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ORIGINAL REPORT

Osimertinib in Pretreated T790M-Positive Advanced Non–Small-Cell Lung Cancer: AURA Study Phase II Extension Component

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ABSTRACT

Purpose

Osimertinib is an irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) selective for both EGFR-TKI sensitizing (*EGFR*m) and T790M resistance mutations. AURA (NCT01802632) is a phase I/II clinical trial to determine the dose, safety, and efficacy of osimertinib. This article reports the results from the phase II extension component.

Patients and Methods

Patients with EGFR-TKI–pretreated *EGFR*m- and T790M-positive advanced non–small-cell lung cancer (NSCLC) received once-daily osimertinib 80 mg. T790M status was confirmed by central testing from a tumor sample taken after the most recent disease progression. Patients with asymptomatic, stable CNS metastases that did not require corticosteroids were allowed to enroll. The primary end point was objective response rate (ORR) by independent radiology assessment. Secondary end points were disease control rate, duration of response, progression-free survival (PFS), and safety. Patient-reported outcomes comprised an exploratory objective.

Results

In total, 201 patients received treatment, with a median treatment duration of 13.2 months at the time of data cutoff (November 1, 2015). In evaluable patients (n = 198), ORR was 62% (95% CI, 54% to 68%), and the disease control rate was 90% (95% CI, 85 to 94). Median duration of response in 122 responding patients was 15.2 months (95% CI, 11.3 to not calculable). Median PFS was 12.3 months (95% CI, 9.5 to 13.8). The most common possibly causally related adverse events (investigator assessed) were diarrhea (43%; grade $\geq$ 3, $<$ 1%) and rash (grouped terms; 40%; grade $\geq$ 3, $<$ 1%). Interstitial lung disease (grouped terms) was reported in eight patients (4%; grade 1, n = 2; grade 3, n = 3; grade 5, n = 3).

Conclusion

In patients with *EGFR*m T790M advanced NSCLC who progress after EGFR-TKI treatment, osimertinib provides a high ORR, encouraging PFS, and durable response.

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INTRODUCTION

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the recommended first-line treatment of patients with advanced lung cancer that harbors an activating *EGFR* mutation (*EGFR*m),[1,2] which is supported by results from several phase III studies.[3-8] Despite high initial responses to first-line EGFR-TKIs and a median progression-free survival (PFS) of 10 to 14 months, resistance eventually develops in most, if not all, patients. The most common mechanism of acquired resistance to EGFR-TKIs, the *EGFR* p.Thr790Met point mutation (T790M), can be detected in 50% to 60% of tissue biopsy samples taken after acquired resistance.[9-12]

Osimertinib is an oral, irreversible EGFR-TKI selective for both *EGFR*m and T790M resistance mutations.[13] The phase I component of the osimertinib AURA (NCT01802632) study showed clinical activity across oral doses of 20 to 240 mg/day.[14] The optimal dose chosen for

ASSOCIATED CONTENT

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further phase II evaluation was 80 mg once daily. The phase I study results suggested that both patients with T790M-positive non–small-cell lung cancer (NSCLC) and patients with T790M not detected derive benefit from osimertinib treatment but with a much higher response rate in patients with T790M-positive disease (objective response rate [ORR], 61% *v* 21%). AURA extension is the phase II component of the AURA study. We report the treatment outcomes, including ORR, by blinded independent central review (BICR), duration of response (DoR), and PFS of patients in the AURA extension phase II study.

PATIENTS AND METHODS

Study Design and Participants

The AURA study was a phase I/II, open-label, multicenter study of osimertinib in patients with advanced NSCLC who had progressed after therapy with an EGFR-TKI agent (with or without additional anticancer regimens). Patients were at least 18 years of age (≥ 20 years in Japan) with a histologically or cytologically confirmed diagnosis of NSCLC that harbored confirmed EGFR-TKI sensitizing *EGFR*m and were enrolled across 46 study centers in Japan (16), the United States (seven), South Korea (four), Australia (three), France (three), Germany (three), Spain (three), Italy (three), Taiwan (two), and the United Kingdom (two).

The AURA study consisted of dose escalation and dose expansion in phase I with the capsule formulation of osimertinib (methods and preliminary results have been previously reported)[14] and a phase II extension component with the tablet formulation at the recommended phase II 80-mg once-daily dose. Two cohorts comprised the phase II extension component: patients whose disease had progressed (confirmed by radiologic documentation) either after only one prior therapy with an EGFR-TKI (second line) or after treatment with at least two lines of prior therapy, including at least one EGFR-TKI (third line or more).

Eligibility criteria are provided in detail in the Appendix (online only). Briefly, patients were required to have a WHO performance status of 0 to 1 and acceptable organ function. Patients with CNS metastases could be enrolled if the disease was asymptomatic, stable, and not requiring corticosteroids for at least 4 weeks before the first dose. Prospective confirmation of T790M mutation status was by a central laboratory that used the cobas EGFR Mutation Test (Roche Molecular Systems, Pleasanton, CA; Appendix) from a tissue biopsy specimen taken after disease progression on the most recent treatment regimen (irrespective of whether EGFR-TKI or chemotherapy).

All participating sites required approval from the independent institutional review board/independent ethics committee. The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonization/Good Clinical Practice and applicable regulatory requirements. All patients provided written informed consent before their participation in the study. The protocol was designed by the sponsor (AstraZeneca) and the study investigators.

Procedure

Eligible patients received 80 mg osimertinib orally once daily and continued treatment until Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST1.1)–defined progression or until a treatment discontinuation criterion was met. Patients could continue to receive osimertinib beyond RECIST1.1–defined progression if they continued to show clinical benefit as judged by the investigator. If osimertinib was discontinued for reasons other than disease progression, the patient continued response assessment every 6 weeks until disease progression.

The primary end point of the AURA phase II extension study was ORR by BICR. Secondary end points were DoR, disease control rate (DCR), tumor shrinkage, PFS, overall survival (OS), safety, tolerability, and pharmacokinetics. Collection of patient-reported outcomes (PROs) and quality of life were exploratory objectives. DoR, DCR, tumor shrinkage, and PFS were determined by using RECIST1.1 assessed by BICR. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4). The Appendix provides further details on procedures related to AEs and the collection of PROs.

Statistical Analysis

The full analysis set was defined as all patients enrolled who received at least one dose of study treatment. The evaluable for response analysis set was defined as all patients who received at least one dose of study treatment and had measurable disease at baseline according to BICR. CNS efficacy was assessed in an evaluable for CNS response analysis set, which included patients with at least one measurable CNS lesion on baseline brain scan (RECIST1.1) by BICR (assessed by neuroradiologists). The primary efficacy end point variable ORR by BICR (according to RECIST1.1) was defined as the percentage of patients with at least one visit response of complete response or partial response confirmed at least 4 weeks later. (Definitions of PFS and DoR are provided in the Appendix.) No formal statistical analysis was done. The study was sized to recruit approximately 175 patients to estimate an ORR with 95% CI within ± 8% and to adequately assess safety and tolerability.

