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# Osimertinib versus standard-of-care EGFR-TKI as first-line treatment for EGFRm advanced NSCLC: FLAURA Japanese subset

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## Abstract

**Background:** The FLAURA study was a multicenter, double-blind, Phase 3 study in which patients with previously untreated epidermal growth factor receptor mutation-positive advanced non-small-cell lung carcinoma were randomized 1:1 to oral osimertinib 80 mg once daily or standard-of-care (gefitinib 250 mg or erlotinib 150 mg, once daily) to compare safety and efficacy. In the overall FLAURA study, significantly better progression-free survival was shown with osimertinib versus standard-of-care.

**Methods:** Selected endpoints, including progression-free survival (primary endpoint), overall survival, objective response rate, duration of response and safety were evaluated for the Japanese subset of the FLAURA study.

**Results:** In Japan, 120 eligible Japanese patients were randomized to osimertinib (65 patients) or gefitinib (55 patients) treatment from December 2014 to June 2017. Median progression-free survival was 19.1 (95% confidence interval, 12.6, 23.5) and 13.8 (95% confidence interval, 8.3, 16.6) months with osimertinib and gefitinib, respectively (hazard ratio, 0.61; 95% confidence interval, 0.38, 0.99). Median overall survival was not reached in either treatment arm (data were immature). In the osimertinib and gefitinib arms, objective response rate was 75.4% (49/65) and 76.4% (42/55), and median duration of response from onset was 18.4 (95% confidence interval, not calculated) and 9.5 (95% confidence interval, 6.2, 13.9) months, respectively. The incidence of adverse events was similar in the two groups. The frequency of Grade ≥3 interstitial lung disease and pneumonitis in the two groups were the same (one patient).

**Conclusions:** As the first-line therapy, osimertinib showed significantly improved efficacy versus gefitinib in the Japanese population of the FLAURA study. No new safety concerns were raised.
**Clinical trial registration:** NCT02296125 (ClinicalTrials.gov)

**Key words:** clinical trials, lung medicine, thoracic

## Introduction

First- and second-generation epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are the recommended first-line treatment for *EGFR* mutation-positive advanced non-small-cell lung cancer (NSCLC) (1,2). While treatment with gefitinib or erlotinib can significantly extend progression-free survival (PFS) compared with combination chemotherapy (3), more than 50% of patients treated with an EGFR-TKI become resistant within the first year of treatment (4–6).

Osimertinib is an oral, third-generation, central nervous system (CNS)-active, irreversible EGFR-TKI that potently and selectively inhibits both EGFR-TKI-sensitizing mutations (EGFRm; exon 19 and 21 mutations) and the T790M resistance mutation (7–11). Osimertinib has recently been approved in the USA and Europe as a first-line treatment for patients with EGFRm advanced NSCLC and for patients with T790M mutation-positive advanced NSCLC (12,13).

In the FLAURA study, a multicenter, double-blind, Phase 3 study with 556 patients with previously untreated *EGFR* mutation-positive advanced NSCLC, osimertinib was found to be statistically and clinically significant in prolonging PFS compared with gefitinib or erlotinib (18.9 months vs 10.2 months; hazard ratio [HR] for disease progression or death, 0.46; 95% confidence interval [CI], 0.37, 0.57; $P < 0.0001$) (14).

Based on the previous studies that demonstrated the usefulness of first- and second-generation EGFR-TKIs for the treatment of Japanese patients with EGFR mutation-positive NSCLC (15,16), these are now regarded as standard therapy in the clinical setting in Japan. However, Japanese NSCLC patients have a high rate of EGFR-TKI-sensitizing mutations (17,18). Furthermore, some issues of concern related to EGFR-TKIs remain, such as acquired resistance primarily involving the T790M mutation and the onset of interstitial lung disease (ILD) (19,20).

New first-line treatment options that circumvent the development of EGFR-TKI-sensitizing mutations in the Japanese population are needed to avoid the development of T790M resistance, delay clinical disease progression and improve treatment outcomes. This report describes a predefined subset analysis of the FLAURA study that compares the safety and efficacy of osimertinib versus standard-of-care in Japanese patients.

