ORIGINAL ARTICLE

Osimertinib with or without Chemotherapy in *EGFR*-Mutated Advanced NSCLC

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ABSTRACT

BACKGROUND

Osimertinib is a third-generation epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI) that is selective for EGFR-TKI–sensitizing and *EGFR* T790M resistance mutations. Evidence suggests that the addition of chemotherapy may extend the benefits of EGFR-TKI therapy.

METHODS

In this phase 3, international, open-label trial, we randomly assigned in a 1:1 ratio patients with *EGFR*-mutated (exon 19 deletion or L858R mutation) advanced non–small-cell lung cancer (NSCLC) who had not previously received treatment for advanced disease to receive osimertinib (80 mg once daily) with chemotherapy (pemetrexed [500 mg per square meter of body-surface area] plus either cisplatin [75 mg per square meter] or carboplatin [pharmacologically guided dose]) or to receive osimertinib monotherapy (80 mg once daily). The primary end point was investigator-assessed progression-free survival. Response and safety were also assessed.

RESULTS

A total of 557 patients underwent randomization. Investigator-assessed progression-free survival was significantly longer in the osimertinib–chemotherapy group than in the osimertinib group (hazard ratio for disease progression or death, 0.62; 95% confidence interval [CI], 0.49 to 0.79; P<0.001). At 24 months, 57% (95% CI, 50 to 63) of the patients in the osimertinib–chemotherapy group and 41% (95% CI, 35 to 47) of those in the osimertinib group were alive and progression-free. Progression-free survival as assessed according to blinded independent central review was consistent with the primary analysis (hazard ratio, 0.62; 95% CI, 0.48 to 0.80). An objective (complete or partial) response was observed in 83% of the patients in the osimertinib–chemotherapy group and in 76% of those in the osimertinib group; the median response duration was 24.0 months (95% CI, 20.9 to 27.8) and 15.3 months (95% CI, 12.7 to 19.4), respectively. The incidence of grade 3 or higher adverse events from any cause was higher with the combination than with monotherapy — a finding driven by known chemotherapy-related adverse events. The safety profile of osimertinib plus pemetrexed and a platinum-based agent was consistent with the established profiles of the individual agents.

CONCLUSIONS

First-line treatment with osimertinib–chemotherapy led to significantly longer progression-free survival than osimertinib monotherapy among patients with *EGFR*-mutated advanced NSCLC. (Funded by AstraZeneca; FLAURA2 ClinicalTrials.gov number, NCT04035486.)

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*A complete list of the FLAURA2 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Osimertinib is a third-generation, irreversible, oral epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI) that potently and selectively inhibits both EGFR-TKI–sensitizing and *EGFR* p.Thr790Met (T790M) resistance mutations, with demonstrated efficacy in *EGFR*-mutated non–small-cell lung cancer (NSCLC), including in central nervous system (CNS) metastases.[1-7] Osimertinib is the preferred first-line treatment for patients with *EGFR*-mutated advanced NSCLC,[8,9] on the basis of results from the phase 3 FLAURA trial, which showed superior progression-free survival and overall survival benefits with first-line osimertinib treatment as compared with first-generation EGFR-TKIs.[2,10]

Despite the efficacy of first-line treatment with osimertinib, most patients will have disease progression. Phase 2 and 3 trials have shown superior efficacy outcomes with the first-generation EGFR-TKI gefitinib plus carboplatin–pemetrexed as compared with gefitinib alone.[11-14] These data support the hypothesis that the addition of a platinum-based agent and pemetrexed to osimertinib, with its superior clinical outcomes as compared with comparator EGFR-TKIs,[2,10] may extend the benefit provided by osimertinib alone.

The phase 3, international, open-label, randomized FLAURA2 trial was designed in two phases: safety run-in and randomized phases. The safety run-in phase showed that osimertinib plus platinum–pemetrexed had a safety profile consistent with the safety profiles of its components without new toxic effects — findings that supported further assessment in the randomized phase.[15] Here, we report efficacy and safety data for first-line osimertinib plus platinum–pemetrexed as compared with osimertinib monotherapy in patients with *EGFR*-mutated advanced NSCLC from the randomized phase of the FLAURA2 trial.

METHODS

TRIAL POPULATION

In this trial, we enrolled eligible patients who were 18 years of age or older (or ≥20 years of age in Japan), had locally advanced or metastatic NSCLC, and had not previously received systemic treatment for advanced disease. Nonsquamous NSCLC was pathologically confirmed, with local or central confirmation of the *EGFR* exon 19 deletion or p.Leu858Arg (L858R) mutation, either alone or in combination with other *EGFR* mutations. Patients had a World Health Organization (WHO) performance-status score of 0 or 1 (scores range from 0 to 5, with higher numbers indicating greater disability). Patients with CNS metastases whose condition was neurologically stable were eligible. Any previous radiation or chemoradiation treatment or glucocorticoid therapy had to be completed at least 2 weeks before initiation of the trial treatment. Full inclusion and exclusion criteria are provided in the trial protocol, which is available with the full text of this article at NEJM.org.

OVERSIGHT

The trial was conducted in accordance with the provisions of the Declaration of Helsinki, the Council for International Organizations of Medical Sciences International Ethical Guidelines, the Good Clinical Practice guidelines of the International Council for Harmonisation, and applicable regulatory requirements. The trial protocol was approved by relevant institutional review boards or ethics committees. All the patients provided written informed consent. Oversight of safety during the randomized period of the trial was provided by an independent data and safety monitoring committee.

The trial was designed by the sponsor (AstraZeneca) in consultation with the investigators. The sponsor was responsible for data collection and analysis and had a role in the interpretation of the data. The first draft of the manuscript was written by the authors, with medical writing assistance funded by the sponsor in accordance with Good Publication Practice guidelines (https://www.ismpp.org/gpp-2022). The authors had access to the data and contributed to the development of the manuscript, including approval of the final version before submission. 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

Results from a nonrandomized safety run-in phase[15] supported continuation to the randomization phase of this trial. Patients were randomly assigned in a 1:1 ratio to receive osimertinib plus chemotherapy (with pemetrexed and a platinum-based agent) or osimertinib monother-

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apy. For the combination, patients received osimertinib (80 mg once daily) and intravenous pemetrexed (500 mg per square meter of body-surface area) plus either cisplatin (75 mg per square meter) or carboplatin (a pharmacologically guided dose defined as an area under the concentration–time curve of 5 mg per milliliter per minute), administered intravenously on day 1 of 21-day cycles for four cycles; the chemotherapy regimen was chosen by the investigator before randomization. This treatment was followed by osimertinib (80 mg once daily) plus pemetrexed maintenance therapy (500 mg per square meter) every 3 weeks. Patients in the monotherapy group received osimertinib at a dose of 80 mg once daily.

