ORIGINAL ARTICLE

# Overall Survival with Osimertinib in Untreated, *EGFR*-Mutated Advanced NSCLC

S.S. Ramalingam, J. Vansteenkiste, D. Planchard, B.C. Cho, J.E. Gray, Y. Ohe, C. Zhou, T. Reungwetwattana, Y. Cheng, B. Chewaskulyong, R. Shah, M. Cobo, K.H. Lee, P. Cheema, M. Tiseo, T. John, M.-C. Lin, F. Imamura, T. Kurata, A. Todd, R. Hodge, M. Saggese, Y. Rukazenkov, and J.-C. Soria, for the FLAURA Investigators*

## ABSTRACT

### BACKGROUND

Osimertinib is a third-generation, irreversible tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR-TKI) that selectively inhibits both EGFR-TKI–sensitizing and *EGFR* T790M resistance mutations. A phase 3 trial compared first-line osimertinib with other EGFR-TKIs in patients with *EGFR* mutation–positive advanced non–small-cell lung cancer (NSCLC). The trial showed longer progression-free survival with osimertinib than with the comparator EGFR-TKIs (hazard ratio for disease progression or death, 0.46). Data from the final analysis of overall survival have not been reported.

### METHODS

In this trial, we randomly assigned 556 patients with previously untreated advanced NSCLC with an *EGFR* mutation (exon 19 deletion or L858R allele) in a 1:1 ratio to receive either osimertinib (80 mg once daily) or one of two other EGFR-TKIs (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily, with patients receiving these drugs combined in a single comparator group). Overall survival was a secondary end point.

### RESULTS

The median overall survival was 38.6 months (95% confidence interval [CI], 34.5 to 41.8) in the osimertinib group and 31.8 months (95% CI, 26.6 to 36.0) in the comparator group (hazard ratio for death, 0.80; 95.05% CI, 0.64 to 1.00; P=0.046). At 3 years, 79 of 279 patients (28%) in the osimertinib group and 26 of 277 (9%) in the comparator group were continuing to receive a trial regimen; the median exposure was 20.7 months and 11.5 months, respectively. Adverse events of grade 3 or higher were reported in 42% of the patients in the osimertinib group and in 47% of those in the comparator group.

### CONCLUSIONS

Among patients with previously untreated advanced NSCLC with an *EGFR* mutation, those who received osimertinib had longer overall survival than those who received a comparator EGFR-TKI. The safety profile for osimertinib was similar to that of the comparator EGFR-TKIs, despite a longer duration of exposure in the osimertinib group. (Funded by AstraZeneca; FLAURA ClinicalTrials.gov number, NCT02296125.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Ramalingam at the Winship Cancer Institute of Emory University, 1365 Clifton Rd., Atlanta, GA 30322, or at ssramal@emory.edu.

*A complete list of the investigators in the FLAURA trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 21, 2019, and updated on December 4, 2019, at NEJM.org.

N Engl J Med 2020;382:41-50.
DOI: 10.1056/NEJMoa1913662

In patients with advanced or metastatic non–small-cell lung cancer (NSCLC) with mutations in the gene encoding epidermal growth factor receptor (*EGFR*) that are sensitive to tyrosine kinase inhibitors (TKIs) (exon 19 deletions or L858R point mutations), guidelines recommend treatment with an EGFR-TKI.[1-4] The clinical practice guidelines of the National Comprehensive Cancer Network recommend osimertinib as the preferred EGFR-TKI option for first-line treatment in such patients.[4]

Osimertinib is a third-generation, irreversible, oral EGFR-TKI that selectively inhibits both EGFR-TKI–sensitizing and *EGFR* p.Thr790Met (T790M) resistance mutations and has shown efficacy in patients with NSCLC who have central nervous system (CNS) metastases.[5-9] The FLAURA trial was a double-blind, phase 3 trial involving patients with previously untreated advanced NSCLC with *EGFR* mutations that compared the efficacy and safety of osimertinib with that of two other EGFR-TKIs, gefitinib or erlotinib (with both drugs included in the comparator group).[9]

The primary analysis (data cutoff on June 12, 2017) showed significantly longer progression-free survival with the osimertinib regimen than with the comparator regimen (median duration, 18.9 months vs. 10.2 months; hazard ratio for disease progression or death, 0.46; P<0.001). At the time of the primary analysis, overall survival data were immature (data maturity, 25%) but showed a trend toward longer overall survival with osimertinib (hazard ratio for death, 0.63; P=0.007).[9] The safety profile of osimertinib was similar to that of the comparator EGFR-TKIs, and the rates of serious adverse events were lower with osimertinib.[9] On the basis of these efficacy and safety data, the indication for osimertinib was extended to include first-line treatment in patients with advanced NSCLC whose tumors have sensitizing *EGFR* mutations.[10,11] Here, we report the results of the planned final analysis of overall survival.

## Methods

### Patients

Full details regarding the FLAURA trial have been published previously[9] and are provided in the trial protocol, available with the full text of this article at NEJM.org. In brief, eligible patients were 18 years of age or older (20 years or older in Japan), had locally advanced or metastatic NSCLC with an *EGFR* mutation (exon 19 deletion or L858R), had not previously received treatment for advanced disease, and were eligible to receive first-line treatment with gefitinib or erlotinib. Patients with known or suspected CNS metastases were eligible to participate if their condition was neurologically stable.

