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Regulatory Issues: FDA

# FDA Benefit-Risk Assessment of Osimertinib for the Treatment of Metastatic Non-Small Cell Lung Cancer Harboring Epidermal Growth Factor Receptor T790M Mutation

Lauretta Odogwu, Luckson Mathieu, Kirsten B. Goldberg, Gideon M. Blumenthal, Erin Larkins, Mallorie H. Fiero, Lisa Rodriguez, Karen Bijwaard, Eunice Y. Lee, Reena Philip, Ingrid Fan, Martha Donoghue, Patricia Keegan, Amy McKee, Richard Pazdur

Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA

*Disclosures of potential conflicts of interest may be found at the end of this article.*

**Key Words.** Osimertinib • Non-small cell lung adenocarcinoma • Epidermal growth factor receptor inhibitor • T790M

## Abstract

On March 30, 2017, the U.S. Food and Drug Administration (FDA) approved osimertinib for the treatment of patients with metastatic, epidermal growth factor receptor (EGFR) T790M mutation-positive, non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, whose disease has progressed following EGFR tyrosine kinase inhibitor (TKI) therapy. Approval was based on demonstration of a statistically significant difference in the primary endpoint of progression-free survival (PFS) when comparing osimertinib with chemotherapy in an international, multicenter, open-label, randomized trial (AURA3). In this confirmatory trial, which enrolled 419 patients, the PFS hazard ratio for osimertinib compared with chemotherapy per investigator assessment was 0.30 (95% confidence interval 0.23–0.41), $p < .001$, with median PFS of 10.1 months in the osimertinib arm and 4.4 months in the chemotherapy arm. Supportive efficacy data included PFS per blinded independent review committee demonstrating similar PFS results and an improved confirmed objective response rate per investigator assessment of 65% and 29%, with estimated median durations of response of 11.0 months and 4.2 months, in the osimertinib and chemotherapy arms, respectively. Patients received osimertinib 80 mg once daily and had a median duration of exposure of 8 months. The toxicity profile of osimertinib compared favorably with the profile of other approved EGFR TKIs and chemotherapy. The most common adverse drug reactions (>20%) in patients treated with osimertinib were diarrhea, rash, dry skin, nail toxicity, and fatigue. Herein, we review the benefit-risk assessment of osimertinib that led to regular approval, for patients with metastatic NSCLC harboring EGFR TKI whose disease has progressed on or after EGFR TKI therapy. ***The Oncologist*** 2018;23:353–359

**Implications for Practice:** Osimertinib administered to metastatic non-small cell lung cancer (NSCLC) patients harboring an EGFR T790M mutation, who have progressed on or following EGFR TKI therapy, demonstrated a substantial improvement over platinum-based doublet chemotherapy as well as durable intracranial responses. The ability to test for the T790M mutation in plasma using the FDA-approved cobas EGFR Mutation Test v2 (Roche, Basel, Switzerland) identifies patients with NSCLC tumors not amenable to biopsy. Since a 40% false-negative rate has been observed with the circulating tumor DNA test, re-evaluation of the feasibility of tissue biopsy is recommended to identify patients with a false-negative plasma test result who may benefit from osimertinib.

## Introduction

Platinum-based doublet chemotherapy was the standard first-line treatment for patients with metastatic non-small cell lung cancer (NSCLC); median survival with this approach is approximately 8–12 months, versus 3–6 months with best supportive care [1]. The discovery of molecular pathways and actionable mutations has led to the development of agents that target specific mutations and pathways in tumor cells [2]. Activating mutations within the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) gene in NSCLC (such as exon 19 deletions or the L858R point mutation in exon 21) were first reported in 2004 and are identified in 10%–20% of patients with NSCLC in the West and 30%–40% in Asia [3]. The presence

Correspondence: Lauretta Odogwu, M.D., Office of Hematology and Oncology Products, CDER, U.S. Food and Drug Administration, WO22 Room 2389, 10903 New Hampshire Avenue, Silver Spring, Maryland 20993, USA. Telephone: 301-796-1384; e-mail: lauretta.odogwu@fda.hhs.gov Received August 30, 2017; accepted for publication October 24, 2017; published Online First on December 14, 2017. http://dx.doi.org/10.1634/theoncologist.2017-0425

of exon 19 deletions or the L858R point mutation in exon 21 predicts sensitivity to EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib, first-generation reversible inhibitors, and afatinib, a second-generation irreversible inhibitor [4, 5]. Most responding patients develop an acquired resistance to an EGFR TKI approximately 9–13 months after initiation of treatment [6]. The most common mechanism of resistance is acquisition of the gatekeeper mutation in EGFR T790M identified in 50%–60% of cases [7, 8]. After emergence of resistance to EGFR TKIs, median survival is typically less than 2 years [9].

