ORIGINAL ARTICLE

Osimertinib versus Standard of Care EGFR TKI as First-Line Treatment in Patients with *EGFR*m Advanced NSCLC: FLAURA Asian Subset

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ABSTRACT

Introduction: Here we report efficacy and safety data of an Asian subset of the phase III FLAURA trial (NCT02296125), which compares osimertinib with standard of care (SoC) EGFR tyrosine kinase inhibitors (TKIs) in patients with previously untreated advanced NSCLC with tumors harboring exon 19 deletion (Ex19del)/L858R EGFR TKI–sensitizing mutations.

Methods: Eligible Asian patients (enrolled at Asian sites) who were at least 18 years of age (≥20 years in Japan) and had untreated *EGFR*-mutated advanced NSCLC were randomized 1:1 to receive osimertinib (80 mg, orally once daily) or an SoC EGFR TKI (gefitinib, 250 mg, or erlotinib, 150 mg, orally once daily). The primary end point was investigator-assessed progression-free survival (PFS). The key secondary end points were overall survival, objective response rate, central nervous system efficacy, and safety.

Results: The median PFS was 16.5 versus 11.0 months for the osimertinib and SoC EGFR TKI groups, respectively (hazard ratio = 0.54, 95% confidence interval: 0.41–0.72, $p < 0.0001$). The overall survival data were immature (24% maturity). The objective response rates were 80% for osimertinib and 75% for an SoC EGFR TKI. The median central nervous system PFS was not calculable for the osimertinib group and was 13.8 months for the SoC EGFR TKI group (hazard ratio = 0.55, 95% confidence interval: 0.25–1.17, $p = 0.118$). Fewer adverse events of grade 3 or higher (40% versus 48%) and fewer adverse events leading to treatment discontinuation (15% versus 21%) were reported with osimertinib versus with an SoC EGFR TKI, respectively.

Conclusion: In this Asian population, first-line osimertinib demonstrated a clinically meaningful improvement in PFS over an SoC EGFR TKI, with a safety profile consistent with that for the overall FLAURA study population.

Keywords: Osimertinib; First-line; Asian; FLAURA; NSCLC

Introduction

EGFR sensitizing mutations are more prevalent in Asian patients (~40%–50%) than in non-Asian patients (~10%–15%) with NSCLC.[1] Treatment with a first-generation or second-generation EGFR tyrosine kinase inhibitor (TKI) such as gefitinib, erlotinib, or afatinib is the standard of care (SoC) for patients with EGFR-mutated (*EGFR*m) locally advanced or metastatic NSCLC.[2,3] Erlotinib, gefitinib, and afatinib have demonstrated superior efficacy versus chemotherapy in the first-line setting for Asian and non-Asian patients with *EGFR*m advanced NSCLC, with phase III studies reporting significant improvements in progression-free survival (PFS) (median PFS ranging between 9 and 13 months) compared with chemotherapy (median PFS ranging between 4 and 6 months).[4–8]

Osimertinib is a third-generation, central nervous system (CNS)-active EGFR TKI that potently and selectively inhibits both *EGFR* mutation and *EGFR* T790M resistance mutations.[9,10] Osimertinib is the recommended treatment for patients with T790M-positive NSCLC who have disease progression during or after first-line treatment.[2,3] In the United States, the U.S. Food and Drug Administration has recently approved osimertinib for first-line treatment of patients with *EGFR*m (exon 19 deletion [Ex19del] or L858R) metastatic NSCLC.[11]

The recently published phase III FLAURA trial (NCT02296125) demonstrated that osimertinib significantly improved PFS, with a 54% lower risk of disease progression or death compared with SoC EGFR TKI therapy (gefitinib or erlotinib) in the first-line treatment of patients with *EGFR*m (Ex19del or L858R) advanced NSCLC.[12] We report efficacy and safety data for 322 Asian patients enrolled at Asian sites in the FLAURA trial.

