

Osimertinib for Previously Treated Patients With Advanced *EGFR* T790M Mutation-Positive NSCLC: Tolerability and Diagnostic Methods From an Expanded Access Program

Edgardo S. Santos · Barry Kaplan · Eli Kirshner · Elisabeth F. Croft ·
Lecia V. Sequist · MyDoanh Chau · Jiefen Munley · Geoffrey R. Oxnard

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ABSTRACT

Introduction: The osimertinib (AZD9291) US Expanded Access Program (EAP) provided compassionate access to osimertinib prior to US Food and Drug Administration (FDA) approval for patients with advanced/metastatic epidermal growth factor receptor (*EGFR*) T790M-positive non-small cell lung cancer (NSCLC) following progression on tyrosine kinase inhibitors (TKIs) targeting *EGFR*. Here, we report the patient demographics, safety and tolerability,

and diagnostic methods used for T790M testing in the EAP.

Methods: Adult patients with *EGFR* T790M-positive NSCLC following progression on prior *EGFR*-TKI therapy (irrespective of line of therapy) were enrolled in the EAP and treated with 80 mg osimertinib once daily until dose reduction, discontinuation, or completion of the EAP following FDA approval (November 2015). Various testing methods were allowed for the required T790M testing.

Results: In total, 248 patients from 25 centers throughout the USA were enrolled in the EAP. The starting dose of 80 mg osimertinib once daily was maintained for 96% ($n = 238$) of patients over the duration of the EAP (median duration of exposure 84 days). Most patients (overall 83% [$n = 205/238$]; patients aged ≥ 75 years 83% [$n = 48/58$]) completed the EAP

MyDoanh Chau is also known as Maiyan Chau.

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E. S. Santos (✉)
Lynn Cancer Institute, Boca Raton, FL, USA
e-mail: esantos@brrh.com

B. Kaplan
Queens Medical Associates, PC–New York-
Presbyterian Queens Hospital, Fresh Meadows, New
York, NY, USA

E. Kirshner
Valley Health System, Westwood, Los Angeles, CA,
USA

E. F. Croft
AstraZeneca, Cambridge, UK

L. V. Sequist
Massachusetts General Hospital, Harvard Medical
School, Boston, MA, USA

M. Chau
AstraZeneca, Gaithersburg, MD, USA

J. Munley
AstraZeneca, Wilmington, DE, USA

G. R. Oxnard
Dana-Farber Cancer Institute, Harvard Medical
School, Boston, MA, USA

and transitioned to commercially available osimertinib following FDA approval. Serious adverse events considered to be treatment related by investigators were reported in five patients (2%), all aged ≥ 65 years, and were dyspnea, deep vein thrombosis, femur fracture, alanine aminotransferase increase, and pneumonitis, respectively. A variety of biospecimen types were collected: solid tumor tissue (73%), blood (20%), cytology (6%), and urine (2%). PCR-based methods were most commonly used for determining *EGFR* mutation status (47%) followed by next-generation sequencing (33%). **Conclusion:** In a real-world setting, osimertinib was well tolerated, and most patients, including patients aged ≥ 75 years, transitioned to commercially available osimertinib following FDA approval. The EAP suggests there has been an uptake of minimally invasive T790M testing methods at some centers.

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Keywords: Compassionate use; EGFR; EGFR-TKI; Non-small cell lung cancer; Osimertinib

INTRODUCTION

The epidermal growth factor receptor (EGFR) pathway is one of the most common oncogenic pathways found either mutated or overexpressed in non-small cell lung cancer (NSCLC) [1–3]. In those patients with EGFR gene (*EGFR*)-sensitizing mutations, the recommended first-line therapy consists of a first- or second-generation tyrosine kinase inhibitor (TKI) that targets EGFR, such as erlotinib, gefitinib, or afatinib [4]. Although EGFR-TKI treatment provides clinical benefit in patients with *EGFR* mutation-positive NSCLC, most patients develop resistance after a median progression-free survival (PFS) of approximately 9–13 months [5–10]. Secondary mutations commonly drive EGFR-TKI-acquired resistance, such as *EGFR* T790M, which is reported in approximately 50–60% of patients with NSCLC following prior TKI therapy [11–15].

