Editorial

AZD9291 in epidermal growth factor receptor inhibitor—resistant non-small-cell lung cancer

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Abstract: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in advanced *EGFR* mutant non-small cell lung cancer have an objective response rate (ORR) of approximately 60–70% and a median progression free-survival (PFS) of approximately 10-13 months. Studies of tumor biopsies performed after progression on EGFR TKI revealed that 50-60% of EGFR mutant NSCLC developed an EGFR exon 20 T790M mutation as a mechanism of acquired resistance. AZD9291 is a third generation irreversible EGFR TKI with activity against the activating *EGFR* mutation, the T790M acquired resistance mutation, and relative sparing of the wild-type EGFR. AZD9291 was investigated in a phase I trial with expansion cohorts in patients with disease progression after EGFR TKI. Patients with and without detectable T790M mutations were enrolled in the trial. The ORR in patients with centrally confirmed and without detectable T790M mutations was 61% (95% CI, 52–70%) and 21% (95% CI, 12–34%), respectively. The PFS observed in patients with centrally confirmed and without detectable T790M mutations was 9.6 months (95% CI, 8.3 to not reached) and 2.8 months (95% CI, 2.1–4.3 months), respectively. At the dose for further investigation, 80 mg daily, the rate of all grade 3-5 drug related adverse events was 11%, and the rates of grade 3 diarrhea and rash were 1% and 0%, respectively. The identification of the T790M resistance mutation and the subsequent development of an agent against the mechanism of resistance provide a template for future drug development for acquired resistance to targeted therapy.

Keywords: Epidermal growth factor receptor mutation; tyrosine kinase inhibitor (TKI); novel therapy; clinical trial

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The identification of epidermal growth factor receptor (*EGFR*) activating mutations, and the subsequent development of EGFR tyrosine kinase inhibitors (TKIs) as first-line therapy for advanced *EGFR* mutant NSCLC represents a fundamental change in the treatment and drug development paradigms. In phase III trials first-line treatment with EGFR TKI's in patients with *EGFR* exon 19 deletions and exon 21 L858R point mutations results in an objective response rate (ORR) of approximately 60-70% and a median progression-free survival (PFS) of approximately 10-13 months. Studies have analyzed the cancer molecular characteristics after progression on EGR TKI's and the most common mechanism of resistance is the *EGFR* exon 20 T790M mutation which is detected in 50-60% of tumor samples (1,2). The T790M mutation increases the tyrosine kinase affinity for adenosine triphosphate (ATP) and consequently reduces the competitive binding of the EGFR TKI to the tyrosine kinase (3). Unfortunately increasing the dose of first-generation or the use of irreversible EGFR TKI's has not been effective in overcoming the acquired resistance by the T790M mutation and causes toxicities related to the EGFR TKI activity on wild-type EGFR on normal tissues, most notably the skin and gastrointestinal tract. Current EGFR TKI's utilized a quinazoline-base and are ATP-competitive inhibitors of binding to EGFR tyrosine kinase. Pyrimidine EGFR TKI's are 30-100 times more potent against the EGFR T790M mutation, are 100 times less potent against the EGFR wild type, and retain activity against the activating EGFR mutation (4).

AZD9291 is a pyrimidine compound that is a potent

irreversible EGFR inhibitor by targeting the cysteine-797 residue in the ATP biding site via covalent binding (5,6). AZD9291 demonstrated significant activity in *EGFR* mutant and *EGFR* mutant/T790M mutant cell lines as well as xenograft and transgenic models (6). This agent was investigated in a phase I trial with expansion cohorts in patients with *EGFR* mutant advanced NSCLC who had experienced disease progression on EGFR TKI (7). Patients with and without confirmed T790M were eligible in the dose escalation phase, but only patients with a confirmed T790M mutation by central testing were eligible for the expansion cohorts. The dose of AZD9291 was escalated from 20 mg daily to 240 mg once daily, and at the 240 mg dose level the rates of all grade diarrhea and rash were numerically higher due to inhibition of the wild-type EGFR. AZD9291 80 mg daily will be used in future clinical trials based on preclinical data, similar ORR across the different dose levels, and the rate of adverse events. At 80 mg daily the rates of all grade and grade 3 diarrhea were 33% and 1%, respectively and the rates of all grade and grade 3 rashes were 32% and 0%, respectively. The rate of grade 3-5 drug-related adverse events at 80 mg daily was 11%. Other adverse events of interest in the entire study population were 6 patients experienced pneumonitis-like events, 6 patients developed hyperglycemia, and 11 patients had prolongation of the corrected QT interval. The ORR observed in the entire study patient population was 51% (95% CI, 45–58%), and the ORRs among patients with a centrally confirmed T790M (n=127) and without detectable T790M mutation (n=61) were 61% (95% CI, 52–70%) and 21% (95% CI, 12–34%), respectively. The median PFS in patients with and without a centrally confirmed T790M was 9.6 months (95% CI, 8.3 to not reached) and 2.8 months (95% CI, 2.1-4.3 months), respectively.

