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Osimertinib after Chemoradiotherapy in Stage III *EGFR*-Mutated NSCLC

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ABSTRACT

BACKGROUND

Osimertinib is a recommended treatment for advanced non–small-cell lung cancer (NSCLC) with an epidermal growth factor receptor (*EGFR*) mutation and as adjuvant treatment for resected *EGFR*-mutated NSCLC. EGFR tyrosine kinase inhibitors have shown preliminary efficacy in unresectable stage III *EGFR*-mutated NSCLC.

METHODS

In this phase 3, double-blind, placebo-controlled trial, we randomly assigned patients with unresectable *EGFR*-mutated stage III NSCLC without progression during or after chemoradiotherapy to receive osimertinib or placebo until disease progression occurred (as assessed by blinded independent central review) or the regimen was discontinued. The primary end point was progression-free survival as assessed by blinded independent central review.

RESULTS

A total of 216 patients who had undergone chemoradiotherapy were randomly assigned to receive osimertinib (143 patients) or placebo (73 patients). Osimertinib resulted in a significant progression-free survival benefit as compared with placebo: the median progression-free survival was 39.1 months with osimertinib versus 5.6 months with placebo, with a hazard ratio for disease progression or death of 0.16 (95% confidence interval [CI], 0.10 to 0.24; P<0.001). The percentage of patients who were alive and progression free at 12 months was 74% (95% CI, 65 to 80) with osimertinib and 22% (95% CI, 13 to 32) with placebo. Interim overall survival data (maturity, 20%) showed 36-month overall survival among 84% of patients with osimertinib (95% CI, 75 to 89) and 74% with placebo (95% CI, 57 to 85), with a hazard ratio for death of 0.81 (95% CI, 0.42 to 1.56; P=0.53). The incidence of adverse events of grade 3 or higher was 35% in the osimertinib group and 12% in the placebo group; radiation pneumonitis (majority grade, 1 to 2) was reported in 48% and 38%, respectively. No new safety concerns emerged.

CONCLUSIONS

Treatment with osimertinib resulted in significantly longer progression-free survival than placebo in patients with unresectable stage III *EGFR*-mutated NSCLC. (Funded by AstraZeneca; LAURA ClinicalTrials.gov number, NCT03521154.)

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CME

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Approximately 20 to 30% of patients with non–small-cell lung cancer (NSCLC) present with locally advanced stage III disease at the time of diagnosis.[1,2] Of these patients, 60 to 90% are considered to have unresectable disease.[3,4] The current standard of care for unresectable stage III NSCLC is concurrent chemoradiotherapy followed by consolidation therapy with durvalumab in patients without progression after chemoradiotherapy.[5]

Epidermal growth factor receptor (*EGFR*) mutations are reported in up to one third of patients with unresectable stage III NSCLC who receive chemoradiotherapy.[6-8] Currently, no targeted treatments are approved for patients with unresectable stage III *EGFR*-mutated NSCLC.[5] Previous studies have suggested that, as compared with patients without *EGFR* mutations, patients with unresectable stage III *EGFR*-mutated NSCLC have shorter or similar progression-free survival and a higher incidence of distant metastases, including in the central nervous system (CNS), after definitive chemoradiotherapy.[9] Of note, data suggest a lower risk of local failure (failure of the primary tumor to regress or reappearance of the tumor at the primary site) in patients with *EGFR*-mutated disease.[9] Therefore, the control of systemic micrometastatic disease is critical to improving long-term outcomes in patients with unresectable stage III *EGFR*-mutated NSCLC.

Although immune checkpoint inhibitors provide substantial overall survival benefit to patients with metastatic NSCLC without detectable *EGFR* mutations, the same benefit has not been shown in patients with *EGFR*-mutated NSCLC.[10,11] Similarly, limited data show that the benefit of consolidation therapy with durvalumab specifically in patients with unresectable stage III *EGFR*-mutated NSCLC is uncertain.[7,12,13] Although no dedicated prospective trial data are available regarding these patients, a small number of exploratory analyses and retrospective studies have shown median progression-free survival ranging from 9.0 to 12.7 months in patients who received consolidation therapy with durvalumab after chemoradiotherapy.[7,12-14]

Osimertinib, a third-generation EGFR tyrosine kinase inhibitor (EGFR-TKI), potently and selectively inhibits both EGFR-TKI sensitizing and *EGFR* p.Thr790Met resistance mutations, with efficacy in NSCLC, including in patients with CNS metastases.[15-20] Osimertinib is the preferred first-line treatment for advanced *EGFR*-mutated NSCLC and is also approved for use in combination with platinum-based chemotherapy in this context.[21,22] In addition, osimertinib is recommended as adjuvant treatment for resected stage IB–IIIA *EGFR*-mutated NSCLC.[23,24]

Here, we report the efficacy and safety of osimertinib as compared with placebo in patients with unresectable stage III *EGFR*-mutated NSCLC, without disease progression during or after chemoradiotherapy, from the international, phase 3 LAURA trial.

