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RAPID COMMUNICATION

Osimertinib As First-Line Treatment of *EGFR* Mutation–Positive Advanced Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose

The AURA study (ClinicalTrials.gov identifier: NCT01802632) included two cohorts of treatment-naïve patients to examine clinical activity and safety of osimertinib (an epidermal growth factor receptor [EGFR] –tyrosine kinase inhibitor selective for EGFR–tyrosine kinase inhibitor sensitizing [*EGFR*m] and *EGFR* T790M resistance mutations) as first-line treatment of *EGFR*-mutated advanced non–small-cell lung cancer (NSCLC).

Patients and Methods

Sixty treatment-naïve patients with locally advanced or metastatic *EGFR*m NSCLC received osimertinib 80 or 160 mg once daily (30 patients per cohort). End points included investigator-assessed objective response rate (ORR), progression-free survival (PFS), and safety evaluation. Plasma samples were collected at or after patients experienced disease progression, as defined by Response Evaluation Criteria in Solid Tumors (RECIST), to investigate osimertinib resistance mechanisms.

Results

At data cutoff (November 1, 2016), median follow-up was 19.1 months. Overall ORR was 67% (95% CI, 47% to 83%) in the 80-mg group, 87% (95% CI, 69% to 96%) in the 160-mg group, and 77% (95% CI, 64% to 87%) across doses. Median PFS time was 22.1 months (95% CI, 13.7 to 30.2 months) in the 80-mg group, 19.3 months (95% CI, 13.7 to 26.0 months) in the 160-mg group, and 20.5 months (95% CI, 15.0 to 26.1 months) across doses. Of 38 patients with postprogression plasma samples, 50% had no detectable circulating tumor DNA. Nine of 19 patients had putative resistance mechanisms, including amplification of *MET* (n = 1); amplification of *EGFR* and *KRAS* (n = 1); *MEK1*, *KRAS*, or *PIK3CA* mutation (n = 1 each); *EGFR* C797S mutation (n = 2); *JAK2* mutation (n = 1); and *HER2* exon 20 insertion (n = 1). Acquired *EGFR* T790M was not detected.

Conclusion

Osimertinib demonstrated a robust ORR and prolonged PFS in treatment-naïve patients with *EGFR*m advanced NSCLC. There was no evidence of acquired *EGFR* T790M mutation in postprogression plasma samples.

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INTRODUCTION

In patients with oncogenic driver mutations, including epidermal growth factor receptor (*EGFR*), treatment with targeted therapies results in superior outcomes compared with chemotherapy.[1] *EGFR* mutations are a predictive biomarker for high response rate and progression-free survival (PFS) benefit with EGFR tyrosine kinase inhibitor (TKI) treatment.[2] EGFR-TKIs are standard first-line therapy for patients with advanced-stage non–small-cell lung cancer (NSCLC) harboring EGFR-TKI–sensitizing mutations (*EGFR*m).[1,3,4]

Erlotinib, gefitinib, and afatinib are approved EGFR-TKIs for patients with treatment-naïve *EGFR*-mutant lung cancer.[1,3,4] A meta-analysis of randomized trials of treatment-naïve patients reported a median PFS of 11.0 months in patients treated with EGFR-TKIs compared with 5.6 months in patients treated with chemotherapy.[5] Despite initial responses to EGFR-TKIs, most patients ultimately develop acquired resistance, with approximately 60% of such patients harboring the *EGFR* T790M resistance mutation.[6,7]

Osimertinib is a potent, irreversible EGFR-TKI, selective for both *EGFR*m and *EGFR* T790M

ASSOCIATED CONTENT

Data Supplement
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resistance mutations.[8-11] Previously reported data from the AURA study have shown osimertinib to be highly active in patients with *EGFR* T790M–mediated resistance to prior EGFR inhibitors (overall response rate [ORR], 62% to 70%; median PFS, 9.9 to 12.3 months),[12,13] and more effective than platinum-based chemotherapy (ORR, 71% with osimertinib *v* 31% with chemotherapy; median PFS, 10.1 *v* 4.4 months, respectively).[14] After these positive outcomes,[12-15] osimertinib is indicated for patients with metastatic *EGFR* T790M–positive NSCLC after experiencing disease progression on or after EGFR-TKI therapy.[16,17]

