The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2020 VOL. 383 NO. 18

Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

Yi-Long Wu, M.D., Masahiro Tsuboi, M.D., Jie He, M.D., Thomas John, Ph.D., Christian Grohe, M.D., Margarita Majem, M.D., Jonathan W. Goldman, M.D., Konstantin Laktionov, Ph.D., Sang-We Kim, M.D., Ph.D., Terufumi Kato, M.D., Huu-Vinh Vu, M.D., Ph.D., Shun Lu, M.D., Kye-Young Lee, M.D., Ph.D., Charuwan Akewanlop, M.D., Chong-Jen Yu, M.D., Ph.D., Filippo de Marinis, M.D., Laura Bonanno, M.D., Manuel Domine, M.D., Ph.D., Frances A. Shepherd, M.D., Lingmin Zeng, Ph.D., Rachel Hodge, M.Sc., Ajlan Atasoy, M.D., Yuri Rukazenkov, M.D., Ph.D., and Roy S. Herbst, M.D., Ph.D., for the ADAURA Investigators*

ABSTRACT

BACKGROUND

Osimertinib is standard-of-care therapy for previously untreated epidermal growth factor receptor (*EGFR*) mutation–positive advanced non–small-cell lung cancer (NSCLC). The efficacy and safety of osimertinib as adjuvant therapy are unknown.

METHODS

In this double-blind, phase 3 trial, we randomly assigned patients with completely resected *EGFR* mutation–positive NSCLC in a 1:1 ratio to receive either osimertinib (80 mg once daily) or placebo for 3 years. The primary end point was disease-free survival among patients with stage II to IIIA disease (according to investigator assessment). The secondary end points included disease-free survival in the overall population of patients with stage IB to IIIA disease, overall survival, and safety.

RESULTS

A total of 682 patients underwent randomization (339 to the osimertinib group and 343 to the placebo group). At 24 months, 90% of the patients with stage II to IIIA disease in the osimertinib group (95% confidence interval [CI], 84 to 93) and 44% of those in the placebo group (95% CI, 37 to 51) were alive and disease-free (overall hazard ratio for disease recurrence or death, 0.17; 99.06% CI, 0.11 to 0.26; P<0.001). In the overall population, 89% of the patients in the osimertinib group (95% CI, 85 to 92) and 52% of those in the placebo group (95% CI, 46 to 58) were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.20; 99.12% CI, 0.14 to 0.30; P<0.001). At 24 months, 98% of the patients in the osimertinib group (95% CI, 95 to 99) and 85% of those in the placebo group (95% CI, 80 to 89) were alive and did not have central nervous system disease (overall hazard ratio for disease recurrence or death, 0.18; 95% CI, 0.10 to 0.33). Overall survival data were immature; 29 patients died (9 in the osimertinib group and 20 in the placebo group). No new safety concerns were noted.

CONCLUSIONS

In patients with stage IB to IIIA *EGFR* mutation–positive NSCLC, disease-free survival was significantly longer among those who received osimertinib than among those who received placebo. (Funded by AstraZeneca; ADAURA ClinicalTrials.gov number, NCT02511106.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Herbst at the Section of Medical Oncology, Yale School of Medicine and Yale Cancer Center, 333 Cedar St., P.O. Box 208028, New Haven, CT 06520, or at roy.herbst@yale.edu; or to Dr. Wu at the Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, and Guangdong Academy of Medical Sciences, Guangzhou, 510080, China, or at syylwu@live.cn; or to Dr. Tsuboi at the National Cancer Center Hospital East, 6 Chome-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577 Japan, or at mtsuboi@east.ncc.go.jp.

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

Drs. Wu and Tsuboi contributed equally to this article.

This article was published on September 19, 2020, at NEJM.org.

N Engl J Med 2020;383:1711-23.
DOI: 10.1056/NEJMoa2027071

A Quick Take is available at NEJM.org

Approximately 30% of patients with non–small-cell lung cancer (NSCLC) present with resectable disease.[1-3] Postoperative adjuvant cisplatin-based chemotherapy is recommended in patients with completely resected stage II to IIIA disease and — subject to postoperative evaluation to assess benefits and risks — in selected patients with stage IB disease. However, this therapy is associated with only a 16% decrease in the risk of disease recurrence or death; at 5 years, it is associated with a 5% decrease in the risk of death.[4,5] Over a median follow-up of approximately 5 years, the percentage of patients who have disease recurrence or who die after surgery remains high (ranging from 45% among patients with stage IB disease to 76% among those with stage III disease), regardless of the use of postoperative chemotherapy.[5]