Randomized treatment continued until the occurrence of disease progression as defined according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; until the occurrence of unacceptable or clinically significant toxic effects; or until another discontinuation criterion was met. Treatment beyond disease progression was permitted if the patient had a continued clinical benefit, according to the judgment of the investigator. After the discontinuation of trial treatment, subsequent therapy was chosen on the basis of the investigator's discretion, and patients were followed for second progression during subsequent treatment, according to local practice, and for survival. Further details on the trial design and measures to minimize bias that was due to the open-label trial design are described in the Supplementary Appendix, available at NEJM.org.

END POINTS

The primary end point was investigator-assessed progression-free survival, which was defined as the time from randomization until objective disease progression or death from any cause in the absence of progression (according to RECIST, version 1.1). The primary analysis of progression-free survival on the basis of investigator assessment occurred when approximately 278 events had occurred among the patients who had undergone randomization (data maturity, approximately 50%). Secondary end points included overall survival, objective response, duration of response, disease control, depth of response, and second progression–free survival (see the Supplementary Appendix). Safety was also assessed.

ASSESSMENTS

Tumor assessments of the chest and abdomen were performed at screening and after 6 weeks (within a window of ±1 week), 12 weeks (window, ±1 week), and then every 12 weeks (window, ±1 week) from randomization until the occurrence of disease progression as assessed radiologically. Brain scans were performed at screening and at the time of progression in all patients. Patients with brain metastases at screening underwent brain scans at each tumor assessment.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Details regarding the collection and reporting of safety data are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The full analysis set, which included all the patients who had undergone randomization, was used for the summaries of demographic and baseline clinical characteristics and for efficacy assessments. The safety analysis set included all the patients who had undergone randomization and received at least one dose of trial treatment, according to the actual treatment received.

Progression-free survival was analyzed with the use of a log-rank test stratified according to patient-reported race (Asian Chinese vs. Asian non-Chinese vs. non-Asian; options were given on a drop-down list at randomization), WHO performance-status score (0 vs. 1), and EGFR mutation tissue testing method (central vs. local). Patients who had not had disease progression or died at the time of analysis had their data censored at the last evaluable RECIST assessment. A Cox proportional-hazards model was used to analyze progression-free survival in prespecified patient subgroups. A sensitivity analysis for progression-free survival as assessed by blinded independent central review was also conducted. To control the type I error at the 5% two-sided level, a prespecified hierarchical testing procedure was used; if significance was shown in the analysis of progression-free survival, then overall survival would be tested.

We calculated that approximately 278 events of disease progression or death (from any cause in the absence of progression) among 556 patients who had undergone randomization would provide the trial with at least 90% power to detect a hazard ratio of 0.68 at a two-sided 5%

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significance level. One interim analysis of progression-free survival (as assessed by the investigator) for futility was planned before the primary analysis in order to evaluate any potential lack of efficacy in the osimertinib–chemotherapy group as compared with the osimertinib group. This interim analysis was reviewed by an independent data and safety monitoring committee, whose members were aware of the trial-group assignments; the sponsor remained unaware of the trial-group assignments until the primary analysis. Two analyses of overall survival were planned as part of the hierarchical testing procedure: the first was to be conducted at the time of the primary analysis of progression-free survival (as reported here), with a final analysis to be performed at approximately 60% data maturity, when approximately 334 deaths (across the two groups) have occurred. The data-cutoff date was April 3, 2023.

RESULTS

PATIENTS AND TREATMENT

Between June 1, 2020, and December 22, 2021, a total of 557 patients were randomly assigned to the osimertinib–chemotherapy group (279 patients) or the osimertinib group (278 patients) (full analysis set). A total of 276 patients received osimertinib plus platinum–pemetrexed, 275 received osimertinib monotherapy, and 6 patients received no treatment (Fig. S1 in the Supplementary Appendix). One patient who had been randomly assigned to the osimertinib–chemotherapy group received only osimertinib and was therefore included in the osimertinib monotherapy group for the safety analysis. A total of 41% of the patients had CNS metastases, and 53% had extrathoracic metastases. The characteristics of the patients at baseline were balanced between the two groups and are summarized in Table 1. The overall representativeness of the trial population is described in Table S1.

As of the data-cutoff date, the median duration of total treatment exposure was 22.3 months in the osimertinib–chemotherapy group and 19.3 months in the osimertinib group. In both groups, the median actual exposure to osimertinib (with dose interruptions taken into consideration) of 21.8 months in the combination group and 19.0 months in the monotherapy group did not differ substantially from the median total osimertinib exposure of 22.3 months and 19.3 months, respectively; these findings suggest that any dose interruptions were of short duration (see the Supplementary Results section).

In the osimertinib–chemotherapy group, patients received a median of 4 cycles (range, 1 to 6) of carboplatin or cisplatin, with 211 patients (76%) completing the planned 4 cycles of carboplatin or cisplatin, and a median of 12 cycles (range, 1 to 48) of pemetrexed. As of the data-cutoff date, 154 patients (56%) were receiving osimertinib and 68 (25%) were receiving ongoing pemetrexed in the osimertinib–chemotherapy group; 123 patients (45%) in the osimertinib monotherapy group continued to receive osimertinib.

The most frequent reasons for the discontinuation of osimertinib were disease progression (in 25% of the patients in the osimertinib–chemotherapy group vs. 43% of those in the osimertinib group) and adverse events (in 11% vs. 6%). The occurrence of adverse events was the most frequent reason for the discontinuation of carboplatin or cisplatin (in 47 patients [17%]) and pemetrexed (in 119 patients [43%]).