Methods

Trial Design and Treatment

Full details of the FLAURA study methodology have been published elsewhere.[12] In brief, the FLAURA trial

was a double-blind, phase III trial comparing the efficacy and safety of osimertinib in patients with previously untreated *EGFR*m advanced NSCLC with that of an SoC EGFR TKI (either gefitinib or erlotinib). This subset analysis assessed the efficacy and safety of osimertinib in Asian patients enrolled at Asian sites (People's Republic of China, Japan, Malaysia, Philippines, Republic of Korea, Republic of China, Thailand, and Vietnam) in the FLAURA trial.

Patients were randomized in a 1:1 ratio to receive osimertinib (80 mg orally, once daily) or an SoC EGFR TKI (gefitinib [250 mg orally, once daily] or erlotinib [150 mg orally, once daily]) and stratified on the basis of *EGFR* mutation status (Ex19del or L858R). Patients randomized to the SoC EGFR TKI arm could cross over to receive open-label osimertinib if objective disease progression was confirmed by blinded independent central review (BICR) and postprogression T790M-positive mutation status was confirmed locally or centrally by plasma or tissue testing. Further details on the study treatment are included in the Supplementary Materials.

Patients

Eligible patients were at least 18 years of age (at least 20 years in Japan), had locally advanced or metastatic NSCLC, were treatment naive for advanced disease, and were eligible to receive gefitinib or erlotinib. Local or central confirmation of the *EGFR* mutations Ex19del or L858R, either alone or co-occurring with other EGFR mutations, was required. Patients with asymptomatic or stable CNS metastases were eligible. In patients with symptomatic CNS metastases, neurological status was required to be stable for at least 2 weeks after completion of definitive therapy and corticosteroids.

Table 1. Demographic and Clinical Characteristics at Baseline

Characteristic	Osimertinib, 80 mg (n = 162)	SoC EGFR TKI (n = 160)
Age, y		
Mean (SD)	62.5 (10.7)	63.2 (11.0)
Median (range)	63.5 (26-85)	64.0 (35-87)
Sex, n (%)		
Male	61 (38)	69 (43)
Female	101 (62)	91 (57)
Race, n (%)		
Asian	162 (100)	160 (100)
Ethnic group, n (%)		
Asian (other than Chinese and Japanese)	71 (44)	85 (53)
Chinese	26 (16)	20 (13)
Japanese	65 (40)	55 (34)
Smoking history, n (%)		
Never-smokers	104 (64)	95 (59)
Current smokers	5 (3)	5 (3)
Former smokers	53 (33)	60 (38)
WHO performance status, n (%)		
0 (normal activity)	65 (40)	62 (39)
1 (restricted activity)	97 (60)	98 (61)
Overall disease classification, n (%)		
Metastatic	154 (95)	156 (98)
Locally advanced	8 (5)	4 (3)
Metastases at study entry, n (%)		
CNS[a]	33 (20)	33 (21)
Extrathoracic visceral[b]	58 (36)	53 (33)
Liver	25 (15)	14 (9)
Bone and locomotor	52 (32)	47 (29)
Comparator, n (%)		
Gefitinib	NA	130 (81)
Erlotinib	NA	30 (19)

[a]Programmatically derived composite end point with a list of contributing data sources.
SoC, standard of care; TKI, tyrosine kinase inhibitor; CNS, central nervous system; NA, not applicable.

Standard Protocol Approvals, Registration, and Patient Consent

FLAURA was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization/Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on bioethics. Informed consent was obtained from all patients before enrolment in the study. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

End Points and Assessments

The primary end point for the Asian subset analysis was PFS according to investigator assessment based on the Response Evaluation Criteria in Solid Tumors, version 1.1. Tumor assessments were performed at baseline and every 6 weeks thereafter for 18 months and then every 12 weeks until objective disease progression. Secondary efficacy end points included overall survival (OS), objective response rate, duration of response, disease control rate, and depth of response (change in target lesion size from baseline). Adverse events (AEs) were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The pharmacokinetics of osimertinib and its metabolites AZ5104 and AZ7550 were assessed, as were patient-reported outcomes; assessment details are included in the Supplementary Materials.