Preclinical studies have shown that osimertinib, an oral third-generation EGFR TKI, demonstrated antitumor activity against NSCLC lines harboring certain mutant forms of EGFR, such as T790M, L858R, and exon 19 deletion, while sparing EGFR wild type [10]. Studies have also shown that osimertinib is distributed to the brain in multiple animals with brain-to-plasma area under the curve ratios of approximately 2 following oral dosing [11]. Tumor regression and increased survival were observed in osimertinib- versus control-treated animals in a preclinical mutant-EGFR intracranial mouse metastasis xenograft model (PC9; exon 19 deletion) [12]. Osimertinib has limited activity in patients with T790M-negative acquired resistance. Data from the AURA study showed osimertinib achieved better response rates (objective response rate [ORR] 61% vs. 21%) in patients with T790M-positive versus T790M-negative tumors [13].

## Regulatory History

On April 16, 2014, the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy designation to osimertinib based on preliminary clinical evidence that osimertinib may provide a substantial improvement over existing therapies for patients with metastatic NSCLC whose disease has progressed on EGFR-targeted therapy and whose tumors harbor a T790M mutation. On November 13, 2015, the FDA granted accelerated approval to osimertinib for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy. Accelerated approval was based on the results of two single-arm clinical trials documenting a 59% objective response rate with a median duration of response of 12 months [14]. On November 13, 2015, the cobas EGFR Mutation Test v2 (Roche, Basel, Switzerland) was originally approved, along with accelerated approval for osimertinib, for the detection of the EGFR exon 20 T790M substitution mutation in formalin-fixed, paraffin-embedded tumor tissue specimens based on performance using patient specimens from the AURA2 study [15]. On September 28, 2016, the indication for the cobas EGFR Mutation Test v2 was expanded to include the detection of the T790M substitution mutation in circulating tumor DNA (ctDNA) isolated from plasma samples [16].

## Clinical Trial Design

The approval of osimertinib for treatment of patients with advanced or metastatic EGFR T790M mutation-positive NSCLC, whose disease had progressed following first-line treatment with an EGFR TKI, was based on efficacy and safety data from the AURA3 trial (NCT02151981), a randomized, multicenter, open-label, active-controlled trial. All patients were required to have EGFR T790M mutation-positive NSCLC identified by the cobas EGFR Mutation Test v2 performed in a central laboratory [17]. Eligible patients were randomized (2:1) to receive osimertinib or platinum-based doublet chemotherapy, respectively. AURA3 included patients with asymptomatic brain metastases not requiring steroids for at least 4 weeks prior to start of study treatment. Patients randomized to the chemotherapy arm with radiological progression according to both the investigator and the blinded independent central review (BICR) were offered treatment with osimertinib at the time of disease progression.

The primary efficacy outcome measure was progression-free survival (PFS) by investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Additional efficacy outcome measures included ORR, duration of

**Table 1.** Baseline demographic and disease characteristics for AURA3

| Characteristics | Osimertinib *n* = 279 % | Chemotherapy *n* = 140 % |
|---|---|---|
| Age, median: years | 62 | 63 |
| Range: years | 25–85 | 20–90 |
| <65 years | 59 | 55 |
| ≥65 years | 41 | 45 |
| Gender | | |
| Female | 62 | 69 |
| Male | 38 | 31 |
| Race | | |
| White | 32 | 31 |
| Asian | 65 | 66 |
| Black | 1.4 | 0.7 |
| Other | 1.4 | 0.7 |
| Smoking Hx | | |
| Never | 68 | 67 |
| Current | 5 | 6 |
| Former | 27 | 27 |
| WHO performance status | | |
| 0 (normal activity) | 37 | 40 |
| 1 (restricted activity) | 63 | 60 |
| Overall disease classification | | |
| Metastatic | 95 | 99 |
| Locally advanced | 4.7 | 1.4 |
| Investigator-assessed CNS metastasis | | |
| Yes | 33 | 36 |
| No | 67 | 64 |
| Extrathoracic visceral metastasis | | |
| Yes | 52 | 57 |
| No | 48 | 43 |
| Baseline plasma T790M mutation status | | |
| Positive | 42 | 40 |
| Negative | 40 | 40 |
| Missing | 18 | 20 |

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; Hx, history; WHO, World Health Organization.