METHODS

PATIENTS

Full details of the trial are provided in the protocol and statistical analysis plan (available with the full text of this article at NEJM.org). The trial design is shown in Figure S1 in the Supplementary Appendix (available at NEJM.org).[25] Eligible patients were at least 18 years of age (20 years of age or older in Japan), with locally advanced, unresectable, stage III NSCLC, with an *EGFR* exon 19 deletion or exon 21 codon p.Leu858Arg point mutation (alone or with other *EGFR* mutations) and a World Health Organization (WHO) performance-status score of 0 or 1 (on a scale of 0 to 5, with higher numbers indicating greater disability).

At the time of recruitment, the disease stage was determined according to the eighth edition of the American Joint Committee on Cancer–Union for International Cancer Control staging guidelines.[26] Eligible patients had completed concurrent or sequential platinum-based chemoradiotherapy within 6 weeks before undergoing randomization and were without investigator-assessed disease progression during or after definitive chemoradiotherapy. Patients with a history of interstitial lung disease before chemoradiotherapy, symptomatic pneumonitis after chemoradiotherapy, or unresolved adverse effects of grade 2 or higher after chemoradiotherapy were ineligible.

TRIAL 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, applicable laws and regulations, and the policy of the trial sponsor, AstraZeneca, regarding bioethics and human biologic samples. The protocol was approved by the relevant institutional review boards or by independent ethics committees. All the patients provided written informed consent.

The trial was funded by the sponsor and designed by the sponsor in collaboration 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 support funded by the sponsor. All the authors had access to the data, contributed to the development of the manuscript, and approved the final version to be submitted for publication. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

TRIAL DESIGN AND TREATMENT

In this phase 3, double-blind, placebo-controlled trial, patients were enrolled on the basis of either a preexisting local or centrally confirmed *EGFR* mutation–positive test result. Results of preexisting local tests were based on the cobas *EGFR* Mutation Test, version 2 (Roche Diagnostics) or the FoundationOne CDx Test (Foundation Medicine); central testing was performed with the use of the cobas *EGFR* Mutation Test, version 2. After completing chemoradiotherapy, patients underwent randomization in a 2:1 ratio to receive either oral osimertinib at a dose of 80 mg once daily or placebo, until disease progression was shown by means of objective radiologic confirmation, as assessed by blinded independent central review (according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1), or until fulfillment of another discontinuation criterion. After the occurrence of disease progression as assessed by blinded independent central review, patients in both treatment groups were offered open-label osimertinib (see the Supplementary Methods section of the Supplementary Appendix).

END POINTS

The primary end point was progression-free survival as assessed by blinded independent central review according to RECIST, version 1.1. Progression-free survival was defined as the time from randomization to objective disease progression or death from any cause in the absence of progression. Key secondary end points were overall survival, survival without progression of CNS disease (CNS progression–free survival) as assessed by blinded independent central review, objective response rate, duration of response, health-related quality of life, and safety. Descriptions of the primary and secondary end points are provided in Table S1.

TRIAL ASSESSMENTS

The assessment of tumors with computed tomography or magnetic resonance imaging (MRI) of the chest and abdomen and MRI of the brain was required at baseline (after the patient had undergone chemoradiotherapy and no later than 28 days before randomization), every 8 weeks from the time of randomization for 48 weeks, and every 12 weeks thereafter until objective radiologic confirmation of disease progression as assessed by blinded independent central review according to RECIST, version 1.1.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Adverse events of special interest were interstitial lung disease (comprising interstitial lung disease, pneumonitis, and pulmonary fibrosis) and radiation pneumonitis (comprising lung radiation fibrosis and radiation pneumonitis). Protocol-specified guidelines for management of adverse events allowed patients with interstitial lung disease or radiation pneumonitis of CTCAE grade 1 or 2 to continue or restart treatment. Additional details regarding the efficacy and safety assessments are provided in the Supplementary Methods section.

STATISTICAL ANALYSIS

The full analysis set, which included all the patients who had undergone randomization, provided the data that were used for summaries of the demographic and baseline characteristics and for efficacy analyses. The safety analysis set included all the patients who received at least one dose of osimertinib or placebo and provided the data that were used for safety analyses.

Progression-free survival that was assessed by blinded independent central review was analyzed with the use of a log-rank test stratified

according to the patients' disease stage (stage IIIA vs. stage IIIB or IIIC) before chemoradiotherapy. The Kaplan–Meier method was used to calculate median progression-free survival. To control for the type I error rate at the 5% two-sided level, a sequential multiple testing procedure was used; if significance was shown in the analysis of progression-free survival, then overall survival would be tested, followed by testing for CNS progression–free survival. For the primary analysis, we calculated that 120 events of disease progression or death would provide the trial with 90% power to detect a hazard ratio of 0.53 at a two-sided 5% significance level. Progression-free survival was analyzed in prespecified subgroups with the use of a Cox proportional-hazards model and was not included in the multiple testing procedure. The data-cutoff date was January 5, 2024. Additional details regarding the statistical analyses are provided in the Supplementary Methods section.