Epidermal growth factor receptor (*EGFR*) mutations such as exon 19 deletions (Ex19del) and exon 21 codon p.Leu858Arg (L858R) point mutations are common oncogenic driver mutations in NSCLC.[6,7] EGFR tyrosine kinase inhibitors (EGFR-TKIs) are the recommended first-line treatment for *EGFR* mutation–positive advanced NSCLC.[8-13] The efficacy of EGFR-TKIs in patients with advanced disease led to investigation of their use as an adjuvant treatment for resectable disease. Studies have shown that disease-free survival may be longer among patients with resected *EGFR* mutation–positive NSCLC who receive adjuvant first-generation EGFR-TKIs than among those who receive adjuvant chemotherapy or placebo.[14,15]

Osimertinib, a third-generation oral EGFR-TKI, potently and selectively inhibits both EGFR-TKI sensitizing and *EGFR* p.Thr790Met resistance mutations, with efficacy in NSCLC central nervous system (CNS) metastases.[16-20] In the phase 3 FLAURA trial, osimertinib was superior to gefitinib or erlotinib with respect to progression-free and overall survival. These findings provided support for osimertinib as the standard-of-care therapy for previously untreated *EGFR* mutation–positive (Ex19del or L858R) advanced NSCLC.[18,21] Furthermore, the incidence of adverse events of grade 3 or higher among patients who received osimertinib was similar to that among patients who received gefitinib or erlotinib, despite longer treatment exposure.[18,21] The efficacy and safety profile of osimertinib in patients with *EGFR* mutation–positive NSCLC advanced disease provide support for investigation of this agent as adjuvant treatment for resected disease.

The phase 3, randomized ADAURA trial assessed the efficacy and safety of osimertinib as compared with placebo in patients with completely resected stage IB to IIIA (as classified according to the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer [AJCC]),[22] *EGFR* mutation–positive (Ex19del or L858R) NSCLC, after adjuvant chemotherapy, according to physician and patient choice. After a planned review by the independent data monitoring committee in April 2020, the committee recommended that the trial be unblinded at a trial level 2 years early because of evidence of an efficacy benefit; we report the results of the unplanned interim analysis based on this recommendation.

Methods

Trial Patients

Full details of the trial have been published previously and are provided in the protocol and statistical analysis plan, available with the full text of this article at NEJM.org.[23] The trial design is shown in Figure S1 in the Supplementary Appendix (available at NEJM.org), and eligibility criteria are summarized in the Supplementary Methods section in the Supplementary Appendix. Eligible patients were at least 18 years of age (20 years of age or older in Japan and Taiwan), with a World Health Organization performance status of 0 or 1 (on a scale of 0 to 5, with higher numbers indicating greater disability); primary nonsquamous NSCLC with postsurgical pathological stage IB, II, or IIIA; and a centrally confirmed *EGFR* mutation (Ex19del or L858R, either alone or in combination with other *EGFR* mutations) on examination of tissue. At the time of recruitment, staging was determined according to the seventh edition of the *Cancer Staging Manual* of the AJCC. Complete resection of the primary NSCLC was mandatory. Administration of standard postoperative adjuvant chemotherapy before randomization was allowed but not mandatory; decisions about whether patients would receive adjuvant chemotherapy were made by the physician and the patient and were made before trial enrollment. Treatment with preoperative, postoperative, or planned radiation therapy was not allowed.

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 for Harmonisation), applicable regulatory requirements, and the policy of the trial sponsor, AstraZeneca, on bioethics and human biologic samples. All the patients provided written informed consent.

The trial was funded by the sponsor and was designed by the investigators and the sponsor. The sponsor was responsible for collection and analysis of the data and had a role in data interpretation. The first draft of the manuscript was written by the first, second, and last authors, with medical-writing support funded by the sponsor and conducted in accordance with Good Publication Practice guidelines. All the authors had full access to the data, reviewed the manuscript before it was submitted for publication, and provided input. 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 phase 3, double-blind, placebo-controlled, randomized, international trial, patients were stratified according to disease stage (IB, II, or IIIA), *EGFR* mutational status (Ex19del 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 placebo. Screening and randomization occurred after the patients had undergone surgery and received chemotherapy. Patients received osimertinib or placebo for 3 years or until disease recurrence or fulfillment of a criterion for discontinuation.

TRIAL END POINTS

The primary end point was disease-free survival according to investigator assessment among patients with stage II to IIIA disease. The secondary end points included disease-free survival in the overall population of patients with stage IB to IIIA disease, overall survival, health-related quality of life, and safety. The analysis of quality-of-life data is ongoing, so those results are not reported here. Assessment of the site or sites of recurrence (including the CNS) and the time to CNS disease recurrence or death were prespecified exploratory end points.

