Published in final edited form as:

Expert Rev Anticancer Ther. 2016 April ; 16(4): 383–390. doi:10.1586/14737140.2016.1162103.

The safety and efficacy of osimertinib for the treatment of *EGFR* T790M mutation positive non-small-cell lung cancer

Xin Gao, MD¹, Xiuning Le, MD, PhD¹, and Daniel B. Costa, MD, PhD^{1,*}

¹Department of Medicine, Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States of America

Abstract

First- and second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the evidence-based first-line treatment for metastatic non-small-cell lung cancers (NSCLCs) that harbor sensitizing *EGFR* mutations (i.e., exon 19 deletions or L858R). However, acquired resistance to EGFR TKI monotherapy occurs invariably within a median time frame of one year. The most common form of biological resistance is through the selection of tumor clones harboring the *EGFR* T790M mutation, present in >50% of repeat biopsies. The presence of the *EGFR* T790M mutation negates the inhibitory activity of gefitinib, erlotinib, and afatinib. A novel class of third-generation EGFR TKIs has been identified by probing a series of covalent pyrimidine EGFR inhibitors that bind to amino-acid residue C797 of EGFR and preferentially inhibit mutant forms of EGFR versus the wild-type receptor. We review the rapid clinical development and approval of the third-generation EGFR TKI osimertinib for treatment of NSCLCs with *EGFR*-T790M.

Keywords

mutation; lung cancer; adenocarcinoma; EGFR; kinase inhibitor; TKI; T790M; osimertinib; resistance

INTRODUCTION

Activating mutations in the kinase domain (exon 18 to 21) of the epidermal growth factor receptor (*EGFR*) gene result in the formation of ligand-independent EGFR proteins that activate downstream signaling pathways and are oncogenic drivers in a subset of non-small-cell lung cancers (NSCLCs). *EGFR* mutations account for approximately 10–15% of NSCLC cases in North America/Europe and 30–40% of NSCLCs in Asian countries [1–4]. The presence of an *EGFR* mutation in advanced NSCLC is predictive of disease responsiveness to EGFR tyrosine kinase inhibitors (TKIs) in preclinical models and patients [5–17]. The most common *EGFR* mutations are in-frame deletions around the LREA motif

* Correspondence to: Daniel B. Costa, MD, PhD - Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, 330 Brookline Av., Boston, MA 02215, Phone: 617-667-9236, Fax: 617-975-5665, dbcosta@bidmc.harvard.edu.

Competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

of amino-acids 747–750 in exon 19 and the L858R point mutation in exon 21, together accounting for approximately 85–90% of all *EGFR* mutations [18]. Multiple randomized trials have shown that the first-generation (gefitinib and erlotinib) and second-generation (afatinib) *EGFR* TKIs confer excellent radiographic overall response rates (ORRs) ranging from 50–75%, improved progression-free survival (PFS) as compared to standard platinum-doublet chemotherapy in patients with advanced NSCLC with *EGFR* mutations, and a trend towards improved overall survival [8–14]. As a result, gefitinib, erlotinib, and afatinib are approved first-line treatments by the United States (U.S.) Food and Drug Administration (FDA) for patients with advanced NSCLCs with *EGFR* exon 19 deletions or the L858R mutation.

Unfortunately, acquired resistance to first- and second-generation *EGFR* TKIs invariably develops within a median period of 9–13 months. Multiple mechanisms of acquired resistance have been identified, including secondary mutations in *EGFR* (e.g., *EGFR*-T790M), amplification of the *MET* oncogene, *ERBB2* amplification, *MAPK1* amplification, *PIK3CA* mutation, *BRAF* mutations, *AXL* activation, and small cell transformation among others [19–24]. The most common mechanism of acquired resistance involves development of the *EGFR* T790M mutation in exon 20 and is seen in approximately 50–60% of patients who experience disease progression on *EGFR* TKIs [19–21]. The *EGFR* T790M mutation was initially thought to develop only as an acquired mutation after *EGFR* TKI treatment, but subsequent studies have also reported existence of pre-treatment *de novo* *EGFR* T790M mutations as a minor clone concomitantly with other *EGFR* activating mutations [25–29]. Tyrosine kinase inhibitors in general compete with ATP to bind to the kinase domain of *EGFR*, and *EGFR* T790M significantly increases the affinity of *EGFR* for ATP, thereby reducing the efficacy of first-generation *EGFR* TKIs [30]. Second-generation *EGFR* TKIs were therefore originally developed to be irreversible *EGFR* inhibitors with the hope of achieving higher potency against *EGFR* T790M-mediated resistance, but the drugs that moved forward in confirmatory clinical trials (afatinib, dacomitinib, and neratinib) have failed to produce meaningful disease response after resistance to gefitinib or erlotinib [31–33]. The failure of second-generation *EGFR* TKIs to overcome T790M resistance is likely related to their potent non-mutant *EGFR* selectivity, resulting in dose-limiting skin and gastro-intestinal toxicities that limit maximum tolerated doses, and the absence of a therapeutic window between inhibition of *EGFR* T790M and wild-type *EGFR* [34,35].

