Targeting the Gatekeeper: Osimertinib in EGFR T790M Mutation-Positive Non-Small Cell Lung Cancer
Ferdinandos Skoulidis and Vassiliki A. Papadimitrakopoulou

Abstract

In 2015, the FDA approved an unprecedented number of new therapies for non–small cell lung cancer (NSCLC), among them therapies addressing specific genomic tumor subsets in the setting of development of resistance to first-line targeted therapy. Osimertinib (Tagrisso, formerly AZD9291; AstraZeneca) is indicated for patients with metastatic EGFR T790M mutation–positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor therapy. It received breakthrough therapy designation, priority review status, and accelerated approval from the FDA. Clin Cancer Res; 23(3): 1–5. ©2016 AACR.

Introduction

The treatment of non–small cell lung cancer (NSCLC) bearing activating mutations in EGFR with EGFR tyrosine kinase inhibitors (TKI) represents a paradigm of science-driven personalized cancer therapy. For patients bearing EGFR TKI–sensitizing mutations, most commonly in-frame microdeletions in exon 19 (Ex19del) and point mutations in exon 21 (leading to L858R or L861Q amino acid substitutions) or exon 18 (G719X), treatment with the first-generation EGFR TKIs erlotinib (Tarceva; Genentech/Formation Pharma) and gefitinib (Iressa; AstraZeneca) or the second-generation inhibitor afatinib (Gilotrif; Boehringer Ingelheim) has resulted in objective responses in 56% to 74% of patients. The acquisition of resistance to these drugs most commonly occurs in-frame microdeletions in exon 19 (Ex19del) and point mutations in exon 21 (leading to L858R or L858R or L861Q amino acid substitutions) or exon 18 (G719X), treatment

Preclinical Data

Osimertinib is a mono-anilino-pyrimidine compound developed by AstraZeneca as a mutant-selective, irreversible inhibitor of EGFR. In keeping with the mode of action of other irreversible inhibitors, osimertinib binds covalently via its acrylamide group to Cys797 in the ATP-binding site, but it is structurally distinct from the other third-generation EGFR TKIs rociletinib (CO-1686) and WZ4002 (12). In EGFR recombinant enzyme assays, it inhibited T790M-mutant EGFR with IC50 of 2.1 nM, which was at least 10-fold lower compared with wild-type EGFR. It further demonstrated limited promiscuity when assayed across an extensive commercial biochemical kinase panel with the exception of moderate inhibition of ERBB2/HER2 (erb-b2 receptor tyrosine kinase 2), ERBB4/HER4 (erb-b2 receptor tyrosine kinase 4), and BLK (BLK proto-kinase) with IC50 in the 10-fold range.
oncogene, Src family tyrosine kinase; ref. 12). In vitro, osimertinib inhibited EGFR phosphorylation and reduced cell viability with comparable potency with first-generation EGFR TKIs in NSCLC cell lines bearing typical EGFR-sensitizing mutations (Ex19del, L858R), but not in those with wild-type EGFR, and exhibited dramatically enhanced activity compared with first-generation TKIs in cell lines bearing the T790M resistance mutation (12). In vivo antitumor activity was demonstrated across a wide spectrum of xenograft models representative of common sensitizing EGFR mutations, including PC-9 (Ex19del) and H3255 (L858R), as well as the T790M gatekeeper mutation in H1975 (L858R/T790M) and PC-9VianR (Exon19del/T790M), and was further confirmed in genetically engineered murine models of EgfrL858R and EgfrL858R/T790M–driven NSCLC (12).