EFFICACY

Overall, events of disease progression according to investigator assessment or death occurred in 120 patients (43%) in the osimertinib–chemotherapy group and in 166 (60%) in the osimertinib group (overall data maturity, 51%). The median follow-up for progression-free survival was 19.5 months in the osimertinib–chemotherapy group and 16.5 months in the osimertinib group. At 24 months, the percentage of patients who were alive and progression-free was 57% (95% confidence interval [CI], 50 to 63) in the osimertinib–chemotherapy group and 41% (95% CI, 35 to 47) in the osimertinib group (Fig. 1A and Table 2). The Kaplan–Meier curves showed an early separation between the trial groups in favor of osimertinib plus chemotherapy that was maintained throughout follow-up. Overall investigator-assessed progression-free survival was significantly longer in the osimertinib–chemotherapy group than in the osimertinib group (hazard ratio for disease progression or death, 0.62; 95% CI, 0.49 to 0.79; P<0.001; median progression-free survival, 25.5 months vs. 16.7 months). The progression-free survival assessment according to blinded independent cen-

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tral review was consistent with the investigator assessment (hazard ratio, 0.62; 95% CI, 0.48 to 0.80) (Fig. 1B). The central review–assessed median values for progression-free survival are reported in the Supplementary Appendix, as are additional sensitivity analyses of progression-free survival.

The progression-free survival benefit with osimertinib plus chemotherapy appeared to be consistent across prespecified subgroups (Fig. 2), including the subgroups defined according to *EGFR* mutation type and the presence or absence of CNS metastases at baseline. Among patients with exon 19 deletion, the median progression-free survival was 27.9 months in the osimertinib–chemotherapy group and 19.4 months in the osimertinib group; among those with L858R mutation, it was 24.7 months and 13.9 months, respectively (Fig. S2A and S2B). Among patients with CNS metastases at baseline, the median progression-free survival was 24.9 months in the osimertinib–chemotherapy group and 13.8 months in the osimertinib group; among those without CNS metastases at baseline, it was 27.6 months and 21.0 months, respectively (Fig. 1C and 1D). The hazard ratio for disease progression or death in the analysis of second progression–free survival was 0.70 (95% CI, 0.52 to 0.93). Further details regarding second progression–free survival and type of subsequent treatment received are provided in Figure S3 and Table S2.

An objective response as assessed by the investigator was observed in 83% of the patients (95% CI, 78 to 87) in the osimertinib–chemotherapy group and in 76% of those (95% CI, 70 to 80) in the osimertinib group (Table 2). An objective response as assessed according to blinded independent central review occurred in 92% (95% CI, 88 to 95) and 83% (95% CI, 78 to 87), respectively. The median duration of response was longer with osimertinib plus platinum–pemetrexed than with osimertinib according to both the investigator assessment (24.0 months [95% CI, 20.9 to 27.8] vs. 15.3 months [95% CI, 12.7 to 19.4]) and the blinded independent central review (Table 2 and Fig. S4). Data regarding the depth of response are provided in Figure S5.

As of the data-cutoff date, 149 patients had died (71 in the osimertinib–chemotherapy group and 78 in the osimertinib group; data maturity, 27%). The hazard ratio for death was 0.90 (95% CI, 0.65 to 1.24; P=0.52) (Fig. S6). Overall survival was 89% (95% CI, 84 to 92) in the osimertinib–chemotherapy group and 92% (95% CI, 88 to 95) in the osimertinib group at 12 months and 79% (95% CI, 73 to 83) and 73% (95% CI, 67 to 78), respectively, at 24 months.

SAFETY

Overall, 551 patients were included in the safety analysis set (276 in the osimertinib–chemotherapy group and 275 in the osimertinib group). Adverse events were reported in 276 patients (100%) in the osimertinib–chemotherapy group and in 268 (97%) in the osimertinib group. Commonly reported adverse events (regardless of causality) are shown in Table 3.

Adverse events of grade 3 or higher were reported in 176 patients (64%) in the osimertinib–chemotherapy group and in 75 (27%) in the osimertinib group (Table S3). Commonly reported adverse events that were considered by the investigator to have a causal relationship to any trial treatment are reported in Table S4. Adverse events of special interest are reported in Table S5. Hematologic toxic effects (as a grouped term) were reported in 197 patients (71%) in the osimertinib–chemotherapy group and in 66 patients (24%) in the osimertinib group. Interstitial lung disease or pneumonitis (as a grouped term) was reported in 9 patients (3%) in the osimertinib–chemotherapy group and in 10 patients (4%) in the osimertinib group, and cardiac effects (as a grouped term) were reported in 26 (9%) and 10 (4%), respectively.

Serious adverse events were reported in 104 patients (38%) in the osimertinib–chemotherapy group and in 53 (19%) in the osimertinib group (Table S6). Adverse events with an outcome of death that were considered by the investigator to be possibly causally related to trial treatment occurred in 5 patients in the osimertinib–chemotherapy group and in 1 patient in the osimertinib group (Table S7, and see the Supplementary Results section).

Adverse events leading to the discontinuation of osimertinib were reported in 30 patients (11%) in the osimertinib–chemotherapy group and in 17 (6%) in the osimertinib group. Dose interruptions of osimertinib occurred in 120 patients (43%) and 52 patients (19%), respectively, and dose reductions of osimertinib in 27 (10%) and 8 (3%), respectively. The mean relative dose in-

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Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