Statistical analyses were performed by Pharmaceutical Product Development (Wilmington, NC). All calculations were performed with SAS 9.2 software (SAS Institute, Cary, NC) unless otherwise stated. We report a November 1, 2015, data cutoff.

RESULTS

Demographics

Between May 14, 2014, and November 1, 2015, 401 patients were screened, and 327 patients' samples were eligible for T790M testing, of which 324 (99%) gave a valid test result; 207 (64%) had positive test results for T790M. The T790M detection rate did not vary by last prior EGFR-TKI treatment (gefitinib, 69%; erlotinib, 68%; afatinib, 68%; Appendix Table A1, online only).

Two hundred one patients received osimertinib treatment (61 as second-line therapy and 140 as third-line or more therapy; Fig 1); three patients had no measurable disease at baseline by BICR and were excluded from the evaluable for response set (n = 198). Baseline characteristics are listed in Table 1. Twenty-five patients were included in a CNS response analysis set.

Duration of Treatment

At the time of analysis, the median duration of exposure was 13.2 months (range, 0.1 to 17.6 months). By investigator assessment, 106 patients were known to be alive after radiologic progression of whom 79 continued to receive osimertinib for at least 7 days after their first radiologic progression for a median duration of 3.4 months (Fig 1). Forty-eight of the 106 patients received at least one subsequent cancer therapy after progression (Fig 1).

Efficacy

Tumor response. One hundred ninety-eight patients were evaluable for response by BICR. ORR was 62% (122 of 198 patients; 95% CI, 54 to 68), and DCR was 90% (179 of 198 patients; 95% CI, 85 to 94). ORRs ranging from 53% to 68% were observed across all presented predefined subgroups (Fig 2). ORRs were similar between the second-line and third-line or more cohorts

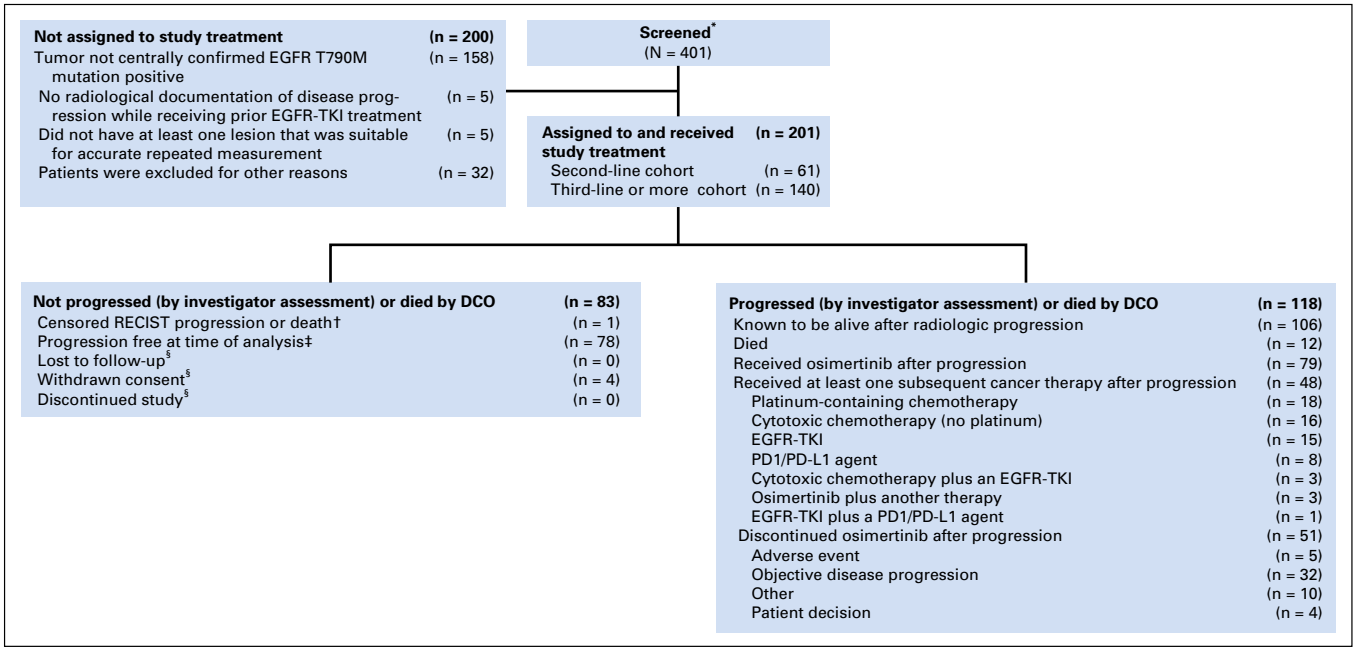

Fig 1. Patient disposition. All treatment decisions were based on investigator interpretation of patient disease status. *Informed consent received. Patients could have had more than one reason for not being assigned to treatment and, hence, would be counted more than once. †Response Evaluation Criteria in Solid Tumors (RECIST) progression event occurred 19 weeks after last evaluable RECIST assessment. ‡Includes patients known to be alive with no evaluable baseline RECIST assessment (censored at day 0). §Patients at last evaluable RECIST assessment. DCO, data cutoff; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

(62% and 61%) and by common EGFR-TKI sensitizing mutation status (exon 19 deletion, 64%; L858R, 57%), respectively (Fig 2). Post hoc analyses of ORR by last prior EGFR-TKI treatment were as follows: gefitinib, 68% (64 of 94 patients; 95% CI, 58 to 77); erlotinib, 57% (56 of 99 patients; 95% CI, 46 to 67); and afatinib/dacomitinib, 50% (two of four patients; 95% CI, 7 to 93).

Overall, 99 (81%) of 122 responders had a documented initial response at their first scheduled follow-up RECIST1.1 scan at 6 ± 1 weeks. Tumor shrinkage was seen in the majority of patients (94%; Fig 3A). The mean best percentage change in target lesion size from baseline was −42.7%.

Of the 122 patients deemed to have an objective response, 46 (38%) had subsequently progressed or died by the time of analysis. The median DoR was 15.2 months (95% CI, 11.3 to not calculable [NC]; range, 1.4 to 15.3 months). The proportion of patients with an objective response who subsequently progressed or died was similar by last EGFR-TKI treatment received before osimertinib (gefitinib, 22 [34%] of 64; erlotinib, 23 [41%] of 56; afatinib/dacomitinib, one [50%] of two).

PFS and OS. At the time of data cutoff, 107 (53%) of 201 patients had progressed or died (by BICR). One hundred four of these patients were on treatment at the time of progression; three had discontinued osimertinib before progression and, therefore, were not censored. Median PFS (by BICR) was 12.3 months (95% CI, 9.5 to 13.8); 11.0 months (95% CI, 6.7 to NC), and 12.4 months (95% CI, 9.5 to 15.5) in the second-line and third-line or more cohorts, respectively (Fig 4A). The proportion of patients progression free at 6, 9, and 12 months was 70%, 58%, and 52%, respectively.