In preclinical studies, osimertinib has demonstrated ability to delay emergence of resistance in *EGFR*m tumors,[18,19] and deeper, more sustained inhibition of tumor growth compared with gefitinib in PC9 (*EGFR* exon 19 deletion [ex19del]) tumor xenograft models.[8] *EGFR* T790M has not emerged as a resistance mechanism to osimertinib in preclinical models.[18,19] Together, these data suggest osimertinib could be effective, and potentially delay emergence of resistance, as initial therapy in patients harboring *EGFR*m. The phase I dose-escalation and expansion parts of AURA, an open-label, multicenter study of patients who had experienced disease progression on prior EGFR-TKIs, have been reported previously.[9] The AURA study also included two cohorts of treatment-naïve patients. We present the clinical activity and safety results in these patients who received osimertinib as first-line treatment of *EGFR*m advanced NSCLC.

PATIENTS AND METHODS

Patients

Eligible patients age at least 18 years had histologic or cytologic documentation of locally advanced or metastatic NSCLC with measurable disease at baseline. Detection of *EGFR*m in tumor tissue was required by local or central test. CNS metastases were allowed, provided patients were asymptomatic, stable, and did not require corticosteroids for at least 4 weeks before starting treatment. Patients with history of interstitial lung disease or who had received prior therapy for advanced disease were not eligible.

Study Design and Treatment

Two first-line treatment cohorts were included in the dose expansion part as a secondary objective of the AURA study (Data Supplement) to investigate safety and tolerability and provide an initial assessment of potential efficacy of osimertinib in treatment-naïve patients with *EGFR*m advanced NSCLC.[20] There was no primary statistical end point used to justify the sample size of these cohorts. Sequential patient cohorts received oral osimertinib at a dose of 80 mg or 160 mg once daily until progression (defined according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) or discontinuation criteria were met. Patients could continue osimertinib beyond RECIST-defined progression provided that clinical benefit continued (as judged by the investigator).

Study Assessments

Clinical assessments. Clinical activity end points included investigator-assessed ORR, duration of response (DOR), and PFS. End point definitions are provided in the Data Supplement. Safety and tolerability were assessed using adverse events (AEs) graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.[21]

Translational assessments. Plasma samples were collected before dose (baseline) during the screening period and at or after radiologic progression according to RECIST, version 1.1. Circulating tumor DNA (ctDNA) extracted from baseline plasma samples was analyzed using BEAMing digital polymerase chain reaction (Sysmex Inostics, Mundelein, IL) for the following three *EGFR* mutations: ex19del, L858R, and T790M, as described previously.[22] Plasma samples collected at or after progression (as well as paired baseline samples, where available) were analyzed using next-generation sequencing (NGS) panels, as previously described (56-gene panel [AstraZeneca, Cambridge, United Kingdom] and 73-gene panel [Guardant Health, Redwood City, CA]; Data Supplement).[23,24] Clinical response was investigated in patients with de novo T790M mutations detected by central tissue testing (cobas; Roche Molecular Diagnostics, Pleasanton, CA) and/or plasma testing at baseline (BEAMing).

Study Oversight

The AURA phase I component was approved by the independent institutional review board or independent ethics committee associated with each study center. The study was performed in accordance with the provisions of the Declaration of Helsinki (as defined by the International Conference on Harmonization), Good Clinical Practice and applicable regulatory requirements, and with the policy on bioethics and human biologic samples of the trial sponsor, AstraZeneca. Informed consent was obtained from all patients before initiation of the study. This trial was funded by the sponsor and designed by the principal investigators and the sponsor. The data cutoff was November 1, 2016.

Statistical Analysis

The evaluable for response analysis set included all dosed patients with a baseline RECIST assessment; all patients assigned to the first-line treatment cohorts received treatment and were therefore evaluable for response. The denominator for calculation of ORR included all patients who could be evaluated for response. DOR and PFS were calculated using the Kaplan-Meier method. The safety analysis set included all patients who received at least one dose of osimertinib.

RESULTS

Patients and Treatment

Of 60 treatment-naïve patients with *EGFR*m NSCLC who received osimertinib treatment, 30 received 80 mg once daily and 30 received 160 mg once daily. Patient demographics and baseline characteristics were similar across doses (Table 1; Data Supplement).