## Materials and methods

### Patients

Inclusion and exclusion criteria for the FLAURA study have been previously published (14). In brief, eligible patients had untreated advanced or metastatic NSCLC and were eligible for treatment with gefitinib or erlotinib. Patients with CNS metastases were eligible if their condition was stable or asymptomatic. Patients with locally or centrally confirmed *EGFR* exon 19 deletion or L858R mutation were eligible for the FLAURA study. Patients who were described as 'Japanese' on the case report form and were enrolled in a study site in Japan were included in the subset analyzed in the current study. All patients provided written informed consent.

### Study design, treatments and blinding

The FLAURA study design, conducted between December 2014 and June 2017, has previously been published (14). The FLAURA study was conducted in accordance with the principles outlined in the Declaration of Helsinki, Good Clinical Practice and local regulatory requirements and was approved by the institutional review boards or independent ethics committees of the participating study centers. 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.

Patients eligible for the FLAURA study were stratified based on *EGFR* mutation status (*EGFR* exon 19 deletion or L858R mutation) and race (Asian and non-Asian) and then randomized 1:1 to either oral osimertinib 80 mg once daily or a standard EGFR-TKI (gefitinib 250 mg once daily or erlotinib 150 mg once daily) (Fig. 1). Each study site prespecified the EGFR-TKI to be used for the standard-of-care arm. In Japan, only gefitinib was chosen as the standard-of-care for comparison. The Japanese patients were enrolled from 18 study sites throughout Japan.

After investigator-assessed objective disease progression was confirmed, a protocol amendment allowed patients allocated to the standard-of-care arm to switch to osimertinib treatment if they had radiological disease progression, had not received interventional therapy after discontinuation of their randomized treatment and had the T790M mutation detected in either tissue or circulating tumor DNA collected after disease progression (Fig. 1).

### Endpoints

The primary endpoint was the duration of PFS. Disease progression was assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Secondary endpoints were overall survival (OS), duration of response (DoR), disease-control rate (DCR), objective response rate (ORR) and safety. Adverse events (AEs) were assessed and graded by the investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Tumors were assessed at baseline, every 6 weeks for the first 18 months and then every 12 weeks until disease progression was detected. Brain imaging was conducted at screening for those with known or suspected CNS metastases, and follow-up scans were conducted for those with confirmed CNS metastases.

The predefined post-progression outcome measures included the time from randomization to second progression or death after the start of subsequent therapy (PFS2), time from randomization to first subsequent therapy or death, time from randomization to discontinuation of treatment or death, and time to second subsequent treatment or death.