The focus therefore shifted toward identification of novel *EGFR* TKIs with selectivity toward mutant forms of *EGFR* [36,37]. WZ4002, a preclinical covalent *EGFR* pyrimidine TKI, was the first such compound to be described in 2009 [36,37]. Osimertinib (previously AZD9291; AstraZeneca), rociletinib (CO-1686; Clovis Oncology), BI-1482694/HM61713 (Boehringer Ingelheim/Hanmi) and ASP8273 (Astellas) are newer third-generation *EGFR* TKIs with selectivity against *EGFR* T790M - as well as other commonly mutated forms of *EGFR* - that have progressed to clinical trials [36,38,39]. Here we review the pharmacodynamics, pharmacokinetics, clinical efficacy, and safety of osimertinib for treatment of NSCLCs harboring the *EGFR* T790M mutation.

OVERVIEW OF THE MARKET

Multiple third-generation EGFR TKIs – osimertinib, rociletinib, BI-1482694/HM61713, and ASP8273 among others – are currently in clinical trials and mid-to-late development. Rociletinib was evaluated in a phase I/II study of patients with *EGFR* mutated NSCLC who had disease progression during prior EGFR TKI treatment [40]. Rociletinib was originally reported to have an objective response rate of 59% in the 46 patients with *EGFR* T790M-positive disease and had an overall tolerable but worrisome safety profile, with clinically-relevant hyperglycemia as the common dose-limiting adverse event and cardiac abnormalities not uncommonly reported [41]. The U.S. FDA granted rociletinib breakthrough therapy designation based on these promising early efficacy results. However, more mature data in late 2015 has subsequently shown lower ORRs (below 35% in updated press releases) at the doses moving forward in clinical development for NSCLCs with *EGFR* T790M-positive disease [42]. In the intent to treat analysis of the 79 patients in the rociletinib 500 mg dose group, the current confirmed ORR is 28%, and of the 170 patients in the 625 mg dose group the ORR is only 34% [42]. Rociletinib is currently undergoing extended review by the U.S. FDA, but the aforementioned severe toxicities coupled with the suboptimal ORR lead most thoracic oncologists to believe the drug approval process will be difficult for rociletinib [43].

BI-1482694/HM61713 and ASP8273 are currently under evaluation in phase I/II trials in patients with advanced *EGFR* mutated NSCLCs who progressed on prior EGFR TKI and/or have confirmed *EGFR* T790M [38]. Final results of the ORR and toxicities of these drugs have not been published in peer-review periodicals.

Osimertinib is the first and only third-generation EGFR TKI to date to have gained approval by major regulatory agencies for treatment of *EGFR* T790M mutated NSCLC.

INTRODUCTION TO OSIMERTINIB

Chemistry and mechanism of action

Osimertinib is a mono-anilino-pyrimidine small molecule that acts as a covalent EGFR TKI. The molecular formula for osimertinib mesylate is $C_{28}H_{33}N_7O_2 \cdot CH_4O_3S$, and the compound possesses a molecular weight of 596 g/mol. Osimertinib was part of a novel series of small-molecule inhibitors developed by AstraZeneca to target double-mutant (i.e., activating mutation + T790M) forms of EGFR that are resistant to first- and second-generation EGFR TKIs [44]. Osimertinib is distinct in both structure and pharmacology from other approved EGFR TKIs [45]. The structural formula of osimertinib and other selected preclinical/clinical third-generation EGFR TKIs are shown in Figure 1.

Osimertinib binds irreversibly, via the C797 amino-acid covalent bond, to certain mutant forms of EGFR (L858R, exon 19 deletion and double mutants containing T790M) at approximately 9-fold lower concentrations than to wild-type EGFR [45,46]. In preclinical models (e.g., NSCLC cell lines and tumor implantation models), osimertinib exhibited potent activity against cancers harboring *EGFR*-mutations (L858R, L858R+T790M, exon 19 deletion, and exon 19 deletion+T790M). Two pharmacologically-active metabolites AZ7550

and AZ5104, circulating at approximately 10% of the parent, have similar inhibitory profiles to osimertinib. AZ7550 maintains a similar potency as osimertinib. AZ5104 possesses a greater potency against EGFR exon 19 deletion and T790M mutation (approximately 8-fold) as well as EGFR wild-type (approximately 15-fold). Osimertinib, AZ7550, and AZ5104 each have half-lives of greater than 50 hours [45]. Osimertinib also inhibits the activity of ERBB2, ERBB3, ERBB4, ACK1, and BLK at clinically relevant concentrations *in vitro* [46].

The commercially available form of osimertinib is distributed by AstraZeneca under the brand name Tagrisso™. Osimertinib is available in tablets of 40 mg or 80 mg, equivalent to 47.7 mg and 95.4 mg of osimertinib mesylate, respectively.

Pharmacodynamics

The pharmacodynamics of the drug has been studied in humans in cardiac electrophysiology studies. The heart rate-corrected QT (QTc) interval prolongation potential of osimertinib was assessed in 210 patients who received osimertinib 80 mg daily, and a pharmacokinetic/pharmacodynamic analysis suggested a concentration-dependent QTc interval prolongation of 14 msec [46]. Pharmacodynamics in other organ systems have not been reported.