TRIAL ASSESSMENTS

Disease-free survival was defined as the time from randomization to disease recurrence (determined by computed tomography or magnetic resonance imaging, pathological disease on biopsy, or both) or death from any cause. Baseline assessments were performed within 28 days before administration of osimertinib or placebo, with follow-up assessments at weeks 12 and 24, then every 24 weeks until 5 years, and yearly thereafter. At disease recurrence, sites of relapse were recorded. The assessment of safety and secondary end points is detailed in the Supplementary Methods section in the Supplementary Appendix.

STATISTICAL ANALYSIS

The full analysis set, which included all the patients who underwent randomization, was used for demographic summaries and efficacy analyses. Safety data were summarized for the patients who received at least one dose of osimertinib or placebo.

Disease-free survival was analyzed with the use of a log-rank test stratified according to disease stage, mutational status, and race. The Breslow approach was used to handle tied events.

For the planned primary analysis, we determined that approximately 247 disease recurrence events or deaths in 490 patients with stage II to IIIA disease (50%) would provide 80% power to detect a hazard ratio of 0.70 at a two-sided alpha level of 5%. To control type I error at the 5% two-sided level, a prespecified hierarchical testing procedure was used; if significance was shown for disease-free survival among patients with stage II to IIIA disease, then disease-free survival would be tested for the overall population (patients with stage IB to IIIA disease). If this result was significant, overall survival would then be tested. The trial was not powered for overall survival.

The independent data monitoring committee met regularly to review safety. After a planned meeting in 2019 to assess futility, but not superiority, when at least 83 disease recurrence events or deaths had occurred in patients with stage II to IIIA disease, the committee requested assessment of efficacy data at the next scheduled meeting for safety (April 2020). On the basis of review of these data, the committee recommended that the trial be unblinded at a trial level early to complete primary reporting. Given these unplanned reviews of efficacy for superiority, the alpha allocation had to be revised to control the overall type I error. Reviews of disease-free survival among patients with stage II to IIIA disease

were conducted when 85 events and 156 events had been observed.

The planned data cutoff date for the primary event-based analysis was February 2022. The data cutoff date for this unplanned interim analysis was January 17, 2020.

RESULTS

PATIENTS AND TREATMENT

From November 2015 to February 2019, a total of 682 patients underwent randomization (339 to receive osimertinib and 343 to receive placebo) (Fig. S2). At the time of unblinding, enrollment was complete, and all the patients had been followed for at least 1 year. Baseline characteristics were balanced between the two groups (Table 1 and Table S1). Most patients with stage II to IIIA disease (76%) and approximately a quarter of the patients with stage IB disease (26%) received adjuvant platinum-based chemotherapy (Table S2).

In the overall population of patients with stage IB to IIIA disease, the median duration of total treatment exposure was 22.5 months (range, 0 to 38) in the osimertinib group and 18.7 months (range, 0 to 36) in the placebo group. The number of patients who discontinued osimertinib or placebo was 92 (27%) and 174 (51%), respectively. In the safety analysis, dose reductions were reported in 49 of 337 patients (15%) in the osimertinib group and in 3 of 343 patients (1%) in the placebo group. At the data cutoff date, 205 of 337 patients (61%) in the osimertinib group and 136 of 343 patients (40%) in the placebo group were continuing the assigned trial regimen.

EFFICACY

Among the 470 patients with stage II to IIIA disease, disease recurrence or death occurred in 156 patients (33% maturity); there were 26 events in the osimertinib group (11% maturity) and 130 events in the placebo group (55% maturity). The median follow-up for disease-free survival was 22.1 months in the osimertinib group and 14.9 months in the placebo group. The percentage of patients who were alive and disease-free at 24 months was 90% (95% confidence interval [CI], 84 to 93) in the osimertinib group and 44% (95% CI, 37 to 51) in the placebo group (overall hazard ratio for disease recurrence or death, 0.17; 99.06% CI, 0.11 to 0.26; P<0.001) (Fig. 1A). This hazard ratio, which was equal to an 83% reduction in the risk of disease recurrence or death, indicated a significantly longer disease-free survival among patients in the osimertinib group than among those in the placebo group. The median disease-free survival was not reached (95% CI, 38.8 to could not be calculated) in the osimertinib group and was 19.6 months (95% CI, 16.6 to 24.5) in the placebo group; Kaplan–Meier event curves showed early separation between the osimertinib and placebo groups.