At data cutoff, 25 (42%) of 60 patients were still receiving study treatment, including 12 patients in the 80-mg group and 13 patients in the 160-mg group. Thirty-five patients (58%) had discontinued study treatment; 24 patients (40%) discontinued as a result of progressive disease, five (8%) as a result of AEs, three (5%) as a result of patient decision, and three (5%) for other reasons (clinical progression, n = 1; to start another anticancer therapy, n = 2). Median duration of RECIST follow-up at data cutoff was 19.1 months (17.0 months for the 80-mg group and 19.3 months for the 160-mg group). Median total treatment duration was 26.3 months (range, 0.5 to 34.6 months).

Clinical Activity

Confirmed ORR was 67% (95% CI, 47% to 83%) in the 80-mg group, 87% (95% CI, 69% to 96%) in the 160-mg group, and 77% (95% CI, 64% to 87%) across doses. ORR by *EGFR* mutation status is listed in Table 2. The overall disease control rate was 93% (95% CI, 78% to 99%) in the 80-mg group, 100% (95% CI, 88% to 100%) in the 160-mg group, and 97% (95% CI, 89% to 100%) across doses. Mean best percentage change in target lesion size was −48% across doses (standard deviation [SD], 22%; Fig 1).

Table 1. Baseline Characteristics Across Dose Levels

Characteristic	Osimertinib Dose		Total (N = 60)
	80 mg (n = 30)	160 mg (n = 30)	
Sex, No. (%)			
Male	10 (33)	5 (17)	15 (25)
Female	20 (67)	25 (83)	45 (75)
Median age, years (range)	62.5 (40-77)	65.0 (38-91)	63.5 (38-91)
Race, No. (%)			
White	7 (23)	8 (27)	15 (25)
Asian	23 (77)	20 (67)	43 (72)
American Indian or Alaska Native	0	1 (3)	1 (2)
Not reported*	0	1 (3)	1 (2)
Central/local T790M, No. (%)			
Positive	4 (13)	1 (3)	5 (8)
Negative	21 (70)	25 (83)	46 (77)
Unknown†	5 (17)	4 (13)	9 (15)
Central/local‡ *EGFR*, No. (%)			
Ex19del	11 (36)	15 (50)	26 (43)
L858R	15 (50)	14 (47)	29 (48)
Other§	4 (13)	1 (3)	5 (8)
WHO performance status, No. (%)			
0	18 (60)	16 (53)	34 (57)
1	12 (40)	14 (47)	26 (43)
CNS metastases at baseline, No. (%)	7 (23)	8 (27)	15 (25)

Abbreviations: EGFR, epidermal growth factor, Ex19del, exon 19 deletion.
*Race not reported for all centers.
†Reasons for unknown central T790M include no data recorded on database, no tumor, and insufficient DNA yield.
‡Twelve patients (20%) had *EGFR* mutation status confirmed by local *EGFR* testing. Central *EGFR* testing was not performed in three (5%) of 60 patients. Central *EGFR* testing results were unknown in nine patients (15%; reasons listed in previous note).
§Other *EGFR* mutations include G719X (n = 2), G719X/S7681 (n = 2), and L861Q (n = 1).

Fifty percent of patients with an objective response had responded at the first scheduled follow-up scan (6 weeks), with a median time to first response of 6.1 weeks (95% CI, 5.6 to 6.4 weeks).

Median DOR (Fig 1) was 19.3 months (95% CI, 12.3 to 24.7 months) in the 80-mg group, 16.7 months (95% CI, 9.7 to 24.8 months) in the 160-mg group, and 18.0 months (95% CI, 12.5 to 24.7 months) across doses. The maximum reported DOR was 33.1 months in the 80-mg group and 27.7 months in the 160-mg group. Across doses, the percentage of patients remaining in response at 12 and 18 months was 73% (95% CI, 57% to 84%) and 50% (95% CI, 35% to 64%), respectively.

At data cutoff, 42 (70%) of 60 patients had developed RECIST-defined progression or died. There were three deaths, all occurring in the 160-mg group. Median PFS was 22.1 months (95% CI, 13.7 to 30.2 months) in the 80-mg group, 19.3 months (95% CI, 13.7 to 26.0 months) in the 160-mg group, and 20.5 months (95% CI, 15.0 to 26.1 months) across doses. Across doses, median PFS was 23.4 months (95% CI, 15.1 to 31.8 months) in patients with an ex19del mutation, 22.1 months (95% CI, 12.2 to 27.4 months) in patients with an L858R mutation, and 8.3 months (95% CI, 2.8 to 19.0 months) in patients with other *EGFR* mutations. At 12 months, 72% (95% CI, 59% to 82%) of patients were alive and progression free. At 18 months, 56% (95% CI, 42% to 68%) of patients were alive and progression free. Clinical activity results are listed in Table 2.

