Clinical Cancer Research

Osimertinib for the Treatment of Metastatic EGFR T790M Mutation–Positive Non–Small Cell Lung Cancer

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Abstract

On November 13, 2015, the FDA granted accelerated approval to osimertinib (TAGRISSO; AstraZeneca), a breakthrough therapy-designated drug for the treatment of patients with metastatic EGFR T790M mutation–positive non–small cell lung cancer, as detected by an FDA-approved test, with progression on or after EGFR tyrosine kinase inhibitor therapy. Approval was based on durable tumor response rates in two single-arm, multicenter trials: the dose extension cohort of a first-in-human trial (FIH; AURA extension; $n = 201$) and a fixed-dose, activity-estimating trial (AURA2; $n = 210$). Osimertinib was administered at 80 mg orally once daily. The objective response rates (ORR) per blinded independent committee review were 57% [95% confidence interval (CI), 50–64) in AURA extension and 61% (95% CI, 54–68) in AURA2. Median duration of response (DOR) could not be estimated. Supportive efficacy data from 63 patients in the dose-finding part of the FIH trial demonstrated an ORR of 51% (95% CI, 38–64), with a median DOR of 12.4 months. Common adverse events (AE) evaluated in 411 patients included diarrhea (42%), rash (41%), dry skin (31%), and nail toxicity (25%). Grade 3 to 4 AEs occurred in 28% of patients, and 5.6% discontinued treatment due to AEs. *Clin Cancer Res; 23(9); 2131–5. ©2016 AACR.*

Introduction

Lung cancer is the leading cause of cancer deaths in the United States, with an estimated incidence of more than 220,000 new cases and approximately 160,000 deaths in 2016 (1). In recent years, several molecularly defined subsets of non–small cell lung cancer (NSCLC) with specific somatic "driver" mutations, thought to be responsible for the initiation and maintenance of tumor growth, have been identified (2, 3). Among these mutations, *EGFR* alterations are the most common, present in about 10% to 15% of patients with NSCLC in the United States (2, 4, 5).

EGFR belongs to the ERBb superfamily of tyrosine kinase receptors, which mediate tumor proliferation, invasion, metastasis, resistance to apoptosis, and angiogenesis (6). There are currently three FDA-approved EGFR tyrosine kinase inhibitors (TKI)—gefitinib, erlotinib, and afatinib—indicated for the initial treatment of metastatic NSCLC patients with tumors harboring *EGFR* deletions in exon 19 or exon 21 L858R substitution mutations. These agents have demonstrated an overall response rate (ORR) of approximately 50% to 70% and median progression-free survival of 9 to 13 months (7, 8, 9).

In approximately half of patients, the mechanism of acquired resistance to first-generation EGFR TKIs is thought to involve the emergence of a second-site *EGFR* point mutation that results in substitution of threonine with methionine at amino acid position 790 (T790M), an amino acid located within the ATP-binding site of the EGFR kinase domain (10).

On April 16, 2014, the FDA granted breakthrough therapy designation to osimertinib based on preliminary clinical evidence that osimertinib was likely to provide a substantial improvement over available therapies to treat patients with metastatic NSCLC who have progressed on EGFR-targeted therapy and whose tumors harbor a T790M mutation. The FDA's review of the new drug application (NDA) for osimertinib is summarized.

Mechanism of Action

Osimertinib binds irreversibly to several mutant forms of EGFR (T790M, L858R, and exon 19 deletion) at approximately 9-fold lower concentrations than wild-type EGFR. In cultured cells and animal tumor implantation models, osimertinib exhibited antitumor activity against NSCLC lines harboring *EGFR* mutations (T790M/L858R, L858R, T790M/exon 19 deletion, and exon 19 deletion) and, to a lesser extent, wild-type *EGFR* amplifications. The major target organs for toxicity in both rats and dogs were the gastrointestinal tract, skin, and eyes (11, 12).