**Table 2.** AURA3 key efficacy results

| Efficacy parameter | Investigator assessment | | BICR assessment | |
|---|---|---|---|---|
| | Osimertinib ($n = 279$) | Chemotherapy ($n = 140$) | Osimertinib ($n = 279$) | Chemotherapy ($n = 140$) |
| Progression-free survival: *n* (%) | | | | |
| Number of events | 140 (50) | 110 (79) | 116 (42) | 103 (74) |
| Progressive disease | 129 (46) | 104 (74) | 105 (38) | 96 (69) |
| Death[a] | 11 (4) | 6 (4) | 11 (4) | 7 (5) |
| Median PFS: months (95% CI) | 10.1 (8.3–12.3) | 4.4 (4.2–5.6) | 11.0 (9.4–NR) | 4.2 (4.1–5.6) |
| Hazard ratio (95% CI)[b,c] | 0.30 (0.23–0.41) | | 0.28 (0.20–0.38) | |
| *p* value[b,d] | <.001 | | <.001 | |
| Objective response rate[e] | | | | |
| Objective response rate (95% CI)[b,f] | 65% (59%–70%) | 29% (21%–37%) | 57% (51%–63%) | 29% (22%–38%) |
| Complete response: % | 1% | 1% | 1% | 0% |
| Partial response: % | 63% | 27% | 56% | 29% |
| *p* value | <.001 | | <.001 | |
| Duration of response | | | | |
| Median duration of response: months (95% CI) | 11.0 (8.6–12.6) | 4.2 (3.9–5.9) | NR (8.9–NR) | 3.9 (3.0–5.6) |

[a]Without documented radiological disease progression.
[b]Stratified by ethnicity (Asian vs. non-Asian).
[c]Pike estimator.
[d]Stratified log-rank test.
[e]Confirmed.
[f]Chi-square test.
Abbreviations: BICR, blinded independent central review; CI, confidence interval; NR, not reached; PFS, progression-free survival.

response (DoR), and overall survival (OS). A prespecified, exploratory, noncomparative subgroup analysis of intracranial ORR by BICR was performed in patients with measurable central nervous system (CNS) metastases at baseline.

A sample size of approximately 410 patients and a total of 221 PFS events were required to provide 80% power to detect superiority in PFS at a two-sided alpha level of 5%. This sample size assumed that PFS followed an exponential distribution with a median PFS of 6 months in the chemotherapy arm and 9 months in the osimertinib arm and a hazard ratio (HR) of 0.67. This sample size provides at least 75% power to detect an OS HR of 0.72 with a two-sided alpha level of 5%, assuming a median OS of 16 months in the chemotherapy arm and 22 months in the osimertinib arm, when approximately 287 events have occurred.

For the secondary endpoint of OS, all efficacy analyses were conducted in the intent-to-treat population, and a hierarchical procedure was used to adjust for multiplicity in testing endpoints in the order of PFS, ORR, and OS. Both PFS and OS were analyzed using a log-rank test stratified by ethnicity (Asian vs. non-Asian). No interim analyses for PFS were planned. Two interim analyses were planned for OS, at 4 months after data cutoff for the primary analysis (~25% maturity) and after approximately 205 (71%) events. The Lan-DeMets method for approximating the O'Brien-Fleming boundary method was used for alpha allocations of 0.001 (two-sided) and 0.016 (two-sided) for the two interim analyses and 0.045 (two-sided) for the final analysis. The secondary endpoints of ORR and DoR were analyzed at the time of the primary PFS analysis.

The primary safety analysis was based on the safety analysis population of AURA3 supported by pooled safety data of patients enrolled across four trials and was of adequate size to characterize the adverse reactions to osimertinib. A total of 833 patients from AURA3 ($n = 279$), AURA Extension ($n = 201$) [18], AURA2 ($n = 210$) [19], and the expansion cohort from the first-in-human trial of osimertinib, AURA1 ($n = 143$) [13], received osimertinib at the recommended 80 mg once daily dose.