Characteristic	Osimertinib + Platinum–Pemetrexed (N = 279)	Osimertinib Monotherapy (N = 278)
Median age (range) — yr	61 (26–83)	62 (30–85)
Sex — no. (%)		
Male	106 (38)	109 (39)
Female	173 (62)	169 (61)
Race or ethnic group — no. (%)†		
Asian	179 (64)	176 (63)
White	74 (27)	83 (30)
American Indian or Alaska Native	11 (4)	6 (2)
Black	2 (1)	3 (1)
Other	13 (5)	10 (4)
WHO performance-status score — no. (%)‡		
0	104 (37)	102 (37)
1	174 (62)	176 (63)
2	1 (<1)	0
Histologic characteristics — no. (%)		
Adenocarcinoma	275 (99)	275 (99)
Adenosquamous carcinoma	2 (1)	0
Other	2 (1)	3 (1)
EGFR mutation at randomization — no. (%)§		
Exon 19 deletion	169 (61)	168 (60)
L858R mutation	106 (38)	107 (38)
Both exon 19 deletion and L858R mutation	3 (1)	1 (<1)
Unknown	1 (<1)	2 (1)
Disease extent at trial entry — no. (%)		
Locally advanced	14 (5)	7 (3)
Metastatic	265 (95)	271 (97)
CNS metastases — no. (%)¶‖		
Yes	116 (42)	110 (40)
No	163 (58)	168 (60)
Extrathoracic metastases — no. (%)‖**		
Yes	147 (53)	149 (54)
No	132 (47)	129 (46)
Liver metastases — no. (%)‖**		
Yes	43 (15)	66 (24)
No	236 (85)	212 (76)
Bone and locomotor-system metastases — no. (%)‖		
Yes	132 (47)	142 (51)
No	147 (53)	136 (49)
Median baseline tumor size (range) — mm††	57 (10–284)	57 (11–221)

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Table 1. (Continued.)

* Patients had been randomly assigned to receive osimertinib plus chemotherapy with pemetrexed and either cisplatin or carboplatin or to receive osimertinib monotherapy. No formal between-group comparison was performed for baseline characteristics. Percentages may not total 100 because of rounding. L858R denotes p.Leu858Arg.
† Race and ethnic group were reported by the patient.
‡ World Health Organization (WHO) performance-status scores are assessed on a scale from 0 to 5, with higher scores indicating greater disability. A score of 0 indicates that the patient is fully active and able to carry out all predisease activities without restrictions, and a score of 1 indicates that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work. A score of 2 indicates that the patients is ambulatory, capable of self-care, and up and about more than 50% of waking hours but unable to carry out any work activities. One patient had a WHO performance-status score of 1 at the time of randomization, but before the administration of trial treatment on day 1 of cycle 1 the patient had a score of 2 (attributed to mobility issues). This condition was transient, and 15 days later (on day 1 of cycle 2), the patient's score was 1.
§ The presence of epidermal growth factor receptor (EGFR) mutations was based on central or local testing.
¶ The presence or absence of central nervous system (CNS) metastases at baseline was assessed according to the investigator on the basis of data in the electronic case-report form regarding CNS lesion site at baseline, medical history, previous surgery, or history of radiotherapy for CNS metastases.
‖ The presence or absence of metastases was programmatically derived as composite end points with a list of contributing data sources.
** Extrathoracic metastases were determined programmatically from baseline data in which the disease site was described by AstraZeneca physicians.
†† The baseline tumor size was defined as the sum of the longest diameters of the target lesions.

tensity of osimertinib was similar in the two groups (95% in the combination group and 98% in the monotherapy group).

DISCUSSION

The results of the phase 3 FLAURA2 trial showed that among patients with *EGFR*-mutated advanced NSCLC, first-line osimertinib plus chemotherapy with pemetrexed and a platinum-based agent was associated with a significant improvement in progression-free survival according to investigator assessment, as compared with osimertinib monotherapy. The hazard ratio for disease progression or death in the analysis of progression-free survival according to investigator assessment was 0.62 (95% CI, 0.49 to 0.79; P<0.001) in favor of osimertinib plus chemotherapy and was consistent with the results of the assessment by means of blinded central independent review. The median prolongation in progression-free survival with the combination as compared with monotherapy was approximately 8.8 months according to the investigator assessment and 9.5 months according to the central review. The safety profile of osimertinib plus pemetrexed and a platinum-based agent was consistent with the established profiles of the individual agents; no new safety concerns were identified.

The prolonged antitumor effect of osimertinib plus chemotherapy, which may have been driven by the longer median duration of response with the combination than with monotherapy (24.0 months vs. 15.3 months), is consistent with effects that have been observed in other clinical trials of first-generation EGFR-TKIs plus chemotherapy in patients with *EGFR*-mutated advanced NSCLC.[12,13] Encouraging activity of osimertinib plus platinum–pemetrexed has also recently been reported in the single-group, phase 2 OPAL trial,[16] in which the median progression-free survival (according to central review) was 31.0 months after a median follow-up of 33.4 months.[16] Of note, the median progression-free survival in the osimertinib group in the present FLAURA2 trial (Fig. 1A) was similar to that reported in the osimertinib group in the FLAURA trial (18.9 months; 95% CI, 15.2 to 21.4).[2] The FLAURA2 trial population was broadly similar to that in the FLAURA trial,[2] although the patients in the present trial had a higher incidence of extrathoracic metastases (53% in FLAURA2 vs. 35% in FLAURA) and CNS metastases (41% vs. 21%) at baseline.[2] All the patients who underwent randomization in the FLAURA2 trial had undergone mandatory brain scans at screening, which was not a requirement in the FLAURA trial and which may account for the discrepancy in the proportion of patients with CNS metas-