### Trial Oversight

The trial was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Conference on Harmonisation), applicable regulatory requirements, and the policy on bioethics and human biologic samples of the trial sponsor, AstraZeneca. All the patients provided written informed consent.

The trial was funded by the sponsor and was designed by the principal investigators (first and last authors) and the sponsor. The sponsor was responsible for the collection and analysis of the data and had a role in data interpretation. All the authors had full access to all the data. The first draft of the manuscript was written by the first and last authors, with medical-writing support funded by the sponsor; all the authors reviewed the manuscript before it was submitted for publication. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol.

### Trial Design and Treatment

In this double-blind, phase 3 trial, patients were stratified according to *EGFR* mutational status (exon 19 deletion or L858R) and race (Asian or non-Asian) and were randomly assigned in a 1:1 ratio to receive either oral osimertinib (at a dose of 80 mg once daily) or a comparator oral EGFR-TKI (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily) until disease progression, unacceptable toxicity, or withdrawal of consent. Patients in the comparator group (a combination of those who received either gefitinib or erlotinib) were eligible for crossover to open-label osimertinib after disease progression had been objectively confirmed on blinded independent central review (or by investigator assessment if disease progression occurred after the primary data cutoff) and after post-progression documentation of the presence of a T790M resistance mutation on local or central testing.

### END POINT

Overall survival was a key secondary end point in the trial. According to the protocol, after the analysis of the primary end point of progression-free survival had been performed (data cutoff, June 12, 2017), central collection of progression events, defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1, was stopped.

### TRIAL ASSESSMENTS

After the primary data cutoff, tumor assessments were performed in accordance with clinical practice, and scans were no longer centrally collected. Assessments for survival were made every 6 weeks after objective disease progression up to the time of the final analysis of overall survival. Overall survival was defined as time from randomization until death from any cause. Adverse events were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

### STATISTICAL ANALYSIS

The final analysis of overall survival was planned after approximately 318 deaths had occurred in the full analysis set. We used the Kaplan–Meier method with a log-rank test, stratified according to race (Asian vs. non-Asian) and mutational status (exon 19 deletion vs. L858R), to compare overall survival in the two groups; the Breslow approach was used to handle tied events. The hazard ratio and confidence interval were obtained directly from a stratified log-rank test.[12] Data from patients who had not died at the time of the analysis were censored on the basis of the last recorded date that the patient was known to be alive.

We calculated that the trial would have a power of 72% to determine a hazard ratio of less than 0.75 (indicating a longer duration of median overall survival, from 25.0 to 33.3 months) with a two-sided significance level of 0.05. The Lan–DeMets approach that approximates the O'Brien–Fleming spending function was used to maintain an overall two-sided 5% type I error rate across the interim and final analyses of overall survival. The P value that was observed at the interim analysis of overall survival was not significant. This finding did not preclude further planned testing of overall survival, and according to the Lan–DeMets approach, a two-sided P value of 0.0495 was considered to indicate statistical significance for the final analysis of overall survival. A 95.05% confidence interval for the final analysis of the hazard ratio for overall survival was calculated because of the remaining alpha of 0.0495 after the interim analysis. All other confidence intervals are reported as 95%, since all P values reported for overall survival are nominal and not part of the multiple-testing strategy. The data cutoff for the final analysis was June 25, 2019.

We used a Cox proportional-hazards model to analyze overall survival in predefined subgroups. There had to be at least 20 deaths in a subgroup for it to be included in the analysis. In the subgroup analysis, all hazard ratios and 95% confidence intervals were adjusted for trial group, subgroup, and a treatment-by-subgroup interaction term for each subgroup. Additional details regarding the statistical analysis are provided in the Supplementary Appendix, available at NEJM.org.

## RESULTS

### PATIENTS AND TREATMENT

From December 2014 through March 2016, a total of 556 patients underwent randomization (279 to receive osimertinib and 277 to receive a comparator EGFR-TKI) and received at least one dose of a trial drug. In the comparator group, 183 patients (66%) received gefitinib and 94 patients (34%) received erlotinib as their assigned treatment. The demographic characteristics of the patients at baseline have been reported previously.[9] The enrollment and outcomes in the two groups are presented in Figure S1 in the Supplementary Appendix.

At the time of the data cutoff, the median duration of treatment exposure was 20.7 months (range, 0.1 to 49.8) in the osimertinib group and 11.5 months (range, 0.0 to 50.6) in the comparator group. The number of patients who were continuing to receive the assigned trial drug at the time of the data cutoff was 61 (22%) in the osimertinib group and 13 (5%) in the comparator group.

### EFFICACY

At the time of data cutoff, 321 deaths had occurred (58% maturity), representing the planned number of events and maturity. All the patients had the opportunity to have a follow-up of 39 months; the median duration of follow-up for overall survival was 35.8 months in the osimertinib group