## Results

A total of 1,036 patients were screened at 126 sites in 18 countries; of these, 419 patients were determined to be eligible, provided consent, and were randomized 2:1 to receive osimertinib ($n = 279$) or platinum-based doublet chemotherapy ($n = 140$). Baseline demographics were similar between treatment arms. Key demographic and disease characteristics are summarized in Table 1. At the time of the data cutoff for the PFS analysis, 113 (41%) patients in the osimertinib arm and 120 (88%) patients in the chemotherapy arm had discontinued assigned treatment. Of those randomized to chemotherapy, 82 (59%) patients initiated osimertinib at the time of disease progression.

### Efficacy

Efficacy results are shown in Table 2 and Figure 1. The FDA accepts PFS as a surrogate endpoint for approval if the results of new treatment compared with available therapies are highly robust and clinically and statistically significant [20]. The results of AURA3 demonstrated a clinically meaningful, highly robust, and statistically significant improvement in the primary efficacy endpoint of PFS, according to RECIST version 1.1 as assessed by the investigator, which was supported by the BICR-assessed

 

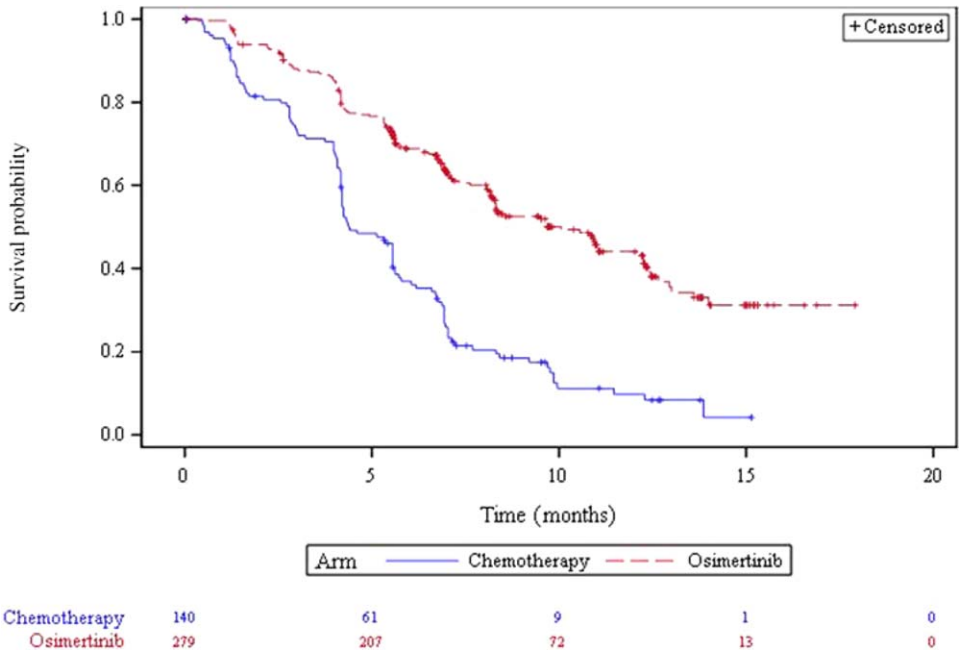


**Figure 1.** Product-limit survival estimates with number of subjects at risk. Kaplan-Meier curves of progression-free survival by investigator assessment in the intent-to-treat population.

**Table 3.** AURA3 exploratory subgroup analysis in 46 (11%) patients with measurable CNS lesions at baseline

| Efficacy parameter | Osimertinib ($n = 30$) | Chemotherapy ($n = 16$) |
|---|---|---|
| CNS objective response rate[a,b] | | |
| Rate (95% CI) | 57% (37%–75%) | 25% (7%–52%) |
| Complete response | 7% | 0% |
| Partial response | 50% | 25% |
| CNS duration of response[c] | | |
| Median DoR, months (range) | NR (1.4–12.5) | 5.7 (1.4–5.7) |

[a]According to RECIST version 1.1.
[b]Based on confirmed response.
[c]Based on patients with response only; DoR defined as the time from the date of first documented response (complete response or partial response) until progression or death event.
Abbreviations: CI, confidence interval; CNS, central nervous system; DoR, duration of response; NR, not reached.