Pharmacokinetics and metabolism

Pharmacokinetics—The area under the plasma concentration-time curve (AUC), maximal plasma concentration (C_{max}), and minimal concentration (C_{min}) of osimertinib have been shown to increase over the 20 to 240 mg dose range (i.e., 0.25 to 3 times the recommended dosage) with linear pharmacokinetics. Oral osimertinib results in 3-fold accumulation and achieves steady state exposure after 15 days. At the steady state, the C_{max}/C_{min} ratio is greater than 1.5-fold. The AUC of osimertinib metabolites AZ5104 and AZ7550 was approximately 10% of the exposure of osimertinib. Pharmacokinetic exposure was not significantly different between Asian versus non-Asian patients [47].

Absorption—The median time to C_{max} was reported at 6 hours. Compared to fasting conditions, administration with a high-fat or high-calorie meal increased osimertinib concentrations by 14% and 19%, respectively [46].

Distribution—The mean volume of distribution of osimertinib was 986 L at steady-state, and plasma protein binding was based on its chemical assets [46].

Elimination—The drug's plasma concentrations decrease with time, with a mean half-life of 48 hours [46].

Metabolism—The main metabolic pathways of osimertinib were oxidation and dealkylation *in vitro* [46].

Excretion—Osimertinib is primarily eliminated in the feces (>65%) and urine (<15%), with unchanged drug accounting for ~2% of total elimination [46].

Specific Populations—No clinically significant differences in the pharmacokinetics of osimertinib have been identified based on age, sex, ethnicity, body weight, smoking status, mild to moderate renal impairment, or mild hepatic dysfunction [46]. Data is unavailable regarding the pharmacokinetics of osimertinib in patients with severe renal impairment or with moderate to severe hepatic impairment.

Drug Interactions—Osimertinib is a competitive inhibitor of CYP3A. It does not inhibit CYP2C8, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 2E1. The drug can induce CYP3A4 and CYP1A2 enzymes. Osimertinib is a substrate of P-glycoprotein and ATP-binding cassette sub-family G member 2, but it is not a substrate of organic anion-transporting polypeptide proteins [46]. The exposure of osimertinib was not affected by concurrent administration of omeprazole in humans [46].

Carcinogenesis, mutagenesis, and fertility—Detailed carcinogenicity studies have not been conducted with osimertinib. The drug did not cause genetic damage in *in vitro* and *in vivo* assays [46]. Animal male fertility may be impaired by treatment with osimertinib. Nonclinical female fertility studies showed the drug may affect the ovaries, uterus, and vagina [46].

CLINICAL EFFICACY

Phase I studies

Osimertinib has been shown to carry significant activity *in vitro* and in mouse models against *EGFR* L858R or exon 19 deletion and compound *EGFR* L858R+T790M or exon 19 deletion+T790M tumors while having significantly reduced activity against wild-type *EGFR* [45]. Based on the promising preclinical data, the phase I AURA trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01802632) identifier NCT01802632) was initiated to assess the safety and efficacy of osimertinib in patients with locally advanced or metastatic *EGFR* mutated NSCLC who had documented disease progression while receiving a first- or second-generation *EGFR* TKI [47]. The study included a total of 253 patients from 33 sites in Japan, South Korea, Taiwan, France, Spain, Germany, Australia, the United Kingdom, and the U.S.

The study included two cohorts. The dose-escalation cohort included 31 patients, and the dose-expansion cohort included 222 patients who received osimertinib at five dosages ranging from 20 mg to 240 mg daily. Osimertinib demonstrated promising efficacy with an ORR of 51%. Of the 239 patients evaluated for disease response, 1 patient demonstrated a complete response, 122 (51%) had partial response, 78 (33%) had stable disease, 34 (14%) had disease progression, and 4 (2%) could not be assessed. The ORR was similar between Asian and non-Asian patients (50% vs 54%). Response rate was also similar at each of the dose levels examined. Based on the data that response rates were similar across all osimertinib dose levels and increasing toxicities at the 160 mg and 240 mg daily doses, a dose of 80 mg daily was adopted for future studies, including registration trials.

Osimertinib exhibited improved efficacy in patients whose tumor harbored the *EGFR* T790M mutation. Of the 127 patients with confirmed *EGFR* T790M on central testing by the sponsor and who were evaluated for disease response, the ORR was 61%. Patients

without detectable *EGFR* T790M mutation on central testing showed an ORR of only 21%. Overall, the median PFS was 8.2 months. Patients with *EGFR* T790M mutation-positive tumors had a median PFS of 9.6 months, while those without the mutation had a median PFS of 2.8 months.

Phase II studies

Additional efficacy data from both the phase II extension cohort of the AURA trial and the phase II AURA2 trial (NCT02094261) were presented at the 2015 World Conference on Lung Cancer and revealed similarly promising results. The AURA trial extension showed previously treated patients with *EGFR* T790M mutation (n=201) had an ORR of 61% to osimertinib 80 mg daily [40]. Median duration of response and median PFS were not yet reached. Similarly, the AURA2 trial found that patients with *EGFR* T790M mutation-positive tumors previously treated with first- or second-generation *EGFR* TKIs (n=210) had an ORR of 71% and a disease control rate (i.e., complete response, partial response, or stable disease) of 92% when treated with osimertinib [48]. Median PFS was reported to be 8.6 months with a median duration of response of 7.8 months. The efficacy data for osimertinib in phase I and II trials are compared to those for rociletinib and summarized in Table 1. The ORR according to RECIST v1.1 as evaluated by a Blinded Independent Central Review in the FDA submission package for osimertinib disclosed an ORR of 57% for AURA and of 61% for AURA2, which formed the basis for the U.S. FDA efficacy approval of the drug [46].