Osimertinib is an oral, central nervous system (CNS)-active, third-generation EGFR-TKI that is selective for both *EGFR*-sensitizing and

EGFR T790M resistance mutations [16–18]. Osimertinib was approved in November 2015 by the US Food and Drug Administration (FDA) for patients with metastatic *EGFR* T790M-positive NSCLC, as detected by an FDA-approved test, following progression on EGFR-TKI therapy. The phase 2 and 3 clinical studies (AURA trials) demonstrated that, following progression on EGFR TKI therapy, patients with T790M-positive NSCLC treated with osimertinib had median PFS ranging from 10 to 12 months [18–20]. The objective response rate (ORR) in the phase 3 trial (AURA 3) was 71% (95% confidence interval [CI] 65–76) in patients treated with osimertinib compared with those on chemotherapy (ORR 31%; 95% CI 24–40) [19]. Osimertinib was well tolerated in these trials with low rates of adverse events (AEs) and drug-related AEs, and few study discontinuations. The most common AEs in osimertinib-treated patients were diarrhea (41%), rash (34%), dry skin (23%), and paronychia (22%) [19]. The phase 3 FLAURA trial demonstrated the superior efficacy of osimertinib compared with standard EGFR-TKIs (erlotinib or gefitinib) as first-line treatment for patients with advanced NSCLC and with at least one of the two most common *EGFR*-TKI-sensitizing mutations (i.e., L858R mutation or exon 19 deletion) (PFS 18.9 vs. 10.2 months, respectively; hazard ratio for disease progression or death 0.46; 95% CI 0.37–0.57; $p < 0.001$) [21]. The safety profiles were similar in the two treatment arms in the FLAURA trial, with lower rates of severe (\geq grade 3) AEs with osimertinib than with the standard EGFR-TKIs (34 vs. 45%) [21]. The US osimertinib (AZD9291) Expanded Access Program (EAP) was developed to provide compassionate access to osimertinib in the USA after enrollment in clinical trials had closed but prior to FDA approval for patients with advanced or metastatic *EGFR* T790M-positive NSCLC following progression on prior EGFR-TKI therapy. Here, we report the real-world patient demographics, the safety and tolerability, and the diagnostic methods used for T790M testing in the EAP in patients treated with osimertinib.

METHODS

Expanded Access Program

The US AZD9291 EAP was open for enrollment from May 29, 2015, to November 20, 2015, prior to FDA approval of osimertinib. Following FDA approval and at investigator discretion, patients benefiting from osimertinib could be transitioned to the commercially available product within approximately 60 days. Patient visits and medical care in the EAP were performed at the discretion of the treating physician and per standard of care.

Adult patients (aged ≥ 18 years) with locally advanced or metastatic *EGFR* T790M-positive NSCLC not amenable to curative surgery or radiotherapy and with a World Health Organization performance status of 0–2 who received ≥ 1 line of prior therapy including ≥ 1 EGFR-TKIs were eligible. T790M-positive status determined from any biospecimen type and any testing platform was considered to be sufficient for EAP entry. Patients with symptomatic CNS metastases who were neurologically unstable or had a past medical history of interstitial lung disease (ILD), previous treatment with osimertinib, treatment with EGFR-TKIs within 7 days before program initiation, cytotoxic chemotherapy within 14 days of program initiation, or any unresolved grade ≥ 3 toxicity from prior therapy (based on Common Terminology Criteria for Adverse Events) were excluded. There were no restrictions on concomitant drugs other than potent cytochrome P450 3A4 inhibitors and inducers. Investigators were advised that medical products known to have interactions with osimertinib, such as those that may increase or decrease osimertinib exposure, should be avoided.

Osimertinib was administered at a dose of 80 mg once daily but could be reduced to 40 mg once daily if patients experienced a grade ≥ 3 and/or unacceptable toxicity (any grade) considered to be related to the osimertinib therapy by the investigator. The once-daily 80 mg dose of osimertinib was chosen based on the available safety, tolerability, pharmacokinetics, and efficacy data from a phase 1 clinical trial in a

similar patient population [15]. Patients (except for those with insulin-dependent diabetes) fasted for ≥ 1 h prior to dosing and ≥ 2 h post dose. Doses were administered approximately 24 h apart at the same time each day. Missed doses were permitted within a 12-h window; otherwise, the next scheduled dose was administered.

Compliance with Ethics Guidelines

This EAP was approved by the FDA and institutional review boards, was performed in accordance with the ethical principles outlined in the Declaration of Helsinki, and was consistent with the International Conference on Harmonisation/Good Clinical Practice Guidelines. Patients provided informed consent prior to enrollment.

