Editorial

AZD9291 in TKI *EGFR* resistance in non-small cell lung cancer and the new concept of phase I trials

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Abstract: Epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors (TKIs) constitute the standard of care for stage IV EGFR mutated non-small cell lung cancer (NSCLC) patients initiating first-line systemic treatment. Despite the initial remarkable activity of targeted treatment in these patients rendering objective response rates (ORR) of 50–80% and progression-free survivals (PFS) of 9–12 months, most patients present disease progression during the first 12 to 24 months. Although the activity of platinum-based doublets has been shown in EGFR mutated NSCLC patients after progression to first-line TKIs, PFS is rather short. Drug development companies have more recently focused their attention on the molecular basis of EGFR TKIs acquired resistance. Secondary resistance mutations have proven to be the most frequent cause of acquired resistance. Among them, T790M mutation in exon 20 seems to be the leading responsible for that resistance. Several agents have shown preliminary preclinical and clinical activity in overcoming acquired resistance to firstline EGFR TKIs. To date, however, only AZD9291, an oral, potent, irreversible EGFR TKI that is selective for EGFR tyrosine kinase inhibitor–sensitizing mutations and the T790M resistance mutation has shown to be not only highly active but also fairly tolerable in a large cohort of patients. Here we present a critical analysis of this trial in its clinical setting and propose some future directions.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR) mutation; AZD9291; acquired resistance; T790M

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In the old days, a well-designed phase I clinical trial evaluating safety and efficacy of a certain non-targeted compound in cancer population constituted more likely a necessary step in drug development but with a low potential for addressing really meaningful clinical activity. In fact, the total number of patients enrolled in those early dose-finding studies was often low, restricting the ability of the trial to make a decision exclusively on whether the drug had to be further evaluated in a phase II/III clinical trial or not.

In the last several years, however, drug development has experienced a dramatic change when evaluating new targeted agents in cancer therapy. It is not uncommon to observe, in some of those trials, a remarkable activity in terms of objective response rates (ORR) and unprecedented improvements in progression-free survival (PFS). In part, that achievement has been due to the new designs used for targeted agents' trials. The so-called umbrella design results especially useful to test the effect of a specific targeted agent on different genomic alterations in a single cancer type.

The article published by Jänne *et al.* (1) reports the preliminary results of the AZD9291 first time in patients ascending dose study (AURA). This phase I/II study probably represents one of those outstanding clinical trials evaluating targeted agents in which a real unmet clinical practice need [in this case, a really active second-line epidermal growth factor receptor (EGFR)-tyrosine-kinase

inhibitors (TKI) after progression to first-line TKI] finally meets a potential answer in a new drug (AZD9291) showing a great balance between clinical benefit and toxicity. In fact, AZD9291 has been granted breakthrough therapy designation, orphan drug and fast track status by the US Food and Drug Administration (FDA) early this year.

AZD9291 is an oral, potent, irreversible, EGFR-TKI that is selective for EGFR-TKI sensitizing mutations and the T790M resistance (2). The AURA trial tested AZD9291 at doses of 20 to 240 mg once daily in 253 patients with advanced *EGFR* mutated non-small cell lung cancer (NSCLC) with radiologically documented disease progression after previous treatment with EGFR-TKIs. It included a dose-escalation cohort (31 patients) and a dose-expansion cohort (222 patients) and tried to address safety, pharmacokinetics and efficacy. The trial design can be considered a variation of an umbrella design trying to define the effect of AZD9291 on different *EGFR* mutations including T790M in a single cancer type.

Of the 239 non-selected patients evaluable for response, 123 (51%) experienced a confirmed partial response (PR) (122 patients) or a complete response (one patient), 78 (33%) had stable disease, 34 (14%) showed progressive disease, and 4 (2%) could not be assessed for response. The disease control rate (DCR) including complete response, PR, or stable disease was as high as 84%. Interestingly enough, of 127 selected patients evaluable for response harboring *EGFR* T790M tumors confirmed by central testing the ORR was 61% (78 of the 127 patients), and the DCR was 95% (121 of the 127 patients). In contrast, of 61 patients with no detectable *EGFR* T790M who were evaluable for response, the ORR was 21% (13 of the 61 patients), and the DCR was 61% (37 of the 61 patients).

Other remarkable finding was that among the 105 patients in the expansion cohorts who showed a confirmed response, 85% had a response duration of 6 months or longer with a median PFS of 8.2 months. When selecting the subgroup of patients with detectable *EGFR* T790M, 88% of them had estimated response duration of 6 months or longer, with a median PFS of 9.6 months among all 138 patients with that mutation. On the contrary, although among patients with no detectable *EGFR* T790M, 69% of the patients experienced estimated response duration of 6 months or longer, the median PFS was only of 2.8 months.