Thirty-seven (62%) of 60 patients received osimertinib treatment beyond RECIST-defined progressive disease for a median of 4.9 months (interquartile range, 1.8 to 11.6 months). Of these, four patients experienced RECIST-defined progression in the CNS, including three patients in the 80-mg treatment group and one patient in the 160-mg treatment group. A summary of RECIST progression in the CNS is included in the Data Supplement. Twenty (33%) of 60 patients (10 patients in each treatment group) received another cancer therapy after RECIST-defined progression (chemotherapy, [n = 14]; EGFR-TKI, [n = 5]; other treatment, [n = 2]); patients may have received more than one postprogression therapy.

Translational Analysis

Baseline central tissue versus plasma EGFR *genotyping.* With central tissue genotyping as a reference, high sensitivity and specificity were observed with plasma genotyping (BEAMing) for T790M and known *EGFR*m L858R and ex19del (Data Supplement). Five patients (8%) had de novo T790M-positive NSCLC confirmed by central tissue testing at study entry. Four of five patients were also plasma T790M positive. Plasma testing identified two additional de novo T790M patients (tissue unknown by central testing). Details of T790M detection and plasma T790M allelic fractions are included in the Data Supplement. All seven de novo T790M mutations were detected alongside L858R. One de novo T790M plasma-positive patient was suspected to have a germline T790M mutation, reflected in the high T790M allelic fraction in the plasma (35%). Six of seven patients with de novo T790M positivity had a partial response, with DOR ranging from 6.9 to 27.7 months (Data Supplement).

Mechanisms of resistance to osimertinib. Forty-two (70%) of 60 patients had experienced RECIST-defined progression at data cutoff, and plasma samples collected at or after progression were available for NGS analysis from 38 (91%) of these patients. Nineteen of these 38 patients did not have detectable ctDNA in their postdose sample. Detectable ctDNA was found in postdose samples from the

Table 2. Clinical Activity Summary

Clinical Activity Output	Osimertinib Dose		Total (N = 60)
	80 mg (n = 30)	160 mg (n = 30)	
Best overall response, No. (%)			
Complete response*	0	2 (7)	2 (3)
Partial response*	20 (67)	24 (80)	44 (73)
Stable disease ≥ 6 weeks, No. (%)	8 (27)	4 (13)	12 (20)
Progressive disease, No. (%)	2 (7)	0	2 (3)
Objective response rate, No./total No. (%)	20/30 (67)	26/30 (87)	46/60 (77)
95% CI, %	47 to 83	69 to 96	64 to 87
Exon 19 deletion†	8/11 (73)	13/15 (87)	21/26 (81)
95% CI, %	39 to 94	60 to 98	61 to 93
L858R†	10/15 (67)	12/14 (86)	22/29 (76)
95% CI, %	38 to 88	57 to 98	57 to 90
Other†	2/4 (50)	1/1 (100)	3/5 (60)
95% CI, %	7 to 93	NC to NC	15 to 95
Disease control rate, No./total No. (%)	28/30 (93)	30/30 (100)	58/60 (97)
95% CI, %	78 to 99	88 to 100	89 to 100
Mean best % change in target lesion size (SD)	−42 (23)	−54 (19)	−48 (22)
Median time to first response, weeks‡ (95% CI)	6.2 (5.6 to 12.1)	6.0 (5.4 to 6.1)	6.1 (5.6 to 6.4)
Duration of response, months‡			
Median (95% CI)	19.3 (12.2 to 24.7)	16.7 (9.7 to 24.8)	18.0 (12.5 to 24.7)
Maximum	33.1	27.7	33.1
Patients remaining in response, % (95% CI)			
12 months	79 (54 to 92)	68 (46 to 83)	73 (57 to 84)
18 months	53 (29 to 72)	48 (28 to 66)	50 (35 to 64)
Median progression-free survival, months‡ (95% CI)	22.1 (13.7 to 30.2)	19.3 (13.7 to 26.0)	20.5 (15.0 to 26.1)
Percentage alive and progression free, % (95% CI)			
12 months	75 (55 to 88)	69 (49 to 83)	72 (59 to 82)
18 months	57 (36 to 73)	55 (36 to 71)	56 (42 to 68)

Abbreviations: NC, not calculable; SD, standard deviation.
*Confirmed responses only.
†*EGFR* mutation status by central or local testing.
‡Calculated using Kaplan-Meier method.

remaining 19 patients (50%). A flowchart outlining patients available for postdose plasma NGS analysis is included in the Data Supplement. Mean time to RECIST-defined progression was 13.1 months (SD, 8.0 months) in patients with detectable ctDNA at resistance, which was shorter than that reported in patients with undetectable ctDNA (19.6 months; SD, 8.9 months). Mean time to osimertinib discontinuation was also shorter in patients with detectable ctDNA (18.2 months; SD, 9.0 months) than in patients with undetectable ctDNA (25.2 months; SD, 8.1 months; Data Supplement).