Diagnostic Testing

For required T790M diagnostics, various testing methods and biospecimen types were permitted for analysis, and all tumor biopsy platforms were accepted. At baseline, information regarding biospecimen samples used for mutational testing was collected, including laboratory name and location, biospecimen type collected (tissue, plasma, urine, cytology), site of tissue-biopsy sample, testing methodology and platforms, and the test result. Descriptions of specific testing methods and platforms were limited to the information provided by each investigator. Samples were submitted to a local Clinical Laboratory Improvement Amendments-certified laboratory for T790M testing using an appropriately validated test when available. Alternatively, the sample was sent to a designated local or central laboratory for analysis.

Data Collection

This program was not designed to assess the real-world effectiveness of osimertinib, and disease response was collected at investigator discretion but not mandated by the EAP protocol. Data collection prior to program initiation

was limited to information required to determine patient eligibility, demographics, and prior cancer treatments. During the program, data on osimertinib exposure, start and stop dates, and reason for discontinuation were collected. Patients were followed for safety evaluation until 30 days following the last dose of osimertinib. Investigators were required to collect and report serious AEs (SAEs) from the time of informed consent through the time of the follow-up contact at 30 days after the last dose. Data on non-serious AEs were not consistently collected by investigators in the EAP.

Statistical Analysis

All analyses were based on the full analysis set, which consisted of patients who received ≥ 1 dose of osimertinib. Statistical analyses were performed using SAS® version 9.3 software (SAS Institute, Cary, NC, USA). Descriptive statistics were used for continuous and categorical variables. Because the incidence of missing measurements was expected to be low, these were not imputed.

RESULTS

Patient Characteristics

A total of 248 patients from 25 centers across the USA were enrolled and treated with osimertinib as part of the EAP. Enrollment in the EAP increased from May through October and decreased around the time of FDA approval of osimertinib, which was November 13, 2015 (Fig. 1). The median age of patients was 65 (range 31–91) years, including 127 patients (51%) aged ≥ 65 years (Table 1), among whom 58 (23%; 58/248) were aged ≥ 75 years. The majority of patients were female (69%) and white (71%). As per the inclusion criteria for the EAP, all patients had received ≥ 1 prior TKI treatment, and most patients (85%) had received ≥ 2 prior cancer treatments. Erlotinib was the most commonly reported prior EGFR-TKI therapy (95%; $n = 236$; Fig. 2). Seventy patients (28%) had received prior treatment

with afatinib, and 36 patients (15%) had received rociletinib. Patients in the EAP were heavily pretreated. The distribution of the most common chemotherapy regimens used (administered to > 20 patients) prior to osimertinib EAP was: carboplatin and pemetrexed ($n = 68$; 27%); cisplatin and pemetrexed ($n = 25$; 10%); pemetrexed ($n = 25$; 10%); nivolumab ($n = 23$; 9%); carboplatin and paclitaxel ($n = 22$; 9%); and carboplatin, paclitaxel, and bevacizumab ($n = 21$; 8%).

Patient Disposition and Duration of Exposure

Once osimertinib was approved in the USA on November 13, 2015, most patients (83%; $n = 205$) transitioned to commercial osimertinib treatment and thus were considered as having completed the EAP (Table 2). Median program duration was 84 (range 3–252) days for the overall population and 90 (range 18–212) days in patients who transitioned to the commercial supply. A total of 115 patients remained on treatment for > 90 days, of whom approximately 90% ($n = 103$) transitioned to commercially available osimertinib. Of the 36 patients with prior treatment with rociletinib, 29 (81%) transitioned to the commercial supply of osimertinib. Among the 43 patients who discontinued the EAP treatment, the most common reasons were disease progression ($n = 17$) and death ($n = 12$; Table 2). In the population aged ≥ 75 years, 48 of 58 patients (83%) converted to the commercial supply; the remaining ten patients discontinued the EAP because of disease progression ($n = 5$), death ($n = 3$), or patient decision ($n = 2$).