RESULTS

PATIENTS AND TREATMENT

From August 2018 through July 2022, a total of 216 patients underwent randomization; 143 were assigned to receive osimertinib, and 73 were assigned to receive placebo. The characteristics of the patients at baseline were generally balanced between the two groups, although the percentage of patients with a WHO performance-status score of 0 was higher in the osimertinib group (56%) than in the placebo group (42%) (Table 1). The demographic and clinical characteristics of the patients were similar to available data from patients with *EGFR*-mutated NSCLC (Table S2); however, the majority of the trial patients were enrolled from Asian countries. Consequently, some racial and ethnic subgroups were underrepresented, and no Black patients were enrolled. Details regarding previous chemoradiotherapy received by the patients are provided in Table S3. All the patients who had undergone randomization received at least one dose of osimertinib or placebo. Discontinuation of the regimen occurred in 63 patients (44%) in the osimertinib group and in 66 patients (90%) in the placebo group, most commonly owing to disease progression (25% vs. 74%) and adverse events (13% vs. 7%). Details regarding patient disposition are provided in Fig. S2.

EFFICACY

A total of 120 events of disease progression (as assessed by blinded independent central review) or death occurred (total data maturity, 56%): 57 in the osimertinib group (data maturity, 40%) and 63 in the placebo group (data maturity, 86%). The median follow-up for progression-free survival was 22.0 months (range, <0.1 to 60.6) with osimertinib and 5.6 months (range, <0.1 to 49.7) with placebo. The median progression-free survival was 39.1 months (95% confidence interval [CI], 31.5 to not calculable) with osimertinib and 5.6 months (95% CI, 3.7 to 7.4) with placebo; the overall hazard ratio for disease progression or death was 0.16 (95% CI, 0.10 to 0.24; P<0.001) (Fig. 1). The percentages of the patients who were alive and progression-free at 12 months and 24 months, respectively, were 74% (95% CI, 65 to 80) and 65% (95% CI, 56 to 73) with osimertinib and 22% (95% CI, 13 to 32) and 13% (95% CI, 6 to 22) with placebo. Beginning with the first postbaseline scan, Kaplan–Meier curves showed early separation between the treatment groups, a separation that was sustained throughout follow-up (Fig. 1). Investigator-assessed progression-free survival results were consistent with the findings of the blinded independent central review (Supplementary Results section and Fig. S3).

The progression-free survival benefit favoring osimertinib was observed in all prespecified subgroups with sufficient events for analysis, with hazard ratios ranging from 0.16 to 0.48 (Fig. 2). A progression-free survival benefit favoring osimertinib was also observed regardless of the patients' WHO performance-status score (assessed in a post hoc analysis). The hazard ratio for disease progression or death was 0.17 (95% CI, 0.10 to 0.28) for patients with a WHO performance-status score of 0 and 0.34 (95% CI, 0.20 to 0.56) for those with a WHO performance-status score of 1.

Lower incidences of local progression and distant metastases were observed in the osimertinib group (21% and 16%, respectively) than in the placebo group (48% and 37%, respectively). The incidence of new lesions was lower with osimertinib (22%) than with placebo (68%), including new brain lesions (8% vs. 29%) and new lung lesions (6% vs. 29%) (Table S4).

Subsequent anticancer treatment of any type was administered in 42 patients (29%) in the

osimertinib group and 57 patients (78%) in the placebo group (Table S5). Among the patients with disease progression, subsequent osimertinib treatment was administered in 15 of 53 patients (28%) in the osimertinib group and in 50 of 62 patients (81%) in the placebo group. As of the data-cutoff date, 43 of the patients had died (data maturity, 20%); the 36-month overall survival was 84% (95% CI, 75 to 89) with osimertinib and 74% (95% CI, 57 to 85) with placebo. The hazard ratio for overall survival was 0.81 (95% CI, 0.42 to 1.56; P=0.53), which was not significant at this interim analysis (Supplementary Results section and Fig. S4).

The objective response rate was higher with osimertinib than with placebo (57% [95% CI, 49 to 66] vs. 33% [95% CI, 22 to 45]; odds ratio, 2.77 [95% CI, 1.54 to 5.08]) (Table 2). The median duration of response was longer with osimertinib (36.9 months) than with placebo (6.5 months) (Table 2 and Fig. S5). The depth of response is described in the Supplementary Results section and shown in Fig. S6.

SAFETY

At the data-cutoff date, the median duration of total treatment exposure (which included the duration of dose interruptions for any reason) was 24.0 months (range, 0.4 to 62.9) with osimertinib and 8.3 months (range, 0.5 to 56.6) with placebo and was similar to the median duration of actual treatment exposure (which excluded the duration of dose interruptions for any reason) — 23.7 months (range, 0.3 to 62.4) with osimertinib and 7.9 months (range, 0.5 to 56.2) with placebo. Adverse events were reported in 140 patients (98%) receiving osimertinib and 64 patients (88%) receiving placebo. The most common adverse events, irrespective of cause, were radiation pneumonitis (48% with osimertinib vs. 38% with placebo), diarrhea (36% vs. 14%), and rash (24% vs. 14%) (Table 3). Adverse events that were considered by the investigator to be possibly causally related to osimertinib or placebo are reported in Table S6.