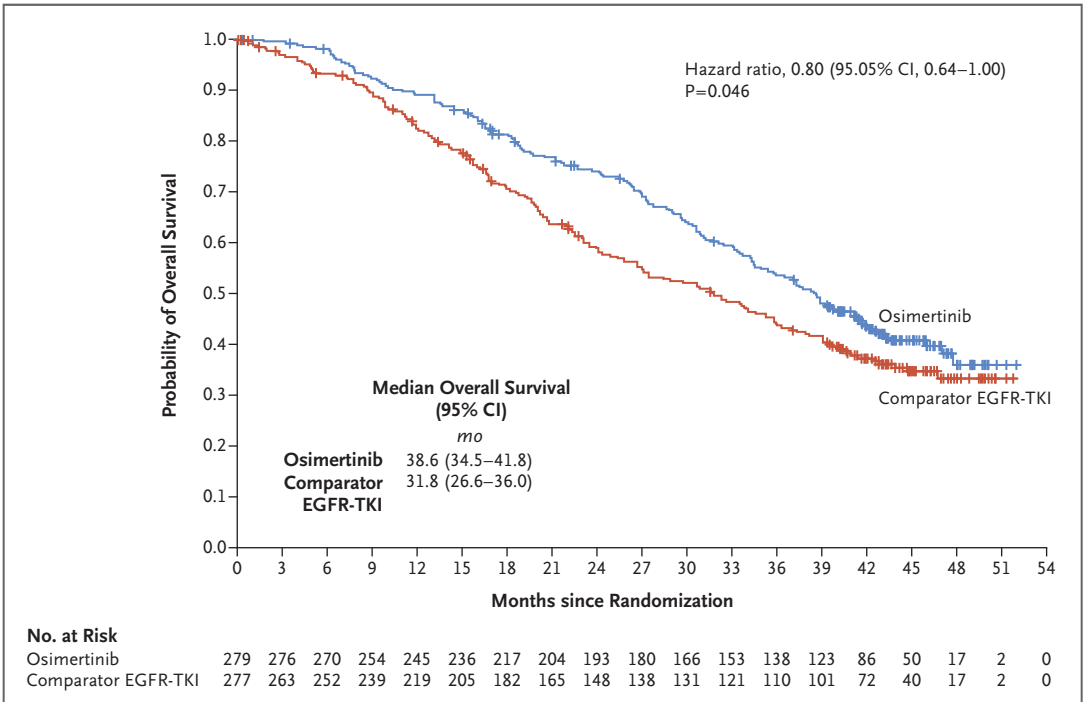


**Figure 1. Overall Survival.**

Shown is the Kaplan–Meier estimate of overall survival in the full analysis set. Censored data are indicated by tick marks. Data from patients who had not died at the time of the analysis were censored on the basis of the last recorded date on which the patient was known to be alive. CI denotes confidence interval, and EGFR-TKI tyrosine kinase inhibitor of epidermal growth factor receptor.

and 27.0 months in the comparator group. The median overall survival was 38.6 months (95% confidence interval [CI], 34.5 to 41.8) in the osimertinib group and 31.8 months (95% CI, 26.6 to 36.0) in the comparator group (hazard ratio for death, 0.80; 95.05% CI, 0.64 to 1.00; P=0.046) (Fig. 1). Survival rates and the number of patients continuing to receive the first-line trial drug were consistently higher in the osimertinib group than in the comparator group at months 12, 24, and 36 (Table 1).

**Table 1. Overall Survival and Continuation of First-Line Trial Drug.***

| Variable | Osimertinib (N=279) | Comparator EGFR-TKI (N=277) |
|---|---|---|
| Overall survival — % (95% CI) | | |
| At 12 mo | 89 (85–92) | 83 (77–87) |
| At 24 mo | 74 (69–79) | 59 (53–65) |
| At 36 mo | 54 (48–60) | 44 (38–50) |
| Patients continuing to receive first-line trial drug — no. (%) | | |
| At 12 mo | 194 (70) | 131 (47) |
| At 24 mo | 118 (42) | 45 (16) |
| At 36 mo | 78 (28) | 26 (9) |

* In the comparator group, patients received one of two tyrosine kinase inhibitors of epidermal growth factor receptor (EGFR-TKI): gefitinib or erlotinib.

The overall survival benefit with osimertinib as compared with the comparator EGFR-TKIs was consistent across most predefined subgroups, with varying magnitude of benefit (Fig. 2). The confidence intervals were overlapping within and across all subgroups. The largest numerical between-group differences in the hazard ratios for overall survival were observed between Asian and non-Asian patients. The Kaplan–Meier estimates for the subgroup comparison between Asian and non-Asian patients and between mutational status (exon 19 deletion vs. L858R) are provided in Figure S2.

### SUBSEQUENT THERAPIES

In total, 133 patients (48%) in the osimertinib group and 180 (65%) in the comparator group started a first subsequent anticancer therapy after