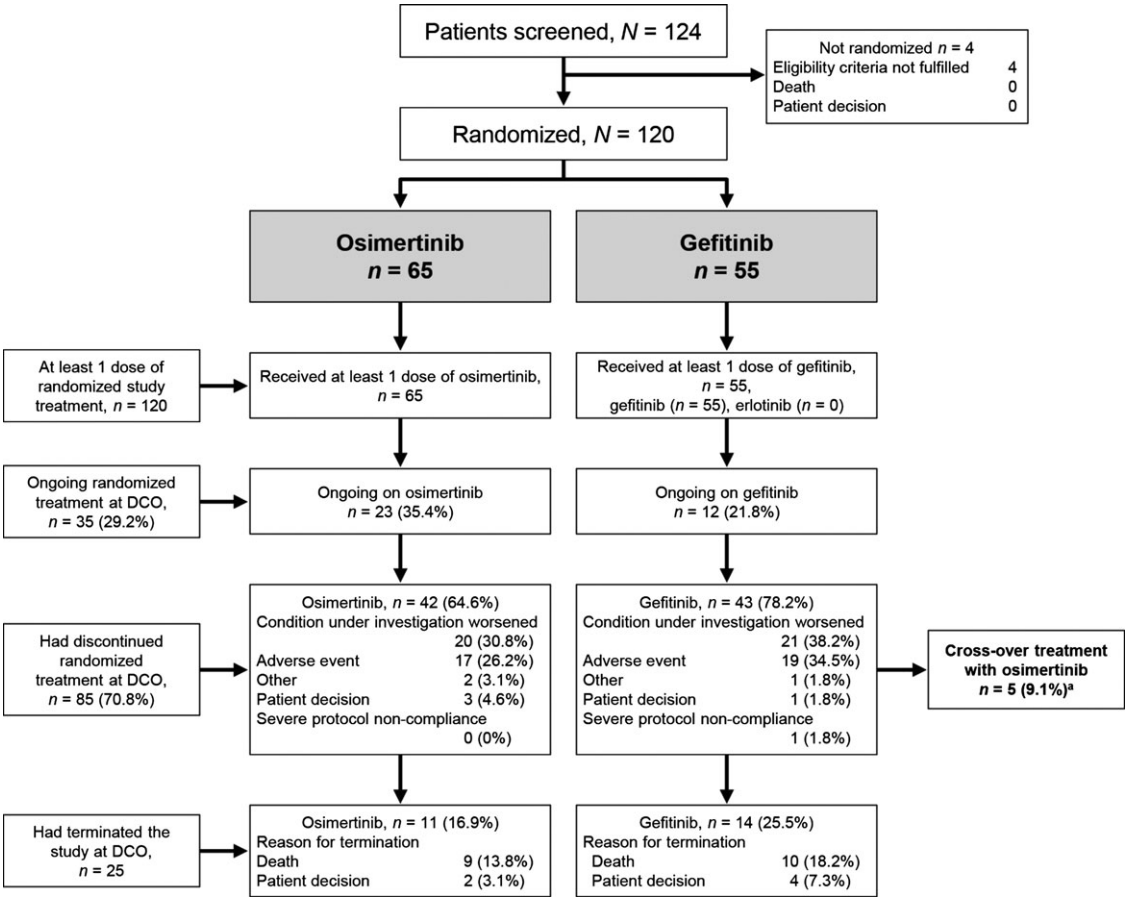


**Figure 1.** Disposition of the Japanese subset in the FLAURA study. DCO, data cutoff. [a]Among patients who requested dispensing of crossover treatment with osimertinib, five patients provided dosing information with osimertinib in the electronic case report form.

### Statistical methods

Considering ~359 events of progression or death in a total of 530 randomly assigned patients, the FLAURA study had a 90% power to detect a HR of 0.71 (representing an improvement in median PFS from 10 to 14.1 months) at a two-sided alpha-level of 5%.

Efficacy was assessed in the full analysis set, including all randomized Japanese patients. AEs were assessed in the safety analysis set, which included all patients receiving at least one dose of the assigned treatment. A Kaplan–Meier survival analysis was performed. An adjusted log-rank test was conducted for an across-treatment comparison, stratified by EGFR mutation type (exon 19 deletion vs L858R), in which the Breslow approach was used to handle tied events. HRs were calculated along with 95% CIs. Adjusted analyses were conducted for DCR and ORR using logistic regression analysis stratified by EGFR mutation type (exon 19 deletion vs L858R). All *P* values are to be considered as nominal in this subgroup analysis, as the study was not powered for the Japanese subset. The data were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

### Patients

In the Japanese subset, a total of 120 eligible Japanese patients were randomized to treatment (osimertinib, 65 [54.2%]; gefitinib, 55 [45.8%]) (Fig. 1). Patients in Japan were randomized between February 2015 and March 2016. Baseline characteristics were well balanced between the two groups (Table 1). Overall, the patients had a median age of 67 years. There was a higher percentage of women in the osimertinib arm (66.2%) than in the gefitinib arm (50.9%). Slightly more than half of the patients were never-smokers (overall, 53.3%; osimertinib, 53.8% and gefitinib, 52.7%).

All randomized patients received at least one dose of the allocated treatment. The median duration of total treatment exposure was 15.3 months (range 0.5 to 25.5) in the osimertinib group and 11.0 months (range 0 to 25.1) in the gefitinib group.

All disease characteristics were similar in the two treatment groups (Table 1). The majority of patients had metastatic NSCLC (overall, 113 [94.2%]; osimertinib, 60 [92.3%] and gefitinib, 53 [96.4%]), with seven (5.8%) patients overall with locally advanced NSCLC. Overall, most patients had adenocarcinomas (116 [96.7%]), including 11 cases of papillary adenocarcinoma. Twenty-seven (22.5%) patients had a CNS metastasis at baseline (osimertinib, 14 [21.5%]; gefitinib, 13 [23.6%]). Overall, 63 (52.5%) patients had exon 19 deletions, and 57 (47.5%) patients had L858R mutations.