Adverse events of grade 3 or higher were reported in 50 patients (35%) with osimertinib and 9 patients (12%) with placebo (Table S7). Adverse events of grade 3 or higher that were considered by the investigator to be possibly causally related to osimertinib or placebo are reported in Table S8. Serious adverse events (irrespective of cause) were reported in 55 patients (38%) receiving osimertinib and in 11 patients (15%) receiving placebo (Table S9). Fatal adverse events occurred in 3 patients (2%) receiving osimertinib (pneumonitis, pneumonia, and a road traffic accident) and in 2 patients (3%) receiving placebo (myocardial infarction and aortic aneurism rupture).

The adverse events that were grouped as interstitial lung disease were reported in 11 patients (8%) receiving osimertinib and 1 patient (1%) receiving placebo and included the preferred terms interstitial lung disease (1% vs. 0%), pneumonitis (6% vs. 1%), and pulmonary fibrosis (2% vs. 0%) (Table S10). The adverse events that were grouped as radiation pneumonitis were reported in 69 patients (48%) receiving osimertinib and in 28 patients (38%) receiving placebo and included the preferred terms of radiation pneumonitis (48% vs. 38%) and lung radiation fibrosis (1% vs. 0). Of the patients in the osimertinib group who reported having radiation pneumonitis, 60 patients (87%) continued or restarted osimertinib treatment according to the trial guidelines for management of adverse events without subsequent recurrence of radiation pneumonitis. Overall, adverse events were responsible for dose interruptions in 80 patients (56%) receiving osimertinib and 18 patients (25%) receiving placebo, dose reductions in 12 patients (8%) and 1 patient (1%), respectively, and discontinuation of osimertinib or placebo in 18 patients (13%) and 4 patients (5%), respectively.

DISCUSSION

The LAURA trial is a prospective phase 3 trial assessing the efficacy and safety of osimertinib in patients with unresectable stage III *EGFR*-mutated NSCLC amenable to curative-intent treatment. The trial met the prespecified criteria for the primary end point of progression-free survival as assessed by blinded independent central review. Osimertinib treatment after definitive chemoradiotherapy showed a significant benefit with regard to progression-free survival as compared with placebo. The hazard ratio for disease progression or death was 0.16 (95% CI, 0.10 to 0.24; P<0.001), indicating an 84% reduction in the risk of disease progression or death with osimertinib as compared with placebo. The

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

Characteristic	Osimertinib (N=143)	Placebo (N=73)
Sex — no. (%)		
Male	53 (37)	31 (42)
Female	90 (63)	42 (58)
Age — yr		
Median	62	64
Range	36 to 84	37 to 83
Smoking status — no. (%)		
Current	4 (3)	1 (1)
Former	37 (26)	23 (32)
Never	102 (71)	49 (67)
Race — no. (%)†		
Asian	116 (81)	62 (85)
Non-Asian	27 (19)	11 (15)
WHO performance-status score — no. (%)‡		
0	80 (56)	31 (42)
1	63 (44)	42 (58)
AJCC–UICC disease stage — no. (%)§		
IIIA	52 (36)	24 (33)
IIIB	67 (47)	38 (52)
IIIC	24 (17)	11 (15)
Histologic type — no. (%)		
Adenocarcinoma	139 (97)	69 (95)
Squamous-cell carcinoma	3 (2)	2 (3)
Other¶	1 (1)	2 (3)
EGFR mutation type at screening — no. (%)‖		
Exon 19 deletion	74 (52)	43 (59)
L858R mutation	68 (48)	30 (41)
Type of chemoradiotherapy — no. (%)**		
Concurrent	131 (92)	62 (85)
Sequential	12 (8)	11 (15)
Best overall response to chemoradiotherapy — no. (%)††		
Complete response	4 (3)	3 (4)
Partial response	67 (47)	27 (37)
Stable disease	61 (43)	37 (51)
Not evaluable‡‡	11 (8)	6 (8)
Target-lesion size — mm§§	33±18	36±17

* Plus–minus values are means ±SD. No formal comparison of baseline characteristics in the two groups was performed. Percentages may not total 100 because of rounding. L858R denotes exon 21 codon p.Leu858Arg.

† Race was reported by the investigators.

‡ World Health Organization (WHO) performance status scores range from 0 to 5, with higher numbers indicating greater disability.

§ Disease stages are classified according to the eighth edition of the American Joint Committee on Cancer (AJCC)–Union for International Cancer Control (UICC) Cancer Staging Manual and are summarized on the basis of data entered in the electronic case-report form.

Table 1. (Continued.)

¶ This category included two patients with adenosquamous histologic characteristics and one patient with adenosquamous carcinoma histologic characteristics. Classification was made on the basis of data entered in the electronic case-report form.
‖ One patient in the osimertinib group underwent randomization without an approved positive local or central *EGFR* test result.
** The type of chemoradiotherapy was summarized on the basis of data entered in the electronic case-report form.
†† Responses were assessed by the investigator.
‡‡ Target lesions that were not evaluable did not meet progressive disease criteria and were not measurable after chemoradiotherapy.
§§ Target-lesion size was determined by independent central reviewers who were unaware of trial-group assignments.

median progression-free survival was 39.1 months with osimertinib and 5.6 months with placebo.