Clinical Data

The regulatory approval of osimertinib was based on efficacy results from two single-arm phase II clinical trials: the phase II extension of the pivotal AURA phase I/II clinical trial (NCT01802632) and the confirmatory AURA2 trial (NCT02094261). Both trials enrolled patients with locally advanced or metastatic NSCLC bearing sensitizing activating EGFR mutations that had progressed following prior EGFR TKI therapy and were positive for the T790M gatekeeper mutation on central testing, using the cobas EGFR Mutation Test (Roche Diagnostics) for patients unable to swallow tablets. Following single-dose administration of the capsule formulation, Cmax is reached after a median of 6 hours, and dose-proportional exposure is observed over the 20- to 240-mg dose range with linear pharmacokinetics (17). Population-estimated mean half-life (t1/2) of osimertinib is 48 hours, and steady-state accumulation following once daily dosing is reached after 15 (or 22) days. The drug is metabolized by oxidation (mostly via the CYP3A pathway) and dealkylation to two active metabolites; therefore, strong CYP3A inducers or inhibitors should be avoided (17). No dose adjustments are recommended for patients with mild or moderate renal impairment (Clcr 30–89 mL/minute) or mild hepatic impairment [bilirubin < upper limit of normal (ULN) and AST between 1 and 1.5 × ULN or total bilirubin between 1.0 and 1.5 ULN and any AST], but no data are available for patients with severe renal impairment or moderate/severe hepatic impairment (17).

Drug Safety

In the dose-escalation phase of AURA, no dose-limiting toxicities were identified at any of the prespecified osimertinib dose levels. Commensurate with the selectivity of osimertinib for mutant EGFR, the frequency and severity of reported “on-target” adverse events of the 80-mg dose in AURA and AURA2 were significantly reduced compared with historical data with first- and second-generation EGFR TKIs. In the AURA phase II extension (N = 201), the most common adverse events were diarrhea (45% all grades, 1% grade 3/4), rash (40% all grades, 1% grade 3/4), dry skin (21% all grades, 0% grade 3/4), and paronychia (20% all grades, 0% grade 3/4). Similar rates of rash (42% all grades, 1% grade 3/4), diarrhea (39% all grades, 1% grade 3/4), dry skin (25% all grades, 0% grade 3/4), and paronychia (15% all grades, 0% grade 3/4) were reported in AURA2 (N = 210; ref. 17).

The incidence of interstitial lung disease/pneumonitis across clinical trials of osimertinib (N = 813) was 3.3%, with fatal outcome in 0.5% of treated patients. In the event of confirmed pneumonitis, osimertinib should be permanently discontinued. Other label warnings include prolongation of the corrected QT interval (QTc; 0.2% greater than 500 msec), cardiomyopathy (recorded in 1.4% of patients, with 0.2% of cases fatal), and fetal toxicity (17).

Mechanisms of Resistance to Osimertinib

The landscape of clinical resistance pathways to third-generation EGFR TKIs, including osimertinib, has recently begun to unfold. In view of the critical importance of the Cys-797 residue for covalent binding of all third-generation inhibitors (as well as second-generation irreversible inhibitors), it is not surprising that acquisition of a C797S somatic mutation that disrupts irreversible
drug binding was identified in cell-free plasma DNA in 22% (15/67) of T790M-positive patients from the phase I AURA trial at the time of progression by digital droplet PCR (18, 19). In all cases with detectable C797S, the T790M mutation also persisted in circulating cell-free DNA (cfDNA). Interestingly, the incidence of C797S at the time of disease progression was more common in patients with Ex19del (30%, 13/43 patients) compared with those bearing L858R (8%, 2/24; ref. 18). Larger studies will be required to fully characterize the incidence of C797S; it is, however, clear that this will represent a dominant mechanism of osimertinib resistance. It is further important to note that the C797S mutation can be present on the same allele as T790M (in cis) or on a different allele (trans configuration; ref. 20). The allelic context of secondary resistance mutations may be clinically relevant, because in vitro EGFR-mutant cell lines bearing T790M and C797S on different alleles were reported to retain sensitivity to the combination of osimertinib with first-generation EGFR TKIs. In contrast, coexistence of T790M and C797S on the same allele confers resistance to all currently available EGFR TKIs, although partial sensitivity to cetuximab may be retained in this setting.

Perhaps less anticipated was the observation that at the time of disease progression, the T790M allele was no longer detectable in 48% of initially T790M-positive patients (32/67) in AURA, despite increased abundance of the primary EGFR-sensitizing mutation (18). This suggests that under the negative selective pressure applied by osimertinib, resistance can develop from T790M-negative clones, thus highlighting intratumoral heterogeneity as a potent barrier to the clinical efficacy of osimertinib monotherapy and indicating a need for upfront combination regimens that simultaneously target more than one resistance mechanism.