### Efficacy

Disease progression occurred in 34 (52.3%) patients in the osimertinib group and 36 (65.5%) in the gefitinib group (Fig. 2A). Median PFS was 19.1 months (95% CI, 12.6, 23.5) in the osimertinib group

and 13.8 months (95% CI, 8.3, 16.6) in the gefitinib group, with a HR of 0.61 (95% CI, 0.38, 0.99; $P = 0.0456$ [nominal $P$ value; this subgroup analysis was not powered for the Japanese subset]). There were nine (13.8%) deaths in the osimertinib group and 10 (18.2%) in the gefitinib group. OS data were immature at the time of this report (Fig. 2B).

Results of the secondary endpoint analyses are summarized in Table 2. The ORR was similar in the two groups. In the osimertinib group, the ORR was 75.4% (49 of 65), with an adjusted response rate of 76.8%. In the gefitinib group, the ORR was 76.4% (42 of 55), with an adjusted rate of 77.1%. Two patients in the osimertinib group achieved a complete response, while no patients in the gefitinib group achieved a complete response. The median DoR from onset in the osimertinib group was almost twice as long as that in the gefitinib group: 18.4 months (no 95% CI) in the osimertinib group and 9.5 months (95% CI, 6.2, 13.9) for the gefitinib group (Fig. 3). At 6 months, an estimated 87.4% (95% CI, 74.1, 94.1) of patients were remaining in response in the osimertinib group and 69.0% (95% CI, 52.0, 81.1) in the gefitinib group. At 12 months, the numbers were 69.9% (95% CI, 54.5, 81.0) in the osimertinib group and 43.6% (95% CI, 27.4, 58.8) in the gefitinib group. The DCR was 96.9% (63 of 65) in the osimertinib group, with an adjusted DCR of 96.9%. In the gefitinib group, the DCR was 96.4% (53 of 55), with an adjusted DCR of 96.4%. The mean (standard deviation) best percent changes from baseline in target lesion size were −50.0 (25.3) mm and −45.6 (24.2) mm in the osimertinib and gefitinib groups, respectively.

**Table 1.** Patients' baseline characteristics

| | Osimertinib ($n = 65$) | Gefitinib ($n = 55$) |
|---|---|---|
| Sex, *n* (%) | | |
| Male | 22 (33.8) | 27 (49.1) |
| Female | 43 (66.2) | 28 (50.9) |
| Age, years, median (range) | 67.0 (34–82) | 67.0 (43–85) |
| Smoking status, *n* (%) | | |
| Never-smokers | 35 (53.8) | 29 (52.7) |
| Current/former smokers | 30 (46.2) | 26 (47.3) |
| CNS metastases at study entry, *n* (%) | 14 (21.5) | 13 (23.6) |
| WHO performance status, *n* (%) | | |
| 0 (normal activity) | 38 (58.5) | 34 (61.8) |
| 1 (restricted activity) | 27 (41.5) | 21 (38.2) |
| Overall disease classification, *n* (%) | | |
| Metastatic | 60 (92.3) | 53 (96.4) |
| Locally advanced | 5 (7.7) | 2 (3.6) |
| EGFR mutation[a] at baseline, *n* (%) | | |
| Exon 19 deletion | 33 (50.8) | 30 (54.5) |
| L858R | 32 (49.2) | 25 (45.5) |

CNS, central nervous system; EGFR, epidermal growth factor receptor; WHO, World Health Organization.

[a]EGFR mutations based on the test (local or central) used to determine randomization strata.

Of the 120 patients in the Japanese subset, 85 patients discontinued study treatment; 61 of 85 (71.8%) patients received several post-investigational anticancer therapies, including radiotherapy, and 58 of 85 (68.2%) patients had at least one post-investigational anticancer therapy. Eleven (20.0%) patients in the gefitinib group (including the five patients who were switched to open-label osimertinib) received osimertinib treatment as a post-investigational treatment therapy; and although no patients in the osimertinib group received osimertinib as a first post-treatment therapy, two (3.1%) patients in the osimertinib group received further osimertinib as a later line of therapy.