Putative genomic resistance mutations were identified in nine of 19 patients with detectable ctDNA, including previously reported mechanisms of second-line osimertinib resistance such as *MET*, *EGFR*, and *KRAS* amplifications and activating mutations of *PIK3CA* and *KRAS*.[25-27] Two cases of acquired *EGFR* C797S resistance mutations were detected: one in a patient with a de novo T790M mutation, and one in absence of T790M. An acquired *MEK1* G128V variant, a known resistance mutation conferring insensitivity to BRAF inhibitors, was identified in one patient alongside *EGFR*m G719S. Known kinase-activating variants were identified in two other patients (*HER2* exon 20 insertion and *JAK2* V617F), both in absence of any detectable *EGFR*m in the postdose plasma. In the remaining 10 patients, no putative resistance mechanisms were identified in postdose plasma, despite clear detection of known *EGFR*m. There was no evidence of acquired T790M mutation in any plasma ctDNA sample analyzed. A summary of resistance to osimertinib is included in the Data Supplement.

Safety and AEs

A safety summary is provided in Table 3. All-causality AEs reported in 15% or more of patients are listed in the Data Supplement. In the 80-mg group, three patients experienced AEs leading to dose reduction; median time to first dose reduction as a result of AEs was 1.7 months. In the 160-mg group, 18 patients (60%) had their dose reduced to 80 mg, of whom 16 (89%) had dose reductions as a result of an AE; median time to first dose reduction as a result of AEs was 3.1 months. A summary of AEs leading to dose reduction is included in the Data Supplement. Three patients (10%) in the 160-mg group had their dose reduced to 80 mg within the first 7 weeks of treatment. Median relative dose-intensity was 100% (range, 50% to 100%) in the 80-mg group, 88% (range, 27% to 100%) in the 160-mg group, and 100% (range, 27% to 100%) across doses. One (2%) of 60 patients experienced an AE leading to death, not causally related to osimertinib.

DISCUSSION

In this first report on the anticancer activity of osimertinib as first-line treatment of patients with *EGFR*m advanced NSCLC, treatment with osimertinib 80 mg once daily (the approved dose for patients with *EGFR* T790M–mediated resistance to prior EGFR-TKIs) was associated with a median PFS of 22.1 months and an ORR of 67%.