Ongoing Phase III studies

Additional phase III trials involving osimertinib are ongoing. The AURA3 trial (NCT02151981) is an open label, randomized study of osimertinib versus platinum-based doublet chemotherapy as second-line therapy for locally advanced or metastatic NSCLC with *EGFR* T790M mutation.

The FLAURA trial (NCT02296125) is a double-blind, randomized study investigating osimertinib versus gefitinib or erlotinib as first-line therapy in patients with *EGFR* mutated locally advanced or metastatic NSCLC. Preliminary data from the first-line expansion cohort of the AURA trial investigating the efficacy and safety of osimertinib in treatment-naïve *EGFR* mutant advanced NSCLC patients showed an ORR of 70% and 6-month progression-free survival of 87% [49].

Finally, the ADAURA trial (NCT02511106) is a double-blind, randomized placebo-controlled trial assessing the efficacy and safety of osimertinib versus placebo as adjuvant therapy in patients with *EGFR* mutated stage IB-IIIa NSCLC following complete tumor resection.

SAFETY AND TOLERABILITY

Osimertinib was relatively well-tolerated in the phase I AURA trial. There were no dose-limiting toxicities observed at any dose level ranging from 20 mg to 240 mg daily during a 28-day evaluation period. Among the combined cohort of 253 patients in the trial, the most common adverse events included diarrhea (47%), rash (40%), nausea (22%), and decreased

appetite (21%). Diarrhea and rash increased with escalating doses of osimertinib. Overall, however, osimertinib was associated with fewer dermatologic and gastro-intestinal toxicities compared to historical data and clinical experience with other approved EGFR TKIs. Any adverse event of grade 3 or higher occurred in 32% of patients, although only 13% of patients experienced a grade 3 or higher adverse event that was thought to be drug-related. Serious adverse events were seen in 22% of patients, with 6% of patients experiencing a serious adverse event that was considered to be drug-related. Adverse events prompted drug reduction in 7% of patients and drug discontinuation in 6% of patients. The frequency and severity of adverse events were similar between Asian and non-Asian patients. The major grade 3 or higher adverse events of osimertinib and rociletinib are summarized in Table 2.

The phase II AURA extension study and the AURA2 trial showed similar results regarding adverse events. Diarrhea and rash were the most common adverse events. Grade 3 or higher adverse events were seen in 21% of patients in the AURA extension study and 18% of patients in AURA2. Interstitial lung disease was reported in 5 (2.5%) patients in AURA extension and 4 (1.9%) patients in AURA2. Both trials had one case each of fatal interstitial lung disease that was considered possibly causally related to osimertinib by the investigator. In both studies, only 4% of patients discontinued treatment due to an adverse event.

REGULATORY AFFAIRS

Based on the results from the phase I AURA trial, the phase II AURA extension study, and the phase II AURA2 trial, the U.S. FDA granted accelerated approval in November 2015 for the use of osimertinib in patients with advanced NSCLC with *EGFR* T790M mutation. U.S. FDA approval of the drug was accompanied by approval of a companion diagnostic test (cobas *EGFR* Mutation Test v2; Roche) to detect the *EGFR* T790M mutation. The newer version (v2) of the cobas *EGFR* Mutation Test adds T790M mutation to other known activating mutations in *EGFR*.

The United Kingdom has also approved osimertinib in December 2015 under the Early Access to Medicines Scheme to meet the urgent unmet need of patients with advanced *EGFR* T790M mutated NSCLC. In December 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended the marketing authorization of osimertinib for the treatment of patients with locally advanced or metastatic *EGFR* T790M mutation-positive NSCLC. The Pharmaceuticals and Medical Devices Agency (PMDA) of Japan has granted priority review for osimertinib.

CONCLUSION

Osimertinib is a covalent third-generation EGFR TKI with significant activity against the *EGFR* T790M resistance mutation and common EGFR-activating mutations, and low activity against wild-type *EGFR* at clinical dosing schemes. Osimertinib is a novel compound with distinct structure and pharmacology from other TKIs, including other covalent third-generation EGFR TKIs. Phase I and II studies of osimertinib have shown ORRs ranging from 57–71% with a favorable cutaneous and gastro-intestinal side effect profile. Several phase III trials are ongoing in evaluating osimertinib as second-line

treatment in *EGFR* T790M mutated NSCLC as well as first-line treatment for NSCLC with any *EGFR* activating mutation.

Osimertinib is the first *EGFR* TKI approved in the U.S. and Europe for the treatment of NSCLC with *EGFR* T790M mutation.