In the Japanese subset, there was a delay in the PFS2 in the osimertinib arm compared with the gefitinib group (HR, 0.73 [95% CI, 0.36, 1.48]). The median PFS2 values for osimertinib could not be calculated. Treatment with osimertinib was associated with a

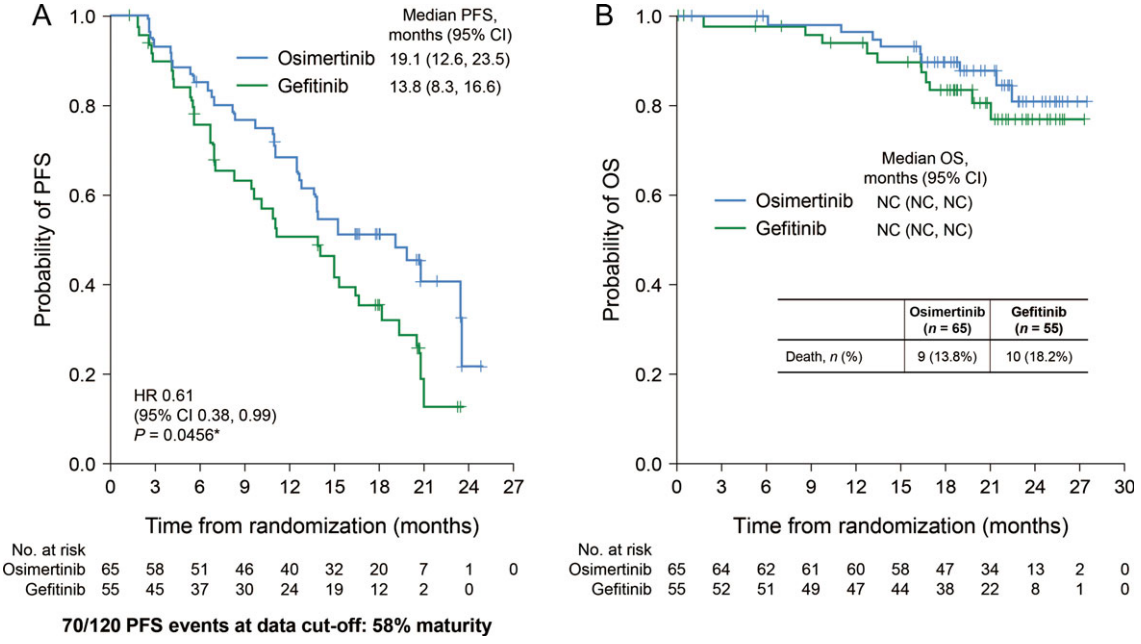


**Figure 2.** PFS (A) and OS (B) in osimertinib and gefitinib treatment groups. *For reference purposes only. The $P$ value is nominal as the present subgroup analysis was not powered for the Japanese subset analysis. CI, confidence interval; HR, hazard ratio; NC, not calculable; OS, overall survival; PFS, progression-free survival.

**Table 2.** Secondary efficacy endpoints

| | Osimertinib ($n = 65$) | Gefitinib ($n = 55$) |
|---|---|---|
| OS, % (95% CI) | | |
| Survival at 12 months | 96.8 (87.7, 99.2) | 94.2 (83.0, 98.1) |
| Survival at 18 months | 90.1 (79.4, 95.5) | 83.7 (69.9, 91.5) |
| Objective response[a] | | |
| Complete response, *n* (%) | 2 (3.1) | 0 |
| Partial response, *n* (%) | 47 (72.3) | 42 (76.4) |
| Adjusted response rate[b], % | 76.8 | 77.1 |
| Odds ratio (95% CI) | 0.98 (0.41, 2.32) | |
| Median DoR from onset[c,d], months (95% CI) | 18.4 (NC, NC) | 9.5 (6.2, 13.9) |
| Disease control[a] | | |
| Patients under control, *n* (%) | 63 (96.9) | 53 (96.4) |
| Adjusted control rate[b], % | 96.9 | 96.4 |
| Odds ratio (95% CI) | 1.19 (0.14, 10.23) | |
| Best percent change from baseline in target lesion size, unadjusted mean (SD) | −50.0 (25.3) | −45.6 (24.2) |

CI, confidence interval; EGFR, epidermal growth factor receptor; NC, not calculable; OS, overall survival; SD, standard deviation; DoR, duration of response.