Baseline brain scans were mandated only in patients with known or suspected CNS metastases at study entry; patients with confirmed CNS metastases received follow-

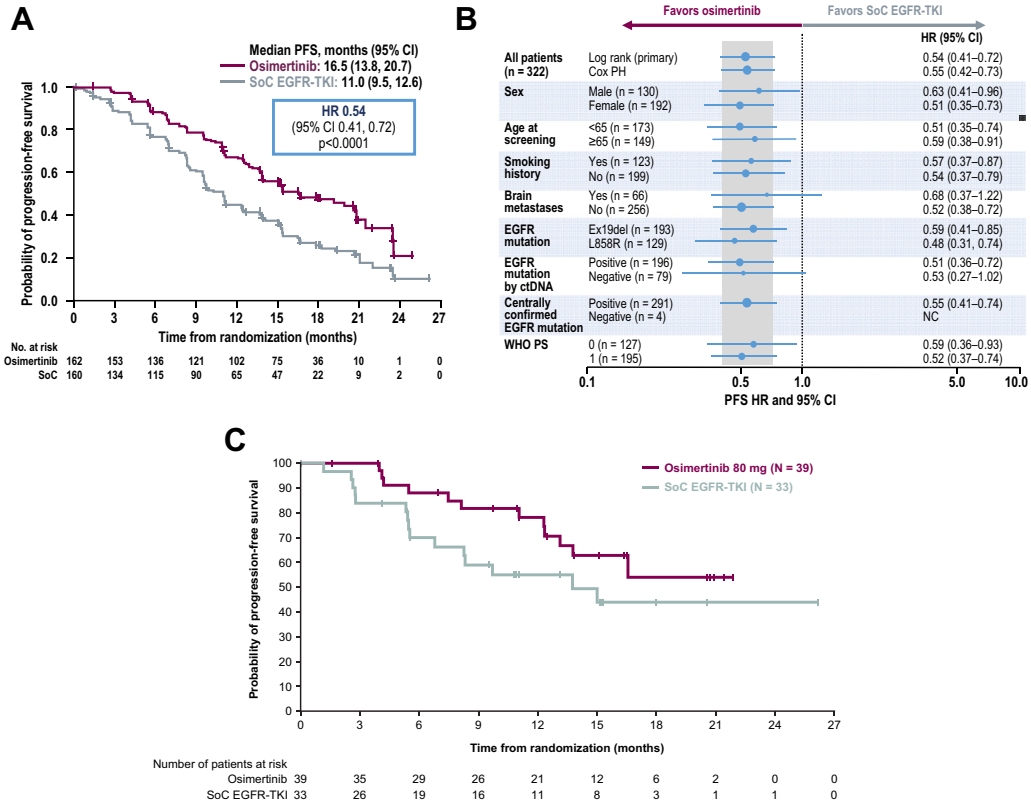

Figure 1. Kaplan-Meier estimates of the duration of progression-free survival (PFS) (*A*) with subgroup analyses of PFS (*B*), and Kaplan-Meier estimates of the duration of PFS for those with central nervous system metastases at study entry (*C*), as assessed by investigators in the Asian subset. For the analysis of PFS, data for patients who had not had a progression event or had not died at the time of the analysis were censored at the time of their last assessment (according to the Response Evaluation Criteria in Solid Tumours) that could be evaluated. A hazard ratio (HR) less than 1 implies a lower risk of disease progression or death with osimertinib than with a standard of care (SoC) EGFR tyrosine kinase inhibitor (TKI). The Cox proportional hazards (PH) model includes randomly assigned treatment, the subgroup covariate of interest, and the treatment-by-subgroup interaction. The size of the circles is proportional to the number of events. Overall population analyses are presented from both a Cox PH model and the primary analysis (U and V statistics from a log-rank test stratified according to EGFR mutation type and race). If there were fewer than 20 events in a subgroup, the analysis was not performed. The shaded area indicates the 95% confidence interval (CI) for the overall hazard ratio (all patients). Subgroup categories with less than 20 events were excluded from the analysis. ctDNA, circulating tumor DNA; Ex19del, exon 19 deletion; NC, not calculable; PS, performance status.