In the overall population (682 patients), 196 patients (37 of 339 patients [11%] in the osimertinib group and 159 of 343 patients [46%] in the placebo group) had disease recurrence or died (29% maturity). The percentage of patients who were alive and disease-free at 24 months was 89% (95% CI, 85 to 92) in the osimertinib group and 52% (95% CI, 46 to 58) in the placebo group (overall hazard ratio for disease recurrence or death, 0.20; 99.12% CI, 0.14 to 0.30; P<0.001) (Fig. 1B). This hazard ratio, which equaled an 80% reduction in the risk of disease recurrence or death, indicated that disease-free survival was significantly longer among patients in the osimertinib group than among those in the placebo group. The median disease-free survival was not reached (95% CI, could not be calculated to could not be calculated) in the osimertinib group and 27.5 months (95% CI, 22.0 to 35.0) in the placebo group. A total of 24 of 37 patients (65%) in the osimertinib group and 149 of 159 patients (94%) in the placebo group were receiving osimertinib or placebo at disease recurrence; the remaining patients had discontinued the regimen before recurrence or had died.

The benefit favoring osimertinib with respect to disease-free survival was observed consistently across all predefined subgroups (Fig. 2), including disease stages IB, II, and IIIA (Fig. S3) and use or nonuse of adjuvant chemotherapy (Fig. S4). Among the patients with stage IB disease, the percentages of those who were alive and disease-free at 24 months were 88% (95% CI, 78 to 94) in the osimertinib group and 71% (95% CI, 60 to 80) in the placebo group (overall hazard ratio for disease recurrence or death, 0.39; 95% CI, 0.18 to 0.76); among those with stage II disease, these percentages were 91% (95% CI, 82 to 95) and 56% (95% CI, 45 to 65), respectively (overall hazard ratio, 0.17; 95% CI, 0.08 to 0.31); and among those with stage IIIA disease, these percentages were 88% (95% CI, 79 to 94) and 32% (95% CI, 23 to 41), respectively (overall hazard

ratio, 0.12; 95% CI, 0.07 to 0.20). Among the patients who received adjuvant chemotherapy, 89% (95% CI, 83 to 93) in the osimertinib group and 49% (95% CI, 41 to 56) in the placebo group were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.16; 95% CI, 0.10 to 0.26). Among the patients who did not receive adjuvant chemotherapy, 89% (95% CI, 81 to 94) in the osimertinib group and 58% (95% CI, 49 to 67) in the placebo group were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.23; 95% CI, 0.13 to 0.40).

In the overall population, locoregional-only recurrence was observed in 23 of 339 patients (7%) in the osimertinib group and in 61 of 343 patients (18%) in the placebo group (Table S3); 14 of 339 patients (4%) and 96 of 343 patients (28%), respectively, had distant recurrence (either distant only or with locoregional recurrence). Two deaths without disease recurrence occurred in the placebo group.

Recurrence of CNS-related disease or death occurred in 45 patients (6 of 339 patients [2%] in the osimertinib group and 39 of 343 patients [11%] in the placebo group); 4 patients (1%) and 33 patients (10%), respectively, had recurrence in the CNS. At 24 months, 98% of the patients (95% CI, 95 to 99) in the osimertinib group and 85% of the patients (95% CI, 80 to 89) in the placebo group were alive without CNS-related disease (overall hazard ratio for CNS disease recurrence or death, 0.18; 95% CI, 0.10 to 0.33). This hazard ratio indicated an 82% reduction in the risk of CNS disease recurrence or death with osimertinib. The median CNS disease-free survival was not reached (95% CI, 39.0 to could not be calculated) in the osimertinib group and was 48.2 months (95% CI, could not be calculated to could not be calculated) in the placebo group (Fig. 3).

At the data cutoff date, 29 patients in the overall population had died (9 in the osimertinib group and 20 in the placebo group) (see the Supplementary Results section and Fig. S5 in the Supplementary Appendix).

SAFETY

Overall, 680 patients were included in the safety analysis set (337 in the osimertinib group and 343 in the placebo group). Adverse events were reported in 329 patients (98%) in the osimertinib group and in 306 patients (89%) in the placebo group. Commonly reported adverse events (irrespective of causality) are listed in Table 2. Interstitial lung disease (grouped terms) was reported in 10 patients in the osimertinib group (3%) and in none of the patients in the placebo group. Adverse events that were considered by the investigator to be causally related to osimertinib or placebo are presented in Table S4. Adverse events of grade 3 or higher were reported in 68 patients (20%) in the osimertinib group and in 46 patients (13%) in the placebo group (Table S5). Serious adverse events were reported in 54 patients (16%) in the osimertinib group and in 42 patients (12%) in the placebo group (Table S6). No fatal adverse events were reported in the osimertinib group; one event (a pulmonary embolism) occurred in the placebo group. Dose interruptions, dose reductions, and discontinuation of the trial regimen owing to adverse events occurred in 80 (24%), 29 (9%), and 37 (11%) patients in the osimertinib group and in 37 (11%), 3 (1%), and 10 (3%) patients in the placebo group, respectively.