[a]Based on investigator assessment.

[b]Adjusted using logistic regression analysis stratified by EGFR mutation type (exon 19 deletion vs L858R).

[c]DoR was the time from the first documentation of response until the date of progression or death in the absence of progression.

[d]Calculated using the Kaplan–Meier method.

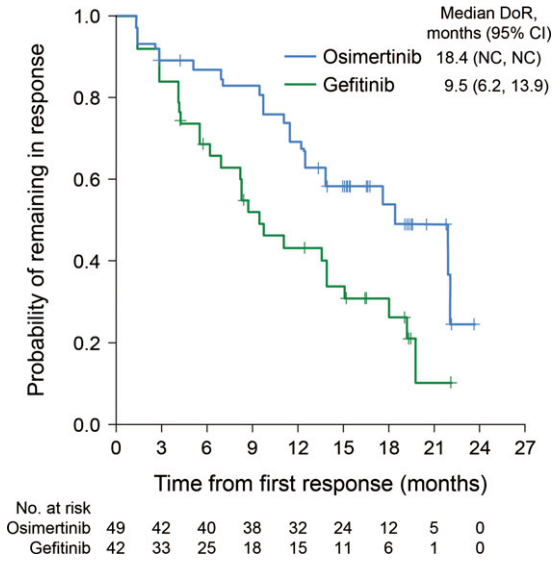


**Figure 3.** DoR in osimertinib and gefitinib treatment groups. CI, confidence interval; NC, not calculable; DoR, duration of response.

delay in the initiation of the first subsequent therapy or death (HR, 0.68 [95% CI, 0.41, 1.12]), a prolongation of the time from randomization to discontinuation of treatment or death (15.3 [95% CI, 11.6, 22.0] months vs 11.0 [95% CI, 5.3, 14.5] months in the osimertinib and gefitinib groups, respectively), and a prolongation of the time to second subsequent treatment or death (HR, 0.86 [95% CI, 0.45, 1.64]).

**Table 3.** Adverse events

| | Osimertinib ($n = 65$) | Gefitinib ($n = 55$) |
|---|---|---|
| AE, any cause, *n* (%) | | |
| Any AE | 65 (100) | 53 (96.4) |
| Any AE Grade ≥3 | 31 (47.7) | 31 (56.4) |
| Any AE leading to death | 0 | 1 (1.8) |
| Any serious AE | 14 (21.5) | 12 (21.8) |
| Any AE leading to discontinuation | 17 (26.2) | 19 (34.5) |
| AE possibly causally related, *n* (%) | | |
| Any AE possibly causally related | 64 (98.5) | 53 (96.4) |
| Any AE possibly causally related Grade ≥3 | 18 (27.7) | 27 (49.1) |
| Any AE possibly causally related leading to death | 0 | 0 |
| Any possibly causally related serious AE | 12 (18.5) | 8 (14.5) |

AE, adverse event.

## Safety

Among the Japanese subset of the FLAURA study, AEs were noted in 118 (98.3%) patients (Table 3). AEs Grade 3 or higher were reported in 31 (47.7%) patients in the osimertinib group and 31 (56.4%) patients in the gefitinib group. Serious AEs were reported in 14 (21.5%) patients in the osimertinib group and 12 (21.8%) patients in the gefitinib group. Only one AE leading to death was reported (in the gefitinib group). This was a case of endocarditis not considered related to treatment. AEs leading to discontinuation were reported in 17 (26.2%) patients in the osimertinib group and 19 (34.5%) patients in the gefitinib group.