up brain scans. In a preplanned exploratory analysis, CNS efficacy was assessed by neuroradiological BICR in patients with measurable and/or nonmeasurable CNS metastases at baseline (CNS full analysis set [cFAS]) and/or in those patients with at least one measurable CNS metastasis at baseline (CNS evaluable-for-response set). Additional detail is included in the Supplementary Materials.

Statistical Methods

The data cutoff was June 12, 2017. The full analysis set included all randomly assigned patients. The safety analysis set consisted of all patients who received at least one dose of study treatment. Sample size and further statistical methods are provided in the Supplementary Materials.

Results

Patients

In total, 322 patients enrolled in FLAURA were included in the Asian subset; of these, 162 received osimertinib and 160 received an SoC EGFR TKI (gefitinib, $n = 130$ [81%], or erlotinib, $n = 30$ [19%]) (Supplementary Fig. 1). Baseline demographics and disease characteristics were representative of the intended target patient population and balanced between treatment groups (Table 1). No protocol deviations were considered to have a meaningful impact on the overall conclusions.

All patients randomized to treatment received at least one dose of study treatment. The median durations of treatment exposure were 15.5 months (range 0.5–25.5) and 11.7 months (range 0–26.2) for the osimertinib and

Table 2. Secondary Efficacy End Points (Full Analysis Set)

End Point, n (%)	Osimertinib (n = 162)	SoC EGFR TKI (n = 160)
Type of response[a]		
Complete	3 (2)	0
Partial	126 (78)	120 (75)
Stable disease ≥6 wk	30 (19)	28 (18)
Progression	0	7 (4)
Death	0	3 (2)
Could not be evaluated	3 (2)	5 (3)
Objective response rate, % of patients (95% CI)	80 (73-86)	75 (68-82)
Adjusted odds ratio[b] (95% CI), *p* value	1.33 (0.78-2.28), $p = 0.2918$	
Disease control rate, % of patients (95% CI)[c]	98 (95-100)	93 (87-96)
Adjusted odds ratio (95% CI), *p* value	4.36 (1.35, 19.42), $p = 0.0123$	
Time to response[d]		
No. of weeks, median (95% CI)	6.1 (6.0-6.3)	6.1 (6.0-6.3)
≤6 wk after first dose, n (%)	91 (71)	87 (73)
≤12 wk after first dose, n (%)	113 (88)	103 (86)
≤18 wk after first dose, n (%)	118 (92)	111 (93)
Median duration of response,[e] mo (95% CI)		
Patients with continued response (95% CI)	18 (12.5-21.9)	9 (7.0-11.0)
At 12 mo	64 (54-71)	38 (29-47)
At 18 mo	48 (38-57)	21 (13-30)
Median overall response,[f] mo (95% CI)	NC (NC-NC)	NC (NC-NC)
Patients alive at 6 mo, % (95% CI)	100 (NC-NC)	94 (88-97)
Patients alive at 12 mo, % (95% CI)	91 (85-94)	84 (77-89)
Patients alive at 18 mo, % (95% CI)	82 (75-88)	72 (64-79)

Note: Efficacy analyses included all randomly assigned patients (full analysis set).
[a]Tumor responses were assessed by the investigators according to the Response Evaluation Criteria in Solid Tumors, version 1.1.
[b]Adjusted for mutation type (exon 19 deletion or L858R).
[c]The disease control rate is the proportion of patients who had a complete response, a partial response, or stable disease lasting at least 6 weeks before any disease progression event.
[d]The time to tumor response was calculated with use of the Kaplan-Meier method from the date of randomization to the date of the first documentation of a partial or complete response. Per the protocol, Response Evaluation Criteria in Solid Tumors assessments occurred every 6 weeks (±1 week) for 18 months, then every 12 weeks (±1 week) until disease progression.
[e]The duration of response was calculated with use of the Kaplan-Meier method from the date of the first documented response until the date of documented disease progression or death in the absence of disease progression.
[f]Overall survival was calculated from the date of randomization to the date of death due to any cause.
SoC, standard of care; TKI, tyrosine kinase inhibitor; CI, confidence interval; NC, could not be calculated.