Concerning the dose, different doses were not associated with significant differences in ORR. However, although AZD9291 treatment was generally associated with mild skin and gastrointestinal adverse effects, at the 160 and 240 mg dose levels, there was an increase in the incidence and severity of adverse events associated with inhibition of non-mutant *EGFR*, including rash, dry skin, pruritus, and diarrhea. In authors' opinion, this may indicate that at higher dose levels, AZD9291 may start inhibiting wild-type *EGFR* more significantly in patients.

A clear limitation of this early report is that the data are still immature (30% maturity) and a further follow up is required.

In addition, other questions remain unsolved. For example, one relevant issue is that the central nervous system (CNS) frequently constitutes the initial failure site after clinical benefit with EGFR-TKIs (3). In the article by Jänne *et al.* (1), no information about the site of progression is available, probably due to the immaturity of the data requiring more events in order to analyze different subgroups. It will be of great interest to find whether AZD9291 is able to cross the brain-blood barrier and prevent from CNS progression or not.

Recently, the implementation of liquid biopsies in monitoring patients with tumors harboring driver mutations has shown to be feasible and of great clinical interest. In NSCLC, circulating tumor plasma DNA has been used for *EGFR* sensitizing and resistance mutation dynamic monitoring showing not only to provide prognostic information but also to result of predictive value (4,5). Moreover, those studies have shown that the detection levels of both activating and resistance mutations can substantially vary during EGFR-TKI treatment associated to clinical outcomes. Potential variations of the detection of T790M in free plasma DNA during AZD9291 treatment and their clinical implications should be prospectively addressed in future clinical trials.

Currently, the phase II, *AZD9291 Open Label Study in NSCLC after Previous EGFR TKI Therapy in EGFR and T790M Mutation Positive Tumors (AURA2)*, clinical trial is ongoing. Its primary goal is to assess the safety and efficacy of AZD9291 (80 mg, orally, once daily) in patients with a confirmed diagnosis of *EGFR* mutation positive and T790M mutation positive NSCLC, who have progressed following prior therapy with an approved EGFR-TKI agent (6). Patients must agree to provide a biopsy for central confirmation of T790M mutation status following confirmed disease progression on the most recent treatment regimen. The primary objective of the study is to assess the efficacy of AZD9291 by assessment of ORR according to RECIST v1.1 by an independent central review. The results

from this study may help to elucidate some of the remaining questions.

Moreover, AURA3 (7) is a global, multicenter, phase III, open-label study comparing the efficacy of AZD9291 with platinum-based chemotherapy (CT) as second-line treatment in patients with progressing advanced/metastatic T790M positive NSCLC, with documented *EGFR* mutations, who have received prior EGFR-TKI therapy. The study will recruit approximately 610 CT-naïve patients. Patients will be randomised 2:1 to receive AZD9291 (80 mg, orally, once daily) or platinum-based doublet CT (pemetrexed 500 mg/m^2 + carboplatin AUC5 or pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2; up to six cycles) in accordance with institutional guidelines on day 1 of every 21-day cycle. The primary objective is to compare the efficacy of AZD9291 *vs.* CT with the primary endpoint of PFS assessed according to RECIST v1.1.

Interestingly, a randomized, phase III study called FLAURA comparing AZD9291, *vs.* gefitinib or erlotinib in treatment-naïve patients with advanced NSCLC showing EGFR-TKI sensitizing mutations has been recently opened to accrual (8). The primary objective is to compare PFS for AZD9291 to standard of care EGFR-TKI. PFS in patients with tumors harboring T790M is a key secondary objective.

Finally, other new compound has shown promising activity in T790M positive NSCLC patients. A phase I/II study evaluated the safety and efficacy of rociletinib (CO-1686) in 130 patients with *EGFR* mutated advanced NSCLC who had experimented disease progression during previous treatment with first or second generation EGFR-TKIs showing similar results to AZD9291 (9). The analysis included patients who received the free-base form (900 mg twice daily) or hydrogen bromide salt (HBr) form (500–1,000 mg twice daily). Efficacy results showed that among the 47 patients with a detectable T790M mutation who could be evaluated for response, ORR was 59%, DCR was 93% and the median PFS was 13.1 months, whereas among 17 patients lacking the T790M mutation available for evaluation of response, ORR was 29%, DCR was 59% and median PFS was 5.6 months. Future clinical trials comparing AZD9219 and CO-1686 in different clinical settings are warranted.

In conclusion, acquired resistance to EGFR-TKIs represents a crucial issue for EGFR mutated NSCLC patients receiving first-line targeted therapy. EGFR T790M resistance mutation is the most frequent responsible for this clinical issue. T790M mutation can be overcome by new compounds. AZD9291 shows an outstanding clinical activity with limited and predictable toxicity. Currently ongoing phase II and III clinical trials further evaluating its activity in second and first-line settings should address some of the remaining questions about the drug dosing and its clinical activity at the CNS.

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Footnote

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