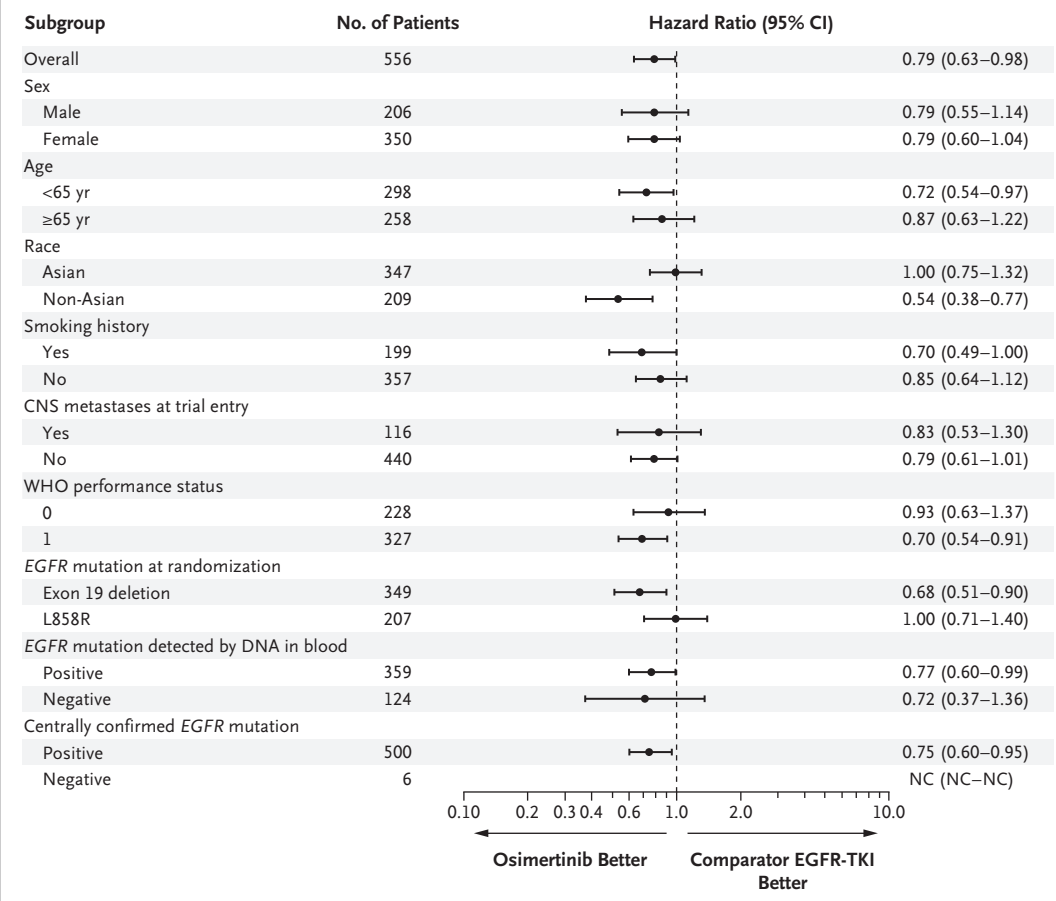


**Figure 2. Subgroup Analyses of Overall Survival.**

Shown is a forest plot of the subgroup analyses, which were performed with the use of a Cox proportional-hazards model that included the trial group, the subgroup covariate of interest, and the treatment-by-subgroup interaction. A hazard ratio of less than 1.00 indicates a lower risk of death with osimertinib than with the comparator EGFR-TKI. The overall population analyses were performed with the use of both a log-rank test stratified according to the *EGFR* mutational status and race and an unstratified Cox proportional-hazards model. The unstratified model was used to analyze the subgroups. If there were fewer than 20 events in a subgroup, the subgroup analysis was not performed. The *EGFR* mutational status at randomization was determined on local or central testing. Data were missing for 1 patient regarding World Health Organization (WHO) performance status and for 73 patients regarding the detection of the *EGFR* mutation in circulating tumor DNA. CNS denotes central nervous system, and NC could not be calculated.

the discontinuation of the assigned treatment. Of these patients, 85 of 180 (47%) in the comparator group received osimertinib as the first subsequent therapy (Fig. 3A); these patients made up 31% of the 277 who had been assigned to the comparator group. Among all the patients who underwent randomization, the number of those who received a second subsequent therapy was 72 of 279 (26%) in the osimertinib group and 92 of 277 (33%) in the comparator group. Among the patients who received a first subsequent therapy, the number of those who received a second subsequent therapy was 72 of 133 (54%) in the osimertinib group and 92 of 180 (51%) in the comparator group (Fig. 3B). (Additional data regarding the time until the first and second subsequent therapies or death and the subsequent therapies received are provided in the Results section in the Supplementary Appendix and in Fig. S3 and Tables S3 and S4.)

### SAFETY

In the analysis of overall survival, the safety profile of osimertinib was consistent with the safety