SoC EGFR TKI groups, respectively. A total of 88 (54%) patients receiving osimertinib and 123 (77%) patients receiving an SoC EGFR TKI discontinued study treatment (see Supplementary Fig. 1). Of those patients who discontinued study treatment, 55 of 88 (63%) in the osimertinib group and 71 of 123 (58%) in the SoC EGFR TKI group started undergoing at least one subsequent therapy.

Efficacy

The efficacy analysis set included all randomized patients. At data cutoff, 74 patients in the osimertinib group (46%) and 37 patients in the SoC EGFR TKI group (23%) continued receiving randomized treatment. An event of Response Evaluation Criteria in Solid Tumors–defined progression or death had occurred in 85 patients in the osimertinib group (53%) and 114 patients in the SoC EGFR TKI group (71%). There was a clinically meaningful improvement in investigator-assessed PFS in the osimertinib group versus in the SoC EGFR TKI group (hazard ratio [HR] for disease progression or death = 0.54, 95% confidence interval [CI]: 0.41–0.72, $p < 0.0001$). The median PFS was 16.5 months (95% CI: 13.8–20.7) in the osimertinib group and 11.0 months (95% CI: 9.5–12.6) in the SoC EGFR TKI group (Fig. 1*A*). The median follow-up times for PFS were 13.8 months and 10.7 months for the osimertinib and SoC EGFR TKI groups, respectively. Clear separation of the Kaplan-Meier curves in favor of osimertinib occurred within the first 3 months and continued for the duration of the follow-up period (see Fig. 1*A*). A sensitivity analysis of PFS by BICR supported the results of investigator-assessed PFS in this patient subset (Supplementary Results and Supplementary Fig. 2). A consistent benefit of

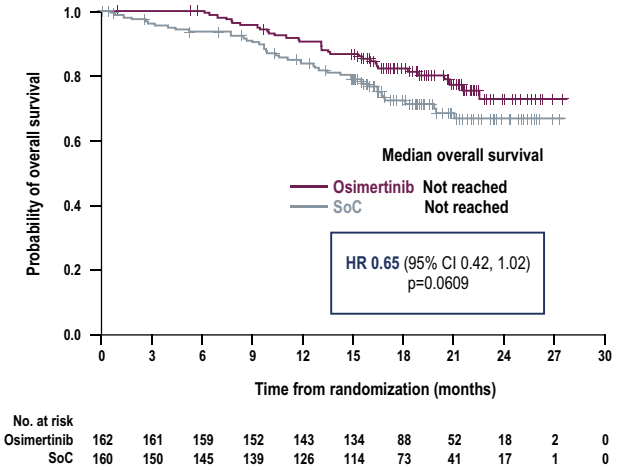

Figure 2. Kaplan-Meier estimates of overall survival. For the analysis of overall survival, data for any patients who were not known to have died at the time of the analysis were censored at the last recorded date on which the patient was known to be alive.CI, confidence interval; HR, hazard ratio; SoC, standard of care.

osimertinib over SoC EGFR TKIs with respect to PFS was observed across all predefined subgroups assessed, with HRs less than 0.70 (Fig. 1*B*); the *p* values for the HRs in the CNS metastases and detection of EGFR mutation by ctDNA categories were greater than 0.05.