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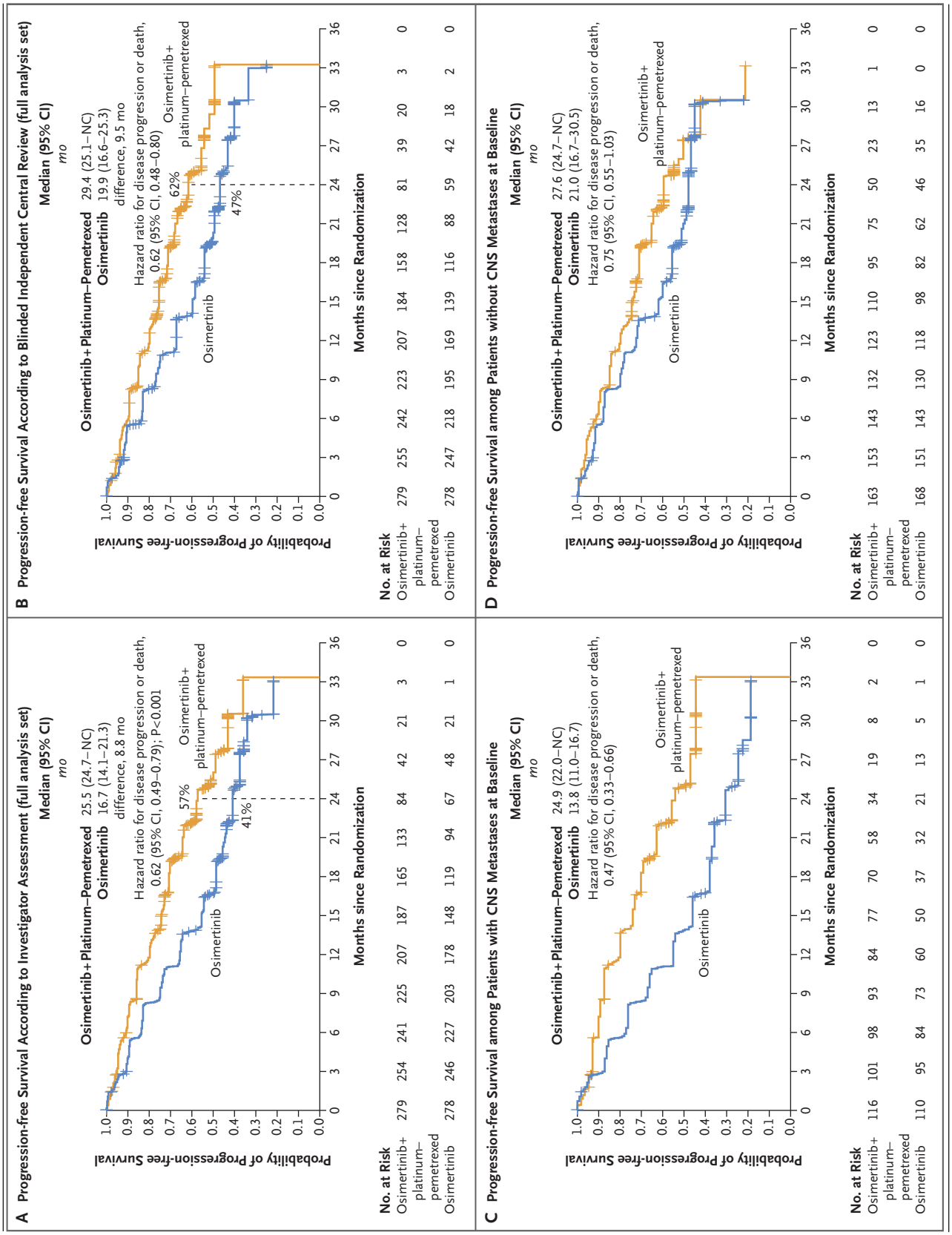

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Figure 1 (facing page). Progression-free Survival.
Shown are Kaplan–Meier estimates of progression-free survival in the full analysis set, as assessed by the investigators (Panel A), as assessed on the basis of blinded independent central review (Panel B), among patients with central nervous system (CNS) metastases at baseline (Panel C), and among those without CNS metastases at baseline (Panel D). Patients had been randomly assigned to receive osimertinib plus chemotherapy with pemetrexed and either cisplatin or carboplatin or to receive osimertinib monotherapy. The subgroups that were defined according to the presence or absence of CNS metastases at baseline were made according to investigator assessment on the basis of data in the electronic case-report form regarding the CNS lesion site at baseline, medical history, previous surgery, or a history of radiotherapy for CNS metastases. Tick marks indicate censored data. Patients who had not had disease progression or died at the time of analysis had their data censored at the time of the latest date of assessment from their last evaluable Response Evaluation Criteria in Solid Tumors, version 1.1, assessment. Disease progression events or death that did not occur within two scheduled visits after the last assessment (or randomization) were censored. The median follow-up among all the patients was 19.5 months (range, 0 to 33.3) in the osimertinib–chemotherapy group and 16.5 months (range, 0 to 33.1) in the osimertinib group; the median follow-up among all the patients with censored data was 22.2 months (range, 0 to 33.1) and 23.7 months (range, 0 to 33.1), respectively. The widths of the confidence intervals for progression free-survival according to investigator assessment (Panel A) have been adjusted for multiplicity; for all other analyses, the widths of the confidence intervals have not been adjusted for multiplicity. NC denotes not calculable.

tases. The CNS tumor burden was broadly similar to or lower than that in the OPAL trial (33%)[16] and in the LASER201 trial (51%),[17] which had mandatory brain scans at screening.

The interim analysis of overall survival is still immature (data maturity, 27%) but indicated that the addition of chemotherapy to osimertinib was not detrimental to survival; further follow-up is required. Second progression–free survival is indicative of the effect of initial treatment on the efficacy of subsequent therapy and is a surrogate end point for overall survival[18,19]; the hazard ratio for disease progression or death in the analysis of second progression–free survival was 0.70 (95% CI, 0.52 to 0.93).

The exact mechanisms for the observed clinical benefit with osimertinib plus platinum–pemetrexed as compared with osimertinib alone are not currently known. Osimertinib is a highly potent and selective EGFR-TKI, whereas therapy with pemetrexed and a platinum-based agent has a nonselective antitumor effect. Thus, it is possible that the combination overcomes intratumor heterogeneity by eliciting an additive effect by means of the killing of different cell populations to improve clinical outcomes. Ongoing exploratory analyses, including circulating tumor DNA–based analyses, may provide insights into predictive biomarkers for the combination.

The FLAURA2 trial was conducted internationally, with a large and diverse geographic distribution, but *EGFR*-mutated NSCLC is more frequently reported in the Asian population.[20] As a consequence, some non-Asian racial and ethnic groups, including Black patients, were underrepresented in this trial. The progression-free survival benefit in the overall population appeared to be consistent across prespecified subgroups, regardless of demographic or disease characteristics. The apparent benefit of the combination therapy over monotherapy was also observed in patient subgroups with greatest unmet need, such as patients with CNS metastases or L858R mutations at baseline — factors that are associated with a poorer prognosis.[21-23] The median progression-free survival was longer with osimertinib–chemotherapy than with osimertinib alone among patients with CNS metastases (24.9 months vs. 13.8 months) and among patients with the L858R mutation (24.7 months vs. 13.9 months).