Subset analysis of PFS by *EGFR*m status before the start of the study showed a nonsignificant trend toward longer PFS in patients who harbored an exon 19 deletion (median, 12.5 months; 95% CI, 9.7 to NC) compared with L858R (median, 9.6 months; 95% CI, 6.9 to 13.8; Fig 4B). Similarly, a nonsignificant trend toward longer PFS was observed in Asian versus non-Asian patients (median, 12.6 months [95% CI, 9.7 to 16.6] *v* 9.7 months [95% CI, 7.0 to 13.8], respectively; Fig 4C). Median PFS by last prior EGFR-TKI treatment was 12.6 months (95% CI, 9.5 to NC) for gefitinib and 11.0 months (95% CI, 6.9 to 13.8) for erlotinib (Fig 4D).

Median PFS generally was consistent across other subgroups analyzed: age at screening (< 65 *v* ≥ 65 years), smoking status (never *v* ever), last treatment before osimertinib (EGFR-TKI *v* non–EGFR-TKI), immediate prior EGFR-TKI treatment (< 30 days before osimertinib *v* ≥ 30 days before osimertinib), and duration of most recent EGFR-TKI treatment (< 6 *v* ≥ 6 months; Appendix Table A2, online only).

At the time of data cutoff, 54 patients (27%) had died; hence, the median OS was not reached (95% CI, 16.4 to NC). The median follow-up for OS was 13.8 months. One-year survival rate was 79% (95% CI, 72 to 84; Appendix Fig A1, online only).

Symptom resolution. Data from European Organization for Research and Treatment of Cancer questionnaires QLQ-LC13 and QLQ-C30 showed that patients had consistent and sustained improvements in key lung cancer symptoms, including dyspnea, cough, chest pain, and pain in arm or shoulder (Appendix Fig A2, online only). Sustained improvements in global health status and physical functioning domains also were recorded.

Osimertinib activity in patients with CNS metastases. Seventy-four patients had CNS metastases at entry. Median PFS was shorter in patients with CNS metastases than in those without (median, 7.1 months [95% CI, 4.2 to 12.3] *v* 13.7 months [95% CI, 11.0 to NC], respectively; Appendix Fig A3, online only). In the CNS response analysis set, the ORR was 64% (16 of 25 patients; 95% CI, 43 to 82); four patients experienced a complete response and 12 patients a partial response. Tumor shrinkage was seen in the majority of patients (Fig 3B)

Table 1. Baseline Characteristics of Study Patients (full analysis set)

Characteristic	Second Line, No. (%)	Third Line or More, No. (%)	Total, No. (%)
No. of patients	61	140	201
Age, years			
Mean (SD)	62.6 (10)	60.9 (11)	61.4 (11)
Median (range)	61 (45-89)	63 (37-84)	62 (37-89)
Sex			
Male	20 (33)	48 (34)	68 (34)
Female	41 (67)	92 (66)	133 (66)
Ethnicity			
White	24 (41)	52 (37)	76 (38)
Asian	32 (54)	82 (59)	114 (57)
Black or African American	0	1 (1)	1 (< 1)
Other	1 (2)	3 (2)	4 (2)
Not reported*	2 (3)	2 (1)	4 (2)
Smoking status			
Never	41 (67)	93 (66)	134 (67)
Former	20 (33)	42 (30)	62 (31)
Current	0	5 (4)	5 (2)
WHO performance status			
0	25 (41)	43 (31)	68 (34)
1	36 (59)	96 (69)	132 (66)
2	0	1 (1)	1 (< 1)†
Histology			
Adenocarcinoma	60 (98)	135 (96)	195 (97)
Adenosquamous carcinoma	0	1 (1)	1 (< 1)
Other	1 (2)	4 (3)	5 (2)
EGFR T790M mutation by cobas central test	59 (97)	138 (99)	197 (98)‡
EGFR mutations co-occurring with T790M by cobas central test			
Exon 19 deletion	44 (72)	98 (70)	142 (71)
L858R	16 (26)	35 (25)	51 (25)
G719X	1 (2)	3 (2)	4 (2)
S768I	0	3 (2)	3 (1)
Exon 20 insertion	1 (2)	1 (1)	2 (1)
T790M only	0	5 (4)	5 (2)
Overall disease classification			
Metastatic	59 (97)	138 (99)	197 (98)
Locally advanced	2 (3)	2 (1)	4 (2)
Metastases			
CNS§	14 (23)	60 (43)	74 (37)
Visceral	50 (82)	123 (88)	173 (86)
Median No. of prior regimens (range)	1	3 (2-11)	2 (1-11)
Prior treatment			
First-generation EGFR-TKIs			
Gefitinib	32 (52)	85 (61)	117 (58)
Erlotinib	28 (46)	88 (63)	116 (58)
Second-generation EGFR-TKIs			
Afatinib	0 (0)	36 (26)	36 (18)
Afatinib + cetuximab		4 (3)	4 (2)
Dacomitinib	1 (2)	3 (2)	4 (2)
Other EGFR-TKI	0	5 (4)	5 (2)
Platinum-containing doublet chemotherapy	0	122 (87)	122 (61)
Platinum-containing doublet chemotherapy + bevacizumab	0	25 (18)	25 (12)

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.
*Some countries do not allow collection of ethnicity data.
†Protocol deviation: inclusion criteria state that patients should have a WHO performance status of 0 or 1.
‡Three patients with *EGFR* T790M mutation status not detected (negative) and one patient not centrally tested entered the study; consequently, these were considered important protocol deviations. Of the three patients with no T790M detected by central testing, one had detectable exon 19 deletion, one had detectable L858R, and one had detectable exon 19 deletion/S768I.
§CNS metastases were determined programmatically from baseline data: patients with a CNS metastatic site, those who reported prior radiotherapy in anatomic locations unequivocally in the CNS, and/or those who reported surgical excision of tumor from anatomic locations unequivocally in the CNS.

Safety

Nearly all patients reported at least one AE (199 [99%] of 201), with 185 (92%) reporting at least one AE possibly casually related to osimertinib treatment. A summary of safety and all-cause AEs are listed in Appendix Tables A3 and A4 (online only). The most common possibly causally related AEs (by investigator assessment) were diarrhea, rash (grouped terms), paronychia (grouped terms), and dry skin (grouped terms; Table 2). The