Clinical Pharmacology

The pharmacokinetics of osimertinib has been characterized following a single-dose administration in healthy volunteers and in patients with advanced NSCLC following single- and

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multiple-dose administration. The area under the plasma concentration–time curve (AUC) and maximal plasma concentration (C_{max}) of osimertinib increased dose proportionally over 20 to 240 mg dose range (0.25 to 3 times the recommended dosage). In cancer patients, the median time to C_{max} (T_{max}) of osimertinib was 6 hours (range, 3–24 hours). Administration of osimertinib once daily resulted in approximately 3-fold accumulation with steady-state exposures achieved after 15 days of dosing. The mean terminal half-life was approximately 48 hours.

The main metabolic pathways of osimertinib were oxidation (predominantly CYP3A) and dealkylation *in vitro*. Two pharmacologically active metabolites (AZ7550 and AZ5104) have been identified in the plasma after oral osimertinib dosing, each with 10% of the exposure of osimertinib at steady state.

On the basis of population pharmacokinetics analyses, no clinically significant differences in the pharmacokinetics of osimertinib were observed based on age, sex, ethnicity, body weight, smoking status, mild (creatinine clearance of 60–89 mL/minute) or moderate (creatinine clearance of 30–59 mL/minute) renal impairment, or mild hepatic impairment (12).

Clinical Trials

The FDA primarily relied on data from two single-arm, multicenter clinical trials to establish the safety and efficacy of osimertinib: the subgroup of patients enrolled in an expansion cohort of a first-in-human (FIH) trial (AURA extension) and all patients enrolled in the fixed-dose, activity-estimating trial AURA2. All patients had metastatic *EGFR* T790M mutation–positive NSCLC, detected in a central laboratory by the cobas® EGFR Mutation Test v2, who had progressed on prior systemic therapy, including an EGFR TKI. Osimertinib was administered at a starting dose of 80 mg once daily. The major efficacy outcome measure of both trials was confirmed ORR according to RECIST v1.1 as evaluated by a blinded independent central review (BICR). Duration of response (DOR) was an additional outcome measure. Safety evaluations included regular physical examinations, laboratory evaluations, and electrocardiograms.

The basis for dose selection relied on data obtained in the FIH AURA trial that consisted of three distinct parts: AURA phase I, with a dose-escalation portion ($n = 31$) and a dose-expansion portion ($n = 252$), followed by a single-dose, activity-estimating portion (AURA extension). In both the dose-escalation and dose-expansion portions of AURA phase I, patients received osimertinib at doses ranging from 20 to 240 mg daily, and preliminary evidence of antitumor activity (objective tumor response) was observed across all doses. Using data from the dose-escalation and dose-expansion parts of AURA phase I, 80 mg was chosen as the recommended phase II dose based on dose–response modeling for efficacy and safety.

In addition to the analyses of efficacy for patients who received osimertinib 80 mg daily in AURA extension and AURA2, the FDA reviewed data on a subset of 63 patients in AURA phase I to allow for better characterization of DOR, given the short follow-up time in AURA extension and AURA2 trials. All 63 patients in this AURA phase I subgroup had metastatic disease, were previously treated with an EGFR TKI, had *EGFR* T790M mutation–positive NSCLC as detected by the cobas® EGFR Mutation Test v2, and received osimertinib 80 mg once daily. The median duration of exposure in this subgroup was 8.1 months. For this subgroup analysis, the assessment of ORR and DOR was based on BICR assessment according to RECIST v1.1 (13).

A premarket application (PMA) supplement was submitted to the FDA's Center for Devices and Radiological Health to support expansion of the intended use and indication for use of the cobas® EGFR Mutation Test v2 for the detection of *EGFR* T790M mutation in NSCLC patients for whom osimertinib is indicated. This device is a real-time PCR test, originally approved as a companion diagnostic assay for the detection of *EGFR* exon 19 deletions and exon 21 (L858R) substitution mutations in patients with metastatic NSCLC for whom erlotinib (TARCEVA; Astellas Pharma) is indicated (8).