EXPERT COMMENTARY

The *EGFR* T790M mutation accounts for the majority of acquired resistance to first- and second-generation *EGFR* TKIs and represents a significant obstacle in the treatment of *EGFR* mutant advanced NSCLCs. Osimertinib has demonstrated efficacy and safety parameters in phase I and II studies, and has become the first *EGFR* inhibitor approved for the treatment of NSCLC with the *EGFR* T790 mutation. Patients with advanced NSCLC with *EGFR* activating mutations who progress on a first-line *EGFR* inhibitor have traditionally been offered platinum-doublet chemotherapy as second-line treatment [50,51]. Platinum-doublet chemotherapy yields a modest ORR of approximately 30%, significantly lower than the 51–71% ORR reported in the phase I and II studies on osimertinib. Whether osimertinib is truly superior to standard platinum-doublet chemotherapy as second-line treatment in patients with T790M acquired resistance is currently being evaluated in the phase III study AURA3. Nevertheless, given the overall favorable side effect profile of osimertinib and the promising phase I and II efficacy data, the majority of oncology providers, including the authors, will likely favor osimertinib and reserve chemotherapy as a third-line therapy. Another option of care for *EGFR* T790M-positive NSCLC is the use of dual *EGFR* inhibition with afatinib plus cetuximab [52], a scheme fraught with severe cutaneous adverse events and an ORR of only 29%. The latter strategy will likely no longer be used in the setting of acquired resistance to *EGFR* TKIs mediated by *EGFR* T790M. Figure 2 illustrates one potential treatment algorithm for *EGFR*-mutated advanced NSCLC.

Additional indications for osimertinib are also being explored in the phase III FLAURA trial comparing osimertinib to gefitinib or erlotinib as first-line therapy for metastatic *EGFR*-mutated NSCLC, as well as the phase III ADAURA trial comparing osimertinib to placebo as adjuvant therapy following resection of *EGFR*-mutated NSCLC. These studies have the potential to significantly expand the role of osimertinib in the treatment algorithm for *EGFR* mutated NSCLC. Specifically, the FLAURA trial has the potential to catapult osimertinib into the first-line setting for treatment of *EGFR* mutated advanced NSCLC, particularly since pre-existing clones with *EGFR*-T790M have been identified in treatment-naïve tumors with sensitizing *EGFR*-activating mutations [29].

The cost for a one-month supply of osimertinib will reportedly be \$12,750 [53], approximately 50% more than the cost of first- and second-generation *EGFR* TKIs. The cost-effectiveness of a strategy of rebiopsying tumors at the point of resistance to first-line *EGFR* TKIs and switching to osimertinib remains unclear. However, multiple cost-effectiveness studies conducted in the U.S. and in Asian countries have shown that a strategy of upfront molecular testing of NSCLCs and treatment with first-generation *EGFR* TKIs is generally more favorable than use of non-targeted chemotherapy, and a similar advantage with targeted therapy may extend to osimertinib [54–57].

Despite the apparent success of osimertinib in *EGFR* T790M-mutated NSCLC, disease progression invariably develops, with preliminary PFS of approximately 10 months. Just as the *EGFR* T790M acquired resistance develops after an initial period of response to first- and second-generation *EGFR* TKIs, tumor heterogeneity and adaptation drives additional resistance mechanisms in patients treated with osimertinib and other third-generation *EGFR* TKIs. The most common mechanism of acquired resistance in patients with the *EGFR* T790 mutation treated with osimertinib appears to be via acquisition of yet another mutation – C797S in exon 20 at the site of covalent bonding of third-generation *EGFR* TKIs. Cell-free plasma DNA analysis of 15 patients with acquired resistance who were treated with osimertinib in the AURA study identified 6 (40%) with the *EGFR* C797 mutation [58], which prevents binding of all third-generation *EGFR* TKIs [23,59,60]. Additional resistance mechanisms that bypass *EGFR* signaling are also likely involved, including *MET* amplification, *ERBB2* amplification, *MAPK1* amplification, *NRAS* mutation or amplification, and neuroendocrine transformation to small cell lung cancer [61].

FIVE-YEAR VIEW

Osimertinib is poised to be the *de facto* evidence-based palliative monotherapy for *EGFR* mutated advanced NSCLCs that acquired resistance to first- and second-generation *EGFR* TKIs mediated by *EGFR* T790M for the foreseeable near future. All other drugs within the same class of third-generation *EGFR* TKIs are either poised to have difficulties during regulatory approval (as is the case detailed above for rociletinib due to low ORR and significant adverse events) or are considerably behind in clinical development plans (as is the case of BI-1482694/HM61713 that only received U.S. FDA breakthrough therapy designation for review in December 2015). Although we expect that either BI-1482694/HM61713 or ASP8273 may receive regulatory approval within the next few years for the same current indication as osimertinib, it is likely that osimertinib will have cemented its status as the go-to *EGFR* TKI for *EGFR* T790M resistance by that time. The clinical development of osimertinib for the first line therapy of TKI-naïve *EGFR* mutated NSCLCs will be more convoluted and require larger phase III trials comparing it to the current evidence-based standards (gefitinib, erlotinib and afatinib).

The main focus of academic research moving forward for osimertinib will hinge on preventing acquired resistance to monotherapy and attempting to combine osimertinib with other anti-cancer therapies. To the latter end, a phase Ib clinical trial called TATTON (NCT02143466) was launched to evaluate osimertinib when given together with one of either durvalumab (immune check point inhibitor), savolitinib (*MET* inhibitor) or selumetinib (*MEK* inhibitor).