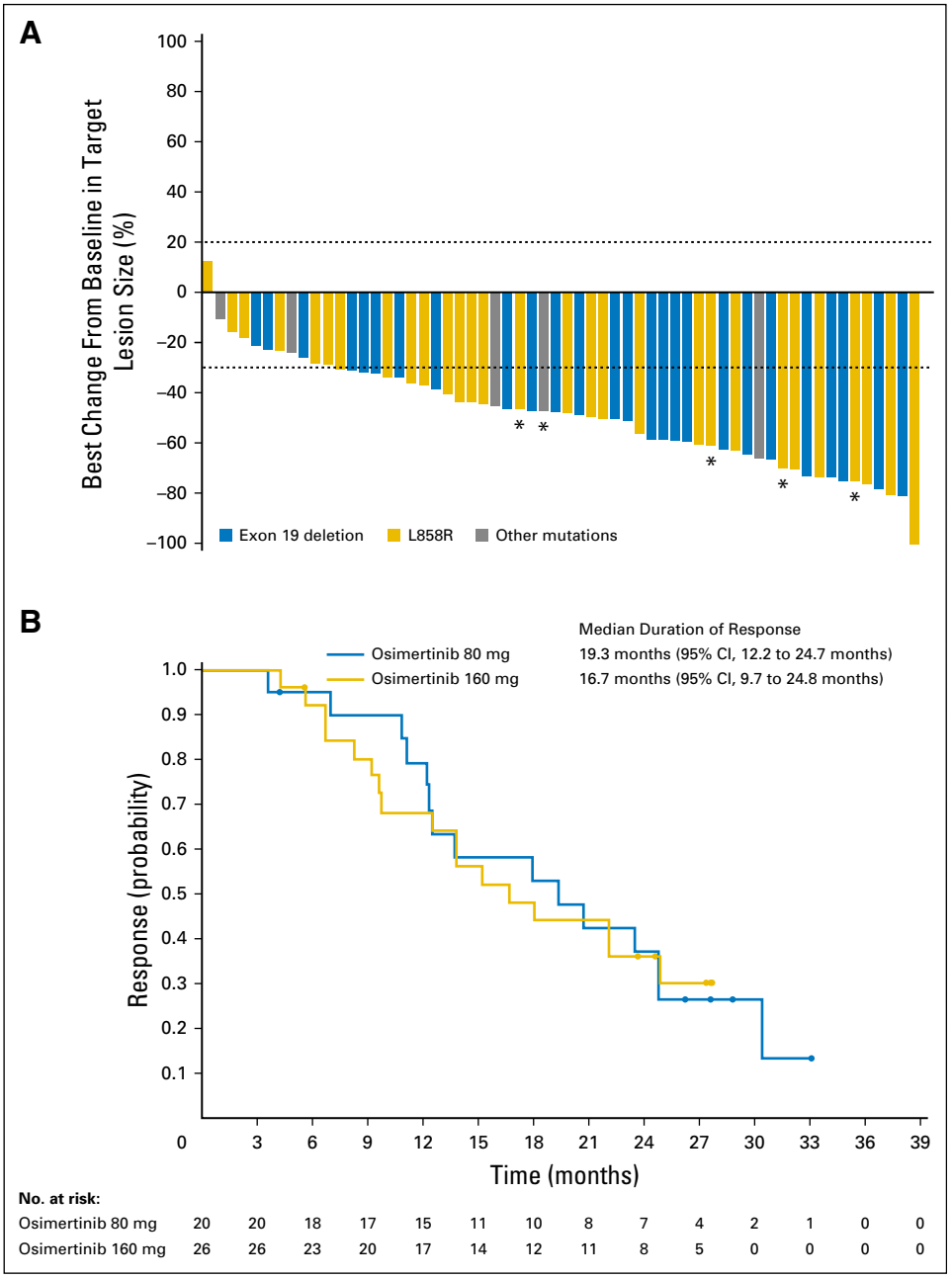

Fig 1. (A) Best percent change in target lesion size. *EGFR* mutation status is indicated on the plot. (*) Patients with de novo T790M mutation by central testing (cobas). Other mutations are shown in gray. (B) Kaplan-Meier estimates showing duration of response (all responding patients) by dose. (C) Kaplan-Meier estimates showing progression-free survival by dose and (D) by *EGFR* mutation status (local and central testing) at study entry. Progression events that did not occur within 14 weeks of the last evaluable assessment (or first dose) were censored at the last evaluable RECIST assessment.

Previous studies of gefitinib and erlotinib in a similar setting report median PFS of 8.4 to 13.1 months.[28] These data suggest osimertinib may result in prolonged PFS as first-line systemic treatment of patients with advanced *EGFR*m NSCLC. This is being evaluated in an ongoing phase III study (FLAURA; ClinicalTrials.gov identifier: NCT02296125) that directly compares osimertinib with erlotinib or gefitinib.

The similar PFS observed between the 80- and 160-mg first-line treatment groups and the better tolerability of the lower dose (a higher number of dose reductions as a result of AEs was observed in the 160-mg treatment group, consistent with available data from later-line patients treated with osimertinib in the AURA phase I study),[15] support the approved 80-mg once-daily dosage. FLAURA evaluates the clinical benefit of 80 mg once daily in the first-line setting, as it was considered to provide the optimum risk/benefit ratio based on a comprehensive review of available safety, tolerability, efficacy, and pharmacokinetic data from first- and later-line patients treated with osimertinib in the AURA phase I study.

EGFR T790M is sometimes detected at baseline, in absence of prior EGFR-targeted therapy, and rarely as a germline variant.[29] In this study, outcomes seemed similar in patients with and without de novo *EGFR* T790M and patients with only an *EGFR* activating mutation, suggesting osimertinib to be appropriate initial treatment in both patient subsets. The relatively high number of de novo *EGFR* T790M patients in this study likely reflects investigator bias, because these patients are expected to have limited clinical benefit in the first-line setting from gefitinib, erlotinib, or afatinib.