Efficacy

Baseline disease and patient characteristics in AURA extension were as follows: median age 62 years (range, 37–89), female (66%), White (38%), Asian (58%), never smoker (67%), World Health Organization (WHO) performance status 0 (34%) or 1 (66%), adenocarcinoma histology (97%), 1 prior line of therapy (30%), and 2 or more prior lines of therapy (70%). Sites of extrathoracic metastasis included liver (32%), bone (51%), and brain (37%). Somatic *EGFR* mutations in addition to T790M were exon 19 deletion (71%), L858R (25%), G719X (2%), and S768I (2%). Baseline disease and patient characteristics in AURA2 were as follows: median age 64 years (range, 35–88), female (70%), White (34%), Asian (63%), never smoker (76%), WHO performance status 0 (40%) or 1 (60%), adenocarcinoma histology (95%), 1 prior line of therapy (32%), and 2 or more prior lines of therapy (68%). Sites of extrathoracic metastasis included liver (26%), bone (43%), and brain (41%). Somatic *EGFR* mutations in addition to T790M were exon 19 deletion (65%), L858R (32%), G719X (2%), and S768I (1%).

The FDA's primary efficacy analyses were based on a total of 411 patients in AURA extension and AURA2 who received at least one dose of osimertinib at 80 mg daily. The FDA's analysis of ORR and DOR according to BICR are shown in Table 1. The efficacy of osimertinib was present across all clinically relevant subgroups in exploratory analyses, and ORR appeared to be higher in Asian patients [64%; 95% confidence interval (CI), 58–70; $n = 247$] according to BICR assessment than non-Asian patients (51%; 95% CI, 43–59; $n = 164$; ref. 13).

Brain metastases were only assessed as nontarget lesions (NTL) or new lesions in these trials; therefore, there were no measurements of metastatic brain lesions, and the tumor responses of all NTLs were combined across all anatomic sites, including non-brain regions, precluding isolation of central nervous system (CNS) antitumor activity. Of the 74 patients with documented disease progression in the data reviewed by

Table 1. Primary efficacy results in AURA extension and AURA2 trials determined by RECIST v1.1 according to BICR

	AURA extension ($n = 201$)	AURA2 ($n = 210$)	Overall[a] ($N = 411$)
ORR (95% CI), (%)	57 (50–64)	61 (54–68)	59 (54–64)
CR (%)	0	1	0.5
PR (%)	57	60	59

[a]Pooled analysis of AURA extension and AURA2.

Abbreviations: CR, complete response; PR, partial response.

the FDA, 9 (12%) had the CNS as the primary site of disease recurrence while on osimertinib.

Safety

The primary safety analysis was based on data obtained in all 411 osimertinib-treated patients included in the primary efficacy analyses from AURA extension and AURA2. This primary safety population had a median duration of exposure to osimertinib of 8 months, with 81% of patients having ≥6 months of exposure to osimertinib and 24% of patients having ≥9 months; no patient was exposed for 12 months. For the assessment of pneumonitis/interstitial lung disease (ILD) and cardiomyopathy, the safety database was supplemented by data from an additional 402 patients ($N = 813$) enrolled in dose-escalation and dose-expansion portions of AURA phase I who received osimertinib at doses ranging from 20 to 240 mg daily, with a median exposure of 8 months.

Adverse events (AE) are described using the NCI Common Terminology Criteria for Adverse Events (version 4.0). Across the primary safety population, the most common AEs (with a per-patient incidence of >25%) were diarrhea (42%) and clustered terms of rash (41%), dry skin (31%), and nail toxicity (25%). The most common, treatment-emergent laboratory abnormalities (incidence >20%) were lymphopenia (63%), thrombocytopenia (54%), anemia (44%), neutropenia (33%), and hyponatremia (26%). Grade 3 neutropenia occurred in 3.4% of patients. Grade 3 to 4 AEs were reported in 28% of patients. Grade 3 to 4 AEs, reported in >2% of patients, included venous thromboembolism (2.4%) and pneumonia (2.2%). Fatal AEs consisted of ILD/pneumonitis (4 patients), pneumonia (4 patients), and cerebrovascular accidents (2 patients). Other fatal AEs included congestive cardiac failure/liver disorder/urinary tract infection, failure to thrive, gastrointestinal hemorrhage, multi-organ failure, and respiratory failure (1 patient each).