Secondary efficacy outcomes, including OS, objective response rate, disease control rate, duration of response, and time to onset of response are presented in Table 2**.** The OS data were immature at the interim analysis (24% maturity), and the median OS was not reached in either arm; the total number of patient deaths in the osimertinib and SoC EGFR TKI groups were 33 (20%) and 44 (28%), respectively. The survival rates at 18 months were 82% (95%: CI: 75–88) with osimertinib and 72% (95% CI: 64–79) with SoC EGFR TKIs (HR for death = 0.65, 95% CI: 0.42–1.02, $p = 0.0609$) (Fig. 2). The median best percentage change in target lesion size is reported in the Supplementary Materials.

CNS BICR Analysis

The CNS BICR analysis assessed the CNS efficacy of osimertinib versus that of an SoC EGFR TKI. In total, 39 and 33 patients were identified by neuroradiological BICR as having at least one measurable and/or nonmeasurable CNS lesion at study entry (the cFAS) in the osimertinib and SoC EGFR TKI groups, respectively. In the cFAS, the median CNS PFS was not reached in the osimertinib group; the 95% CI lower limit was 13.1 months. In the SoC arm, the median CNS PFS was 13.8 months (95% CI: 6.8–not calculable) (HR = 0.55, 95% CI: 0.25–1.17, $p = 0.118$) (Fig. 1*C*). Additional CNS data are reported in the Supplementary Materials.

Safety

The safety analysis set included all patients who received at least one dose of treatment (full analysis set). In both treatment groups, 99% of patients experienced an AE (all causality). Fewer grade 3 or higher AEs occurred with osimertinib than with an SoC EGFR TKI (40% versus 48%, respectively). The most commonly reported all-causality AEs in the osimertinib and SoC EGFR TKI groups were rash (58% and 81%, respectively), diarrhea (54% in each group), and paronychia (40% and 37%) (Table 3). AEs considered by the investigator to be possibly related to a study drug are reported in Supplementary Table 1. Fewer AEs leading to treatment discontinuation occurred with osimertinib (15%) than with an SoC EGFR TKI (21%). The difference in incidence of AEs of grade 3 or higher and treatment discontinuation due to an AE was driven largely by the greater incidence of hepatic events in the SoC EGFR TKI group. Serious AEs occurred in 38 patients (23%) and 36 patients (23%) in the osimertinib and SoC EGFR TKI groups, respectively. AEs of special interest, including prolongation of the QT interval corrected for heart rate using Fridericia's formula, cardiac contractility, and interstitial lung disease, were broadly consistent with the known safety profile of osimertinib and consistent with the overall FLAURA safety profile (data not shown).

Pharmacokinetics and patient-reported outcomes data are reported in the Supplementary Materials.

Discussion

In FLAURA, osimertinib showed superior efficacy compared with SoC EGFR TKIs in the first-line treatment of *EGFR*m advanced NSCLC, with an early separation of the PFS Kaplan-Meier curves that continued throughout the study. A longer median duration of PFS was observed with osimertinib (18.9 months versus 10.2 months), and there was a similar safety profile between the two treatment groups.[12] Consistent with the overall study, in this FLAURA Asian subset analysis osimertinib demonstrated superior efficacy over SoC EGFR TKIs as a first-line therapy for Asian patients, with a 46% reduction in the risk of disease progression.

The PFS benefit with osimertinib reported for this Asian subset is consistent with the results observed in the predefined subgroup analysis by race reported in the overall FLAURA population (HR = 0.55, 95% CI: 0.42–0.72).[12] Patients recruited into FLAURA were stratified by race (Asian or non-Asian), irrespective of location. In this subset analysis, only Asian patients enrolled in Asian countries were included. As such, 25 Asian patients enrolled in non-Asian countries were excluded.