The starting dose of 80 mg osimertinib administered once daily was maintained over the entire program duration for 96% ($n = 238$) of patients. Ten patients (4%) had their dose of osimertinib reduced from 80 to 40 mg once daily because of treatment intolerance ($n = 3$), AEs ($n = 1$), or other reasons ($n = 6$; Table 2). Most dose reductions ($n = 9$) were reported in patients aged ≥ 65 years. One dose reduction was reported for a patient in the population aged < 65 years, and six were reported in the

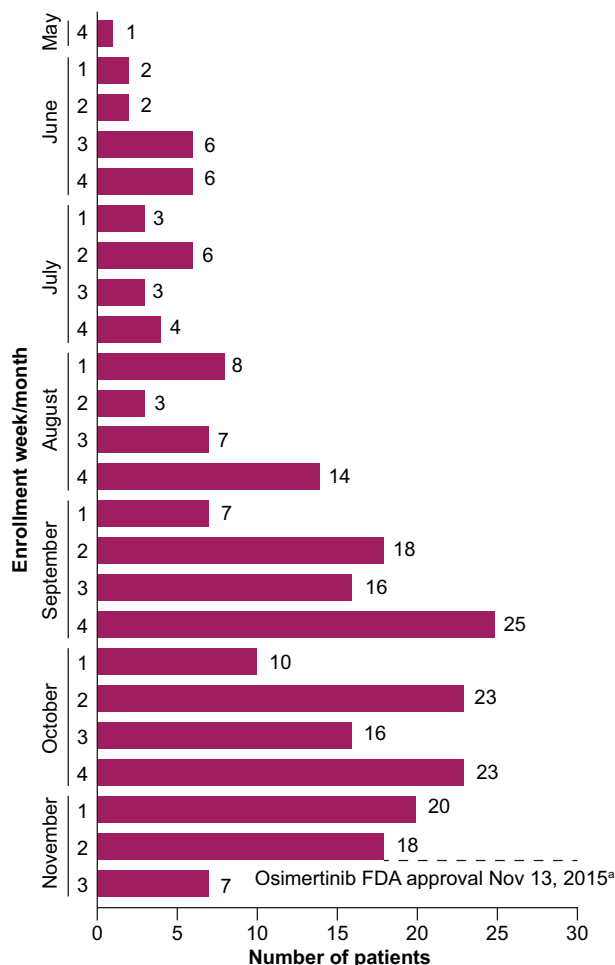


Fig. 1 Enrollment chart of the Expanded Access Program. Date of informed consent indicates when a patient was enrolled. ^aOsimertinib was approved in the USA by the US Food and Drug Administration (FDA) on November 13, 2015 for the treatment of patients with metastatic

epidermal growth factor receptor gene (*EGFR*) T790M-positive non-small cell lung cancer, as detected by a US FDA-approved test, whose disease had progressed on or after therapy with a tyrosine kinase inhibitor targeting EGFR

population aged ≥ 75 years. Dose interruption occurred in 12 patients (5%), with the most common reason being SAEs ($n = 1$), intolerance ($n = 1$), or other ($n = 10$); the majority of these SAEs ($n = 9$) were observed in patients aged ≥ 75 years.

Safety

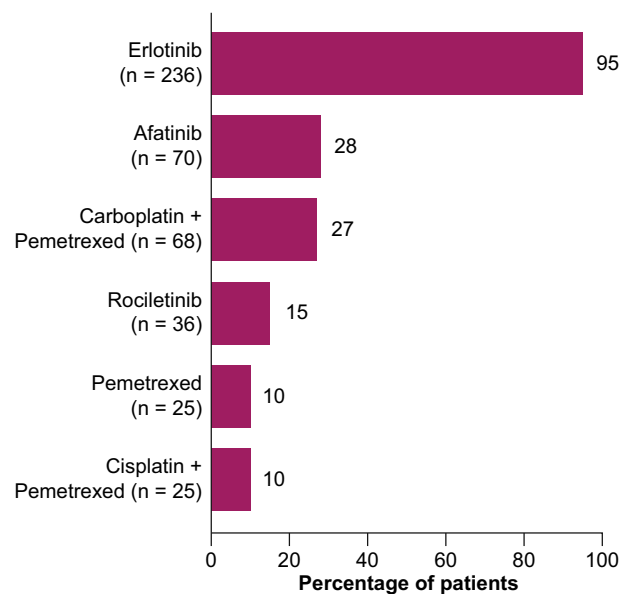
During the EAP, SAEs were reported in 19% (48/248) of all patients (Table 3) and in 28% (16/58) of patients aged ≥ 75 years. The majority of SAEs were considered by the investigators to be

unrelated to osimertinib, with the exception of five patients (2%) who developed dyspnea, deep vein thrombosis (DVT), femur fracture, alanine aminotransferase (ALT) increase, and pneumonitis. Investigators considered the SAEs in these five patients to be related to osimertinib. All five patients were aged ≥ 65 years, including four patients aged ≥ 75 years.