determination of PFS. The treatment effect on PFS is consistent with the findings of a meta-analysis performed by the FDA, showing that in advanced NSCLC, a drug with a large magnitude of effect on ORR is likely to result in a large improvement in PFS [21]. AURA3 also verified the clinical benefit of osimertinib predicted by the BICR-assessed overall response rate of 51%–59% across three trials and the estimated median duration of response of 12.4 months in one of these trials among patients with EGFR T790M mutation-positive, metastatic NSCLC with disease progression on an EGFR TKI. The results from the analysis of CNS ORR and CNS DoR in patients with measurable CNS lesions at baseline provide additional supportive evidence of effectiveness for osimertinib. Table 3 shows intracranial efficacy results by BICR. Approximately 57% (17/30; 95% confidence interval [CI] 39%–74%) of those with CNS metastases at baseline achieved an intracranial response, with 2 patients achieving a complete response in intracranial metastases. In comparison, the CNS response rate in the chemotherapy arm was 25% (4/16; 95% CI 4%–46%).

At the time of the PFS analysis, there were 109 deaths, corresponding to 38% of the events for the planned final analysis. At the time of this interim analysis, there was no significant difference in survival between arms, and the median survival could not be estimated in either arm. Estimates of OS were not reliable because of immaturity of the data.

The approval of the cobas EGFR Mutation Test v2 using ctDNA obtained from K2-ethylenediamine tetraacetic acid (EDTA) plasma specimens was based on the results from a proportion of patients who were screened for enrollment into the AURA2 study. The patients included in the approval were those with valid EGFR T790M mutation-positive or -negative results from tissue who had plasma samples available for testing [14]. The comparison of T790M results between ctDNA and tissue specimens, excluding invalid results, yielded a positive percent agreement of 58.4% (128/219; 95% CI 51.8%–64.8%), a negative percent agreement of 80.4% (90/112; 95% CI 72.0%–86.7%), a positive predictive value of 85.3% (128/150; 95% CI 78.8%–90.1%), and a negative predictive value of 49.7% (90/181; 95% CI 42.5%–56.9%). As limited data were provided for patients who were EGFR T790M mutation-positive in plasma and EGFR mutation-negative or -unknown in tissue, the ctDNA plasma test is indicated to be most appropriate for patients from whom a tumor biopsy cannot be obtained.

## Safety

The safety database was considered adequate in terms of size, exposure to osimertinib, duration of treatment, and disease characteristics with reference to the U.S. target population. The median duration of exposure to osimertinib in the entire safety

**Table 4.** Adverse reactions occurring in ≥10% of patients receiving osimertinib in AURA3

| | Osimertinib ($n = 279$) | | Chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) ($n = 136$) | |
|---|---|---|---|---|
| **Adverse reaction** | **All grades[a]: %** | **Grade 3/4[a]: %** | **All grades[a]: %** | **Grade 3/4[a]: %** |
| Gastrointestinal disorders | | | | |
| Diarrhea | 41 | 1.1 | 11 | 1.5 |
| Nausea | 16 | 0.7 | 49 | 3.7 |
| Stomatitis | 15 | 0 | 15 | 1.5 |
| Constipation | 14 | 0 | 35 | 0 |
| Vomiting | 11 | 0.4 | 20 | 2.2 |
| Skin disorders | | | | |
| Rash[b] | 34 | 0.7 | 5.9 | 0 |
| Dry skin[c] | 23 | 0 | 4.4 | 0 |
| Nail toxicity[d] | 22 | 0 | 1.5 | 0 |
| Pruritus[e] | 13 | 0 | 5.1 | 0 |
| Metabolism and nutrition disorders—Decreased appetite | 18 | 1.1 | 36 | 2.9 |
| Respiratory, thoracic, and mediastinal disorders—Cough | 17 | 0 | 14 | 0 |
| Musculoskeletal and connective tissue disorders—Back pain | 10 | 0.4 | 9 | 0.7 |
| General disorders and administration site conditions—Fatigue[f] | 22 | 1.8 | 40 | 5.1 |

National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
[a]No grade 4 events were reported.
[b]Includes rash, rash generalized, rash erythematous, rash macular, rash maculopapular, rash papular, rash pustular, erythema, folliculitis, acne, dermatitis, and acne dermatitis.
[c]Includes dry skin, eczema, skin fissures, and xerosis.
[d]Includes nail disorders, nail bed disorders, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail ridging, nail toxicity, onychoclasis, onychomadesis, and paronychia.
[e]Includes pruritis, pruritis generalized, and eyelid pruritis.
[f]Includes fatigue and asthenia.