Emulating previous findings with first-generation EGFR TKIs (21), reactivation of downstream signal transduction pathways in the context of persistence of the T790M mutation and ongoing potent inhibition of EGFR signaling has also been reported at the time of clinical osimertinib progression. Signalizing bypass mechanisms that have so far been validated in patient samples include high-level amplification of ERBB2/HER2 or MET (MET proto-oncogene, receptor tyrosine kinase) and emergence of BRAF (B-Raf proto-oncogene, serine/threonine kinase) V600E-mutant clones (18). In cell line models of acquired resistance to third-generation EGFR TKIs, several additional mechanisms have been reported, including mutations in NRAS and amplification of wild-type NRAS (neuroblastoma Ras viral oncogene homologue) or KRAS (KRAS proto-oncogene GTPase; ref. 22). Enhanced sensitivity to the MAP2K1 (mitogen-activated protein kinase kinase 1-MEK1)/MAP2K2 (mitogen-activated protein kinase kinase 2-MEK2) inhibitor selumetinib (AZD6244), when used in conjunction with the initial EGFR TKI, was observed in some of these cellular resistance models. Importantly, concomitant administration of the potent MEK1/2 inhibitor trametinib with the third-generation EGFR TKI WZ4002 tool compound was demonstrated to prevent the development of acquired resistance by both T790M-dependent and T790M-independent mechanisms in preclinical models, although treatment of resistant tumors was effective only in the context of T790M (23).

Phenotypic transformation to small-cell carcinoma coupled with the acquisition of its genetic hallmarks, mutational inactivation or deletion of TP53 (tumor protein p53) and RB1 (RB transcriptional coresspressor 1), with downregulation of EGFR expression and loss of dependence on EGFR signaling has also been reported in EGFR T790M-positive patients at the time of progression on osimertinib, similar to what has been reported previously for first-generation EGFR TKIs (18, 24, 25).

Finally, it remains unclear whether acquired resistance to EGFR TKIs is a stochastic phenomenon or whether preexisting molecular features of the primary tumor channel development of resistance toward a specific molecular trajectory. Indeed, a recent provocative study highlighted that emergence of gefitinib-resistant, T790M-mutant clones of the PC9 EGFR Ex19del-mutant cell line could either occur rapidly, as a result of the expansion of preexisting drug-resistant T790M-positive clones, or, alternatively, emerge with a proscribed latency from dormant drug-resistant cells following de novo acquisition of secondary T790M mutations (26). Importantly, latent T790M-positive clones exhibited diminished apoptotic response to osimertinib compared with early resistant clones that could be restored with navitoclax (ABT-263), a potent BCL2 (BCL2, apoptosis regulator)/BCL2L1 (BCL2-like 1)/BCL2L2 (BCL2-like 2) inhibitor, which led to a phase Ib clinical trial (NCT02520778) of combined therapy with osimertinib and navitoclax in EGFR T790M mutation-positive NSCLC.

**Comparison with Alternative Therapies**

Rociletinib (also known as CO-1686; Clovis) is a third-generation, mutant-selective, pyrimidine-based, irreversible EGFR TKI that followed an analogous clinical development path to osimertinib. The rate of confirmed responses with rociletinib was 22.8% (95% CI, 14.1–33.6) at the 500-mg twice a day dose level, with a median DoR of 9.1 months (95% CI, 6.8–12.9) among patients treated in TIGER-X and TIGER-2. Hyperglycemia (54% all grades, 31% grade 3/4 at the 500-mg twice a day dose) and QTc prolongation (33% all grades, 8% grade 3/4) represent two major, clinically significant adverse events of rociletinib. QTc prolongation resulted in Toursade de Pointes in one patient. One further important point in the comparison between the two compounds relates to the inferior CNS penetration of rociletinib compared with osimertinib. It is also notable that among nine patients who developed resistance to rociletinib in TIGER-X who were subsequently enrolled in AURA2, seven derived clinical benefit, including three patients who developed brain metastases on rociletinib (8). This suggests incomplete target inhibition at clinical doses of rociletinib and is in keeping with patterns of acquired resistance that are characterized by loss of the EGFR T790M in approximately 31% of cases (4/13), small-cell transformation with associated loss of T790M (~15%, 2/13 cases), EGFR amplification (~23%, 3/13), and retention of T790M without other identified mechanisms in 31% (4/13; ref. 8). Importantly, the typical C797S mutation that prevents irreversible binding of third-generation EGFR TKIs was not observed in this cohort. In May 2016, Clovis announced that further clinical development of rociletinib was stopped.