DISCUSSION

In the phase 3, double-blind, randomized international ADAURA trial, patients with resected *EGFR* mutation–positive NSCLC who received osimertinib had significantly longer disease-free survival than those who received placebo. With respect to the primary end point of disease-free survival, among patients with stage II to IIIA disease, 90% of those in the osimertinib group and 44% of those in the placebo group were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.17; 99.06% CI, 0.11 to 0.26; P<0.001). With respect to the key secondary end point of disease-free survival in the overall population of patients with stage IB to IIIA disease, 89% of those in the osimertinib group and 52% of those in the placebo group were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.20; 99.12% CI, 0.14 to 0.30; P<0.001), equating to an 80% reduction in the risk of disease recurrence or death with osimertinib. The disease-free survival benefit with osimertinib was observed consistently across all predefined subgroups, including all disease stages. Among the patients with stage IB disease, the percentages of those who were alive and disease-free at 24 months were 88% in the

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

Characteristic	Osimertinib (N=339)	Placebo (N=343)
Sex — %		
Male	32	28
Female	68	72
Age — yr		
Median	64	62
Range	30–86	31–82
Smoking		
History — %		
Yes	32	25
No	68	75
Status — %		
Former	31	24
Never	68	75
Current	1	1
Pack-yr — mo		
Median	22	18
Range	0–360	0–130
Race — %†		
Asian	64	64
Non-Asian	36	36
WHO performance status — %‡		
0	64	64
1	36	36
AJCC stage — %§		
IB	32	32
II	34	34
IIIA	35	34
Histologic type — %		
Adenocarcinoma	96	97
Acinar adenocarcinoma	25	24
Malignant papillary adenocarcinoma	13	13
Malignant adenocarcinoma	54	55
Bronchioloalveolar adenocarcinoma	3	4
Solid adenocarcinoma with mucus formation	1	1
Non-adenocarcinoma	4	3
Bronchial gland carcinoma (not otherwise specified)	<1	1
Malignant adenosquamous carcinoma	1	1
Other	2	1

Table 1. (Continued.)

Characteristic	Osimertinib (N = 339)	Placebo (N = 343)
Lung cancer resection type — %		
Lobectomy	97	94
Other	<4	6
Sleeve resection	<1	1
Bilobectomy	2	2
Pneumonectomy	1	3
Regional lymph nodes — %		
N0	41	42
N1	29	28
N2	31	30
EGFR mutation type at randomization — (%)¶		
Ex19del	55	55
L858R	45	45
p.Thr790Met	1	1
Adjuvant chemotherapy — (%)		
Yes	60	60
No	40	40

* Percentages may not total 100 because of rounding. *EGFR* denotes epidermal growth factor receptor, Ex19del exon 19 deletion, L858R exon 21 codon p.Leu858Arg, and p.Thr790Met *EGFR* T790M resistance mutation.
† Race was reported by the investigators.
‡ A World Health Organization (WHO) performance status of 0 indicates that the patient is fully active and able to carry out all predisease activities without restrictions, and a WHO performance status 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.
§ Staging was determined according to the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer (AJCC).[22]
¶ *EGFR* mutational status at randomization was centrally tested. Patients may have had more than one *EGFR* mutation.

osimertinib group and 71% in the placebo group (overall hazard ratio for disease recurrence or death, 0.39); among those with stage II disease, these percentages were 91% and 56%, respectively (overall hazard ratio, 0.17); and among those with stage IIIA disease, these percentages were 88% and 32%, respectively (overall hazard ratio, 0.12).

The use of adjuvant chemotherapy according to disease stage before randomization in the ADAURA trial was consistent with the uptake reported in clinical trials and with practice in the community observed in real-world studies across different regions.[24-27] The majority of patients with stage II to IIIA disease and approximately a quarter of patients with stage IB disease received adjuvant chemotherapy; use was balanced across the two groups. The disease-free survival benefit with osimertinib was observed irrespective of whether patients received adjuvant chemotherapy or not. Of patients who received adjuvant chemotherapy, 89% who received osimertinib and 49% who received placebo were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.16); of patients who did not receive adjuvant chemotherapy, these percentages were 89% and 58%, respectively (overall hazard ratio, 0.23).