A total of 19 deaths (8%) were reported during the EAP, most of which were attributed to disease progression and/or respiratory complications ($n = 16$; 84%). The reported case of pneumonitis in a 75-year-old female patient was

Table 1 Patient demographics

Patient demographics	All patients (N = 248)	Patients aged < 65 years (n = 121)	All patients aged ≥ 65 years (n = 127)	All patients aged ≥ 75 years (n = 58)
Median age, years (range)	65 (31–91)	56 (31–64)	74 (65–91)	79 (75–91)
Sex, n (%)				
Female	171 (69)	81 (67)	90 (71)	42 (72)
Male	77 (31)	40 (33)	37 (29)	16 (28)
Race, n (%)				
White	175 (71)	84 (69)	91 (72)	48 (83)
African American	12 (5)	6 (5)	6 (5)	1 (2)
Asian	51 (21)	25 (21)	26 (20)	8 (14)
Other	10 (4)	6 (5)	4 (3)	1 (2)

**Fig. 2** Overall prior cancer treatments (includes prior cancer treatments received by $\geq 10\%$ of overall population). A patient can have more than one prior cancer treatment

fatal and deemed by the investigator to be related to treatment; however, because the patient died outside of the clinical trial, and the case was retrospectively reported, the diagnosis could not be confirmed owing to the limited clinical information available. Other causes of

death unrelated to osimertinib included cerebrovascular diseases and CNS infection ($n = 1$), hypotension and kidney failure ($n = 1$), and acute cerebrovascular accident and disseminated intravascular coagulation ($n = 1$).

Table 2 Patient disposition: drug exposure and dose modifications

	All patients (<i>N</i> = 248)	Patients aged < 65 years (<i>n</i> = 121)	All patients aged ≥ 65 years (<i>n</i> = 127)	All patients aged ≥ 75 years (<i>n</i> = 58)
Patients who converted to commercial supply ^a , <i>n</i> (%)	205 (83)	99 (82)	106 (84)	48 (83)
Reasons for withdrawal prior to EAP completion, <i>n</i> (%)				
Disease progression	17 (7)	8 (7)	9 (7)	5 (9)
Death	12 ^b (5)	5 (4)	7 (6)	3 (5)
Other	6 ^c (2)	5 (4)	1 (1)	0
Patient decision	3 (1)	0	3 (2)	2 (3)
Adverse event	2 ^d (1)	1 (1)	1 (1)	0
Lost to follow-up	2 ^e (1)	2 (2)	0	0
Investigator decision	1 (0.4)	1 (1)	0	0
Median duration of exposure, days (range)	84 (3–252)	NR	NR	NR
Median duration of exposure in EAP-completed patients, days (range)	90 (18–212)	NR	NR	NR
Dose modifications, <i>n</i> (%)				
Dose reduction	10 (4)	1 (1)	9 (7)	6 (10)
Treatment intolerance	3 (1)	0	3 (2)	2 (3)
SAE	1 ^f (0.4)	0	1 (1)	1 (2)
Other	6 ^g (2)	1 (1)	5 (4)	3 (5)
Dose interrupted	12 (5)	3 (3)	9 (7)	9 (16)
Treatment intolerance	1 (0.4)	0	1 (1)	1 (2)
SAE	1 ^h (0.4)	1 (1)	0	0
Other	10 ⁱ (4)	2 (2)	8 (6)	8 (14)

EAP Expanded access program, NR not reported; SAE serious adverse event

^a Approval by the US Food and Drug Administration (FDA) was received November 13, 2015

^b There were 19 deaths reported in the EAP; 7 had study disposition categories other than death reported before the date of death

^c Other includes 2 comorbidities, 3 international patients, and 1 patient decision

^d Adverse events were mental status change (unrelated) and dyspnea (drug-related)

^e Unsuccessful contact with patient despite every effort made by clinician

^f Fatigue and dyspnea (unrelated to drug)

^g Other reasons for dose reduction included adverse events such as rash, diarrhea, vomiting, fatigue, tachycardia, physician discretion, and dry mouth

^h Constipation and seizure (unrelated to drug)

ⁱ Other reasons for dose interruption included feeling unwell, brain radiation, urinary tract infection, thrombocytopenia, respiratory issues, fatigue, hospitalization, suspected pneumonitis that was subsequently ruled out by X-ray, and insurance coverage

