The Role of Osimertinib in Treatment Naïve Epidermal Growth Factor Receptor–Mutated Stage IIIB or IV Non–Small-Cell Lung Cancer Patients

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The epidermal growth factor receptor (EGFR) mutation occurs in about 10% (Western) to 50% (Asian) of patients with locally advanced or metastatic non–small-cell lung cancer (NSCLC).[1] The first-line treatment for these patients with sensitizing EGFR mutation (exon 19 deletion or Leu858Arg mutation) includes reversible EGFR inhibitors like erlotinib, gefitinib, or afatinib as these were found to be superior to platinum-based therapy. In addition to survival benefit, these agents also offer health-related quality of life (QoL).[2,3] However, majority of these patients will eventually progress and osimertinib remains an option for selective number of patients who develop acquired resistance secondary to T790M mutation which overcomes the competitive binding of EGFR-Tyrosine Kinase Inhibitor (TKI) to adenosine triphosphate (ATP).[4]

Osimertinib formerly known as AZD9291 is an oral, third-generation irreversible EGFR-TKI that was developed to selectively inhibit EGFR-TKI sensitizing mutation and the T790M resistance mutation. It has little activity against wild type EGFR and hence a better side effect profile.[5] In preclinical studies, osimertinib was found to be more potent than afatinib in tumors harboring both EGFR L858R and T790M mutation.[5] Osimertinib's activity in the second-line setting has since been proven in phase I/II and phase III studies and has been the standard of care for patients who progress on firstline EGFR-TKI who harbor a T790M mutation.[4,6]

In the *New England Journal of Medicine*, Soria et al[7] report the result of phase III FLAURA study, which evaluated the role of osimertinib in treatment naïve EGFR-mutated stage IIIB or IV NSCLC. A total of 556 patients were randomly assigned in a 1:1 fashion, to either receive oral osimertinib (n = 279) or standard oral EGFR-TKI (either gefitinib or erlotinib, n = 277). There was a substantial improvement in progression free survival (PFS) with osimertinib—18.9 months (95% confidence interval [CI], 15.2-21.4) in osimertinib arm vs 10.2 months (95% CI, 9.6-11.1) in the standard EGFR-TKI arm. Benefit was observed irrespective of age, race, and smoking status. The overall survival (OS) data are yet to mature, and as there was no significant difference in objective response rate and disease control rate between the 2 arms, one may argue that it may not necessarily increase OS. However, we must realize that, PFS still remains an important surrogate marker for OS in NSCLC[8] and a PFS benefit of almost 9 months will most likely produce a clinically meaningful OS benefit. Also, a new brain lesion is an important surrogate marker for worsening OS and QoL.[9] Approximately one-fifth of patients in FLAURA trial had central nervous system (CNS) metastases. Osimertinib is known to have activity in CNS and is superior to platinum-based therapy in patients with known CNS disease. This was demonstrated in AURA-3 trial where osimertinib was compared with platinum-based therapy in second-line setting.[4] FLAURA trial also demonstrates a striking difference in rates of CNS progression between osimertinib arm and EGFR-TKI arm (6% vs 15%). Skin rash or acne, diarrhea, dry skin, paronychia, stomatitis, and pyrexia were common adverse effects from osimertinib and mostly were mild. Serious adverse events were reported in 22% of patients in osimertinib arm and 25% in the EGFR-TKI. Fatal adverse events occurred in 6 patients (2%) in osimertinib arm. Adverse effects of grade 3 or higher were less frequent with osimertinib than with standard EGFR-TKI arm. Mutation analysis for T790M was not done in the patients enrolled in this trial and we do not know if the patients who had significantly prolonged PFS compared with standard oral EGFR-TKI had concurrent EGFR T790M mutation in addition to the EGFR L858R mutation. De novo EGFR T790M mutations although are rare and occurs in <1% of all lung cancers and approximately 2% of all *EGFR*-mutant lung cancers.[10]

In treatment naïve EGFR-mutated NSCLC, various trials utilizing erlotinib or gefitinib showed median PFS from 9 to 13 months,[11,12] which is similar to the observed PFS (10.2 months) in the standard EGFR-TKI arm in FLAURA

trial depicting consistently similar efficacy of standard EGFR-TKI. It is important to note that, FLAURA trial only included patients with World Health Organization (WHO) performance status of either 0 or 1. Few randomized trials utilizing EFGR-TKI had included patients even with worse performance status.[12,13]

Second-generation EGFR-TKI have shown to improve PFS but at the expense of increased toxicity. In phase 2, LUX-Lung 7 study, afatinib was compared head-to-head with gefitinib in treatment naïve patients. Afatinib did not result in meaningful PFS or OS benefit.[14] More recently, Yi-Long Wu and colleagues presented the result of the ARCHER 1050 trial, where dacomitinib was compared head-to-head with gefitinib in treatment naïve EGFR-mutated NSCLC. Median PFS was 14.4 months in the dacomitinib arm vs 9.2 months in the gefitinib arm. This PFS benefit is much less than the median PFS offered by osimertinib in the FLAURA study. Also, dacomitinib was clearly more toxic than gefitinib: significant grade 3 or 4 dermatitis (14% vs none) and diarrhea (8% vs 1%). A total of 63% of patients had grade ⩾3 adverse effects, 9% of patients had serious treatment-related adverse events, and 10% of patients had treatment-related deaths in dacomitinib arm raising some concern about drug safety and overall QoL.[15]

The financial burden should be an important consideration factor while using it in the firstline setting. Wu et al[16] conducted a mathematical model to evaluate cost-effectiveness of osimertinib for EGFR-mutated NSCLC after disease progression on standard EGFR-TKI. Osimertinib yielded more positive health-related outcomes compared with chemotherapy but this benefit was associated with a substantial augmentation of cost with an average incremental cost-effectiveness ratio higher than $200 000 in the United States. On the contrary, if we consider using it sequentially after progression on standard EGFR-TKI, subset of patient will be lost due to global deterioration of health from disease progression. The APPLE trial will possibly solve this dispute (upfront vs sequenced strategy). In addition, the trial will also explore the potential mechanism of acquired resistance to osimertinib.[17] Various trials are underway to evaluate the role of combination therapy with osimertinib (including check point inhibitor, bevacizumab, gefitinib, and dasatinib). Hopefully with the combination therapy, we can overcome resistance and produce a durable response.

In summary, osimertinib has impressive median PFS of 18.9 months, favorable side effects profile, and decreased rates of CNS progression but several questions remain unanswered regarding the use of osimertinib in the firstline setting vs using it at the time of disease progression. Does PFS benefit translate to OS benefit? Is osimertinib better than standard EGFR-TKI for improving Q-TWIST (Quality-adjusted Time without Symptoms of Toxicity)? Is osimertinib alone sufficient to treat CNS disease and if not, is it safe to use it with radiation? Where are we in developing a targeted agent for patients who progress on osimertinib? Nevertheless, a debate has started, and we do not have a clear guidance yet to support upfront treatment with osimertinib.

Author Contributions

DU, AB, YV and LA contributed equally to the manuscript.

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