Acknowledgments

Financial

This work was funded in part through an American Cancer Society grant RSG 11-186 (DBC), a Lung Cancer Foundation of America - International Association for the Study of Lung Cancer grant (DBC) and a National Cancer Institute grant P50CA090578 (DBC). DB Costa has received consulting fees from Pfizer Inc and Ariad pharmaceuticals, honoraria from Boehringer Ingelheim Inc, plus clinical research funding from AstraZeneca and Clovis Oncology.

REFERENCES

1. Shi Y, Au JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol*. 2014; 9(2):154–162. [PubMed: 24419411]
2. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst*. 2005; 97(5):339–346. [PubMed: 15741570]
3. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004; 304(5676):1497–1500. [PubMed: 15118125]
4. Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T. Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. *Cancer Res*. 2004; 64(24):8919–8923. [PubMed: 15604253]
5. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004; 350(21):2129–2139. [PubMed: 15118073]
6. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A*. 2004; 101(36):13306–13311. [PubMed: 15329413]
7. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005; 353(2):123–132. [PubMed: 16014882]
8. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009; 361(10):947–957. [PubMed: 19692680]
9. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010; 11(2):121–128. [PubMed: 20022809]
10. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010; 362(25):2380–2388. [PubMed: 20573926]
11. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012; 13(3):239–246. [PubMed: 22285168]
12. Wu YL, Zhou C, Liam CK, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. *Ann Oncol*. 2015; 26(9):1883–1889. [PubMed: 26105600]
13. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011; 12(8):735–742. [PubMed: 21783417]
14. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013; 31(27):3327–3334. [PubMed: 23816960]
15. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol*. 2011; 29(21):2866–2874. [PubMed: 21670455]
16. Lee CK, Brown C, Gralla RJ, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. *J Natl Cancer Inst*. 2013; 105(9):595–605. [PubMed: 23594426]
17. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet*. 2008; 372(9652):1809–1818. [PubMed: 19027483]

18. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. *Nat Rev Cancer*. 2007; 7(3):169–181. [PubMed: 17318210]
19. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med*. 2011; 3(75):75ra26.
20. Ji W, Choi CM, Rho JK, et al. Mechanisms of acquired resistance to EGFR-tyrosine kinase inhibitor in Korean patients with lung cancer. *BMC Cancer*. 2013; 13:606. [PubMed: 24369725]
21. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res*. 2013; 19(8):2240–2247. [PubMed: 23470965]
22. Nguyen KS, Kobayashi S, Costa DB. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancers dependent on the epidermal growth factor receptor pathway. *Clin Lung Cancer*. 2009; 10(4):281–289. [PubMed: 19632948]
23. Ercan D, Choi HG, Yun CH, et al. EGFR Mutations and Resistance to Irreversible Pyrimidine-Based EGFR Inhibitors. *Clin Cancer Res*. 2015; 21(17):3913–3923. [PubMed: 25948633]
24. Stewart EL, Tan SZ, Liu G, Tsao MS. Known and putative mechanisms of resistance to EGFR targeted therapies in NSCLC patients with EGFR mutations-a review. *Transl Lung Cancer Res*. 2015; 4(1):67–81. [PubMed: 25806347]
25. Inukai M, Toyooka S, Ito S, et al. Presence of epidermal growth factor receptor gene T790M mutation as a minor clone in non-small cell lung cancer. *Cancer Res*. 2006; 66(16):7854–7858. [PubMed: 16912157]
26. Li H, Hu H, Wang R, et al. Primary concomitant EGFR T790M mutation predicted worse prognosis in non-small cell lung cancer patients. *Onco Targets Ther*. 2014; 7:513–524. [PubMed: 24729716]
27. Su KY, Chen HY, Li KC, et al. Pretreatment epidermal growth factor receptor (EGFR) T790M mutation predicts shorter EGFR tyrosine kinase inhibitor response duration in patients with non-small-cell lung cancer. *J Clin Oncol*. 2012; 30(4):433–440. [PubMed: 22215752]
28. Watanabe M, Kawaguchi T, Isa S, et al. Ultra-Sensitive Detection of the Pretreatment EGFR T790M Mutation in Non-Small Cell Lung Cancer Patients with an EGFR-Activating Mutation Using Droplet Digital PCR. *Clin Cancer Res*. 2015; 21(15):3552–3560. [PubMed: 25882755]
29. Costa C, Molina MA, Drozdowskyj A, et al. The impact of EGFR T790M mutations and BIM mRNA expression on outcome in patients with EGFR-mutant NSCLC treated with erlotinib or chemotherapy in the randomized phase III EURTAC trial. *Clin Cancer Res*. 2014; 20(7):2001–2010. [PubMed: 24493829]
30. Yun CH, Mengwasser KE, Toms AV, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci U S A*. 2008; 105(6):2070–2075. [PubMed: 18227510]
31. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol*. 2012; 13(5): 528–538. [PubMed: 22452896]
32. Ellis PM, Shepherd FA, Millward M, et al. Dacomitinib compared with placebo in pretreated patients with advanced or metastatic non-small-cell lung cancer (NCIC CTG BR.26): a double-blind, randomised, phase 3 trial. *Lancet Oncol*. 2014; 15(12):1379–1388. [PubMed: 25439692]
33. Sequist LV, Besse B, Lynch TJ, et al. Neratinib, an irreversible pan-ErbB receptor tyrosine kinase inhibitor: results of a phase II trial in patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2010; 28(18):3076–3083. [PubMed: 20479403]
34. Janne PA, Boss DS, Camidge DR, et al. Phase I dose-escalation study of the pan-HER inhibitor, PF299804, in patients with advanced malignant solid tumors. *Clin Cancer Res*. 2011; 17(5):1131–1139. [PubMed: 21220471]
35. Yap TA, Vidal L, Adam J, et al. Phase I trial of the irreversible EGFR and HER2 kinase inhibitor BIBW 2992 in patients with advanced solid tumors. *J Clin Oncol*. 2010; 28(25):3965–3972. [PubMed: 20679611]
36. Zhou W, Ercan D, Chen L, et al. Novel mutant-selective EGFR kinase inhibitors against EGFR T790M. *Nature*. 2009; 462(7276):1070–1074. [PubMed: 20033049]