Table 3 Patient safety

Patient safety	All patients (<i>N</i> = 248)	Patients aged < 65 years (<i>n</i> = 121)	All patients aged ≥ 65 years (<i>n</i> = 127)	Patients aged ≥ 75 years (<i>n</i> = 58)
Patients with SAEs, <i>n</i> (%)	48 (19)	20 (17)	28 (22)	16 (28)
Number of reported SAEs, <i>n</i>	92	37	55	33
Patients with drug- related SAEs, <i>n</i> (%)	5 (2)	0	5 (4)	4 (7)
Number of drug-related SAEs, <i>n</i>	5	0	5	4
Drug-related SAEs	See age group results	None	ALT increase, DVT, dyspnea, femur fracture, pneumonitis	

ALT Alanine aminotransferase; *DVT* deep vein thrombosis; *SAE* serious adverse event

Diagnostic Testing and Program Centers

All 248 patients had *EGFR* T790M-positive NSCLC, which was determined at screening. In this real-world setting, various biospecimen types (tissue, blood, cytology, and urine) and diagnostic testing methods were used to confirm T790M mutation status (Table 4). Overall, the majority of biospecimens tested (73%; *n* = 180) were solid tumor tissue samples; blood specimens were collected from 49 patients (20%).

Variation in biospecimen type was reported among and within EAP centers, which were located across the USA (Fig. 3). The majority of EAP centers (*n* = 19) used more than one biospecimen type for testing, and the remaining six centers used only one biospecimen type. Of the 25 centers conducting diagnostic testing, 23 used tissue, 19 used blood, six used cytology, and three used urine. Overall, a total of 80% (*n* = 20) of EAP centers obtained specimens for testing using minimally invasive methods from blood or urine.

PCR-based methods as well as sequencing methods, such as bidirectional and next-generation sequencing (NGS), were the most common methodologies for determining T790M mutation status and varied within the EAP (Table 4). PCR-based methods were the most

commonly used among the different EAP centers (47%; *n* = 117). NGS was utilized in 33% (*n* = 82) of testing cases and was the only method used across all biospecimen collection types. Specific platforms commonly reported (≥ 10 samples) included Guardant360 (*n* = 30; Guardant Health, Redwood City, CA, USA), FoundationOne® (*n* = 18; Foundation Medicine, Cambridge, MA, USA), SNaPshot® (*n* = 17; Life Technologies, Carlsbad, CA, USA), the cobas® *EGFR* Mutation Test (*n* = 11; Roche Molecular Diagnostics, Pleasanton, CA, USA), and GeneStrat® (*n* = 10; Biodesix®, Boulder, CO, USA).

DISCUSSION

In this article, we report data obtained from 248 patients who received expanded access to osimertinib, an oral, CNS-active, third-generation TKI that is selective for both *EGFR*-sensitizing and *EGFR* T790M resistance mutations. The US osimertinib EAP provided compassionate access to the agent for patients with *EGFR* T790M-positive NSCLC following the development of resistance to first- and second-generation *EGFR*-TKIs. As the EAP was not intended to evaluate the real-world effectiveness of osimertinib for treating these patients, the focus of our report is on the demographics and disposition

Table 4 Diagnostic biospecimen type and testing methods

Biospecimen type	PCR			Sequencing				Other ^b	Unknown		
	PCR			Bidirectional		Total sequencing					
	PCR	RT-PCR	Digital	Other ^c	Total PCR	NGS	Other			Total sequencing	
Tissue, <i>n</i> = 180	52	26	5	5	88	4	41	1 ^d	46	4	42
Blood, <i>n</i> = 49	2	0	15	2	19	0	30	0	30	0	0
Cytology, <i>n</i> = 14	8	1	1	0	10	0	1	1 ^e	2	0	2
Urine, <i>n</i> = 4	0	0	0	0	0	0	4	0	4	0	0
Total, <i>N</i> = 247 ^a	117				82					4	44

NGS Next-generation sequencing; RT-PCR real-time PCR

^a *N* = 247; there was one unknown biospecimen sample type for which the data are not shown

^b Other diagnostic testing methods include those biospecimens analyzed by mass spectrometry (*n* = 3) and restriction fragment length polymorphisms (*n* = 1)

^c Detailed data regarding “PCR Other” diagnostic testing methods were not available

^d Diagnostic testing method was pyrosequencing

^e Diagnostic testing method was Sanger sequencing

of patients, the safety and tolerability of the agent, and the methods of evaluation of T790M mutation status. The data obtained suggest that osimertinib was generally well tolerated and that there is uptake of minimally invasive T790M testing methods at some centers that use blood and urine as biospecimens.

