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Targeting *EGFR* T790M in Advanced Adenocarcinoma of the Lung

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Abstract

The tyrosine kinase inhibitors (TKI) against epidermal growth factor receptor (*EGFR*) are widely used in patients with non-small cell lung cancer (NSCLC). However, *EGFR* T790M mutation leads to resistance to most clinically available *EGFR* TKIs including Gefitinib and erlotinib. Third-generation *EGFR* TKIs against the T790M mutation have been developed and they are in active clinical development. These agents include osimertinib, rociletinib, HM61713, ASP8273, EGF816 and PF-06747775. Osimertinib and rociletinib have shown clinical efficacy in phase I/II trials in patients who had acquired resistance to first- or second-generation TKIs. Osimertinib (AZD9291, TAGRISSO) was recently approved by FDA for metastatic *EGFR* T790M mutation-positive NSCLC. HM61713, ASP8237, EGF816, and PF-06747775 are still in early clinical development. We are discussing the emerging role of 3rd generation anti-*EGFR* in the treatment of locally advanced and metastatic adenocarcinoma of the lung.

Keywords: Adenocarcinoma, lung, *EGFR*, T790M

Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers with 5-years survival rate of less than 5% in advanced cases. The activating mutations of epidermal growth factor receptor (*EGFR*) occur in approximately 10–15 % of NSCLC cases in Caucasian patients and approximately 30–40 % in East Asian patients [1,2]. The first- and second-generation *EGFR* tyrosine kinase inhibitors (TKI), erlotinib, gefitinib, and afatinib, have been widely used in advanced cases of adenocarcinoma presented with mutations in exon 19 and/or exon 21 [3,4]. However, acquired resistance to these inhibitors frequently develops after a median of 8-12 months [5-7]. The common acquired *EGFR* mutations with clinical implications are exon 19 deletions (del19), L858R mutation, and the T790M mutation [2]. Cell lines harboring these mutations have been used for screening novel agents targeting these mutations [8]. The *EGFR* T790M mutation was present in approximately 50 to 60 % of resistant cases [9,10]. The median survival is less than 2 years after the emergence of T790M mutation [9]. Recently, the third-generation *EGFR* inhibitors, AZD9291 (osimertinib, mereletinib), CO-1686 (rociletinib), HM61713 (BI 1482694), ASP8273, EGF816 and PF-06747775, have emerged as potential therapeutics to block the growth of *EGFR* T790M-positive tumors [11-13]. More importantly, unlike the first- and second-generation *EGFR* TKIs, the third-generation TKIs have a significantly increased potency for *EGFR* mutants than for wild-type *EGFR*.

AZD9291 (osimertinib, mereletinib, tagrisso)

AZD9291 is structurally different from the first- and second-generation *EGFR* TKIs. This compound is an irreversible mutant-selective *EGFR* TKI. It is the only approved *EGFR* TKI currently indicated for patients with metastatic *EGFR* T790M mutation-positive NSCLC [14]. AZD9291 has been examined in the first-line treatment in an expansion cohort from AURA trial, doses of 80 or 160 mg/day were administered to 60 treatment-naïve patients with *EGFR*-mutated advanced NSCLC at the time of inclusion [15]. The median age of the patients was 63.5, stable brain metastasis was allowed. *EGFR* mutation subtypes included *EGFR* exon 19 deletion (37%), *EGFR* exon 21 L858R (40%), other *EGFR* sensitizing mutations (3%) and T790M in 8% of patients. ORR at the cutoff date was 70% (95% CI 57–81). A third of the patients had grade ≥3 adverse events, mainly including skin rash and diarrhea. These results appeared to be promising but clearly preliminary.