The percentage of patients with disease recurrence was high in the placebo group, in line with similar historical data in unselected patients and *EGFR* mutation–positive patient popu-

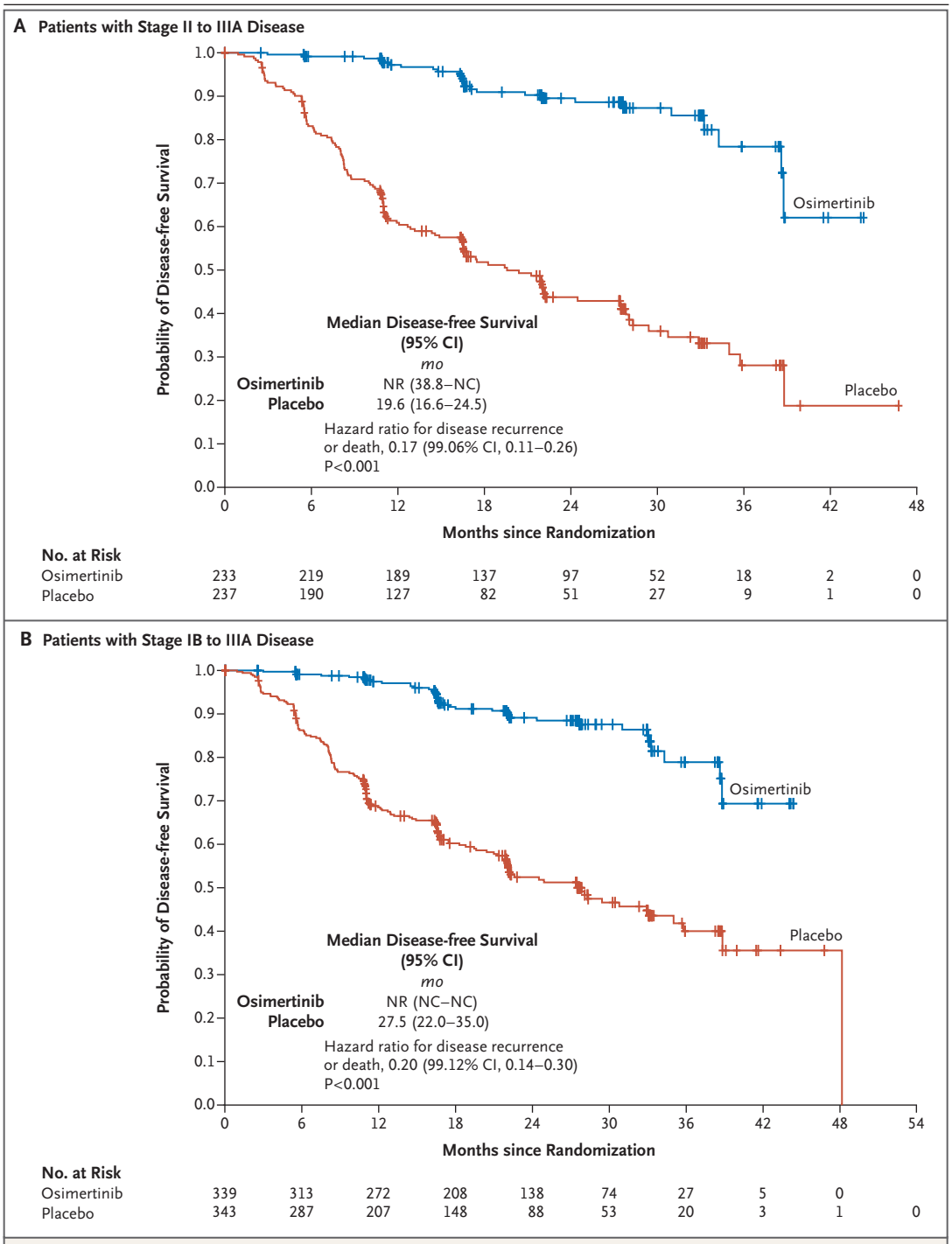

Figure 1. Disease-free Survival, According to Investigator Assessment.

Panel A shows Kaplan–Meier estimates of the duration of disease-free survival among patients with stage II to IIIA disease. At this interim analysis, a two-sided P value of less than 0.0094 was considered to be statistically significant. Panel B shows Kaplan–Meier estimates of the duration of disease-free survival in the overall population of patients with stage IB to IIIA disease. At this interim analysis, a two-sided P value of less than 0.0088 was considered to be statistically significant. Tick marks indicate censored data. CI denotes confidence interval, NC could not be calculated, and NR not reached.