Other mutant-selective third-generation EGFR TKIs include BI 1482694 (olmutinib, formerly HM61713; Boehringer Ingelheim), EGFR816 (Novartis), ASP8273 (Astellas), and PF-06747775 (Pfizer). Among T790M mutation–positive patients from South Korea who were treated with BI 1482694 at the recommended phase II dose of 800 mg once daily in the phase I/II HM-EMSI-101 clinical trial (NCT01588145), a 54% rate of confirmed objective responses was reported, with a median DoR of 8.3 months (27). BI 1482694 was granted breakthrough therapy designation by the FDA in December 2016.
Future Directions and Ongoing Clinical Trials

The impressive clinical activity and favorable toxicity profile of osimertinib for EGFR-mutant NSCLC bearing the T790M secondary resistance mutation, culminating in its regulatory approval in the United States, the European Union, and Japan, spearheaded an extensive clinical development program, with several phase I to III clinical trials currently open or planned. The randomized, double-blind, multinational phase III FLAURA trial (NC102296125) compares osimertinib with erlotinib/gefitinib for the first-line treatment of locally advanced or metastatic, EGFR-mutant NSCLC (N = 530). This trial is designed to address the key unanswered question regarding the optimal sequencing of EGFR TKIs in EGFR-mutant NSCLC. The primary efficacy endpoint is PFS. Crossover to osimertinib at the time of disease progression in the standard-of-care arm (erlotinib or gefitinib) is allowed. AURA 3 (NC102151981) is a randomized, open-label phase III clinical trial of osimertinib versus pemetrexed/platinum (cisplatin or carboplatin) doublet chemotherapy in T790M mutation–positive patients who progressed during or after EGFR TKI therapy (N = 410). PFS is the primary endpoint, and crossover to the osimertinib arm is allowed following progression on chemotherapy. The role of osimertinib in the adjuvant setting is evaluated in the randomized, double-blind phase III ADAURA clinical trial (NCT02511106) of osimertinib versus placebo following surgical resection of stages IB to IIIA EGFR-mutant NSCLC with or without adjuvant chemotherapy (N = 700). Two additional open-label phase II clinical trials are assessing the efficacy of osimertinib for locally advanced/metastatic, EGFR T790M mutation–positive NSCLC in different ethnic populations (NCT02442349 and NCT02504346), whereas the large multinational open-label phase II ASTRIS trial (NCT02474355) is assessing the efficacy and safety of osimertinib in T790M mutation–positive advanced NSCLC following failure of EGFR TKI therapy in a real-world setting (N = 1,500), with overall survival representing the primary efficacy outcome. The combination of osimertinib at a dose of 80 mg daily with promising additional targeted therapies, including the MEK1/2 inhibitor selumetinib (two different dosing schedules), the MET inhibitor savolitinib, and the PD-L1 inhibitor durvalumab (MEDI4736), is evaluated in the multiaxial phase Ib TATTON trial in patients with EGFR-mutant, locally Advanced or metastatic NSCLC that progressed during or following a prior EGFR TKI. The efficacy of the combination of osimertinib with durvalumab (MEDI4736) versus osimertinib monotherapy is further evaluated in the randomized phase III CALIRAL trial (NCT02454933) in patients with advanced, EGFR T790M mutation–positive NSCLC patients who progressed during or following prior EGFR TKI therapy. However, this trial was temporarily suspended following reports of elevated rate of pneumonitis (3/23 patients) in the combination arm.

Disclosure of Potential Conflicts of Interest

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Development of methodology: F. Skoulidis
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): V.A. Papadimitrakopoulou
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): V.A. Papadimitrakopoulou
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