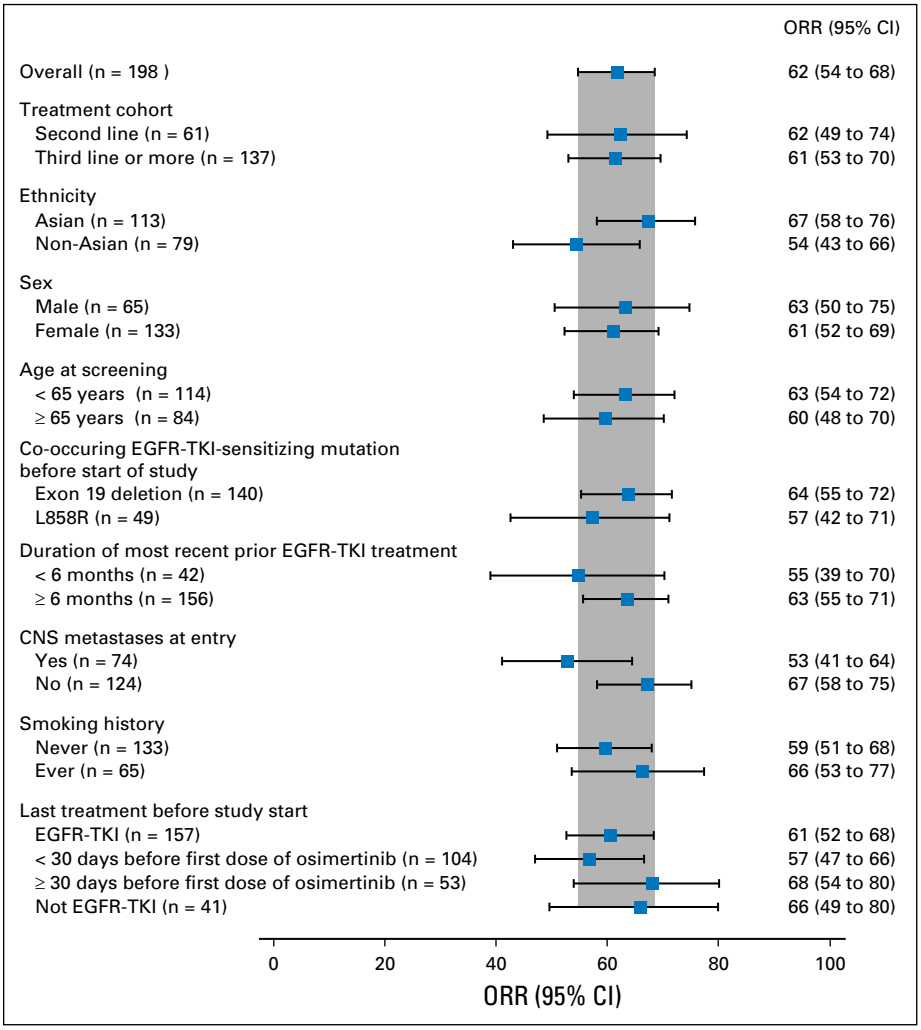

Fig 2. Objective response rate (ORR) by central review by subgroup in the evaluable for response set. The 95% CIs were calculated by using Clopper-Pearson exact method for binomial proportions. The gray band represents the 95% CI for the overall patient ORR. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

majority of these possibly causally related AEs were mild (grade 1 in severity).

Interstitial lung disease (ILD) grouped term AEs were reported in eight patients, all deemed possibly causally related (4%; grade 1, n = 2; grade 3, n = 3; grade 5, n = 3). Three AEs resolved, two were ongoing at the time of data cutoff, and three were reported as fatal (two reports of ILD and one of pneumonitis). Three (4%) of 76 AEs were reported in white patients, three (9%) of 35 in Japanese patients, and two (4%) of 45 in non-Japanese Asian patients. The median time to onset for ILD grouped term AEs was 5.1 months. QT prolongation AEs were recorded in six patients (3%; grade 1, n = 5; grade 2, n = 1), possibly causally related in three patients (2%; grade 1, n = 2; grade 2, n = 1). In two reports, QT prolongation led to a dose reduction.

Forty-three patients (21%) experienced AEs that led to dose interruption of osimertinib treatment, and 10 patients (5%) experienced AEs that led to dose reduction. Nine patients (3%) discontinued osimertinib treatment as a result of possibly causally related AEs (seven because of ILD grouped terms [discontinuation mandated by protocol]; one because of neutrophil count decrease; and one because of decreased appetite, asthenia, diarrhea, and vomiting).

DISCUSSION

In this study, oral osimertinib 80 mg once daily resulted in a high ORR and DCR with significant DoR and PFS in patients with EGFR-TKI–resistant *EGFR*m lung cancer with tumors harboring T790M. This finding is consistent with the previous analysis of the AURA phase I study that demonstrated high response rates across the 20- to 240-mg dose range of osimertinib in patients with T790M-positive tumors.[14] The current study demonstrates a median PFS of 12.3 months and a DoR of 15.2 months in responding patients. The phase II study AURA2 (NCT02094261 [independent phase II study with a similar design conducted in different centers]) demonstrated a similar ORR and PFS, which further confirms the efficacy of osimertinib in patients who