The current standard of care for unresectable stage III NSCLC is consolidation therapy with durvalumab for patients without progression after definitive concurrent chemoradiotherapy.[5,23] However, the benefit of immune checkpoint inhibitors is uncertain in *EGFR*-mutated NSCLC, with limited data available.[7,12-14,27] In a post hoc subgroup analysis of 35 patients with *EGFR*-mutated NSCLC from the PACIFIC trial, the median progression-free survival with durvalumab (11.2 months; 95% CI, 7.3 to 20.7) was similar to that with placebo (10.9 months; 95% CI, 1.9 to not evaluable).[13] Before the current trial, studies of EGFR-TKI plus chemoradiotherapy or radiotherapy showed promising efficacy in patients with unresectable stage III *EGFR*-mutated NSCLC.[9,28] The phase 2 RECEL trial showed longer median progression-free survival with erlotinib plus radiotherapy that was followed by consolidation erlotinib than with chemoradiotherapy (24.5 vs. 9.0 months; hazard ratio, 0.104 [95% CI, 0.03 to 0.39]).[28]

In this phase 3 trial, the median progression-free survival was 33.6 months longer with

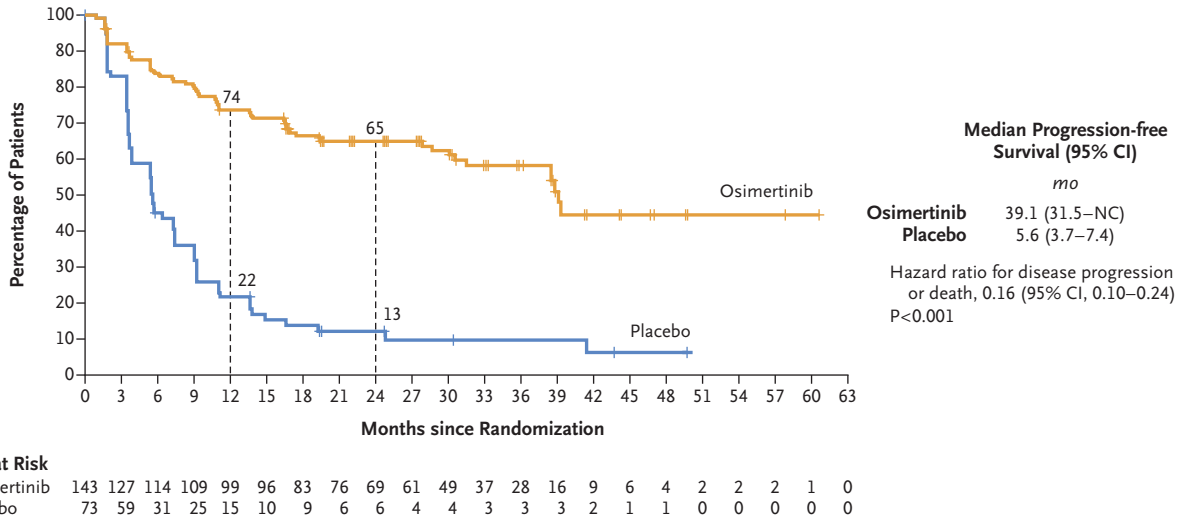

Figure 1. Progression-free Survival According to Blinded Independent Central Review.

The figure shows Kaplan–Meier estimates of the duration of progression-free survival (assessed by blinded independent central review with the use of Response Evaluation Criteria in Solid Tumors, version 1.1). Tick marks indicate censored data, and vertical dashed lines indicate the times of landmark analyses of progression-free survival. The median duration of follow-up for progression-free survival in all patients was 22.0 months (range, <0.1 to 60.6) in the osimertinib group and 5.6 months (range, <0.1 to 49.7) in the placebo group; the median duration of follow-up for progression-free survival in patients whose data were censored was 27.7 months (range, <0.1 to 60.6) in the osimertinib group and 19.5 months (range, <0.1 to 49.7) in the placebo group. CI denotes confidence interval, and NC not calculable.

osimertinib than with placebo after definitive chemoradiotherapy; 87% of the patients in the placebo group had disease progression or died within 2 years after randomization. The placebo group had a median progression-free survival of 5.6 months (95% CI, 3.7 to 7.4), a result consistent with that in previous phase 3 studies involving patients with stage III unresectable NSCLC without biomarker selection, including the PACIFIC trial (intention-to-treat population, 5.6 months; 95% CI 4.6 to 7.8) and the GEMSTONE-301 trial (5.8 months; 95% CI 4.2 to 6.6),[29,30] although comparison between the studies is limited owing to the differences in patient characteristics. The CNS is a common site of distant progression in patients with unresectable stage III *EGFR*-mutated