Dose reductions occurred in 4.4% of patients receiving osimertinib. The most frequent AEs that led to dose reductions or interruptions were prolonged corrected QT interval (QTc; 2.2%) and neutropenia (1.9%). AEs leading to drug discontinuation occurred in 6% of patients, most commonly ILD/pneumonitis and cerebrovascular accidents. QTc prolongation at steady state was observed, with a maximum mean change from baseline in QTc of 16 ms.

Pneumonitis/ILD occurred in 3.3% of patients (grade 1–2, 1.4%; grade 3–4, 1.5%; fatal, 0.5%), and its onset was not predictable (median day of onset 54; range, 14–240). Patients in AURA extension and AURA2 were required to have assessment of left ventricular ejection fraction (LVEF) by multigated acquisition scan or echocardiogram at baseline and every 3 months. LVEF decline >10% and a drop to <50% occurred in 2.4% of 375 patients who had baseline and >1 follow-up assessment. Cardiomyopathy was reported in 1.4% of patients (fatal 0.2%).

Exposure–Response Relationships

A logistic regression model, using data from patients treated on AURA phase I, AURA extension, and AURA2, was used to assess the relationship between osimertinib exposure (AUC_{ss}) and efficacy/safety endpoints. There was no significant exposure–response relationship identified for the primary efficacy endpoint of ORR in *EGFR* T790M mutation–positive patients with advanced NSCLC who have progressed on or after EGFR TKI therapy. The probability of a patient experiencing rash and diarrhea (all grades) increased with osimertinib exposure, although the incidence of experiencing grade 3 or higher rash or diarrhea was less than 1% (12).

Discussion

Osimertinib has shown a favorable benefit–risk profile for the treatment of patients with EGFR T790M mutation–positive metastatic NSCLC with disease progression on or after one prior EGFR TKI based on the demonstration of a large magnitude of durable tumor responses in two single-arm trials (Table 2). The FDA's review of the FIH trial indicated early evidence of clinical activity that was a substantial improvement over available therapy with an acceptable safety profile, leading the agency to grant breakthrough designation for osimertinib to help expedite clinical development and review of the drug. AstraZeneca submitted the NDA on June 5,

Table 2. Benefit–risk analysis for osimertinib in the treatment of patients with metastatic NSCLC who have progressed on or after EGFR TKI therapy and who have developed a T790M resistance mutation

Disease	Patients with *EGFR* mutation–positive metastatic NSCLC who have progressed on or after EGFR TKI therapy and who have developed a T790M resistance mutation.
Unmet need	Metastatic *EGFR* T790M mutation–positive NSCLC that has progressed on or after EGFR TKI therapy is often treated with cytotoxic chemotherapy, which is generally associated with marginal clinical benefit and significant toxicity.
Clinical benefit	Osimertinib was associated with an ORR as assessed by a BICR of 57% (95% CI, 50–64; AURA extension) and 61% (95% CI, 54–68; AURA2). The activity of osimertinib was generally consistent across clinically relevant subgroups. Tumor responses were durable, with a median DOR that had not been reached at the time of the primary analysis.
Risk	The primary safety evaluation was based on 411 patients. The most common AEs (≥25%) were diarrhea, rash, dry skin, and nail toxicity. Grade 3–4 AEs were reported in 28% of patients. Dose reductions occurred in 4.4% of patients, and 5.6% of patients discontinued therapy due to AEs.
Uncertainties	Although ORR is considered an endpoint that can reasonably predict clinical benefit in metastatic NSCLC, no correlation with overall survival or how a patient feels or functions has yet been established. Therefore, traditional approval for osimertinib requires confirmation of clinical benefit. Additional data are needed to assess the safety and efficacy of osimertinib: in patients with hepatic impairment; in patients with CNS metastasis; in combination with CYP3A4 inhibitors, inducers, substrates, as well as BCRP substrates; and in patients with germline and *de novo* EGFR T790M–mutated NSCLC.
Conclusions	Osimertinib meets the criteria for accelerated approval under the provisions of subpart H of 21 C.F.R. 314 (16). Osimertinib has a favorable benefit–risk profile for the treatment of patients with *EGFR* mutation–positive metastatic NSCLC who have progressed on or after EGFR TKI therapy and who have developed a T790M resistance mutation. Osimertinib is associated with a large magnitude of durable responses in a population of patients for whom available treatment options generally offer marginal clinical benefit. The risks associated with osimertinib are acceptable in the context of the disease being treated.