An ongoing first-line phase III trial is comparing the efficacy and safety of AZD9291 (80 mg/day) in combination with gefitinib or erlotinib in patients with common *EGFR* mutations. The primary end point is PFS, and the secondary end points include assessment of PFS by pretreatment T790M mutation status and by *EGFR* mutation subtype (exon 19 deletion or L858R) detected in circulating

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tumor DNA. Patients were allowed to cross over to AZD9291 after disease progression in the control arm. Using *EGFR* mutant cell lines, investigators discovered additional resistance mechanisms, such as NRAS and KRAS mutations and over expression. A combination of AZD9291 with the MEK inhibitor, selumetinib, was shown to cause regression of AZD9291-resistant tumors in an *EGFR*m/T790M transgenic model [16].

Rociletinib (CO-1686)

Rociletinib is another novel, oral, irreversible mutant-selective inhibitor of commonly mutated forms of *EGFR* (exon 19 deletion, L858R and T790M). Preclinical studies have shown that rociletinib has minimal activity against wild-type *EGFR* [12]. A phase I/II study of rociletinib was done in patients with *EGFR*-mutated NSCLC with acquired resistance to first- or second-generation *EGFR* inhibitors [17]. In the phase II part of the study, patients with NSCLC positive for *EGFR* T790M received rociletinib at doses of 500, 625, or 750 mg twice daily. At the time of report, 130 patients were enrolled. MTD was not identified. One common DLT was hyperglycemia. Among the 46 patients with T790M-positive disease who could be evaluated, the ORR was 59% (95% CI 45 to 73). For the 17 patients with T790M-negative disease, the ORR was 29% (95% CI 8 to 51). Therefore, rociletinib was active in NSCLC patients with *EGFR* T790M mutation.

HM61713 (BI 1482694)

HM61713 is an irreversible kinase inhibitor and covalently binds to a cysteine residue near the kinase domain of mutant *EGFR*. HM61713 has a half-life of over 24 h for *EGFR* inhibition [18]. This compound caused potent inhibition in cell lines H1975 (L858R and T790M) and HCC827 (exon 19 deletion). In the phase II expansion part of the study, 800 mg QD was the dose given to patients with centrally confirmed T790M-positive NSCLC. In the latest update, 173 patients were enrolled, including 55 in the phase I and 118 in the phase II cohorts. Eight hundred milligrams once daily was the MTD. DLTs mainly involved GI symptoms and elevation of aspartate aminotransferase, alanine aminotransferase, amylase, and lipase. The ORR was 58.8% in the 34 patients who received HM61713 with a dose more than 650 mg. In addition, ten patients had unconfirmed partial responses, and 13 achieved disease stabilization [13]. Therefore, HM61713 represents another promising agent for patients with T790M-positive NSCLC.

EGF816

EGF816 is another third-generation covalent *EGFR* inhibitor that has potent inhibitory activity against activating (L858R, del19) and resistant T790M mutants with low IC_{50} in various cellular assays [11]. In mouse xenograft models, EGF816 was better than earlier generation *EGFR* inhibitors. A phase I multicenter, dose escalation study of EGF816 enrolled NSCLC patients with confirmed T790M status. The starting dose was 75 mg daily. The doses were escalated according to an adaptive Bayesian logistic regression model. At the cutoff date of 26 January 2015, 57 patients were treated across six cohorts (75, 150, 225, 300, and 350 mg for capsules; 225 mg for tablets). Diarrhea, stomatitis, rash, and pruritus were the most common AEs. ORR was 54.5% in 22 evaluable patients.

Resistance to 3rd generation anti *EGFR*

New mutations to induce resistance to 3rd generation anti *EGFR* were documented including C797S which is the major mutation behind resistance to AZD9291.the former mutation may arise within 6-9 months of treatment in patients with T790M [19].

Conclusion

Osimertinib (AZD9291, TAGRISSO) was recently approved by FDA for metastatic *EGFR* T790M mutation-positive NSCLC. The other inhibitors are still in clinical development. However, new agents are needed to overcome the C797S tertiary *EGFR* mutation. New mutation will emerge sooner or later to pave the street for the novel trends in treatment of refractory disease.

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