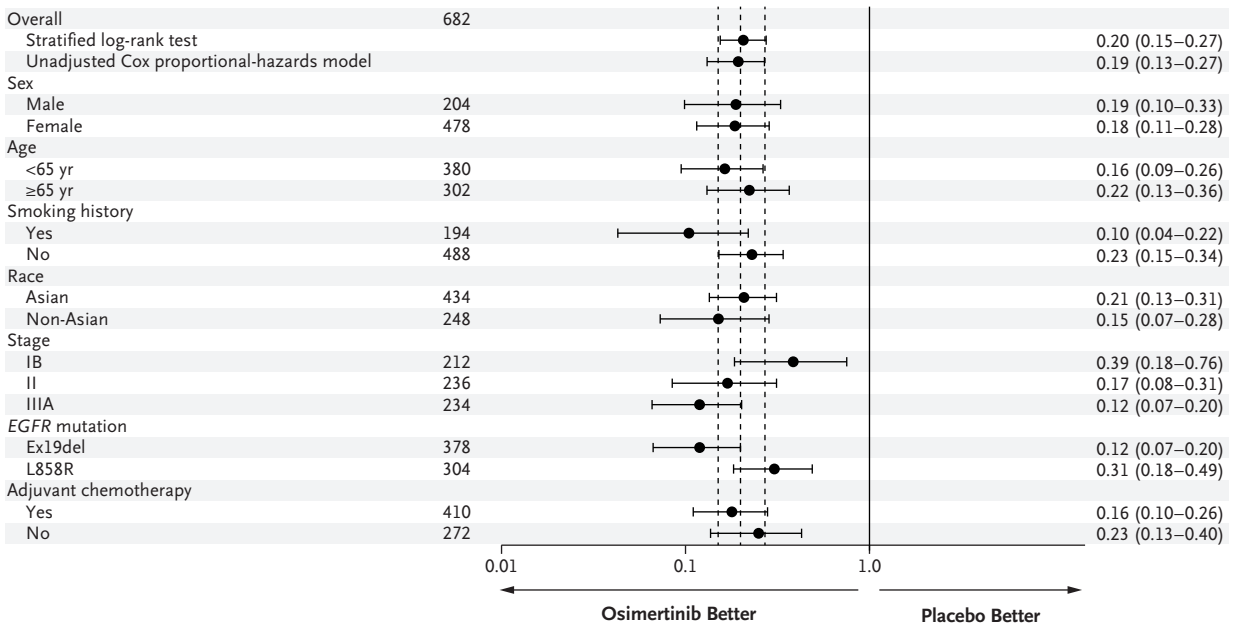

Figure 2. Subgroup Analysis of Disease Recurrence or Death, According to Investigator Assessment.

The subgroup analysis was performed with the use of a Cox proportional-hazards model that included trial regimen, subgroup, and the treatment-by-subgroup interaction term. Subgroup categories with less than 20 events were excluded from the analysis. Race was reported by the patients. The middle vertical dashed line indicates the median and the outer dashed lines indicate the 95% confidence interval for the overall hazard ratio (all patients). A hazard ratio of less than 1 implies a lower risk of disease recurrence or death with osimertinib than with placebo.

lations; these results highlight the need for more effective adjuvant treatment options.[24,28-32] Patients who received osimertinib had fewer locoregional and distant relapses and fewer CNS recurrence events than those who received placebo (1% vs. 10%). The CNS is a common site of metastasis in NSCLC, and this metastasis indicates a poor prognosis.[33] In particular, *EGFR* mutations have been suggested to be a predictor of brain metastases in patients with stage I to III NSCLC.[34] In the ADAURA trial, a clinically meaningful increase in CNS disease-free survival was noted with osimertinib. At 24 months, 98% of the patients who received osimertinib and 85% of those who received placebo were alive without CNS disease (overall hazard ratio for CNS disease recurrence or death, 0.18; 95% CI, 0.10 to 0.33). Thus, adjuvant osimertinib reduced the risk of CNS recurrence among patients with resected *EGFR* mutation–positive NSCLC.