**Table 5.** FDA benefit-risk analysis

| Parameter | Summary |
|---|---|
| Disease | Patients with metastatic NSCLC who have progressed on or after EGFR TKI have a serious and life-threatening condition with a median survival of approximately 2 years. Treatment with standard chemotherapy is associated with limited benefit and results in a wide range of serious toxicities. |
| Unmet medical need | EGFR-positive, metastatic NSCLC is a life-threatening disease. First-line treatment for these patients is primarily first- or second-generation EGFR TKIs (e.g., erlotinib, gefitinib, or afatinib); however, patients typically develop treatment-resistant disease within the first year of treatment. The majority (60%) of these resistances involves the development of EGFR T790M mutations. |
| Clinical benefit | Osimertinib met efficacy standards for accelerated approval based on demonstration of durable ORR of large magnitude in two single-arm trials and now meets efficacy standards for traditional approval based on confirmation of clinical benefit in a large, randomized, adequate, and well-controlled trial (AURA3). The magnitude of effect in the confirmatory trial (AURA3) is large and clinically meaningful and demonstrates a significant improvement in the treatment of an advanced EGFR-mutant NSCLC population with 5-year survival less than 15%. [23] |
| Risk | Overall, the safety of osimertinib appears to be acceptable relative to the benefit. The safety profile compares favorably with the profile of other approved EGFR TKIs and compares favorably with chemotherapy. The larger datasets coupled with longer duration of exposure for the pooled safety analysis did not reveal an increased incidence of the adverse drug events of ILD/pneumonitis, prolonged QTc interval, or decrease in cardiac contractility and are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in the product labeling to allow appropriate management by treating oncologists. |
| Uncertainties | None |
| Conclusions | Osimertinib meets the criteria for regular approval based on a favorable benefit-risk profile for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after TKI therapy. Osimertinib demonstrated an improvement over currently available therapies with a risk profile acceptable compared with the clinical benefit offered. |

Abbreviations: EGFR, epidermal growth factor receptor; FDA, U.S. Food and Drug Administration; ILD, interstitial lung disease; NSCLC, non-small cell lung carcinoma; ORR, objective response rate; QTc, QT interval adjusted for heart rate; TKI, tyrosine kinase inhibitor.

 

database was 16.9 months. In AURA3, the median duration of exposure to osimertinib was 8 months, and all 279 patients randomized to receive osimertinib received at least one dose. Important identified risks of osimertinib include interstitial lung disease (ILD)/pneumonitis, QT interval adjusted for heart rate (QTc) prolongation, and cardiomyopathy. As shown in Table 4, the most common adverse reactions (≥20% of patients) in the osimertinib arm were diarrhea, rash, dry skin, nail toxicity, and fatigue, whereas the most common adverse reactions (≥20% of patients) in the platinum-pemetrexed arm were nausea, decreased appetite, constipation, anemia, rash, and vomiting.

Serious adverse events were reported in 18% of patients treated with osimertinib and 26% of patients treated with chemotherapy. No single serious adverse reaction was reported in 2% or more of patients treated with osimertinib. One patient (0.4%) treated with osimertinib experienced a fatal adverse reaction attributed to ILD/pneumonitis, and one patient treated with chemotherapy died from hypovolemic shock.

The incidence of serious and clinical significant adverse reactions was also evaluated in the pooled safety database ($n = 833$). ILD/pneumonitis occurred in 3.5% ($n = 29$) of osimertinib-treated patients ($n = 833$); 0.6% ($n = 5$) of cases were fatal. These clinical trials did not enroll patients with baseline QTc of greater than 470 msec. Of the 833 patients treated with osimertinib, 0.7% ($n = 6$) developed a QTc greater than 500 msec, and 2.9% of patients ($n = 24$) experienced an increase from baseline QTc greater than 60 msec. No QTc-related arrhythmias were reported. Cardiomyopathy (defined as cardiac failure, congestive heart failure, pulmonary edema, or decreased ejection fraction) occurred in 1.9% ($n = 16$) of 833 patients treated with osimertinib and included 1 (0.1%) fatal event. Left ventricular ejection fraction (LVEF) decline greater than or equal to 10% and a drop to less than 50% occurred in 4.0% (26/655) of patients who had a baseline and at least one follow-up LVEF assessment and was similar between the two treatment arms. Keratitis was reported in 0.7% ($n = 6$) of 833 patients treated with osimertinib.

