicated. Although detailed data on the efficacy of these regimens were not reported, the proportion of participants with CNS lesions in these trials was close to that in actual NSCLC patients. Given the promising efficacy of osimertinib against CNS metastasis, combination strategies that include osimertinib as an EGFR-TKI might further improve the survival of patients with EGFR-mutation-positive NSCLC, including those with lesions of the CNS. The combination therapy of osimertinib and bevacizumab is now being investigated in a phase I/II trial of patients with asymptomatic CNS metastasis (NCT0283203). As for dacomitinib, although patients with CNS metastasis were excluded from the

ARCHER 1050 trial, the brain was the primary site of disease progression for more patients in the gefitinib arm (n=11) than the dacomitinib arm (n=1). Although dacomitinib is a potential standard treatment option for this population, further verification with a larger number of patients is warranted. Second, there is no established standard of care for patients harboring uncommon EGFR mutations, which account for approximately 10% of all EGFR mutations (12). The clinical benefits of first-generation EGFR-TKIs are insufficient for uncommon EGFR mutations, and the key phase III trials in the first-line settings described above included only patients with activating EGFR mutations (exon 19 deletion or L858R). In a combined post-hoc analysis of the LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trials (n=75), afatinib was beneficial for those certain types of uncommon EGFR mutations. The median OS duration was 19.4 months for patients with point mutations or duplications in exon 18–21 (n=38; 95% CI, 16.4–26.9 months), 14.9 months for those with the *de novo* T790M mutation of exon 20 either alone or in combination with other mutations (n=14; 95% CI, 8.1–24.9 months), and 9.2 months for those with exon 20 insertions mutations (n=23; 95% CI, 4.1–14.2 months) (13). On the basis of these results, the US Food and Drug Administration approved afatinib for patients with uncommon EGFR mutations. These data and the results of preclinical studies suggest the heterogeneity of uncommon mutations and the potential role of second-generation EGFR-TKIs (e.g., afatinib and neratinib) as a therapeutic strategy. However, there is a significant paucity of prospective data regarding the survival benefit for such populations. In particular, the prognosis of patients with exon 20 insertion mutations is poor. The results of a recent preclinical study implicated that osimertinib may have a wider selectivity margin than afatinib for patients with some forms of exon 20 insertion mutations, as compared with the wild type. At the World Conference on Lung Cancer meeting held in 2018, the preliminary results of a phase II trial of poziotinib, a potent and clinically active inhibitor of EGFR and HER2 exon 20 mutations, were presented. The best overall response rate as the primary endpoint was 55% in the EGFR cohort (n=44) and 50% in the HER2 cohort (n=12). The median duration of PFS as a secondary endpoint was 5.5 months in the EGFR cohort and not-reached in the HER2 cohort (14).

In the second- or subsequent-line setting, osimertinib is an established standard of care for patients with an acquired EGFR T790M mutation after disease progression with the previous use of EGFR-TKIs (grade A, in the consensus article by Jiang *et al.*). Even in the era of first-line osimertinib, the detection of EGFR mutations, including the T790M mutation, plays a significant role in the management of NSCLC patients. In the near future, the same may be also true for those treated with novel second-generation EGFR-TKIs (e.g., dacomitinib) or the combination of TKIs and chemotherapy as a first-line treatment. However, we need to keep in mind the fact that not all patients initially treated with other EGFR-TKIs will benefit from osimertinib. A recent prospective observational study conducted in Japan showed that only one-quarter of the patients eventually became eligible for osimertinib following disease progression with the use of first- or second-generation EGFR-TKIs (15). For patients with acquired resistance to first- or second-generation EGFR-TKIs not based on the EGFR T790M mutation (or did not obtain T790M-positive results), cytotoxic chemotherapy remains an essential option. Also, there is currently no effective targeted therapy for patients who developed resistance to osimertinib either as a first- or subsequent-line treatment. As mentioned in the consensus article, several studies have described the underlying resistance mechanisms, such as the EGFR C797S mutation of acquired resistance to third-generation EGFR-TKIs. A preclinical study suggested conducting a sequential biopsy to determine if the C797S mutation is either cis or trans with the T790M mutation, which could be an important clinical step in the treatment sequence for NSCLC patients harboring EGFR mutations (16). As for immune checkpoint inhibitors (ICIs), subgroup analyses of prior clinical trials suggest that the effect of ICIs might decrease in populations with EGFR mutations (17-19). The cohort of a phase II trial of pembrolizumab for PD-L1-positive previously untreated NSCLC was small, and no patient had responded to treatment; thus, the trial was stopped early. A retrospective analysis conducted at the MD Anderson Cancer Center (Houston, TX, USA) suggested that the efficacy of ICI may be better for patients with uncommon EGFR mutations (20). The CheckMate 722 and WJOG8515L trials are now ongoing to examine the efficacy of ICIs in combination with other agents. Notably, in the subgroup analysis of the Impower 150 trial, the therapeutic benefit of the combination regimen of atezolizumab, bevacizumab, carboplatin, and paclitaxel was superior to that of the combination of bevacizumab, carboplatin, and paclitaxel even in patients with EGFR or ALK genetic alterations (n=108; median PFS duration of 9.7

and 6.1 months, respectively; HR =0.59; 95% CI, 0.37–0.94; P=0.025) (21). These results allude to the potential value of ICIs for patients harboring EGFR mutations to prevent early death within the first 3 months.

The treatment strategy for advanced EGFR-mutant NSCLC is more complex, and several choices are available, including singlet EGFR-TKI, combination strategies of cytotoxic agents, bevacizumab, or ICIs. Hence, thoracic oncologists must redeliberate the optimal sequential strategy in future clinical trials by sensibly taking into account the results of pivotal studies and emerging preclinical evidence.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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