Although osimertinib plus platinum–pemetrexed was associated with significantly improved efficacy as compared with osimertinib, the combination regimen was accompanied by a higher incidence of grade 3 adverse events. The adverse-event profile for the combination regimen during the randomized phase of this trial was consistent with observations in the safety run-in population.[15] Despite a higher incidence of osimertinib dose modifications in the osimertinib–chemotherapy group than in the monotherapy group, dose interruptions had a minimal overall effect on actual exposure to osimertinib. Previous studies of EGFR-TKIs combined with chemotherapy have also shown increased toxic effects with the combination as compared with an EGFR-TKI alone.[12,13] A higher incidence of hematologic toxic effects (in 71% of the patients in the osimertinib–chemotherapy group vs. 24% of those in the osimertinib group), which was consistent

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

End Point	Analysis according to the Investigator		Analysis according to Central Review	
	Osimertinib + Platinum–Pemetrexed (N=279)	Osimertinib Monotherapy (N=278)	Osimertinib + Platinum–Pemetrexed (N=279)	Osimertinib Monotherapy (N=278)
Median progression-free survival (95% CI) — mo	25.5 (24.7–NC)	16.7 (14.1–21.3)	29.4 (25.1–NC)	19.9 (16.6–25.3)
Hazard ratio for disease progression or death (95% CI)	0.62 (0.49–0.79)†	—	0.62 (0.48–0.80)	—
Progression-free survival (95% CI) — %				
At 12 mo	80 (74–84)	66 (60–71)	80 (75–84)	67 (61–73)
At 18 mo	71 (65–76)	49 (42–54)	71 (65–76)	54 (48–60)
At 24 mo	57 (50–63)	41 (35–47)	62 (55–68)	47 (40–53)
Objective response (95% CI) — %	83 (78–87)	76 (70–80)	92 (88–95)	83 (78–87)
Best objective response — no. (%)‡				
Complete response	1 (<1)	2 (1)	2 (1)	1 (<1)
Partial response	231 (83)	208 (75)	254 (91)	229 (82)
Stable disease for ≥35 days§	34 (12)	51 (18)	10 (4)	29 (10)
Disease progression	1 (<1)	9 (3)	3 (1)	12 (4)
Death¶	6 (2)	3 (1)	6 (2)	3 (1)
Could not be evaluated	6 (2)	5 (2)	4 (1)	4 (1)
Disease control (95% CI) — %‖	95 (92–98)	94 (90–96)	95 (92–98)	93 (90–96)
Median duration of response (95% CI) — mo**	24.0 (20.9–27.8)	15.3 (12.7–19.4)	28.3 (23.7–NC)	21.0 (17.8–NC)
Continued response (95% CI) — %				
At 12 mo	80 (74–84)	64 (57–70)	81 (76–86)	73 (66–78)
At 18 mo	69 (62–75)	44 (37–51)	70 (63–75)	56 (49–63)
At 24 mo	49 (41–57)	35 (27–42)	56 (48–64)	45 (36–52)

* Efficacy analysis included all the patients who had undergone randomization (full analysis set). Aside from investigator-assessed progression-free survival (primary end point), the widths of the confidence intervals have not been adjusted for multiplicity. Central review was a blinded independent central review. NC denotes not calculable.
† P<0.001.
‡ Tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1.
§ Stable disease must have been observed for at least 6 weeks minus 1 week to allow for an early assessment within the assessment window (trial day 35) after randomization.
¶ The deaths reported here are those that occurred in the absence of disease progression.
‖ Disease control was defined as a complete response, a partial response, or stable disease.
** Duration of response was calculated with the use of the Kaplan–Meier method from the date of the first documented response until the date of documented progression or death in the absence of disease progression.

with chemotherapy-induced bone marrow suppression, appeared to drive the higher incidence of adverse events in the osimertinib–chemotherapy group. Gastrointestinal adverse events are also typically observed after the initiation of chemotherapy,[24,25] and accordingly, we observed a higher incidence of nausea from any cause in the osimertinib–chemotherapy group than in the osimertinib group (in 43% vs. 10%), as well as decreased appetite (in 31% vs. 9%), constipation (in 29% vs. 10%), and vomiting (in 26% vs. 6%) (Table 3). Taken together, the results of this trial support the combination of osimertinib plus platinum–pemetrexed as a new treatment option for patients.

The trial may be limited by the following factors. First, the trial included only patients with common *EGFR* mutations (exon 19 deletion or L858R), which account for the majority of *EGFR* mutations in advanced NSCLC. Second, FLAURA2 was an open-label trial; however, the similarity that was seen between the assessment by the