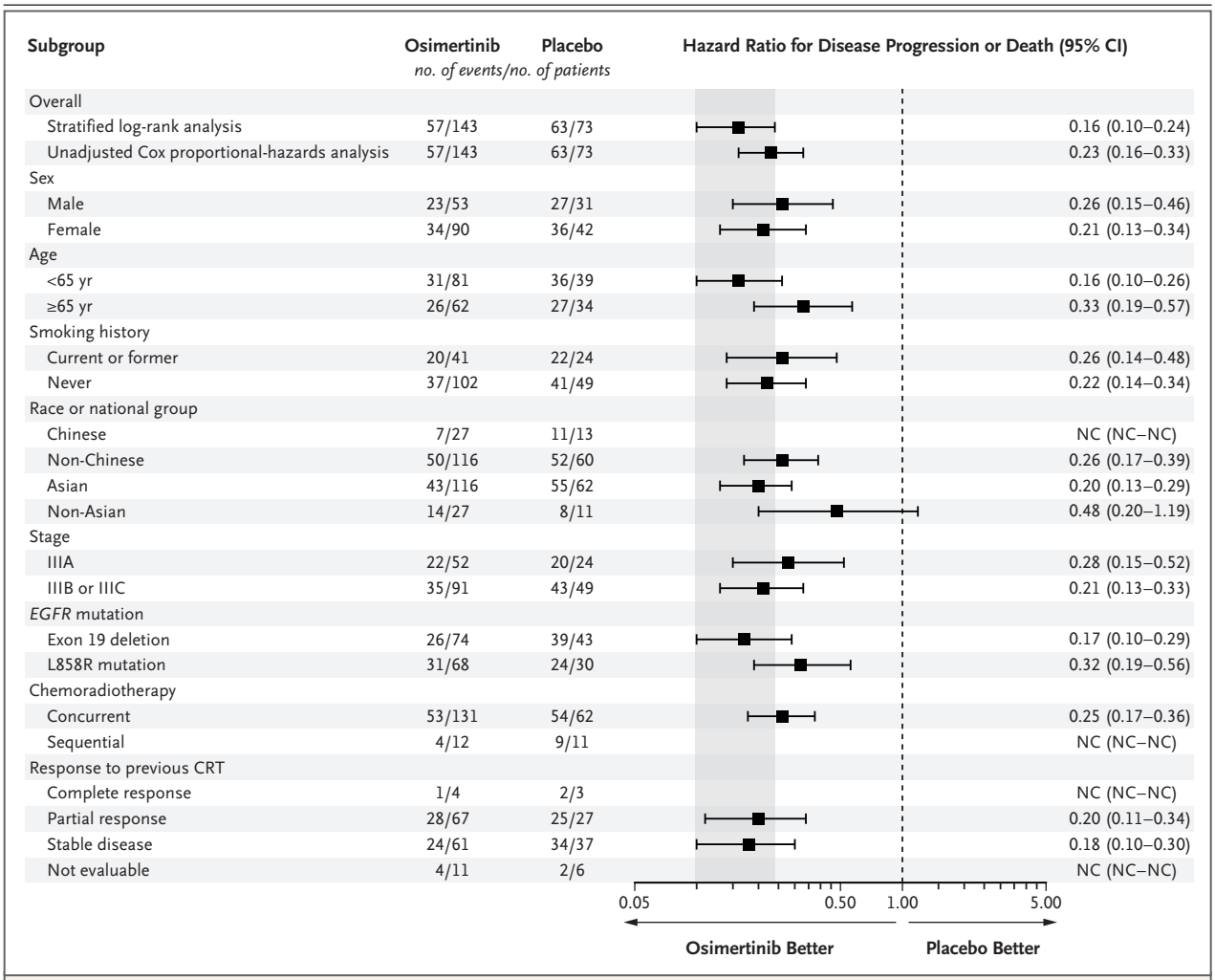

Figure 2. Subgroup Analysis of Progression-free Survival According to Blinded Independent Central Review.

Progression-free survival was assessed by blinded independent central review according to RECIST, version 1.1. The subgroup analysis was performed with the use of a Cox proportional-hazards model and the Efron method of handling ties. Prespecified subgroup categories are shown. Subgroup categories with fewer than 20 events across the two groups were excluded from the analysis, and hazard ratios were not calculable (NC). The shaded area denotes the 95% confidence interval for the overall hazard ratio from the stratified log-rank analysis in the overall population. A hazard ratio of less than 1 indicates a lower risk of disease progression or death with osimertinib than with placebo. Subgroups defined by the stratification factors (chemoradiotherapy [CRT] strategy, disease stage, and China cohort) are derived from values entered in the electronic case-report form. Disease stage, determined before the patients had undergone CRT, is categorized according to the eighth edition of the American Joint Committee on Cancer–Union for International Cancer Control Cancer Staging Manual. One patient in the osimertinib group did not have a central or local *EGFR*-mutation test result at screening and was not included in the analysis. L858R denotes exon 21 codon p.Leu858Arg.

NSCLC treated with chemoradiotherapy, occurring more frequently in those patients than in patients with *EGFR* wild-type NSCLC.[9] In the LAURA trial, new brain metastases were less frequent with osimertinib than with placebo (8% vs. 29%), suggesting that osimertinib provides a protective effect against CNS progression. Osimertinib treatment also led to a lower incidence of local and systemic disease progression than placebo, with similar patterns of progression with regard to local versus distant sites in the two groups.