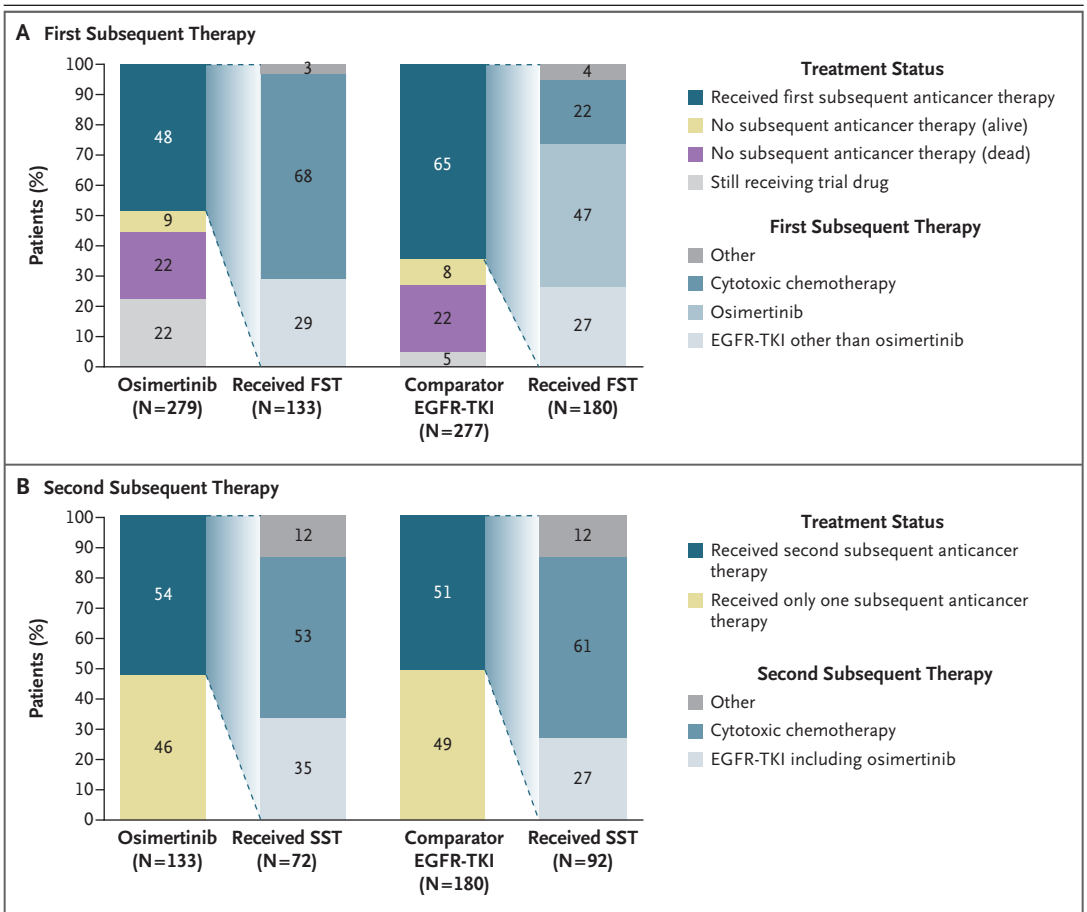


**Figure 3. Summary of First and Second Subsequent Therapies Received.**

Shown are bar plots illustrating the percentage of patients who received a first subsequent therapy (FST) (Panel A) and a second subsequent therapy (SST) (Panel B) after the discontinuation of their assigned treatment. The linked bar plot shows the type of therapy that the patients subsequently received. "Other" therapy refers to a treatment that did not include either chemotherapy or an EGFR-TKI. The majority of patients who underwent cytotoxic chemotherapy received a platinum-based chemotherapy regimen. Percentages may not total 100 because of rounding.

profile in the primary analysis. Overall, 98% of the patients in the two trial groups had at least one adverse event (Table 2). Adverse events that were deemed to be possibly related to the trial drug are listed in Table S5. Adverse events of grade 3 or higher were reported in 42% of the patients in the osimertinib group and in 47% of those in the comparator group (Table S6). Serious adverse events were reported in 27% of the patients in each trial group (Table S7). A decrease in the ejection fraction was reported in 13 patients (5%) in the osimertinib group and in 5 (2%) in the comparator group, with no associated symptoms reported. QT prolongation on electrocardiography was reported in 28 patients (10%) in the osimertinib group and in 12 patients (4%) in the comparator group. There were no new reports of interstitial lung disease, which was reported in 6 patients (2%) in the osimertinib group and in 4 (1%) in the comparator group, or of pneumonitis, which was reported in 5 (2%) and 2 (1%), respectively.[9]

Fatal adverse events were reported in 9 patients (3%) in the osimertinib group and in 10 (4%) in the comparator group. None of the deaths in the osimertinib group and 2 in the comparator group were deemed by investigators to be treatment-related.

In the osimertinib group, dose interruptions occurred in 120 patients (43%), dose reductions in 14 (5%), and permanent discontinuation of treatment because of adverse events in 41 (15%); in the comparator group, the corresponding num-