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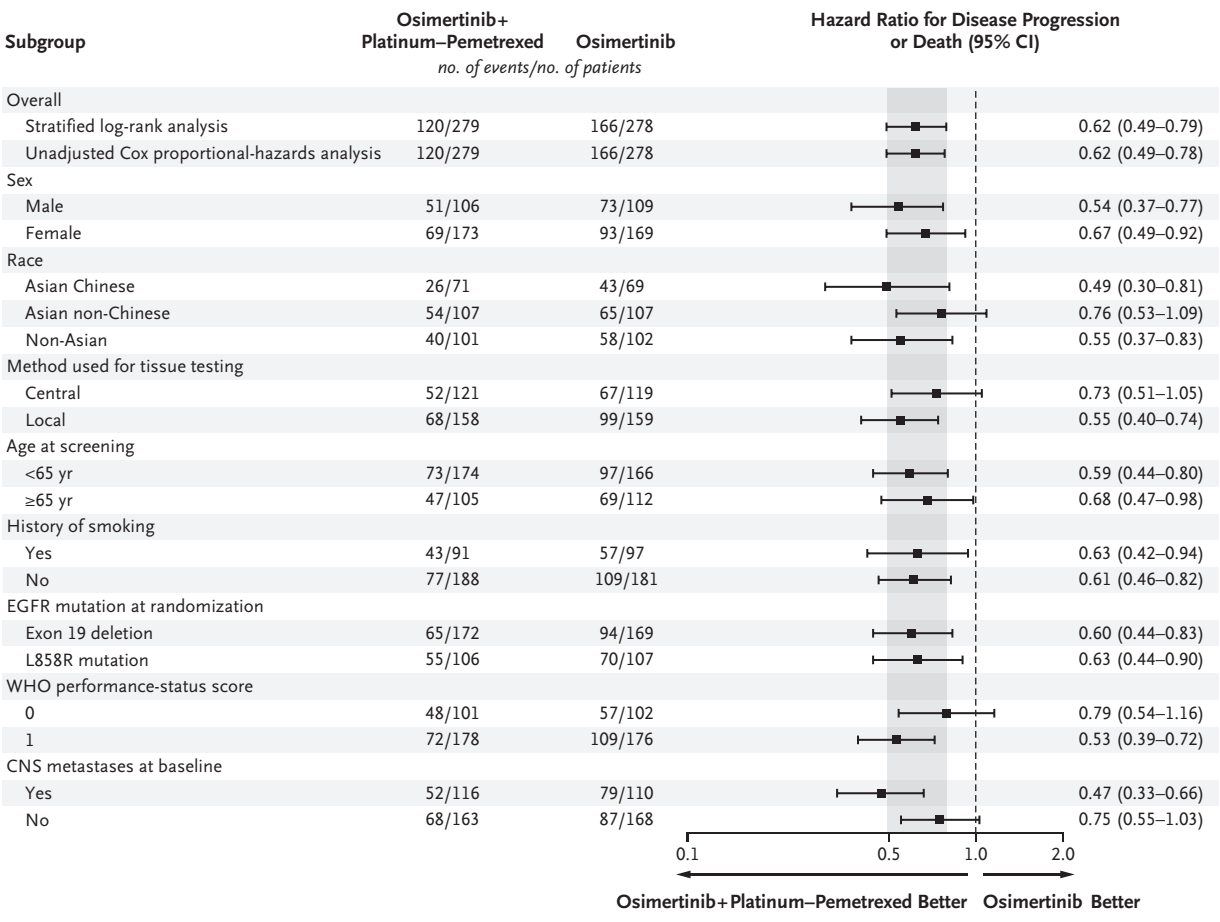

Figure 2. Subgroup Analysis of Progression-free Survival.

A hazard ratio of less than 1 indicates a lower risk of progression or death with osimertinib plus chemotherapy than with osimertinib monotherapy. The Cox proportional-hazards model includes randomized treatment, the subgroup covariate of interest, and the treatment according to subgroup interaction. Subgroups that were defined according to CNS metastases at baseline were made according to investigator assessment on the basis of data in the electronic case-report form regarding the CNS lesion site at baseline, medical history, previous surgery, or history of radiotherapy for CNS metastases. Race was reported by the patient; options were given on a drop-down list at randomization. World Health Organization (WHO) performance-status scores are assessed on a scale from 0 to 5, with higher scores indicating greater disability. A score of 0 indicates that the patient is fully active and able to carry out all predisease activities without restrictions, and a score of 1 indicates that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work. Two additional subgroups that were analyzed to fulfill regulatory requirements for diagnostics are not included here: EGFR mutations as assessed by a central Cobas tissue test and EGFR mutations as assessed by a central Cobas circulating tumor DNA test. The shaded area indicates the 95% confidence interval for the overall hazard ratio (among all the patients). Other than in the analysis in the overall population, the widths of the confidence intervals have not been adjusted for multiplicity. Patients with co-occurring exon 19 deletion and L858R mutations were included in the subgroup for exon 19 deletion. EGFR denotes epidermal growth factor receptor, and L858R p.Leu858Arg.

investigator and that conducted on the basis of blinded independent central review was also observed in the phase 3, randomized, open-label AURA3 trial, which assessed second-line therapy with osimertinib as compared with pemetrexed and a platinum-based agent.[1] Moreover, the sensitivity analysis of evaluation-time bias showed no effect on the primary analysis of progression-free survival.

In this trial, osimertinib plus chemotherapy with pemetrexed and a platinum-based agent significantly improved progression-free survival as compared with osimertinib alone in the context of first-line treatment of patients with *EGFR*-

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Table 3. Adverse Events.*

Event	Osimertinib + Platinum–Pemetrexed (N = 276)					Osimertinib Monotherapy (N = 275)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	128 (46)	30 (11)	43 (16)	55 (20)	0	22 (8)	15 (5)	6 (2)	1 (<1)	0
Diarrhea	120 (43)	83 (30)	29 (11)	8 (3)	0	112 (41)	89 (32)	22 (8)	1 (<1)	0
Nausea	119 (43)	81 (29)	34 (12)	4 (1)	0	28 (10)	22 (8)	6 (2)	0	0
Decreased appetite	85 (31)	49 (18)	28 (10)	8 (3)	0	26 (9)	18 (7)	6 (2)	2 (1)	0
Constipation	81 (29)	60 (22)	20 (7)	1 (<1)	0	28 (10)	23 (8)	5 (2)	0	0
Rash	77 (28)	55 (20)	21 (8)	1 (<1)	0	57 (21)	46 (17)	11 (4)	0	0
Fatigue	76 (28)	45 (16)	23 (8)	8 (3)	0	26 (9)	24 (9)	1 (<1)	1 (<1)	0
Vomiting	73 (26)	50 (18)	20 (7)	3 (1)	0	17 (6)	13 (5)	4 (1)	0	0
Stomatitis	68 (25)	40 (14)	27 (10)	1 (<1)	0	50 (18)	32 (12)	17 (6)	1 (<1)	0
Neutropenia	68 (25)	4 (1)	27 (10)	30 (11)	7 (3)	9 (3)	3 (1)	4 (1)	2 (1)	0
Paronychia	65 (24)	28 (10)	35 (13)	2 (1)	0	73 (27)	37 (13)	35 (13)	1 (<1)	0
Neutrophil count decrease	62 (22)	5 (2)	26 (9)	25 (9)	6 (2)	16 (6)	6 (2)	8 (3)	2 (1)	0
Covid-19†	57 (21)	23 (8)	31 (11)	2 (1)	0	39 (14)	18 (7)	21 (8)	0	0
ALT increase	56 (20)	36 (13)	16 (6)	4 (1)	0	21 (8)	17 (6)	3 (1)	1 (<1)	0
Platelet count decrease	51 (18)	19 (7)	11 (4)	18 (7)	3 (1)	19 (7)	18 (7)	1 (<1)	0	0
Thrombocytopenia	51 (18)	19 (7)	13 (5)	16 (6)	3 (1)	12 (4)	6 (2)	3 (1)	3 (1)	0
Dry skin	50 (18)	43 (16)	7 (3)	0	0	66 (24)	62 (23)	4 (1)	0	0
AST increase	48 (17)	42 (15)	5 (2)	1 (<1)	0	13 (5)	12 (4)	0	1 (<1)	0
Blood creatinine increase	46 (17)	33 (12)	13 (5)	0	0	12 (4)	10 (4)	2 (1)	0	0
White-cell count decrease	44 (16)	7 (3)	28 (10)	8 (3)	1 (<1)	18 (7)	9 (3)	8 (3)	1 (<1)	0
Peripheral edema	42 (15)	33 (12)	9 (3)	0	0	12 (4)	9 (3)	3 (1)	0	0