Dermatitis acneiform was more common in the gefitinib group, affecting 30 (46.2%) patients in the osimertinib group and 38 (69.1%) in the gefitinib group. Increases in liver enzymes were also more common in the gefitinib group. Aspartate aminotransferase increased was reported in seven (10.8%) patients in the osimertinib group and 25 (45.5%) in the gefitinib group. Alanine aminotransferase increase was reported in five (7.7%) patients in the osimertinib group and 27 (49.1%) in the gefitinib group. White blood cell (WBC) count decrease, QTc prolongation, ILD and pneumonitis were all more common in the osimertinib group. WBC count decrease was reported in 14 (21.5%) patients in the osimertinib group and one (1.8%) in the gefitinib group. QTc prolonged was reported in 14 (21.5%) and 5 (9.1%) patients in the osimertinib and gefitinib groups, respectively. There were no safety concerns identified in the underlying laboratory data. In the osimertinib group, the events of QTc prolongation and WBC count decrease were not associated with arrhythmias or infections. ILD and pneumonitis were reported in eight (12.3%) patients in the osimertinib group and one (1.8%) in the gefitinib group. The number of patients with Grade 1–2 ILD and pneumonitis reported was seven (10.8%) and zero in the osimertinib and gefitinib groups, respectively. The number of patients with Grade ≥3 ILD and pneumonitis reported was the same in both groups (one patient [2%] each). In most cases, no symptoms were reported, and these were the only radiological findings. In both arms, all patients with ILD discontinued treatment. All ILD events in the osimertinib arm were reported as recovered and patients were subsequently treated with another EGFR-TKI (Supplementary data, Table S1).

The number of dose interruptions was similar in the two treatment groups. Dose interruption due to an AE occurred in 26 (40.0%) patients in the osimertinib group and 25 (45.5%) in the

gefitinib group. Dose reduction due to an AE occurred in nine (13.8%) patients in the osimertinib group and seven (12.7%) in the gefitinib group.

## Discussion

The overall FLAURA study demonstrated that osimertinib had superior efficacy as a first-line treatment compared with treatment with gefitinib or erlotinib, without raising new safety concerns (14). The reduction in the risk of progression or death in the Japanese subset was consistent with that in the overall population (14). The PFS Kaplan–Meier curves for the Japanese subset show a clear separation between treatment arms within 3 months, which remain separated for the duration of the follow-up. Although PFS in the gefitinib group in the Japanese subset was longer than expected based on historical data (Supplementary data, Table S2), patients in the Japanese subset treated with osimertinib had a clinically meaningful improvement in PFS compared with the gefitinib group: median PFS was 5.3 months longer (osimertinib, 19.1 months [95% CI, 12.6, 23.5] vs gefitinib, 13.8 months [95% CI, 8.3, 16.6]). The HR for the Japanese subset was 0.61 (95% CI, 0.38, 0.99), indicating a 39% reduction in the risk of disease progression or death in the absence of RECIST progression in the osimertinib group compared with the gefitinib group. Afatinib was not included as a comparator in the FLAURA study; however, a recent meta-analysis concluded there is no difference in efficacy between afatinib, gefitinib and erlotinib in NSCLC (21). Historical studies of first-, second- and third-generation EGFR-TKIs show osimertinib has a superior efficacy over first- and second-generation EGFR-TKIs (Supplementary data, Table S2) (22–24).

A numerical improvement in OS in favor of osimertinib was observed in the Japanese subset and was consistent with that seen in the overall population. High responses rates (>75%) were seen in both arms, with a large majority of responses being partial responses. The responses in the osimertinib arm were durable: more patients treated with osimertinib remained in response at 6 months and beyond than patients treated with gefitinib. The improvement in DoR with osimertinib in the Japanese subset was consistent with the overall population.

The prespecified post-progression outcome measures were included in this study because the OS data were expected to be immature at the time of the primary PFS analysis. These measures provide information on whether any observed PFS advantage could be maintained during the administration of subsequent anticancer therapies. They also may provide preliminary evidence of any detrimental effect beyond PFS that could potentially be associated with a poorer OS, such as long-term toxicity, biological changes leading to a more aggressive disease or development of resistance that would affect the efficacy of the next line of therapy. Although the patient numbers are small, and the data are immature, all post-progression outcomes favor the osimertinib treatment group.

A delay was observed in the PFS2 in the osimertinib arm compared with the gefitinib group. This might have been because of the benefit accrued from the time from randomization to first progression (PFS). It might also be because of the limited number of PFS2 events among Japanese patients. Therefore, interpretation of the PFS2 results can be difficult and requires caution.

Treatment with osimertinib showed associations with a delay in terms of prolongation of the time to discontinuation of treatment or death and prolongation of the time to second subsequent treatment or death. These results suggest that the treatment benefit provided by osimertinib in prolonging PFS is maintained with longer follow-up and during subsequent therapy.