AZD9291 clearly demonstrated activity and a favorable toxicity profile in patients with *EGFR* mutant NSCLC who had progressed on an EGFR TKI, and approval by regulatory agencies is anticipated in the near future. The development of AZD9291 demonstrates that a better understating of the molecular biology of NSCLC will result in a more rational and efficient drug development process. This study has answered several important questions, but as with any scientific advance it has created several new questions. The ORR and PFS observed in the T790M mutation negative patient population is intriguing and potentially explained by retreatment effect, lack of sensitivity in the T790M mutation testing, or activity of AZD9291 in the T790M negative patient population. However, the efficacy of AZD9291in the T790M negative patient population is similar to chemotherapy alone in a recent phase III trial of patients who have progressed after EGFR TKI (8). Additional trials in the T790M negative patient population will be required before AZD9291 can be considered an advance in this patient population. If the initial use AZD9291 will be restricted to patients with a confirmed T790M mutation then it will necessitate a repeat biopsy at the time of disease of progression on EGFR TKI therapy. In some patients repeat biopsies or biopsy of the areas of disease progression is not feasible, the disease progression is in the bone which prevents accurate mutational analysis, or the repeat biopsy sample is insufficient for molecular testing. The development of cell-free tumor DNA testing from peripheral blood samples that can detect the T790M mutation would be a significant advance and potentially avoid biopsies, detect T790M missed on standard tumor biopsies or in patients with disease not amendable to biopsy (9,10). The most likely clinical scenario would be patients with a T790M detect using cell-free tumor DNA could forgo biopsy while patients who do not have a T790M detected on cell-free DNA testing would undergo biopsy to confirm the absence of a T790M mutation and investigate for other mechanisms of resistance. The future development of this method of testing could make these agents more widely utilized and reduce the burden of repeat biopsies on patients.

While the efficacy results are preliminary it is clear from the Kaplan-Meier curve for PFS that the majority of patients will experience disease progression and preliminary studies have been performed investigating the mechanisms of resistance to AZD9291. Using cell-free DNA collected from 15 patients who developed resistance at AZD9291, six cases of an acquired the resistance mutation C797S, a cysteine point mutation which is believed to block drug binding, were detected; five cases retained the T790M mutation and did not acquire the C797S mutation, and four cases with loss the T790M mutation while retaining the underlying EGFR activating mutation (11). This small study illustrates the role cell-free DNA in investigating the mechanisms of resistance, and suggests that there will be multiple mechanisms of resistance to AZD9291 and some patients will have disease progression with T790M negative disease. The early investment in collection of tumor and plasma samples in patients who have progressed on AZD9291 will accelerate that development of the next generation of EGFR TKI, and the most obvious target will be agents active against the C979S resistance mutation.

The trial of AZD9291 and the phase I/II trial of rociletinib (CO-1686) in patients with *EGFR* mutant NSCLC were published simultaneously (12). These two agents are frequently thought of together as third generation EGFR TKIs for convenience and inevitably compared to one and another. At this point the ORR and PFS in the *EGFR* mutant T790M patient population appear similar, and the efficacy data are limited by small sample size and are relatively immature. Thus, it would be hazardous to conclude that one agent has superior efficacy based on the data available and the inherent problems with cross trial comparisons. The rates of the adverse events of hyperglycemia and QT prolongation are numerically higher with rociletinib than AZD9291 which may influence some physician's and/or patient's preference for one agent. Both agents will be used clinically and represent a significant advance in the treatment in patients with *EGFR* mutant and T790M mutations.

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Footnote

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