37. Costa DB, Kobayashi SS. Whacking a mole-cule: clinical activity and mechanisms of resistance to third generation EGFR inhibitors in EGFR mutated lung cancers with EGFR-T790M. *Translational Lung Cancer Research*. 2015; 4(6):809–815. [PubMed: 26798593]
38. Kim DW, Lee DH, Kang JH, et al. Clinical activity and safety of HM61713, an EGFR-mutant selective inhibitor, in advanced non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations who had received EGFR tyrosine kinase inhibitors (TKIs). *J Clin Oncol*. 2014; 32:5s, 2014(suppl abstr 8011)
39. Walter AO, Sjin RT, Haringsma HJ, et al. Discovery of a mutant-selective covalent inhibitor of EGFR that overcomes T790M-mediated resistance in NSCLC. *Cancer Discov*. 2013; 3(12):1404–1415. [PubMed: 24065731]
40. Yang, JC.; Ahn, M.; Ramalingam, SS., et al. AZD9291 in Pre-Treated T790M Positive Advanced NSCLC: AURA Study Phase II Extension Cohort. Presented at. 16th World Conference on Lung Cancer; 6–9 September 2015; Denver, Colorado. 2015. Abstract 943
41. Sequist LV, Goldman JW, Wakelee HA, et al. Efficacy of rociletinib (CO-1686) in plasma-genotyped T790M-positive non-small cell lung cancer (NSCLC) patients (pts). *J Clin Oncol*. 2015; 33, 2015(suppl, abstr 8001)
42. Clovis Oncology I. Clovis Oncology Announces Regulatory Update for Rociletinib NDA Filing. 2015 Nov 16. (Ed.^(Eds).
43. Sequist LV, Piotrowska Z, Niederst MJ, et al. Osimertinib Responses After Disease Progression in Patients Who Had Been Receiving Rociletinib. *JAMA Oncol*. 2015:1–3.
44. Ward RA, Anderton MJ, Ashton S, et al. Structure- and reactivity-based development of covalent inhibitors of the activating and gatekeeper mutant forms of the epidermal growth factor receptor (EGFR). *J Med Chem*. 2013; 56(17):7025–7048. [PubMed: 23930994]
45. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov*. 2014; 4(9):1046–1061. [PubMed: 24893891]
46. AstraZeneca Pharmaceuticals LP. Wilmington, DE., editor. TAGRISSO(TM) [package insert]. 2015 Nov.
47. Janne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*. 2015; 372(18):1689–1699. [PubMed: 25923549]
48. Mitsudomi, T.; Tsai, C.; Shepherd, F., et al. AZD9291 in Pre-Treated T790M Positive Advanced NSCLC: AURA2 Phase II Study. Presented at 16th World Conference on Lung Cancer; 6–9 September 2015; Denver, Colorado. 2015. Abstract 1406
49. Ramalingam, SS.; Yang, JC.; Lee, C., et al. AZD9291 in Treatment-Naïve EGFRm Advanced NSCLC: AURA First-Line Cohort. 16th World Conference on Lung Cancer; 6–9 September 2015; Denver, Colorado. 2015. Abstract 1232
50. Delbaldo C, Michiels S, Syz N, Soria JC, Le Chevalier T, Pignon JP. Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis. *JAMA*. 2004; 292(4):470–484. [PubMed: 15280345]
51. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008; 26(21):3543–3551. [PubMed: 18506025]
52. Janjigian YY, Smit EF, Groen HJ, et al. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. *Cancer Discov*. 2014; 4(9):1036–1045. [PubMed: 25074459]
53. Hirschler, B. AstraZeneca's Tagrisso to cost \$12,750 for a month's supply. Neely, J., editor. (Reuters)
54. de Lima Lopes G Jr, Segel JE, Tan DS, Do YK, Mok T, Finkelstein EA. Cost-effectiveness of epidermal growth factor receptor mutation testing and first-line treatment with gefitinib for patients with advanced adenocarcinoma of the lung. *Cancer*. 2012; 118(4):1032–1039. [PubMed: 21792863]
55. Handorf EA, McElligott S, Vachani A, et al. Cost effectiveness of personalized therapy for first-line treatment of stage IV and recurrent incurable adenocarcinoma of the lung. *J Oncol Pract*. 2012; 8(5):267–274. [PubMed: 23277762]