In our trial, osimertinib was offered to patients in both treatment groups after disease progression. In the placebo group, 81% of the patients who had disease progression received subsequent osimertinib treatment. In the osimertinib group, continued osimertinib use was allowed if it was deemed to be clinically beneficial by the investigator; 28% of the patients who had disease progression received subsequent osimertinib treatment. Interim overall survival data showed no evidence of a significant difference between the two groups at the current data maturity (20%).

The treat-to-progression approach was selected for the LAURA trial on the basis of results available at the time of the protocol design. Data from adjuvant trials of EGFR-TKIs in *EGFR*-mutated disease showed that Kaplan–Meier curves for disease-free survival converged or declined after the completion of the planned trial treatment for up to 2 years.[31-33] In unresectable stage III *EGFR*-mutated NSCLC, the same effect was observed in the RECEL study, in which the Kaplan–Meier curve for progression-free survival for the group that received erlotinib plus radiotherapy started to decline at approximately 24 months.[28] These data suggest that EGFR-TKIs prolong disease-free or progression-free survival after curative-intent treatment in patients with nonmetastatic *EGFR*-mutated NSCLC; however, patients may benefit from a longer treatment duration or a treatment-to-progression approach to ensure they maintain a disease-free or progression-free state.[31,34] In addition, in patients with unresectable stage III disease treated with chemoradiotherapy alone, progression-free survival rates are poor,[35,36] with studies showing a high incidence of distant metastases, including CNS metastases,[8,9] a finding supportive of the clinical benefit that long-term treatment may provide after curative-intent treatment.

Table 2. Antitumor Activity.*

	Osimertinib (N=143)	Placebo (N=73)
Best objective response — no. (%)		
Complete response	3 (2)	1 (1)
Partial response	79 (55)	23 (32)
Stable disease†	45 (31)	34 (47)
Disease progression	11 (8)	12 (16)
Not evaluable	5 (3)	3 (4)
Objective response rate		
No. of patients with a response	82	24
Percentage of patients with a response (95% CI)‡	57 (49–66)	33 (22–45)
Duration of response — mo		
Median	36.9	6.5
95% CI	30.1–NC	3.6–8.3

* Tumor responses were assessed by blinded independent central review with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. All scans (scheduled and unscheduled) that were reviewed by blinded independent central review were analyzed. NC denotes not calculable.
† Data shown are for patients with disease that had been stable for at least 8 weeks.
‡ Odds ratio, 2.77 (95% CI, 1.54 to 5.08).

The overall safety profile of osimertinib after chemoradiotherapy was consistent with the established profile of osimertinib[19,20] and chemoradiotherapy.[29] Although the median duration of total treatment exposure was longer with osimertinib than placebo (24.0 months vs. 8.3 months), the majority of adverse events reported with osimertinib were mild or moderate in severity and did not lead to treatment discontinuation. Total and actual treatment exposures were similar, suggesting that dose interruptions had minimal effect on treatment exposure. The incidence of fatal adverse events was low in both treatment groups. The most frequently reported adverse event of any cause of grade 3 or higher in both treatment groups was pneumonia, which is typically associated with the disease under study[19,20]; all other events of grade 3 or higher that were reported in more than two patients in the osimertinib group were either a previously known adverse drug reaction (e.g., diarrhea) or an adverse event that was expected in patients previously treated with chemoradiotherapy (e.g., radiation pneumonitis). Overall, the frequency and profile of adverse events of grade 3 or higher with osimertinib was consistent with the findings in previous studies.[19,20]

Table 3. Most Common Adverse Events of Any Cause in >5% of Patients in Either Group.*