**Table 2. Adverse Events.***

| Adverse Event | Osimertinib (N=279) | | | | Comparator EGFR-TKI (N=277) | | | |
|---|---|---|---|---|---|---|---|---|
| | Any Grade | Grade 1 | Grade 2 | Grade 3 | Any Grade | Grade 1 | Grade 2 | Grade 3 |
| | *number of patients (percent)* | | | | | | | |
| Diarrhea | 167 (60) | 119 (43) | 41 (15) | 7 (3) | 162 (58) | 118 (43) | 35 (13) | 7 (3) |
| Rash or acne† | 164 (59) | 132 (47) | 29 (10) | 3 (1) | 219 (79) | 111 (40) | 88 (32) | 20 (7) |
| Nail effects† | 108 (39) | 61 (22) | 45 (16) | 2 (1) | 95 (34) | 58 (21) | 35 (13) | 2 (1) |
| Dry skin† | 106 (38) | 89 (32) | 16 (6) | 1 (<1) | 102 (37) | 78 (28) | 21 (8) | 3 (1) |
| Stomatitis | 82 (29) | 66 (24) | 14 (5) | 1 (<1) | 60 (22) | 51 (18) | 8 (3) | 1 (<1) |
| Decreased appetite | 66 (24) | 32 (11) | 27 (10) | 7 (3) | 58 (21) | 29 (10) | 24 (9) | 5 (2) |
| Cough | 60 (22) | 42 (15) | 18 (6) | 0 | 50 (18) | 33 (12) | 17 (6) | 0 |
| Nausea | 55 (20) | 37 (13) | 18 (6) | 0 | 55 (20) | 31 (11) | 23 (8) | 0 |
| Constipation | 51 (18) | 42 (15) | 9 (3) | 0 | 39 (14) | 29 (10) | 10 (4) | 0 |
| Pruritus | 50 (18) | 41 (15) | 8 (3) | 1 (<1) | 44 (16) | 30 (11) | 14 (5) | 0 |
| Renal symptoms‡ | 50 (18) | 32 (11) | 13 (5) | 3 (1) | 32 (12) | 24 (9) | 7 (3) | 1 (<1) |
| Fatigue | 45 (16) | 25 (9) | 17 (6) | 3 (1) | 35 (13) | 23 (8) | 10 (4) | 2 (1) |
| Anemia | 44 (16) | 22 (8) | 15 (5) | 7 (3) | 27 (10) | 19 (7) | 5 (2) | 3 (1) |
| Dyspnea | 42 (15) | 28 (10) | 12 (4) | 2 (1) | 22 (8) | 10 (4) | 9 (3) | 3 (1) |
| Vomiting | 41 (15) | 32 (11) | 9 (3) | 0 | 32 (12) | 24 (9) | 4 (1) | 4 (1) |
| Headache | 39 (14) | 29 (10) | 8 (3) | 2 (1) | 25 (9) | 17 (6) | 8 (3) | 0 |
| Back pain | 36 (13) | 22 (8) | 14 (5) | 0 | 29 (10) | 15 (5) | 14 (5) | 0 |
| Upper respiratory tract infection | 36 (13) | 20 (7) | 16 (6) | 0 | 23 (8) | 12 (4) | 11 (4) | 0 |
| Pyrexia | 32 (11) | 28 (10) | 4 (1) | 0 | 12 (4) | 9 (3) | 2 (1) | 1 (<1) |
| Insomnia | 31 (11) | 23 (8) | 8 (3) | 0 | 21 (8) | 12 (4) | 9 (3) | 0 |
| Nasopharyngitis | 31 (11) | 17 (6) | 14 (5) | 0 | 16 (6) | 11 (4) | 5 (2) | 0 |
| Prolonged QT interval | 28 (10) | 12 (4) | 12 (4) | 4 (1) | 12 (4) | 7 (3) | 3 (1) | 2 (1) |
| Increase in aspartate aminotransferase | 28 (10) | 19 (7) | 7 (3) | 2 (1) | 69 (25) | 39 (14) | 18 (6) | 12 (4) |
| Musculoskeletal pain | 28 (10) | 19 (7) | 9 (3) | 0 | 14 (5) | 8 (3) | 6 (2) | 0 |
| Alopecia | 22 (8) | 18 (6) | 4 (1) | 0 | 35 (13) | 31 (11) | 4 (1) | 0 |
| Increase in alanine aminotransferase | 19 (7) | 11 (4) | 6 (2) | 2 (1) | 74 (27) | 30 (11) | 19 (7) | 21 (8) |

* Listed are adverse events that were reported in at least 10% of the patients in either trial group. The safety analyses included all the patients who had received at least one dose of a trial drug (safety analysis set). Some patients had more than one adverse event. In the osimertinib group, the only grade 4 adverse events were stomatitis and renal symptoms (1 patient each); the only grade 5 adverse event was renal symptoms (1 patient). In the comparator group, the only grade 4 adverse event was an increase in the alanine aminotransferase level (4 patients); the only grade 5 adverse event was diarrhea (1 patient). In the comparator group, 1 patient had an adverse event of diarrhea of unknown grade, and 1 patient had an adverse event of nausea of unknown grade.
† This category is a grouped term.
‡ The most common renal adverse events in the two trial groups were an increase in the blood creatinine level, acute kidney injury, proteinuria, dysuria, and hematuria.

bers were 113 (41%), 10 (4%), and 50 (18%). (Additional details regarding adverse events are provided in the Results section in the Supplementary Appendix.)

## DISCUSSION

In the FLAURA trial, a double-blind, randomized phase 3 trial involving untreated patients with

*EGFR* mutation–positive advanced NSCLC, those who received osimertinib had significantly longer progression-free survival leading to significantly longer overall survival than those who received a comparator EGFR-TKI (either gefitinib or erlotinib) (hazard ratio for disease progression or death, 0.46 [P<0.001]; hazard ratio for death, 0.80 [P=0.046]).[9] With an opportunity to conduct at least 39 months of follow-up in the two groups, the median overall survival was longer by 6.8 months in the osimertinib group than in the comparator group, with a 20% lower risk of death, even in the presence of crossover from the comparator group to the osimertinib group. Furthermore, at 36 months, three times as many patients were continuing to receive the assigned trial drug in the osimertinib group as in the comparator group. No new safety signals were observed, and adverse events of grade 3 or higher and rates of treatment discontinuation because of adverse events were similar in the two groups, despite the longer duration of exposure to osimertinib.

An overall survival benefit with osimertinib was observed across most of the predefined subgroups. The magnitude of benefit varied, with hazard ratios close to 1.00 among both the Asian and L858R *EGFR* mutational subgroups. The Kaplan–Meier curve for survival among Asian patients showed an early advantage for osimertinib that remained until approximately 3 years of follow-up. As a secondary end point, the trial and the analysis of the Asian subgroup of patients were not powered for overall survival analysis.

Osimertinib is more effective in pretreated patients in whom the *EGFR* T790M resistance mutation develops than are other earlier-generation EGFR-TKIs.[6,13,14] Therefore, crossover from the comparator group to the osimertinib group probably contributed to the duration of overall survival in the comparator group (31.8 months). Previous clinical trials of first- and second-generation EGFR-TKIs have shown results for median overall survival ranging from approximately 18 to 28 months.[15-19] More recently, the ARCHER 1050 trial[20] showed a median overall survival of 26.8 months for gefitinib and 34.1 months for dacomitinib. However, unlike the FLAURA trial, the ARCHER 1050 trial excluded patients with CNS metastases, a complication that is associated with shorter survival.