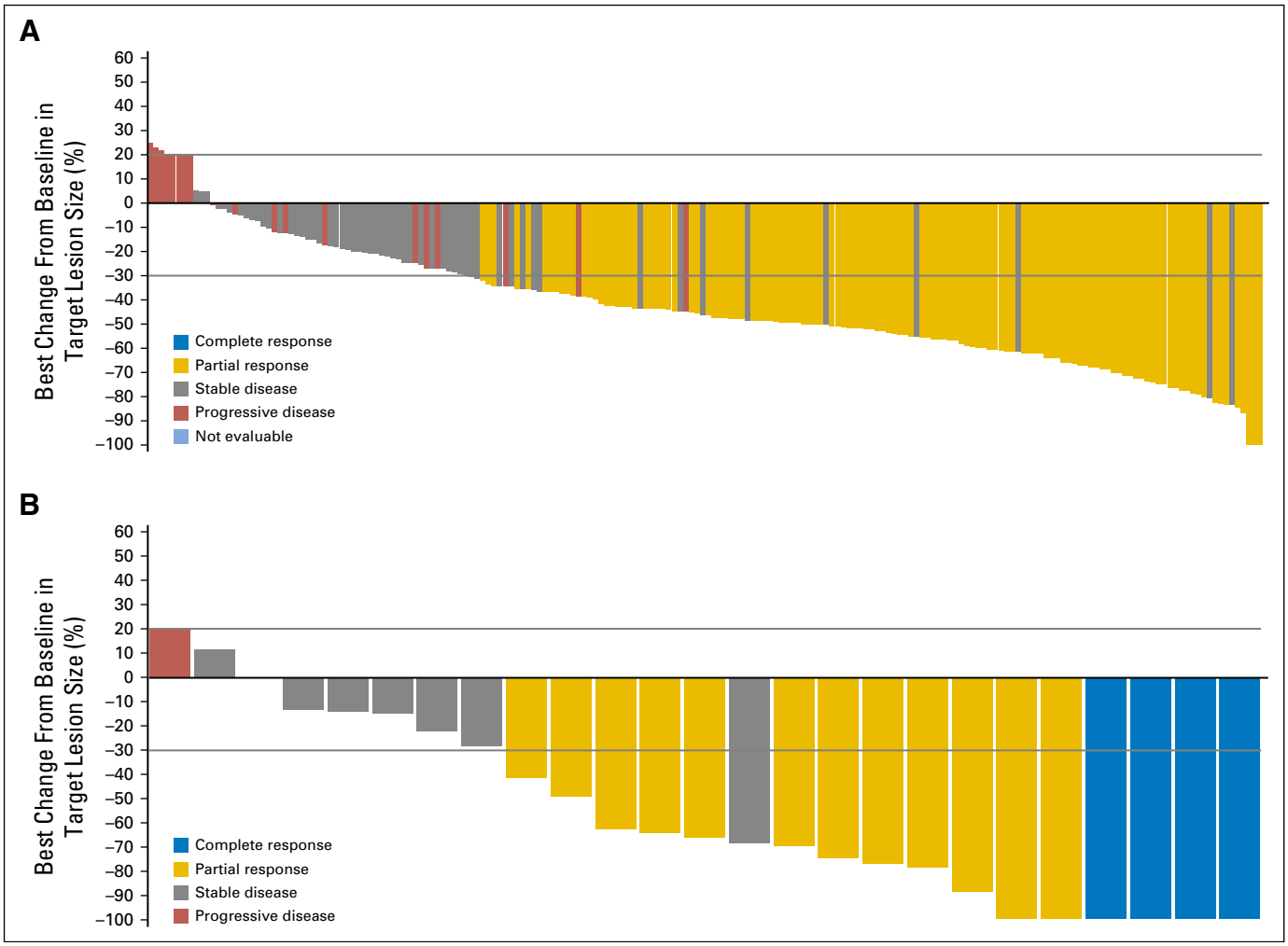

Fig 3. Best percentage change from baseline in target lesion size by central review in (A) the evaluable for response set and in (B) the CNS response analysis set. The line at 20% represents the boundary for determination of progressive disease, and the line at −30% represents the boundary for determination of partial response.

harbor T790M.[15] We also report encouraging systemic PFS with osimertinib in patients with CNS metastases and a high CNS response (64%) in those with measurable CNS lesions. The latter is particularly relevant because new pharmacologic strategies are needed to treat brain metastases given the long-term complications of brain radiation.[16]

The standard recommendation for patients with *EGFR*m who progress after first-line EGFR-TKI treatment is chemotherapy, for which the maximum PFS reported to date is < 6 months.[17] For these patients, alternative treatment strategies have been explored. A study of treatment with paclitaxel and afatinib resulted in an ORR of 32% and PFS of 5.6 months.[18] In a phase II study that evaluated afatinib in combination with cetuximab, the response rate in patients with T790M-positive tumors was 32% and the median PFS 4.7 months.[19] However, a high rate of grade 3 (44%) and 4 (2%) AEs were reported with this combination. The ORR, PFS, and safety profile with osimertinib in both the AURA extension and the AURA2 studies compare favorably with historical results. These data support the current recommendation of osimertinib for the treatment of patients with T790M-positive advanced NSCLC after progression with prior EGFR-TKI therapy.[1]

The response rates to osimertinib were similar across all patient subgroups regardless of the line of therapy or the specific prior EGFR-TKI treatment they had received. Of note, some patients had received many (up to 11) lines of cancer therapy before osimertinib. The response rate and PFS were numerically, although not statistically, higher for patients with co-occurring T790M and *EGFR* exon 19 deletion–activating mutations compared with those with co-occurring T790M and *EGFR* L858R mutations documented before the study start. Prior studies of early-generation EGFR-TKIs (gefitinib, erlotinib, and afatinib) demonstrated greater clinical benefit in patients who harbored an *EGFR* exon 19 deletion than in patients with an L858R mutation.[20,21] We also observed a numerically higher response rate and longer PFS in Asian patients treated with osimertinib, similar to previous observations with early-generation EGFR-TKIs.[3-6,8,22] The reasons behind these observations are not clear because prior pharmacokinetic analyses demonstrated that osimertinib exposure is similar in both Asian and non-Asian patients.[23]

Osimertinib was well tolerated and associated with a low incidence of discontinuations and dose reductions as a result of possibly causally related AEs. Osimertinib was associated with

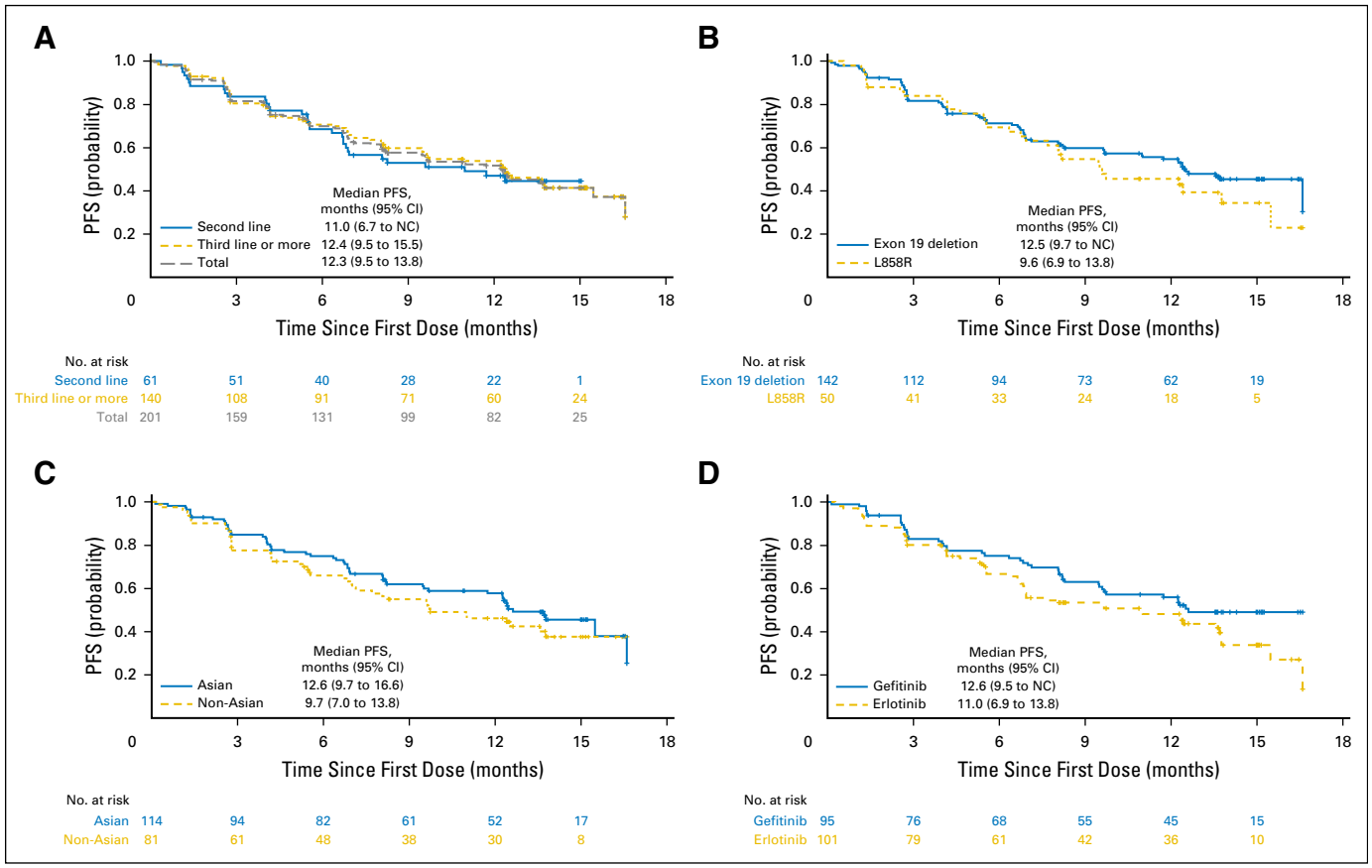

Fig 4. Progression-free survival (PFS) by blinded independent central review (full analysis set) by (A) line of therapy, by (B) co-occurring epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)–sensitizing mutation documented before start of study, (C) by ethnicity (Asian and non-Asian), and (D) by last prior EGFR-TKI treatment (gefitinib, erlotinib). Tick marks indicate censored observations. NC, not calculable.

symptomatic improvements, and PRO data in the AURA extension suggest that patients treated with osimertinib show benefits in symptoms, functioning, and health status/quality of life from baseline assessments.