The EAP was terminated when osimertinib was made commercially available following its FDA approval in November 2015 for the treatment of this patient population. Because the majority of patients were continuing to receive benefit from osimertinib therapy at the end of the EAP, most patients (83%) transitioned to commercial use. The rate of completers was the same regardless of age, including patients aged ≥ 75 years (83%). This suggests that osimertinib was well tolerated, even in those who potentially had significant comorbidities or who were in generally poorer health, and is consistent with previous studies that have shown that EGFR-TKIs are well tolerated with a mild toxicity profile in elderly patient populations [22, 23]. Historically, clinicians have been reluctant to aggressively treat older patients owing to a fear of a greater risk of toxicities [24], but 50% of patients with NSCLC are aged > 70 years at diagnosis [23]. Thus, identifying agents, such as osimertinib, that are well tolerated in this population is clinically relevant.

A requirement for entry into the EAP was that all patients had to have received ≥ 1 prior TKI treatment regardless of the number of treatments received; most patients (85%) had received ≥ 2 prior cancer treatments. Prior TKI therapies included erlotinib (95%), afatinib (28%), and rociletinib (15%). It should be noted that gefitinib was not approved in the USA until after the initiation of the EAP. Thus, this was a heavily pretreated population, and although efficacy was not assessed as part of the EAP, the high proportion of patients who transitioned to a commercial supply of osimertinib indicates that these patients continued to derive clinical benefit from T790M inhibition following progression. These results support the clinical trials program (AURA trials) for osimertinib that demonstrated clinical benefit in patients who had previously received prior EGFR-TKI therapy

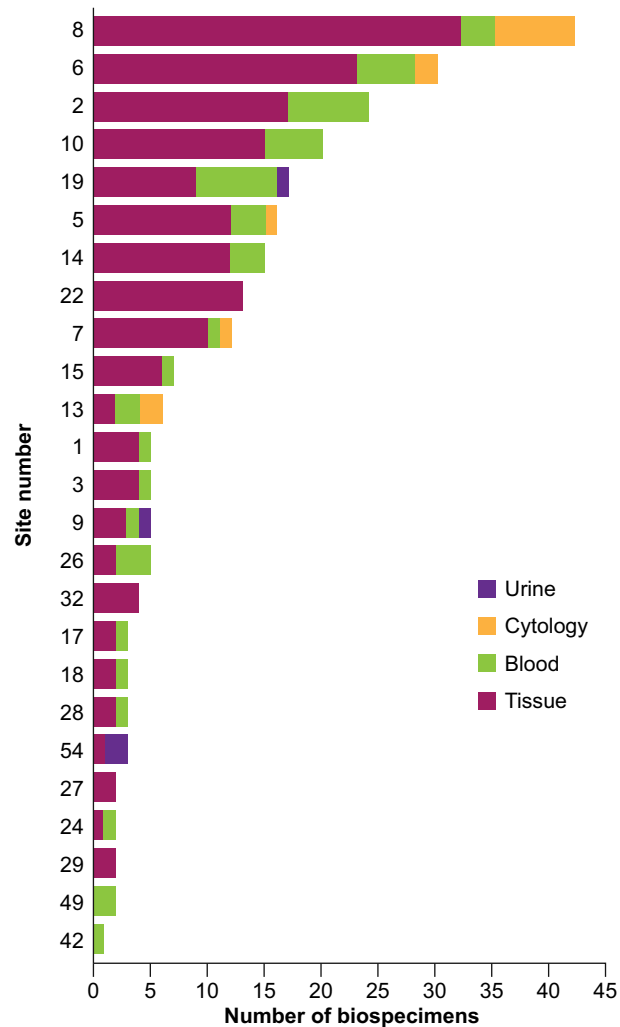


Fig. 3 Diagnostic biospecimen type by program site. $N = 247$ known biospecimens; data for unknown biospecimen sample type ($n = 1$) are not shown

with gefitinib (52–62%), erlotinib (34–63%), or afatinib (3–26%) [18–20]. Additional studies have also investigated the use of osimertinib in patients treated with rociletinib [25, 26]. In one study, of the nine patients treated with rociletinib and subsequent osimertinib, three patients experienced a partial response, four had stable disease, and two had progressive disease, resulting in a 78% disease control rate [25]. In a retrospective analysis of patients treated with osimertinib following prior rociletinib treatment (US AZD9291 EAP and commercial patients), the ORR and disease control rates were 33 and 82%, respectively [26]. Together, these studies demonstrate that, in the real-

world setting, patients can receive clinical benefit from osimertinib following the development of EGFR-TKI resistance, also including resistance to prior third-generation EGFR-TKIs.