In the FLAURA trial, patients with documentation of a T790M-positive mutation after disease progression were eligible for crossover from the comparator group to receive second-line osimertinib. After disease progression, the *EGFR* T790M resistance mutation develops in approximately 50% of the patients who are receiving earlier-generation EGFR-TKIs,[21,22] thus creating a biologically driven limit to the number of patients who are eligible to receive osimertinib as a second-line therapy. In the real-world setting, it has been reported that 25 to 39% of patients who receive first- or second-generation EGFR-TKIs go on to receive osimertinib as a second-line therapy, in line with the crossover rate of 31% (in 85 of 277 patients) observed in all the patients who were assigned to the comparator group in FLAURA (i.e., 85 of 180 patients [47%] who discontinued the comparator EGFR-TKI and received osimertinib as the first subsequent therapy).[23-25]

Subsequent therapies that were received in each trial group were consistent with expectations on the basis of the treatment guidelines for this patient population.[1,2] The majority of patients in the osimertinib group received chemotherapy as the first subsequent therapy, whereas crossover to osimertinib was the most common first subsequent therapy in the comparator group. The proportions of patients who received another EGFR-TKI–containing regimen (other than osimertinib) were similar in the two groups. Similar proportions of patients received a second subsequent therapy in the two groups, and the types of therapies that they received were similar.

In the two groups, approximately 30% of the patients discontinued the trial drug and did not receive a first subsequent therapy, owing to death in approximately 70% of these patients. This percentage is consistent with the results from previous studies involving patients with *EGFR* mutations who received EGFR-TKI therapies.[23-25] This observation has been the basis for use of the most effective therapies in the first-line treatment for patients with advanced-stage cancers.

Among the patients with NSCLC who have *EGFR* mutations, CNS metastases are detected in approximately 25% of the patients at the time of diagnosis and develop in approximately 50% of all the patients within 3 years after diagnosis.[26] As we reported in the primary analysis of data from the FLAURA trial, osimertinib also had activity in patients with CNS metastases.[8] Progression-free survival at 18 months among patients with CNS

metastases was 58% (95% CI, 40 to 72) in the osimertinib group and 40% (95% CI, 25 to 55) in the comparator group (hazard ratio for disease progression or death, 0.48; 95% CI, 0.26 to 0.86).

Understanding resistance mechanisms after first-line treatment and determining appropriate therapies on the basis of molecular-resistance profiles remain important considerations. Preliminary data suggest that first-line osimertinib resistance mechanisms are similar to those observed in patients with the T790M mutation who are receiving osimertinib as a second-line therapy; such resistance mechanisms are also similar to those associated with less frequent mutations (i.e., other than T790M) that are seen in patients who have resistance to other first- and second-generation EGFR-TKIs.[27] Further research is ongoing in the phase 2 ELIOS trial (ClinicalTrials.gov number, NCT03239340). Research to understand the most effective treatment on the basis of resistance patterns after disease progression while patients are receiving first-line osimertinib therapy is also ongoing in two phase 2 studies: the ORCHARD trial (NCT03944772) and the SAVANNAH trial (NCT03778229).

Thus, we found that first-line treatment with osimertinib was associated with significantly longer overall survival than treatment with comparator EGFR-TKIs in patients with *EGFR* mutation–positive, locally advanced or metastatic NSCLC and had a similar safety profile.

Supported by AstraZeneca.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the patients who participated in this trial and their families; all the trial site coordinators and investigators; Andrew Walding, M.Sc., and Kwame Atuah, Ph.D., of AstraZeneca for their review and guidance on the reporting of safety data; and Natalie Griffiths, Ph.D., of Ashfield Healthcare Communications for medical-writing support.

## APPENDIX

The authors' full names and academic degrees are as follows: Suresh S. Ramalingam, M.D., Johan Vansteenkiste, M.D., Ph.D., David Planchard, M.D., Ph.D., Byoung Chul Cho, M.D., Ph.D., Jhanelle E. Gray, M.D., Yuichiro Ohe, M.D., Ph.D., Caicun Zhou, M.D., Ph.D., Thanyanan Reungwetwattana, M.D., Ying Cheng, M.D., Busyamas Chewaskulyong, M.D., Riyaz Shah, M.D., Manuel Cobo, M.D., Ki Hyeong Lee, M.D., Ph.D., Parneet Cheema, M.D., Marcello Tiseo, M.D., Ph.D., Thomas John, M.D., Ph.D., Meng-Chih Lin, M.D., Fumio Imamura, M.D., Ph.D., Takayasu Kurata, M.D., Ph.D., Alexander Todd, M.Sc., Rachel Hodge, M.Sc., Matilde Saggese, M.D., Yuri Rukazenkov, M.D., Ph.D., and Jean-Charles Soria, M.D., Ph.D.