ILD was observed in eight patients (4%), and osimertinib-associated ILD was observed in both white and Asian patients. The mechanistic basis and risk factors that led to osimertinib-associated ILD remain unclear. Presently, patients in whom ILD develops should discontinue osimertinib therapy and receive appropriate supportive care.

For the AURA extension, central confirmation of T790M was carried out by using tumor tissue samples. In a recent study that analyzed plasma-derived circulating tumor DNA as a biomarker for osimertinib response, Oxnard et al[24] concluded that patients positive for T790M in plasma have outcomes with osimertinib equivalent to patients with positive tissue-based assay results, which highlights the feasibility of plasma testing for selecting patients for osimertinib treatment. Recently, plasma-based T790M testing was approved by the US Food and Drug Administration.[25]

Table 2. Most Common Possibly Causally Related Adverse Events

	Grade, No. (%)			
Possibly Causally Related Adverse Event*	1	2	≥ 3	Total
Diarrhea	74 (37)	11 (5)	1 (< 1)	86 (43)
Rash (grouped terms)	67 (33)	12 (6)	1 (< 1)	80 (40)
Paronychia (grouped terms)	46 (23)	17 (8)	0	63 (31)
Dry skin (grouped terms)	56 (28)	6 (3)	0	62 (31)
Stomatitis	21 (10)	6 (3)	0	27 (13)
Pruritus	21 (10)	6 (3)	0	27 (13)
Platelet count decreased	23 (11)	0	2 (1)	25 (12)
Nausea	18 (9)	3 (1)	1 (< 1)	22 (11)
Decreased appetite	16 (8)	3 (1)	1 (< 1)	20 (10)

*That occurred in ≥ 10% of patients overall (as assessed by the investigator; N = 201).

Given that osimertinib is effective in treating patients with T790M-positive tumors and is a potent inhibitor of *EGFR*-activating mutations, the drug is under evaluation in patients with EGFR-TKI–naive advanced NSCLC. These studies will help to determine whether the development of T790M can be prevented and whether this approach is associated with a longer PFS than observed with gefitinib, erlotinib, or afatinib. Preliminary findings from a cohort of patients treated as part of the phase I trial demonstrated an encouraging response rate of 77% and a median PFS of 19.3 months.[26] A randomized phase III trial to compare osimertinib with gefitinib and erlotinib in EGFR-TKI–naive advanced *EGFR*m NSCLC has completed enrollment (FLAURA [Osimertinib Versus Gefitinib or Erlotinib in Patients With Locally Advanced or Metastatic NSCLC]; NCT02296125). To date, the strategy of using a more potent kinase inhibitor capable of overcoming resistance mechanisms to existing kinase inhibitors as initial therapy, including alectinib in *ALK*-rearranged NSCLC or nilotinib or dasatinib in chronic myeloid leukemia, has resulted in improved patient outcomes.[27-29]

In summary, the results from the AURA extension study show that osimertinib 80 mg once daily provides high response rates, encouraging PFS, and a long DoR with a manageable safety profile in patients with T790M-positive pretreated advanced 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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Appendix

Study Design and Participants

Eligibility criteria included the prospective confirmation of *EGFR* T790M mutation status by a central laboratory that used the cobas EGFR Mutation Test (Roche Molecular Systems, Pleasanton, CA) from a tissue biopsy specimen taken after confirmed disease progression while receiving the most recent treatment regimen (irrespective of whether epidermal growth factor receptor [EGFR] tyrosine kinase inhibitor [TKI] or chemotherapy), a WHO performance status of 0 to 1, acceptable organ function, and at least one measurable lesion not previously irradiated or chosen for biopsy during study screening. Patients with spinal cord compression or brain metastases could be enrolled if the disease was asymptomatic, stable, and not requiring corticosteroids for at least 4 weeks before first dose of study treatment.

Patients were excluded from the study if they had received treatment with an EGFR-TKI within 8 days or 5 half-lives of the first dose of study treatment; chemotherapy, investigational agents, or other anticancer drugs from a previous regimen within 14 days of the first dose of study treatment and medications or supplements known to inhibit cytochrome P450 isoenzyme 2C8 and inhibitors or inducers of cytochrome P450 isoenzyme 3A4 within 7 days of the first dose of study treatment. Patients with unresolved toxicity from prior treatment of more than National Cancer Institute Common Terminology Criteria for Adverse Events (version 4) grade 1 were excluded. Patients with a medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis that required corticosteroid treatment, or any evidence of clinically active ILD also were excluded.

cobas EGFR *Mutation Test*

The limit of detection for *EGFR* T790M detection with the cobas EGFR Mutation Test version 1 is 2.04% (O'Donnell et al: BMC Cancer 13:210, 2013). Compared with next-generation sequencing (two-tube amplicon assay run on MiSeq, read depth $\times$5,000; Roche Molecular Systems), positive and negative percent agreements for *EGFR* T790M detection were 91% and 97%, respectively (Appendix Table A5, online only).

Procedures

If a patient experienced a Common Terminology Criteria for Adverse Events (version 4) grade 3 or an unacceptable adverse event, osimertinib dosing was interrupted for up to 21 days. If the toxicity resolved to grade ≤ 2 within 21 days and the patient showed clinical benefit, treatment could be restarted at the same or lower dose of 40 mg/day. Patients with persistent QTc prolongation for > 21 days or ILD were permanently withdrawn from study treatment but followed up postdiscontinuation for disease progression.

Patient-reported outcomes were collected by using the European Organization for Research and Treatment of Cancer questionnaires QLQ-LC13 (disease-specific symptoms) and QLQ-C30 (general cancer symptoms, functioning, and global health status/quality of life) completed at baseline and then every 6 weeks.

Definitions of Progression-Free Survival and Duration of Response

Progression-free survival was defined as the time from date of first dose until the date of objective disease progression or death, regardless of whether the patient withdrew from study treatment or received another anticancer therapy before progression. Duration of response was defined as the time from date of first documented response (subsequently confirmed) until date of documented progression or death in the absence of disease progression.