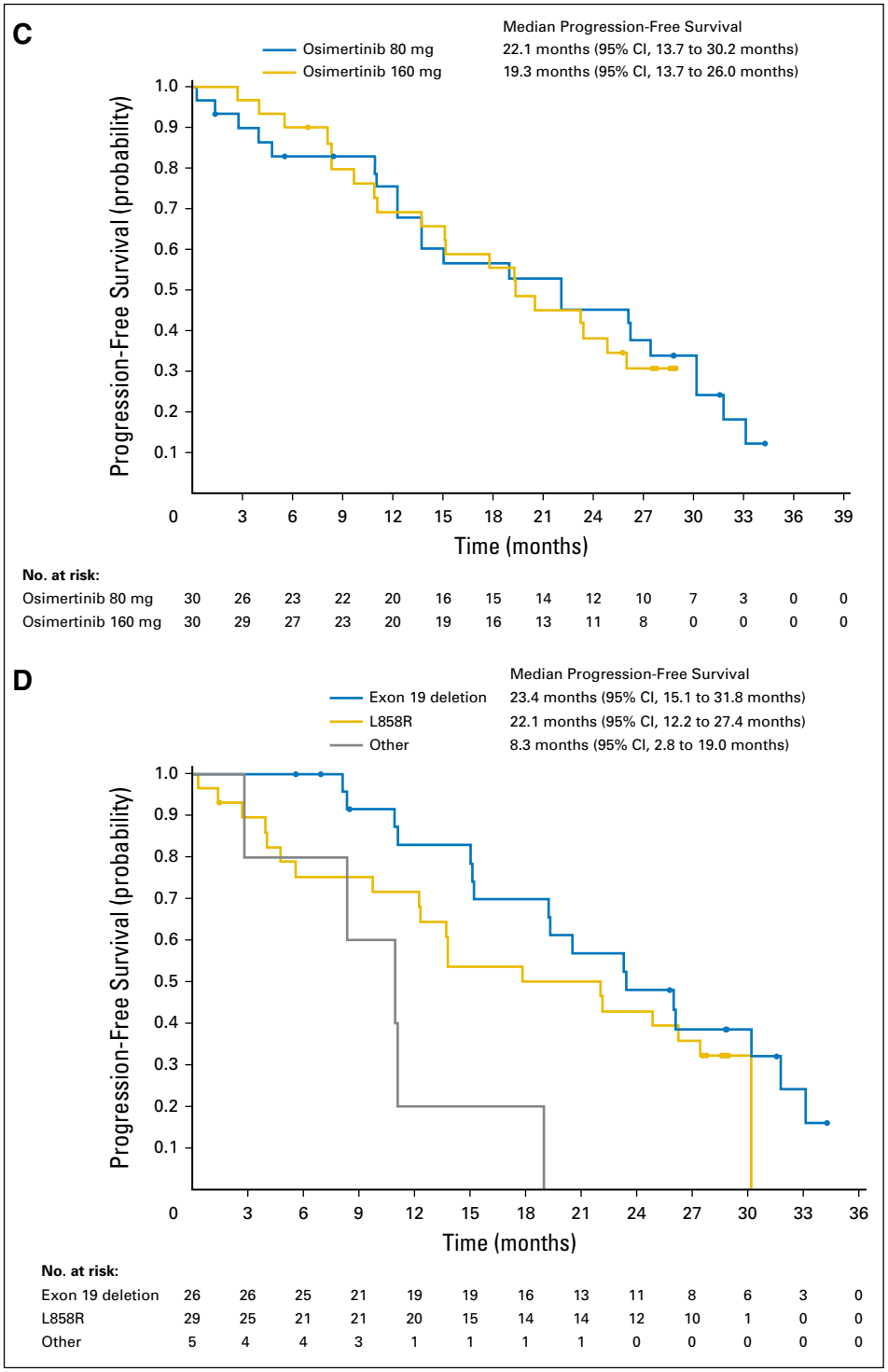

Fig 1. (Continued).

