Editorial

Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients with EGFR inhibitor—resistant non-small cell lung cancer

Tao Jiang, Caicun Zhou

Department of Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai 200433, China
Correspondence to: Caicun Zhou. Shanghai Pulmonary Hospital, 507 Zhengmin Road, Yangpu District, Shanghai 200433, China.
Email: caicunzhoudr@163.com.

Abstract: The first generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are effective in advanced non-small cell lung cancer (NSCLC) with EGFR mutations. Unfortunately, disease progression generally occurs after 9 to 14 months of targeted therapy. The substitution of threonine with methionine at amino acid position 790 (T790M), as the second mutation in EGFR, is the most common resistance mechanism and is detected in tumor cells from more than 50-60% of patients after disease progression. However, current targeted therapeutic strategies for patients with acquired resistance are limited. This has led to the development of "third generation" EGFR-TKIs that are designed to target T790M and EGFR-TKI sensitizing mutations more selectively than wild-type. AZD9291, as a mono-anilino-pyrimidine compound, is a novel, irreversible EGFR-TKI, has proved to be more effective against both EGFR-TKI sensitizing and resistance T790M mutations in preclinical models. This phase I clinical study showed that AZD9291 has robust efficacy and is well tolerated in EGFR mutant NSCLC patients with acquired resistance to EGFR-TKIs.

Keywords: Epidermal growth factor receptor mutation (EGFR); tyrosine kinase inhibitor (TKI); non-small cell lung cancer (NSCLC); T790M

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Lung cancer still remains the most common cancer-related mortality worldwide with about 80-85% patients suffering from non-small cell lung cancer (NSCLC) (1). More than 80% of NSCLC cases are in advanced stage (IIIB or IV) when diagnosed, which systemic chemotherapy could just provide marginal improvement in survival. The first generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), including gefitinib and erlotinib, have proved to be effective in advanced NSCLC patients whose tumors harbor recurrent somatic activating mutations (2-5). These mutations are commonly observed in the exons encoding the kinase domain of EGFR, such as small multi-nucleotide in-frame deletions in exon 19 (Del 19) and a point mutation in exon 21 with the substitution of leucine for arginine at position 858 (L858R) (6). Unfortunately, despite the impressive initial response to treatment, disease progression generally occurs after 9 to 14 months of erlotinib or gefitinib therapy. Moreover, the adverse effects, including skin rash and diarrhea, are due to the non-selective inhibition of wild-type EGFR in skin and gastrointestinal tissue.

The second mutation in EGFR, resulting in the substitution of threonine with methionine at amino acid position 790 (T790M) is the most common resistance mechanism and is detected in tumor cells from more than 50-60% of patients after disease progression (7,8). Current targeted therapeutic strategies for patients with acquired resistance are limited. Second generation irreversible EGFR-TKIs such as afatinib (9) and dacomitinib (10) are effective in untreated EGFR mutant lung cancer. However, as monotherapy, they have failed to overcome T790M-mediated resistance in patients with NSCLC. Therefore, there remains a significant unmet need for EGFR-TKIs that can more effectively target T790M tumors while sparing the

activity of wild-type EGFR. This has led to the development of "third generation" EGFR-TKIs that are designed to target T790M and EGFR-TKI sensitizing mutations more selectively than wild-type EGFR. AZD9291, as a mono-anilino-pyrimidine compound, is a novel, irreversible EGFR-TKI, whose structure and pharmacology are distinct from other third generation EGFR-TKIs including CO-1686 and WZ4002 (11-13). It has proved to be more effective against both EGFR-TKI sensitizing and resistance T790M mutations in preclinical models.

Based on these developments, the phase I study of AZD9291 in EGFR mutant NSCLC patients (14) was presented by Pasi and coworkers at the Annual Meeting of American Society of Clinical Oncology. One hundred and ninety-nine NSCLC patients, with acquired resistance to EGFR-TKIs, were enrolled in a multicenter trial into dose escalation and expansion cohorts. AZD9291 was administered orally, at doses of 20-240 mg once daily. The results showed that overall response rate (ORR) was 51% (91/177). The ORR in 89 EGFR T790M positive patients was 64% (95% CI: 53%, 74%) and in 43 EGFR T790M negative patients was 23% (95% CI: 12%, 39%).The overall disease control rate in T790M positive patients was 96% (85/89). Adverse effects consisted mainly of diarrhea, rash and nausea. Most common adverse events (≥15%) were mostly CTCAE Grade 1. However, Grade 3/4 AEs occurred in 16% of patients. No dose limiting toxicities were observed since the selective inhibition of mutant EGFR instead wild-type EGFR in skin and gastrointestinal tissue. AZD9291 proved to be clinically effective by the higher ORR (51%) in NSCLC patients with positive EGFR T790M and higher overall disease control rate (96%) in T790M positive patients. Moreover, RECIST responses were observed at all dose levels and in brain metastases. Therefore, the current report demonstrates that AZD9291 has robust efficacy and is well tolerated in EGFR mutant NSCLC patients with acquired resistance to EGFR-TKIs.

The first generation TKIs have sometimes the unavoidable and unacceptable adverse effects, since the non-selective inhibition of wild-type EGFR in skin and gastrointestinal tissue. AZD9291 has the high selectivity of mutant EGFR. In the phase I study, no dose limiting toxicities were observed. Most common AEs are acceptable. Therefore, it will overcome these limitations and improve markedly the treatment options to patients who have progressed on TKI treatment due to T790M. Other third generation TKIs, including CO-1686 and WZ4002 have also presented with impressive efficacy and are thus under development in phase I to III studies which will be presented to us in the not too distant future. Thus, the present abstract on the clinical efficacy of AZD9291 is one more part of the fascinating results successfully linking the high selectivity to mutant EGFR, which could be more beneficial to the clinical control of EGFR mutant NSCLC.

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