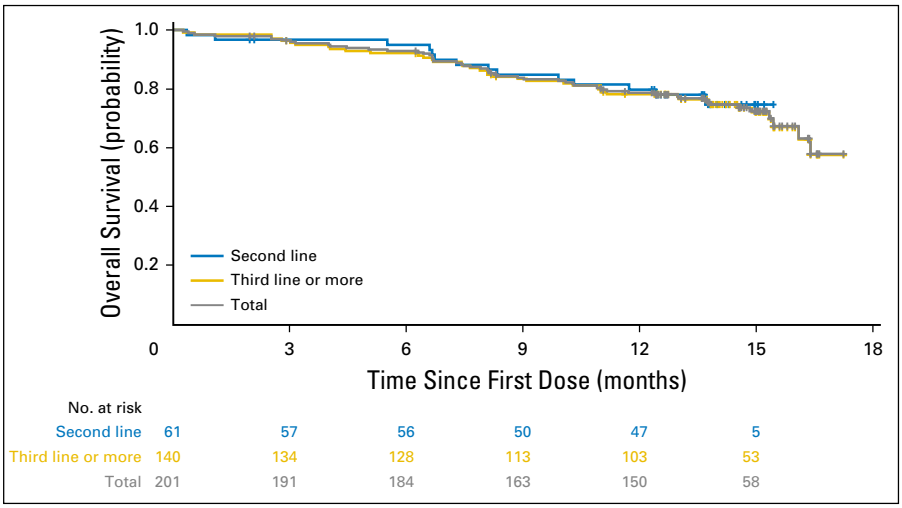

Fig A1. Overall survival by line of therapy.

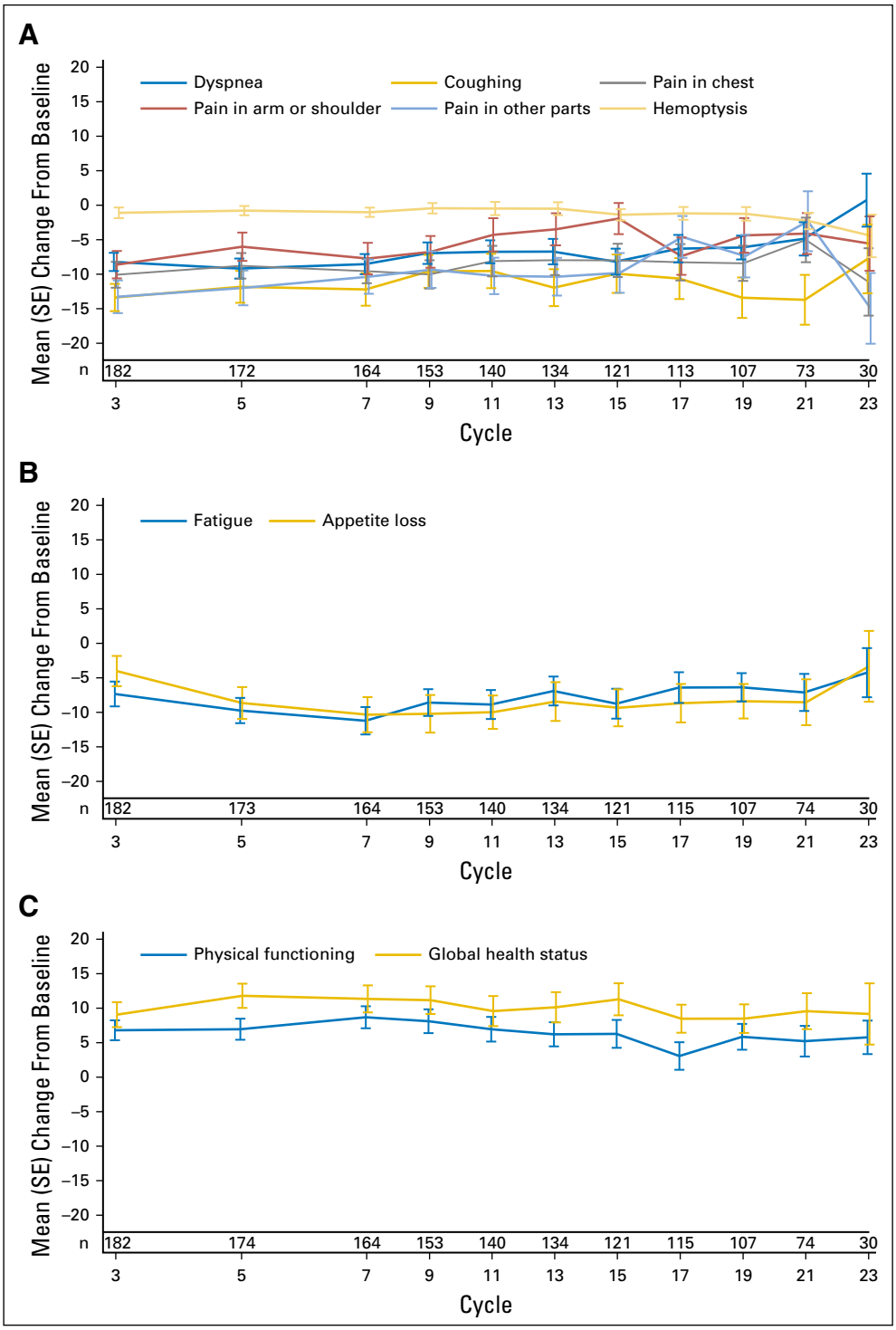

Fig A2. Patients showed consistent and sustained improvements in key lung cancer symptoms, including (A) dyspnea, cough, pain, and hemoptysis; (B) fatigue and appetite loss; and (C) physical functioning and global health status.

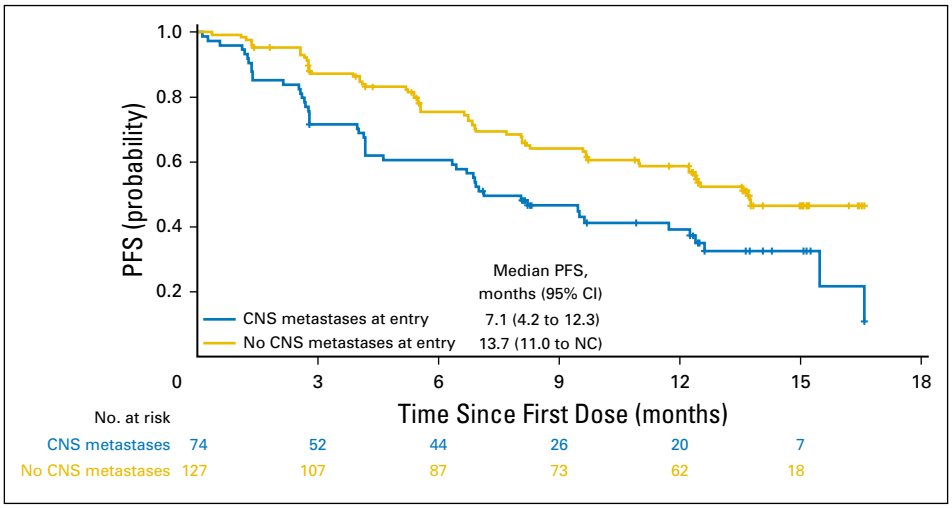

Fig A3. Progression-free survival (PFS) by CNS metastases at study entry. Tick marks indicate censored observations.