## Discussion

On March 31, 2017, the FDA granted regular approval to osimertinib based on a favorable benefit-risk assessment for the treatment of T790M mutation-positive metastatic NSCLC following treatment with an EGFR TKI. Table 5 summarizes the FDA benefit-risk analysis. Additionally, an improvement in ORR over chemotherapy was demonstrated, with a similar magnitude to that observed in the trials supporting initial approval (ORR 65%, with median duration of response of 11.0 months).

In an interim analysis of OS, the prespecified boundary was not crossed; patient follow-up will continue until the planned second interim analysis of OS after 205 events and final analysis of OS after 287 events. The extent to which treatment after progression with osimertinib in 59% of those randomized to chemotherapy may impact the overall survival results may present challenges in interpretation of this data.

No important new adverse reactions were identified by the FDA during review of the data supporting the regular approval of osimertinib. The FDA concluded that the risks of osimertinib are acceptable in light of these efficacy results, the seriousness of the disease reflected by the short expected survival times for patients with metastatic EGFR T790M-positive NSCLC, and the lack of satisfactory and safer alternative treatments. Programmed cell death 1/programmed cell death ligand 1 inhibitors, although available in the second line, have demonstrated low response rates in patients harboring EGFR-sensitizing mutations [22]. Based on this favorable benefit-risk assessment, the FDA granted regular approval to osimertinib, providing patients with metastatic NSCLC harboring an EGFR T790M mutation an available option for second-line treatment following treatment with an EGFR TKI. The approval of osimertinib marks the first effective drug developed for use against the emergence of the gatekeeper mutation T790M following prior treatment with EGFR TKI therapy. With regard to approval of the cobas EGFR v2 companion diagnostic, the low agreement observed between plasma and tissue led to the recommendations that (a) presence of T790M mutation should be confirmed in tumor or plasma specimens, (b) testing in plasma is recommended only in patients for whom a tumor biopsy cannot be obtained, and (c) if the mutation is not detected in plasma, then the feasibility for a tumor biopsy should be re-evaluated. Also, the absence of data in the plasma-positive, tissue-negative/unknown population led to a postmarket commitment to study outcomes in this patient population.

## Conclusion

The magnitude of PFS improvement demonstrated in AURA3 was sufficiently large to be considered by the FDA to be direct evidence of clinical benefit; the hazard ratio of 0.30 corresponding to a 5.7-month increase in median PFS is similar to that observed with other targeted agents for treatment of oncogenically driven NSCLC. These results were confirmed by analysis of BICR-assessed PFS, which showed a slightly larger treatment effect; thus, in contrast to usual practice, the FDA included the results of the investigator-assessed PFS in the product labeling. These results, together with the safety profile of osimertinib, resulted in a favorable overall benefit-risk assessment and formed the basis of the FDA's decision to approve osimertinib for the treatment of patients with metastatic NSCLC harboring an EGFR T790M mutation whose disease has progressed on or after EGFR TKI therapy.

## Author Contributions

**Conception/design**: Lauretta Odogwu, Luckson Mathieu, Gideon M. Blumenthal, Erin Larkins, Mallorie H. Fiero, Lisa Rodriguez, Martha Donoghue

**Collection and/or assembly of data**: Lauretta Odogwu, Luckson Mathieu, Gideon M. Blumenthal, Erin Larkins, Mallorie H. Fiero, Lisa Rodriguez, Ingrid Fan, Martha Donoghue

**Data analysis and interpretation**: Lauretta Odogwu, Luckson Mathieu, Gideon M. Blumenthal, Erin Larkins, Mallorie H. Fiero, Lisa Rodriguez, Karen Bijwaard, Eunice Y. Lee, Reena Philip, Martha Donoghue, Patricia Keegan

**Manuscript writing**: Lauretta Odogwu, Luckson Mathieu, Kirsten B. Goldberg, Gideon M. Blumenthal, Erin Larkins, Mallorie H. Fiero, Martha Donoghue, Patricia Keegan, Amy McKee, Richard Pazdur

**Final approval of manuscript**: Lauretta Odogwu, Luckson Mathieu, Kirsten B. Goldberg, Gideon M. Blumenthal, Erin Larkins, Mallorie H. Fiero, Lisa Rodriguez, Karen Bijwaard, Eunice Y. Lee, Reena Philip, Ingrid Fan, Martha Donoghue, Patricia Keegan, Amy McKee, Richard Pazdur

## Disclosures

The authors indicated no financial relationships.

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