* Safety analyses included all the patients who received at least one dose of trial treatment (safety analysis set), according to the treatment received. Each patient has been represented only with the maximum reported Common Terminology Criteria for Adverse Events grade for each preferred term. Listed are adverse events from any cause according to preferred term that were reported in at least 15% of patients in either group. Adverse events with an onset date on or after the date of first dose and up to and including 28 days after the discontinuation of treatment but before the start of a subsequent anticancer therapy are reported. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

† One patient in the group that received osimertinib plus platinum–pemetrexed died from coronavirus disease 2019 (Covid-19).

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mutated advanced NSCLC. Although hematologic toxic effects were reported, these were as expected with chemotherapy use and were in line with known safety profiles of the individual agents.

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

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APPENDIX

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REFERENCES

1. 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.
2. 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.
3. Cross DAE, 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.
4. Wu Y-L, Tsuboi M, He J, et al. Osimertinib in resected *EGFR*-mutated non–small-cell lung cancer. N Engl J Med 2020;383:1711-23.
5. Wu Y-L, Ahn M-J, 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.
6. 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;36:3290-7.
7. Tsuboi M, Herbst RS, John T, et al. Overall survival with osimertinib in resected *EGFR*-mutated NSCLC. N Engl J Med 2023;389:137-47.
8. Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 2023;34:339-57.
9. Hanna NH, Robinson AG, Temin S, et al. Therapy for stage IV non-small-cell lung cancer with driver alterations: ASCO and OH (CCO) joint guideline update. J Clin Oncol 2021;39:1040-91.
10. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. N Engl J Med 2020;382:41-50.
11. Miyauchi E, Morita S, Nakamura A, et al. Updated analysis of NEJ009: gefitinib-alone versus gefitinib plus chemotherapy for non-small-cell lung cancer with mutated EGFR. J Clin Oncol 2022;40:3587-92.
12. Hosomi Y, Morita S, Sugawara S, et al. Gefitinib alone versus gefitinib plus chemotherapy for non-small-cell lung cancer with mutated epidermal growth factor receptor: NEJ009 study. J Clin Oncol 2020;38:115-23.
13. Noronha V, Patil VM, Joshi A, et al. Gefitinib versus gefitinib plus pemetrexed and carboplatin chemotherapy in EGFR-mutated lung cancer. J Clin Oncol 2020;38:124-36.
14. Han B, Jin B, Chu T, et al. Combination of chemotherapy and gefitinib as first-line treatment for patients with advanced lung adenocarcinoma and sensitive EGFR mutations: a randomized controlled trial. Int J Cancer 2017;141:1249-56.
15. Planchard D, Feng P-H, Karaseva N, et al. Osimertinib plus platinum-pemetrexed in newly diagnosed epidermal growth factor receptor mutation-positive advanced/metastatic non-small-cell lung cancer: safety run-in results from the FLAURA2 study. ESMO Open 2021;6:100271.
16. Saito R, Sugawara S, Ko R, et al. Phase 2 study of osimertinib in combination with platinum and pemetrexed in patients with previously untreated EGFR-mutated advanced non-squamous non-small cell lung cancer: the OPAL Study. Eur J Cancer 2023;185:83-93.
17. Cho BC, Han J-Y, Kim S-W, et al. A phase 1/2 study of lazertinib 240 mg in patients with advanced EGFR T790M-positive NSCLC after previous EGFR tyrosine kinase inhibitors. J Thorac Oncol 2022;17:558-67.
18. European Medicines Agency. Evalua-

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tion of anticancer medicinal products in man — scientific guideline. 2019 (https://www.ema.europa.eu/en/evaluation-anticancer-medicinal-products-man-scientific-guideline).
19. Woodford RG, Zhou DD-X, Kok P-S, et al. The validity of progression-free survival 2 as a surrogate trial end point for overall survival. Cancer 2022;128:1449-57.
20. Costa PA, Saul EE, Paul Y, et al. Prevalence of targetable mutations in black patients with lung cancer: a systematic review and meta-analysis. JCO Oncol Pract 2021;17(5):e629-e636.
21. Bhatt VR, D'Souza SP, Smith LM, et al. Epidermal growth factor receptor mutational status and brain metastases in non–small-cell lung cancer. J Glob Oncol 2016;3:208-17.
22. Peters S, Bexelius C, Munk V, Leighl N. The impact of brain metastasis on quality of life, resource utilization and survival in patients with non-small-cell lung cancer. Cancer Treat Rev 2016;45:139-62.
23. Lee CK, Davies L, Wu Y-L, et al. Gefitinib or erlotinib vs chemotherapy for EGFR mutation-positive lung cancer: individual patient data meta-analysis of overall survival. J Natl Cancer Inst 2017;109(6).
24. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2013;31:2895-902.
25. Cortellini A, Gambale E, Cannita K, et al. Multicentric retrospective analysis of platinum-pemetrexed regimens as first-line therapy in non-squamous non-small cell lung cancer patients: a "snapshot" from clinical practice. Thorac Cancer 2018;9:241-52.
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