Table A1. *EGFR* Mutations Detected by Last Prior EGFR-TKI Treatment (by Central cobas EGFR Mutation Test)

Mutation	Last Prior Treatment, No. (%; 95% CI)		
	Afatinib	Erlotinib	Gefitinib
No. of patients (N = 225)	31	109	85
T790M	21 of 31 (68; 49 to 83)	74 of 109 (68; 58 to 77)	59 of 85 (69; 59 to 79)
T790M + exon 19 deletion	14 of 21 (67; 43 to 85)	54 of 74 (73; 61 to 83)	42 of 59 (71; 58 to 82)
T790M + L858R	5 of 21 (24; 8 to 47)	17 of 74 (23; 14 to 34)	17 of 59 (29; 18 to 42)
T790M + G719X	0 of 21 (0; 0 to 16)	2 of 74 (3; < 1 to 9)	1 of 59 (2; < 1 to 9)
T790M + other/unknown *EGFR*m	0 of 21 (0; 0 to 16)	1 of 74 (1; < 1 to 7)	1 of 59 (2; < 1 to 9)
T790M only	2 of 21 (10; 1 to 30)	2 of 74 (3; < 1 to 9)	0 of 59 (0; 0 to 6)
T790M not detected	10 of 31 (32; 17 to 51)	35 of 109 (32; 24 to 42)	26 of 85 (31; 21 to 42)
Exon 19 deletion without T790M	5 of 10 (50; 19 to 81)	16 of 35 (46; 29 to 63)	12 of 26 (46; 27 to 67)
L858R without T790M	4 of 10 (40; 12 to 74)	13 of 35 (37; 22 to 55)	11 of 26 (42; 23 to 63)
G719X without T790M	0 of 10 (0; 0 to 31)	0 of 35 (0; 0 to 10)	1 of 26 (4; < 1 to 20)
Other/unknown *EGFR*m without T790M	2 of 10 (20; 3 to 56)	0 of 35 (0; 0 to 10)	1 of 26 (4; < 1 to 20)

Abbreviation: *EGFR*m, *EGFR* mutation.

Table A2. Subset Analysis of Median PFS by Blinded Independent Central Review (full analysis set)

Patient Characteristic	Median PFS, Months (95% CI)
Sex	
Male (n = 68)	12.5 (9.6 to NC)
Female (n = 133)	11.0 (8.1 to 15.5)
Age at screening, years	
< 65 (n = 116)	11.7 (8.2 to 13.7)
≥ 65 (n = 85)	12.5 (7.0 to 16.6)
Smoking status	
Never (n = 134)	12.5 (9.5 to NC)
Ever* (n = 67)	12.3 (6.9 to 13.8)
Last treatment before osimertinib	
EGFR-TKI (n = 159)	12.3 (8.1 to 13.8)
Non–EGFR-TKI (n = 42)	12.5 (7.1 to 15.5)
Immediate prior EGFR-TKI treatment	
< 30 days before osimertinib (n = 105)	11.0 (6.9 to 17.0)
≥ 30 days before osimertinib (n = 54)	12.5 (8.1 to NC)
Duration of most recent EGFR-TKI treatment	
< 6 months (n = 43)	9.5 (4.2 to 13.7)
≥ 6 months (n = 158)	12.4 (9.7 to NC)

NOTE. Calculated by Kaplan-Meier technique.
Abbreviations: EGFR, epidermal growth factor receptor; NC, not calculable; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
*Current and former options are combined in the ever category.

Table A3. Safety Summary by AE Category

AE Category*	No. (%)†
No. of patients	201
Any AE	199 (99)
Any possibly causally related AE‡	185 (92)
Any grade ≥ 3 AE	77 (38)
Any grade ≥ 3 possibly causally related AE‡	30 (15)
Any AE with outcome of death	7 (3)
Any possibly causally related AE with outcome of death‡	3 (1)
Any SAE (including events with outcome of death)	55 (27)
Any possibly causally related SAE (including events with outcome of death)‡	12 (6)
Any AE that led to interruption of osimertinib	43 (21)
Any AE that led to reduction of osimertinib	10 (5)
Any AE that led to discontinuation of osimertinib	15 (7)
Any possibly causally related AE that led to discontinuation of osimertinib‡	9 (4)

Abbreviations: AE, adverse event; SAE, serious adverse event.
*Includes adverse events with an onset date on or after the date of first dose and up to and including 28 days following 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.

Table A4. Safety Summary by Most Common AEs (all causality) That Occurred in ≥ 10% of Patients Overall

AE*	Grade, No. (%)			
	1	2	≥ 3	Total (N = 201)
Diarrhea†	78 (39)	16 (8)	2 (1)	97 (48)§
Rash (grouped terms)	74 (37)	14 (7)	1 (< 1)	89 (44)
Dry skin (grouped terms)	60 (30)	7 (3)	0	67 (33)
Paronychia (grouped terms)	47 (23)	18 (9)	0	65 (32)
Decreased appetite	32 (16)	8 (4)	2 (1)	42 (21)
Cough	35 (17)	6 (3)	0	41 (20)
Nausea	30 (15)	8 (4)	3 (1)	41 (20)
Constipation	31 (15)	7 (3)	1 (< 1)	39 (19)
Back pain	26 (13)	8 (4)	1 (< 1)	35 (17)
Stomatitis	26 (13)	6 (3)	0	32 (16)
Platelet count decreased	26 (13)	3 (1)	2 (1)	31 (15)
Pruritus	25 (12)	6 (3)	0	31 (15)
Anemia	13 (6)	10 (5)	7 (3)	30 (15)
Fatigue	14 (7)	12 (6)	2 (1)	28 (14)
Vomiting	20 (10)	5 (2)	3 (1)	28 (14)
Headache	25 (12)	1 (< 1)	1 (< 1)	27 (13)
Asthenia	12 (6)	7 (3)	5 (2)	24 (12)
Dyspnea	12 (6)	7 (3)	5 (2)	24 (12)
Insomnia	20 (10)	4 (2)	0	24 (12)
Upper respiratory infection	16 (8)	8 (4)	0	24 (12)

Abbreviations: AE, adverse event.
*Includes AEs with an onset date on or after the date of first dose of study medication and up to and including 28 days after the date of the last dose of study medication.
†The grade of diarrhea in one patient was unknown.

Table A5. Concordance Data Between cobas *EGFR* Mutation Test Version 1 and Next-Generation Sequencing for the Detection of *EGFR* T790M From Tissue Samples

Test Result	Next-Generation Sequencing,* No.				
	Positive	Negative	Invalid	No Sample	Total
cobas					
Positive	190	3	0	14	207
Negative	18	82	0	17	117
Invalid	0	0	0	3	3
No sample	0	0	0	74	74
Total	208	85	0	108	401
Without invalid results, % (95% CI)					
Positive percent agreement			91 (87 to 95)		
Negative percent agreement			97 (90 to 99)		
Overall percent agreement			93 (89 to 96)		

*Two-tube amplicon assay run on MiSeq, read depth ×5,000 (Roche Molecular Systems, Pleasanton, CA).