2015, and FDA approval occurred approximately 5 months from receipt of the NDA [approximately 2.5 years after receipt of the original investigational new drug (IND) application].

The FDA concurrently approved a PMA supplement for the cobas® EGFR Mutation Test v2, expanding the intended use and indication for use of the assay for detection of *EGFR* T790M mutation in formalin-fixed paraffin-embedded human NSCLC tumor tissue. Given the difficulties of obtaining tumor tissue following disease progression and the challenges in interpretation of the results due to potential effects of tumor heterogeneity, plasma genotyping has been proposed as a noninvasive alternative for the detection of *EGFR* mutations, including T790M, in patients with advanced NSCLC (14). The FDA recently approved the use of the cobas® EGFR Mutation Test v2 for the detection of EGFR exon 19 deletions and L858R mutations in plasma specimens to select patients with metastatic NSCLC for treatment with erlotinib (15). Plasma genotyping is a viable strategy for personalization of cancer therapies and is expected to expand in scope as evidence on the analytic validity and clinical utility of the approach accumulates.

The FDA's exploratory analyses showed that osimertinib's efficacy was generally consistent in clinically relevant subgroups. Asian patients, who made up the majority of the patients in AURA extension and AURA2, appeared to have a higher ORR for unclear reasons. Pharmacokinetic differences of osimertinib do not appear to be clinically meaningful between Asian and non-Asian patients, although a small decrease in the metabolite AZ5104 AUC_{ss} (approximately 10%–23%) may be expected in Asian and non-Asian–non-White patients compared with White patients. There may be other intrinsic (e.g., genetic) and/or extrinsic (e.g., dietary and environmental) factors that may influence response to treatment, and more research is needed to better characterize predictors of response in subpopulations. In the AURA and AURA2 trials, 24% and 15% of patients had treated and untreated brain metastases, respectively. Given that baseline brain metastases were assessed as NTLs in the two trials, there was no measurement of metastatic brain lesion diameter. Therefore, it was not possible to calculate an ORR or DOR for CNS disease. The proportion of patients with the CNS as first site of progression was 12% (9/74 patients with documented disease progression). Given that approximately half of patients with *EGFR*-positive metastatic NSCLC treated with first-line chemotherapy develop CNS relapse, the low rate of primary CNS relapse in AURA and AURA2 trials may suggest a measure of CNS antitumor activity. Data to further characterize osimertinib's CNS antitumor activity are needed for a more accurate estimation of the drug's CNS treatment effect.

Pneumonitis/ILD has been observed with all FDA-approved EGFR TKIs and the cause of four (0.5%) fatalities among osimertinib-treated patients. The FDA's review suggests that pneumonitis/ILD may be difficult to diagnose and mostly occurs in the setting of overlapping lung infection and intraparenchymal progression of disease. Given that pneumonitis/ILD can occur both early and late in the course of therapy, prompt recognition and treatment of the signs and symptoms throughout the course of therapy is warranted, with permanent discontinuation of osimertinib if the diagnosis is confirmed.

On the basis of the observed incidence of LVEF dysfunction and cardiomyopathy, patients receiving osimertinib should have LVEF assessments with multigated acquisition scan or echocardiogram at baseline and at 3-month intervals, with treatment held for LVEF declines >10% and to a value of <50%. Permanent discontinuation is recommended for persistent or symptomatic congestive heart failure.

The accelerated approval for osimertinib was supported by an ORR of large magnitude and long duration, which is considered an endpoint reasonably likely to predict clinical benefit. Confirmation of clinical benefit will be through the ongoing randomized trial of osimertinib versus standard therapy (NCT02151981) in patients with metastatic NSCLC whose disease has progressed with previous EGFR TKI and whose tumors harbor an *EGFR* T790M mutation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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