The authors' affiliations are as follows: Winship Cancer Institute, Emory University School of Medicine, Atlanta (S.S.R.); the Respiratory Oncology Unit, Department of Respiratory Medicine, University Hospital KU Leuven, Leuven, Belgium (J.V.); the Thoracic Unit, Department of Medical Oncology, Institut Gustave Roussy, Villejuif (D.P., J.-C.S.), and University Paris Sud, Orsay (J.-C.S.) — both in France; the Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul (B.C.C.), and the Division of Medical Oncology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheong-ju (K.H.L.) — both in South Korea; the Department of Thoracic Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL (J.E.G.); the Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo (Y.O.), the Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka (F.I.), and the Department of Thoracic Oncology, Kansai Medical University Hospital, Osaka (T.K.) — all in Japan; Pulmonary Hospital of Tongji University, Shanghai (C.Z.), and Jilin Provincial Cancer Hospital, Changchun (Y.C.) — both in China; the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok (T.R.), and the Oncology Unit, Department of Medicine, Chiang Mai University, Chiang Mai (B.C.) — both in Thailand; Kent Oncology Centre, Maidstone Hospital, and Tunbridge Wells NHS Trust, Maidstone (R.S.), and Late Oncology Statistics (A.T., R.H.) and Oncology Research and Development (M.S., Y.R.), AstraZeneca, Cambridge — both in the United Kingdom; Hospital Regional Universitario Málaga, Instituto de Investigación Biomédica de Málaga, Malaga, Spain (M.C.); William Osler Health System, University of Toronto, Toronto (P.C.); the Department of Medicine and Surgery, University of Parma and Medical Oncology Unit, University Hospital of Parma, Parma, Italy (M.T.); the Department of Medical Oncology, Austin Health, Melbourne, VIC, Australia (T.J.); the Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan (M.-C.L.); and Early Oncology Research and Development, AstraZeneca, Gaithersburg, MD (J.-C.S.).

## REFERENCES

1. Hanna N, Johnson D, Temin S, et al. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2017;35:3484-515.
2. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:Suppl 4:iv192-iv237.
3. Wu YL, Planchard D, Lu S, et al. Pan-Asian adapted clinical practice guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS. Ann Oncol 2019;30:171-210.
4. Clinical practice guidelines in oncology: NCCN guidelines for non-small cell lung cancer V.7. Fort Washington, PA: National Comprehensive Cancer Network, 2019 (https://www.nccn.org).
5. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 2014;4:1046-61.
6. Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or platinum–pemetrexed in *EGFR* T790M–positive lung cancer. N Engl J Med 2017;376:629-40.
7. Wu YL, Ahn MJ, Garassino MC, et al. CNS efficacy of osimertinib in patients

with T790M-positive advanced non-small-cell lung cancer: data from a randomized phase III trial (AURA3). J Clin Oncol 2018;36:2702-9.
**8.** Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. J Clin Oncol 2018;36:JCO2018783118.
**9.** Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated *EGFR*-mutated advanced non–small-cell lung cancer. N Engl J Med 2018;378:113-25.
**10.** Tagrisso (osimertinib): summary of product characteristics. London: European Medicines Agency, 2018 (https://www.ema.europa.eu/documents/product-information/tagrisso-epar-product-information_en.pdf).
**11.** Tagrisso (osimertinib): highlights of prescribing information. Silver Spring, MD: Food and Drug Administration, 2018 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208065s008lbl.pdf).
**12.** Berry G, Kitchin RM, Mock PA. A comparison of two simple hazard ratio estimators based on the log-rank test. Stat Med 1991;10:749-55.
**13.** Ellis PM, Shepherd FA, Millward M, et al. Dacomitinib compared with placebo in pretreated patients with advanced or metastatic non-small-cell lung cancer (NCIC CTG BR.26): a double-blind, randomised, phase 3 trial. Lancet Oncol 2014;15:1379-88.
**14.** Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;13:528-38.
**15.** Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
**16.** Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
**17.** Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015;16:141-51.
**18.** Yang JJ, Zhou Q, Yan HH, et al. A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations. Br J Cancer 2017;116:568-74.
**19.** Paz-Ares L, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol 2017;28:270-7.
**20.** Mok TS, Cheng Y, Zhou X, et al. Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. J Clin Oncol 2018;36:2244-50.
**21.** Wang Z-F, Ren S-X, Li W, Gao G-H. Frequency of the acquired resistant mutation T790 M in non-small cell lung cancer patients with active exon 19Del and exon 21 L858R: a systematic review and meta-analysis. BMC Cancer 2018;18:148.
**22.** John T, Akamatsu H, Delmonte A, et al. EGFR mutation analysis for prospective patient selection in AURA3 phase III trial of osimertinib versus platinum-pemetrexed in patients with EGFR T790M-positive advanced non-small-cell lung cancer. Lung Cancer 2018;126:133-8.
**23.** Roeper J, Falk M, Tiemann M, et al. Risk of not receiving 2nd line therapy is high in EGFR mt+ pts: real world data of certified lung cancer centers on treatment sequence in EGFR mt+ pts. J Thorac Oncol 2018;13:Suppl:S94-S95. abstract.
**24.** Gray JE, Thakrar B, Sun P, Maclachlan S, Chehab N, Potter D. Treatment (tx) patterns in patients (pts) with lung cancer starting 1st or 2nd generation (1G/2G) EGFR-TKI: a US insurance claims database analysis. Ann Oncol 2018;29:Suppl 9:mdy425.020. abstract.
**25.** Chiang A, Fernandes A, Pavilack M, et al. Real world biomarker testing and treatment patterns in patients with advanced NSCLC receiving EGFR-TKIs. J Thorac Oncol 2018;13:Suppl:S410-S111. abstract.
**26.** Rangachari D, Yamaguchi N, VanderLaan PA, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer 2015;88:108-11.
**27.** Ramalingam SS, Cheng Y, Zhou C, et al. Mechanisms of acquired resistance to first-line osimertinib: preliminary data from the phase III FLAURA study. Presented at the European Society for Medical Oncology (ESMO) 2018 Congress, Munich, Germany, October 19–23, 2018.