The overall safety profile of osimertinib in this real-world setting was consistent with that reported in controlled clinical trials [15, 18–20]. It should be noted that there were five reports of SAEs that were deemed to be treatment-related by the investigator: dyspnea, ALT increase, DVT, femur fracture, and pneumonitis. All of these five patients, however, had other comorbidities or underlying conditions that could provide possible alternative explanations for the development of these SAEs. The frequency of

pneumonitis was also similar to that observed in previous studies in which single cases of serious or fatal pneumonitis were reported [18–20]. ILD was not observed in this patient population but has been reported in 2–4% of patients in previously published clinical trials [18–20]. The low incidence rates of dose reduction (4%) and discontinuation (5%) in the EAP are similar to those observed in published clinical studies [15, 18–20]. The phase 2 study (AURA2) in patients with *EGFR* T790M-positive NSCLC treated with osimertinib reported dose reductions and discontinuations in 3 and 5% of patients, respectively [20], with the phase 2 study extension component (AURA Extension) reporting rates of 5 and 7%, respectively [18]. In the phase 3 trial (AURA3), 7% of patients treated with osimertinib discontinued therapy [19].

Current National Comprehensive Cancer Network (NCCN) guidelines recommend testing for T790M with disease progression after first-line *EGFR*-TKI therapy [4]. A positive T790M mutation status can guide the decision to switch to osimertinib, which targets both *EGFR*-sensitizing and *EGFR* T790M resistance mutations [16–18]. Prior to FDA approval of osimertinib, diagnostic testing upon disease progression while on *EGFR*-TKIs had not been routine in the USA outside of clinical trials. Now, the guidelines recommend not only *EGFR* T790M testing using standard biopsy samples, but also the use of the so-called “liquid biopsy” if tissue biopsy is not feasible [4]. However, if a plasma-based test is negative for the T790M mutation, re-testing via a tissue-based method should be considered [4, 27, 28].

The type of biospecimen collected or the method used for diagnostic analysis was not restricted in this EAP. Although the majority (92%) of EAP centers used tissue-collection methods, many EAP centers (80%) also used minimally invasive collection methods for testing involving blood or urine, indicating early uptake of these minimally invasive methods at some centers and providing real-world evidence of their feasibility. Descriptions of the testing methods were limited to the data provided by each investigator, and information on why specific methods were used was not collected in the EAP. Other studies have

demonstrated the feasibility of minimally invasive testing in both real-world and clinical trial settings [18, 19, 28–31]. With the introduction of osimertinib, an FDA-approved companion diagnostic test, the cobas® *EGFR* Mutation Test v2, for both tissue and plasma *EGFR* T790M testing was also approved [32].

Although the EAP we describe here provided real-world data regarding the safety of osimertinib and the testing methodology used for T790M analysis, there were some limitations to this program. Because most patients transitioned to the commercial supply of osimertinib after FDA approval, thus completing the EAP, the total duration of treatment with osimertinib was not captured. Furthermore, this EAP did not mandate the collection of patient response data, and, therefore, data on the efficacy of osimertinib for the entire patient population are not available. This contrasts with expanded access and compassionate-use programs conducted with other *EGFR*-TKIs in patients with NSCLC that have been reported in the literature [33–37]. We did not aim to provide outcomes-related data for enrolled patients, primarily because the anticipated length of the osimertinib program would preclude any meaningful data collection. The EAP lasted approximately 6 months, which was much shorter than the expected median PFS of 10–12 months as previously reported for osimertinib [18–20]. Other published access programs were designed differently (patient population and duration) and were long enough to provide sufficient outcomes relative to the therapy of interest [33–37].

CONCLUSIONS

This assessment of the short (approx. 6-month) EAP for osimertinib with robust enrollment due to an unmet need in thoracic oncology at that time shows that osimertinib was well tolerated in previously and heavily treated patients with *EGFR* T790M-positive NSCLC, as demonstrated by the low rates for both dose reduction and discontinuation of osimertinib and the high rates of conversion to the commercially available agent after approval of osimertinib by the

FDA. The results also show that testing at disease progression for T790M in patients with *EGFR* mutation-positive NSCLC is achievable in a real-world, non-trial setting and that there is uptake of minimally invasive collection methods for testing in this population. Testing for T790M remains an important step in patients with advanced *EGFR* mutation-positive NSCLC following disease progression and serves as a guide to the selection of osimertinib for appropriate patients.

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Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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