The tolerability and safety profile of osimertinib in the Japanese subset was generally consistent with that seen in the overall population (14). No new safety issues were identified for osimertinib in the Japanese subset. The safety findings of osimertinib in the Japanese subset were consistent with the known safety profile of osimertinib characterized in the AURA studies (11). While the frequency of Grade 1–2 ILD and pneumonitis was higher in the osimertinib group versus the gefitinib group, the frequency of Grade ≥3 ILD and pneumonitis in the osimertinib group was the same as that in the gefitinib group. The pattern of AEs reported in the treatment groups are as expected for a population of patients receiving an EGFR-TKI as first-line treatment for advanced NSCLC.

The incidence of AEs was broadly similar in the two treatment groups in the Japanese subset, despite the longer exposure in the osimertinib arm. Rates of Grade ≥3 AEs were lower in the osimertinib group than in the gefitinib group. Common AEs, including diarrhea, paronychia, stomatitis, dermatitis acneiform, dry skin and decreased appetite were reported in at least 20% of patients in both treatment groups. Dermatitis acneiform was more common in the gefitinib group, likely because osimertinib has higher selectivity against wild-type EGFR than gefitinib. Increases in liver enzymes were also more common in the gefitinib group. In the osimertinib arm, these AEs were generally mild, with only three Grade 3 or higher events. In the gefitinib group, 15 Grade 3 or 4 hepatic-related AEs were reported. ILD, QTc prolongation and decreases in WBC counts were all more common in the osimertinib group but still infrequent and generally Grade 1 or 2. The events of QTc prolongation and decreases in WBC counts reported in the osimertinib group were not associated with clinical sequelae such as arrhythmias or infections. Laboratory data for QTc prolongation and WBC count decrease in the Japanese subset were consistent with that observed in the overall population (14). In the Japanese subset, comparison of the safety profiles between the two treatment arms in FLAURA confirms that osimertinib is generally well tolerated and has an acceptable safety profile compared with gefitinib.

In Japan, EGFR-TKI therapy is currently recommended for first-line treatment of EGFRm advanced NSCLC, but patients treated with first- and second-generation EGFR-TKIs typically develop resistance due to T790M mutations. In contrast, osimertinib can effectively target T790M mutations. The availability of osimertinib as a first-line treatment for patients with *EGFR* exon 19 deletions or L858R mutations could prevent resistance and provide potent and durable targeting of *EGFR* mutations.

Future studies are needed to address the mechanisms of resistance to osimertinib. As the PFS survival curves separate within the first 3 months of treatment, the initial evidence suggests that resistance to osimertinib does not arise early in treatment as it does in some patients receiving gefitinib.

The T790M mutation arises in about 50–60% of patients treated with standard EGFR-TKIs. Twenty-eight Japanese patients in the gefitinib group had a first post-investigational treatment in the FLAURA study. Of these, about 14–17 would be expected to have the T790M mutation. Eleven (20.0%) patients in the gefitinib group received osimertinib treatment as a post-investigational treatment therapy. Thus, the number of patients who received osimertinib as post-therapy in the gefitinib group was reasonable.

The FLAURA study was not powered for the subanalysis of the Japanese patients; thus, the *P* value presented in this report is for reference purposes only. Although OS analysis was performed, the HR

could not be evaluated because the data were immature. The number of patients with CNS metastases in the Japanese subset did not reach the minimum threshold for a separate analysis. Furthermore, brain imaging was limited to patients with known or suspected CNS metastases, so the study did not assess asymptomatic CNS metastases. The study does not compare osimertinib as a first-line treatment to sequential treatment with gefitinib followed by osimertinib. However, the treatment effect of osimertinib on PFS observed in this study suggests that starting treatment with osimertinib could potentially be more effective than sequential EGFR-TKIs.

As a first-line therapy, osimertinib demonstrated a clinically meaningful improvement in efficacy versus gefitinib in the Japanese subset of the FLAURA study. The safety profile in this study was consistent with the known AEs characteristic of respective EGFR-TKIs (such as low-grade ILD-like events and QTc prolongation in the osimertinib group and hepatic and skin toxicities in the gefitinib group). These data support osimertinib as a first-line treatment for Japanese patients with *EGFR* mutation-positive metastatic NSCLC.

## Supplementary data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

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## Conflicts of interest statement

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