Adverse Event	Osimertinib (N=143)					Placebo (N=73)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)									
Any adverse event	140 (98)	16 (11)	74 (52)	42 (29)	5 (3)	64 (88)	23 (32)	32 (44)	6 (8)	1 (1)
Radiation pneumonitis	68 (48)	21 (15)	44 (31)	3 (2)	0	28 (38)	14 (19)	14 (19)	0	0
Diarrhea	51 (36)	45 (31)	3 (2)	3 (2)	0	10 (14)	6 (8)	4 (5)	0	0
Rash	34 (24)	28 (20)	6 (4)	0	0	10 (14)	10 (14)	0	0	0
Coronavirus 2019	29 (20)	4 (3)	24 (17)	1 (1)	0	6 (8)	4 (5)	2 (3)	0	0
Paronychia	24 (17)	16 (11)	8 (6)	0	0	1 (1)	0	1 (1)	0	0
Cough	23 (16)	11 (8)	12 (8)	0	0	7 (10)	5 (7)	2 (3)	0	0
Decreased appetite	21 (15)	11 (8)	9 (6)	1 (1)	0	4 (5)	3 (4)	1 (1)	0	0
Dry skin	18 (13)	15 (10)	2 (1)	1 (1)	0	4 (5)	4 (5)	0	0	0
Pruritus	18 (13)	17 (12)	1 (1)	0	0	5 (7)	5 (7)	0	0	0
Stomatitis	17 (12)	11 (8)	6 (4)	0	0	2 (3)	2 (3)	0	0	0
Decreased white-cell count	17 (12)	6 (4)	10 (7)	1 (1)	0	2 (3)	0	2 (3)	0	0
Pneumonia	16 (11)	3 (2)	9 (6)	3 (2)	0	6 (8)	1 (1)	2 (3)	3 (4)	0
Anemia	14 (10)	6 (4)	7 (5)	1 (1)	0	3 (4)	1 (1)	2 (3)	0	0
Herpes zoster	13 (9)	3 (2)	10 (7)	0	0	2 (3)	1 (1)	1 (1)	0	0
Urinary tract infection	11 (8)	2 (1)	8 (6)	1 (1)	0	2 (3)	1 (1)	1 (1)	0	0
Increased ALT level	10 (7)	7 (5)	2 (1)	1 (1)	0	2 (3)	2 (3)	0	0	0
Arthralgia	10 (7)	5 (3)	4 (3)	1 (1)	0	6 (8)	4 (5)	2 (3)	0	0
Upper respiratory tract infection	10 (7)	3 (2)	7 (5)	0	0	1 (1)	1 (1)	0	0	0
Acneiform dermatitis	9 (6)	9 (6)	0	0	0	2 (3)	2 (3)	0	0	0
Decreased platelet count	8 (6)	7 (5)	1 (1)	0	0	0	0	0	0	0
Dyspnea	8 (6)	7 (5)	1 (1)	0	0	5 (7)	4 (5)	1 (1)	0	0
Increased AST level	8 (6)	7 (5)	1 (1)	0	0	1 (1)	1 (1)	0	0	0
Nasopharyngitis	8 (6)	2 (1)	6 (4)	0	0	0	0	0	0	0
Pneumonitis	8 (6)	2 (1)	4 (3)	1 (1)	0	1 (1)	1 (1)	0	0	0
Sinus tachycardia	8 (6)	3 (2)	5 (3)	0	0	1 (1)	1 (1)	0	0	0
Productive cough	7 (5)	3 (2)	4 (3)	0	0	4 (5)	4 (5)	0	0	0
Musculoskeletal chest pain	5 (3)	3 (2)	2 (1)	0	0	9 (12)	8 (11)	1 (1)	0	0
Myalgia	5 (3)	4 (3)	1 (1)	0	0	6 (8)	6 (8)	0	0	0
Headache	2 (1)	2 (1)	0	0	0	4 (5)	4 (5)	0	0	0

* Safety analyses included all the patients who had undergone randomization and received at least one dose of osimertinib or placebo. Data reported in the table include adverse events with an onset date on or after the date of the first trial dose and up to and including 28 days after the date of the last trial dose and on or before the start of a subsequent anticancer treatment. Patients reporting multiple events for the same preferred term were counted only once for that preferred term. Each patient could have had more than one adverse event. Grade 5 adverse events of any cause occurred in 3 patients (2%) in the osimertinib group (pneumonitis, pneumonia, and a road traffic accident in 1 patient each [1%]) and 2 patients (3%) in the placebo group (myocardial infarction and aortic aneurism rupture in 1 patient each [1%]). ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

Previous reports suggested that EGFR-TKIs plus chemoradiotherapy or radiotherapy may be associated with an increased risk of radiation pneumonitis or pneumonitis.[28,37,38] In our trial, the incidence of radiation pneumonitis was high in both treatment groups (48% with osimertinib and 38% with placebo), although the difference was not clinically significant. With osimertinib, the majority of radiation pneumonitis events were mild to moderate in severity, consistent with previous data for EGFR-TKI plus radiotherapy and with data from the PACIFIC trial,[29,38] and were managed effectively in accordance with the trial guidelines for management of adverse events. The overall incidence of grade 3 radiation pneumonitis was low (2%), and no grade 4 or 5 radiation pneumonitis was reported. Although the incidence of interstitial lung disease was higher with osimertinib than placebo (8% vs. 1%), the majority of events with osimertinib were attributed to pneumonitis and were of grade 1 or 2. Chemoradiotherapy is a risk factor for the development of interstitial lung disease or pneumonitis,[9,39,40] and in our trial, patients with asymptomatic pneumonitis after chemoradiotherapy were eligible for enrollment, which may have contributed to the incidence of pneumonitis observed with osimertinib. Taken together, these results highlight the importance of *EGFR* testing before chemoradiotherapy to ensure that patients receive appropriate treatment.

Additional analyses and follow-up related to the current trial would be of interest, including final overall survival, CNS progression–free survival, safety, health-related quality of life, and exploratory analyses based on circulating tumor DNA. Future research on the efficacy and safety of EGFR-TKIs, either as induction treatment before chemoradiotherapy or concomitantly with chemoradiotherapy, in this disease setting will also be of interest.

In the international phase 3 LAURA trial, treatment with osimertinib after chemoradiotherapy resulted in significantly longer progression-free survival than placebo among patients with unresectable stage III *EGFR*-mutated NSCLC.

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APPENDIX

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