56. Narita Y, Matsushima Y, Shiomiwa T, et al. Cost-effectiveness analysis of EGFR mutation testing and gefitinib as first-line therapy for non-small cell lung cancer. *Lung Cancer*. 2015; 90(1):71–77. [PubMed: 26259876]
57. Wang S, Peng L, Li J, et al. A trial-based cost-effectiveness analysis of erlotinib alone versus platinum-based doublet chemotherapy as first-line therapy for Eastern Asian nonsquamous non-small-cell lung cancer. *PLoS One*. 2013; 8(3):e55917. [PubMed: 23520448]
58. Thress KS, Paweletz CP, Felip E, et al. Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M. *Nat Med*. 2015; 21(6):560–562. [PubMed: 25939061]
59. Niederst MJ, Hu H, Mulvey HE, et al. The Allelic Context of the C797S Mutation Acquired upon Treatment with Third-Generation EGFR Inhibitors Impacts Sensitivity to Subsequent Treatment Strategies. *Clin Cancer Res*. 2015; 21(17):3924–3933. [PubMed: 25964297]
60. Song HN, Jung KS, Yoo KH, et al. Acquired C797S Mutation upon Treatment with a T790M-Specific Third-Generation EGFR Inhibitor (HM61713) in Non-Small Cell Lung Cancer. *J Thorac Oncol*. 2015
61. Eberlein CA, Stetson D, Markovets AA, et al. Acquired Resistance to the Mutant-Selective EGFR Inhibitor AZD9291 Is Associated with Increased Dependence on RAS Signaling in Preclinical Models. *Cancer Res*. 2015; 75(12):2489–2500. [PubMed: 25870145]
62. Project TP. 2016 Feb 1.

KEY ISSUES

- Osimertinib is a small molecule third-generation covalent inhibitor of both EGFR-sensitizing and T790M resistance mutations with lesser activity against wild-type EGFR.
- Osimertinib has shown significant activity as second-line therapy in patients with advanced *EGFR* T790M mutated NSCLC with ORRs that exceed 50% in clinical trials.
- Osimertinib has a tolerable side effect profile. The most common adverse events include diarrhea, nausea, and decreased appetite.
- Osimertinib was granted accelerated approval by the U.S. FDA in November 2015 for the treatment of advanced NSCLC with *EGFR* T790 mutation.

INFORMATION RESOURCES

- Cross DA, Ashton SE, Ghiorghiu S et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov*, 4(9), 1046–1061 (2014).
- Jänne PA, Yang JC, Kim DW et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*, 372(18), 1689–1699 (2015).

	preclinical	clinical

	WZ4002	rociletinib	osimertinib
Molecular weight	494.97 g/mol	555.55 g/mol	499.61 g/mol
Molecular Formula	$C_{25}H_{27}ClN_6O_3$	$C_{27}H_{28}F_3N_7O_3$	$C_{28}H_{33}N_7O_2$
Preclinical activity EGFR T790M	+++++	+++++	+++++
Activity against EGFR T790M in NSCLC patients	- N/A	+ (ORR <30-35%)	++++ (ORR >50-70%)

Figure 1.

Chemical structures and basic information on selected preclinical and clinical third-generation EGFR inhibitors based on data deposited on the PubChem Compound and Substance databases [62]. Clinical responses reflect data from references [42] and [46]. Activity is grade from minimum (+) to maximum (++++).

Figure 2.
Treatment algorithm for patients with *EGFR*-mutated advanced NSCLC.

Table 1

Efficacy of osimertinib vs rociletinib in *EGFR* T790M mutated non-small-cell lung cancer.

Trial	Phase	Treatment	Patients with <i>EGFR</i> T790M positive tumors	ORR EGFR T790M positive tumors (independent central review and/or confirmed responses)
AURA extension	II	osimertinib 80 mg/day	201	57%
AURA2	II	osimertinib 80 mg/day	210	61%
TIGER-X and TIGER-2	I/II	rociletinib 500 mg/twice day	79	28%
		rociletinib 650 mg/twice day	170	34%

ORR, overall response rate.

Table 2

CTCAE grade 3 or higher adverse events of osimertinib and rociletinib in the AURA and TIGER trials.

Trial	Treatment	CTCAE name	Percentage with grade 3 or higher adverse event
AURA	osimertinib	Dyspnea	2%
		Diarrhea	2%
		Anemia	2%
		Rash/Acne	1%
		Decreased appetite	1%
		Fatigue	1%
		Paronychia	<0.5%
		Nausea	<0.5%
TIGER-X	rociletinib	Hyperglycemia	22%
		QTc prolongation	5%
		Fatigue	4%
		Nausea	2%
		Vomiting	2%
		Decreased appetite	1%
		Muscle spasms	1%

CTCAE, Common Terminology Criteria for Adverse Events