Mechanisms of resistance to treatment with early-generation EGFR-TKIs have been described previously, with *EGFR* T790M being the most common resistance mutation.[6,7] Mechanisms of resistance to osimertinib have also been described, including *KRAS* amplification and acquired *EGFR* C797S mutation.[24,26] Consistent with preclinical data and its mechanism of action, initial treatment with osimertinib did not result in emergence of T790M as the mechanism of drug resistance, as assessed using ctDNA from plasma samples at or after clinical progression. Nine patients had putative genomic resistance mechanisms identified. Two instances of acquired C797S were identified, one in absence of a T790M mutation. This finding has potentially important clinical implications, because quinazoline-based EGFR inhibitors, including gefitinib, have been shown to effectively inhibit C797S when T790M is absent.[30,31] Other genomic resistance mechanisms identified involved either activation of pathways downstream of *EGFR* (MAPK

Table 3. Safety Summary

AE Category*	No. of Patients (%)†		
	Osimertinib Dose		
	80 mg (n = 30)	160 mg (n = 30)	Total (N = 60)
Any AE	30 (100)	30 (100)	60 (100)
Any possibly causally related AE‡	29 (97)	30 (100)	59 (98)
Any grade ≥ 3 adverse event	18 (60)	19 (63)	37 (62)
Any grade ≥ 3 possibly causally related AE‡	4 (13)	7 (23)	11 (18)
Any AE with outcome of death	0	1 (3)	1 (2)
Any AE with outcome of death that was possibly causally related	0	0	0
Any serious AE (including events with outcome of death)	14 (47)	9 (30)	23 (38)
Any possibly causally related serious AE (including events with outcome of death)‡	4 (13)	1 (3)	5 (8)
Any AE leading to interruption of osimertinib	13 (43)	11 (37)	24 (40)
Any AE leading to reduction of osimertinib§	3 (10)	16 (53)	19 (32)
Any AE leading to discontinuation of osimertinib	3 (10)	3 (10)	6 (10)
Any possibly causally related AE leading to discontinuation of osimertinib‡	2 (7)	1 (3)	3 (5)

Abbreviation: AE, adverse event.
*Includes adverse events with an onset date on or after the date of first dose and up to and including 28 days after the date of the last dose of study medication.
†Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
‡As assessed by the investigator.
§Three of three patients in the 80-mg group had a single dose reduction to 40 mg; 13 of 14 patients in the 160-mg group had a single dose reduction to 80 mg, and one patient had two dose reductions, first to 80 mg then to 40 mg.

pathway signaling) or those that activate parallel signaling pathways (*MET* and *HER2*), suggesting the possibility of combination approaches after progression on first-line osimertinib therapy.

In 10 patients, we identified *EGFR*m but no putative resistance mechanism at the time of progression. It is possible that molecular changes only detectable at the tissue level (eg, small-cell lung cancer transformation) and any nongenomic mechanisms of resistance were not identified in this analysis. Future tissue-based analyses of resistance mechanisms will be necessary to understand the full spectrum of osimertinib resistance.

In this study, we collected ctDNA samples at or after progression. Low levels of ctDNA shedding correlate with low tumor burden,[32,33] suggesting that disease in these nonshedding patients may remain sufficiently controlled at RECIST-defined progression. Consistent with this, patients with undetectable levels of ctDNA received osimertinib for approximately 7 months beyond RECIST-defined progression, demonstrating that emergence of clinically significant resistance may correlate with presence of detectable ctDNA in plasma. Previous studies have shown lack of detectable ctDNA early in EGFR-TKI therapy to be associated with better clinical prognosis.[34] Detectable ctDNA may be useful in determining treatment on RECIST progression.

The safety profile for osimertinib in the first-line setting was broadly similar to that reported previously.[14,15] The proportion of patients experiencing AEs possibly causally related to osimertinib (97% any grade, 13% ≥ grade 3 in the 80-mg group) was higher overall than in the second-line setting (AURA3 phase III study: 83% any grade, 6% ≥ grade 3),[14] likely a result of no prior sensitization to *EGFR* wild-type inhibition. Cross-trial comparisons are not possible as a result of differences in trial design and exposure; however, the most commonly reported AEs were rash, diarrhea, and dry skin, some of the more frequently reported AEs with other EGFR-TKIs including erlotinib, gefitinib, afatinib, and dacomitinib.[1,3,4,35,36]

Overall, this first-line study shows encouraging results with evidence of durable clinical activity and manageable tolerability. Osimertinib at 80 mg once daily is considered to be the most appropriate dose in this setting and is being investigated in FLAURA. There was no evidence to suggest the emergence of *EGFR* T790M as an acquired resistance mechanism, consistent with the biologic activity profile of osimertinib. Osimertinib is an effective treatment approach as initial therapy for treatment-naïve patients with advanced *EGFR* mutation–positive NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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