The median PFS reported in the SoC EGFR TKI group is consistent with that in previous clinical trials in Asian

Table 3. Most Common Adverse Events (All Causality; All Patients Who Received at Least One Dose of Randomized Treatment)

	Osimertinib, 80 mg (n = 162)		SoC EGFR TKI (n = 160)	
Adverse Event	Any Grade, n (%)	Grade ≥3, n (%)	Any Grade, n (%)	Grade ≥3, n (%)
Rash[a]	94 (58)	1 (1)	130 (81)	13 (8)
Diarrhea	88 (54)	3 (2)	86 (54)	4 (3)
Paronychia[a]	67 (41)	1 (1)	61 (38)	2 (1)
Stomatitis	56 (35)	1 (1)	41 (26)	0
Dry skin[a]	58 (36)	1 (1)	55 (34)	2 (1)
Decreased appetite	32 (20)	5 (3)	31 (19)	5 (3)
Constipation	27 (17)	0	20 (13)	0
White blood cell count decreased	24 (15)	1 (1)	5 (3)	0
Pruritus	24 (15)	0	24 (15)	0
Electrocardiogram QT prolonged	24 (15)	5 (3)	8 (5)	0
Viral upper respiratory tract infection	22 (14)	0	14 (9)	0
Anemia	23 (14)	2 (1)	18 (11)	3 (2)
Upper respiratory tract infection	22 (14)	0	14 (9)	0
Aspartate aminotransferase level increased	19 (12)	2 (1)	57 (36)	10 (6)
Insomnia	18 (11)	0	15 (9)	0
Cough	17 (10)	0	15 (9)	0
Nausea	15 (9)	0	25 (16)	0
Interstitial lung disease[a]	9 (6)	1 (1)	3 (2)	2 (1)

Note: Includes adverse events with onset date on or after date of first dose up to and including 28 days after discontinuation of randomized treatment or the day before first administration of crossover treatment.
[a]These categories represent a grouped term for the event. If a patient had multiple preferred-term events within a specific grouped-term adverse event, then the maximum grade (according to the Common Terminology Criteria for Adverse Events) across those events was counted.
SoC, standard of care; TKI, tyrosine kinase inhibitor.

patients harboring *EGFR* mutation–positive tumors in a first-line setting (approximately 9–13 months).[7,8] The ARCHER trial (dacomitinib versus gefitinib) showed that dacomitinib has a superior median PFS of 14.7 months in patients with previously untreated *EGFR*m advanced NSCLC. Patients were predominantly Asian (>75%), and those with metastases were excluded from the trial.[13]

CNS metastases are common in patients with NSCLC and are associated with a worse prognosis.[14] In this subset analysis, osimertinib demonstrated a numerically greater CNS PFS for patients receiving osimertinib versus for an SoC EGFR TKI, although this difference was not statistically significant. These data are comparable with the those for the overall FLAURA population,[12] and with the findings of previous reports showing greater CNS efficacy of osimertinib versus chemotherapy in patients with T790M-positive NSCLC and CNS metastases.[10,15]

The safety profile of osimertinib in this Asian subset was consistent with that in the overall FLAURA study population in terms of the nature and severity of reported AEs.[12] The frequency of treatment-related AEs associated with osimertinib in the Asian patients (94%) was comparable with the rate reported in the overall FLAURA population (91%).[13] The safety profile of osimertinib was similar to that of the SoC EGFR TKIs, but with a lower rate of grade 3 or higher AEs and lower discontinuation rates, which is consistent with the rates for the overall FLAURA population (13% and 18%, respectively).[12]

A limitation of the FLAURA study was the exclusion of afatinib and icotinib from the comparator group. This was because afatinib and icotinib were not licensed in all participating countries at study initiation. However, clinical outcomes with afatinib have been reported extensively, and a recent meta-analysis concluded that there is no difference in efficacy among afatinib, erlotinib, and gefitinib.[16] Similarly, the ICOGEN study reported that icotinib and gefitinib have similar efficacy in patients with NSCLC.[17]

In conclusion, our analysis of a subset of Asian patients enrolled in the FLAURA study has shown that osimertinib has a clinically meaningful PFS benefit compared with SoC EGFR TKI therapy in Asian patients with advanced *EGFR*m NSCLC, with consistent improvements in PFS across predefined subgroups. Although immature, the interim OS results show promising survival, favoring osimertinib. Furthermore, the safety profile was consistent with that for the overall FLAURA study population. These data support osimertinib as a standard first-line treatment for this patient population.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2018.09.004.

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