In patients with advanced NSCLC, EGFR-TKIs are well-established therapies, and *EGFR* mutation testing is the standard of care.[8-10] However, these advances have not been successfully applied in patients with resected NSCLCs. Results of the single-group SELECT trial suggested longer disease-free survival with adjuvant erlotinib among patients with *EGFR* mutation–positive stage IA to IIIA disease than among historical genotype-matched controls.[35] In the randomized, placebo-controlled RADIANT trial involving patients with stage IB to IIIA disease, adjuvant erlotinib was associated with longer disease-free survival in a post hoc analysis involving patients with *EGFR* mutation–positive disease, although this result was not significant and 37% of relapses in patients who received erlotinib involved the CNS.[24] The randomized EVAN trial showed longer disease-free survival at 2 years with adjuvant erlotinib than with chemotherapy among patients with *EGFR* mutation–positive stage IIIA disease.[31] The randomized ADJUVANT/CTONG1104 trial involving patients with *EGFR* mutation–positive stage II to IIIA disease showed longer dis-

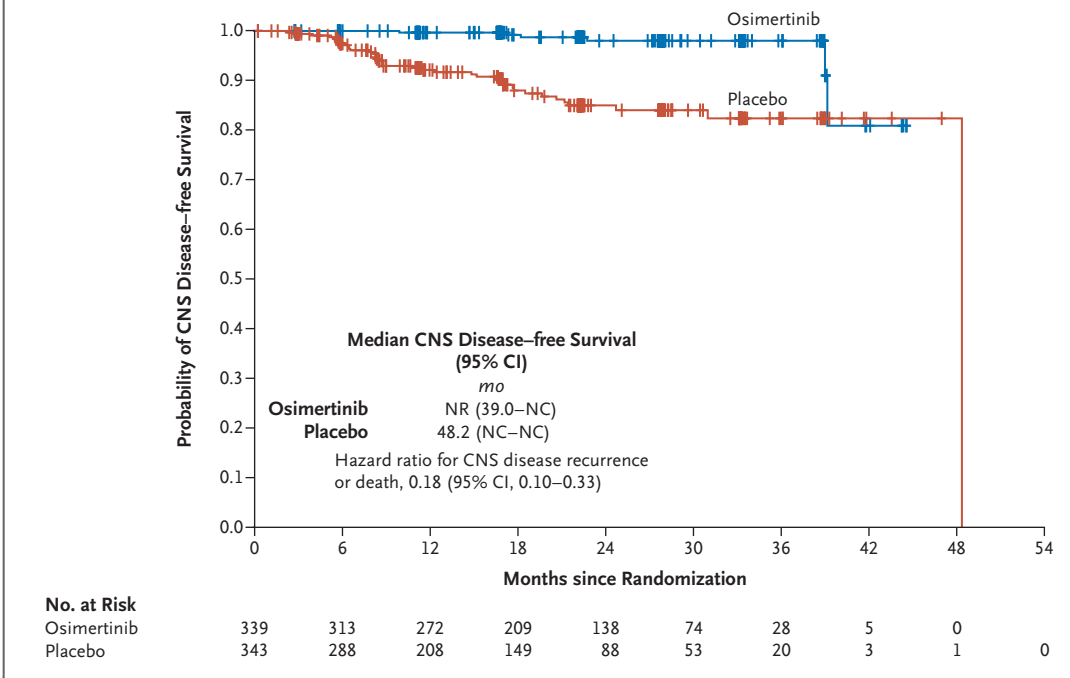

Figure 3. Central Nervous System (CNS) Disease–free Survival, According to Investigator Assessment in the Overall Population.

Shown is the Kaplan–Meier estimate of the duration of CNS disease–free survival in the overall population of patients with stage IB to IIIA disease. Tick marks indicate censored data.

ease-free survival among patients who received adjuvant gefitinib than among those who received chemotherapy (hazard ratio for disease recurrence or death, 0.60; 95% CI, 0.42 to 0.87; P=0.005).[30] However, the disease-free survival advantage did not translate to overall survival,[36] and recurrence in the CNS was common.[37] Although these results suggested a potential role of EGFR-TKIs in patients with resected *EGFR* mutation–positive NSCLC, they did not lead to changes in clinical practice.

The use of a highly potent and selective EGFR-TKI as adjuvant therapy in patients with tumors that may be less heterogeneous and more exclusively driven by *EGFR* mutations than tumors in those with advanced disease is hypothesized to lead to improved treatment outcomes.[16,38,39] Previous preclinical studies and clinical studies involving patients with advanced disease indicated that osimertinib could improve outcomes in patients with resected disease. Osimertinib has been shown to induce apoptosis and to have higher potency against mutant *EGFR* than gefitinib and erlotinib, with a profound and sustained effect in mutant *EGFR* tumor xenograft and transgenic models.[16,40] In addition, osimertinib has been shown to have more clinically significant exposure in the brain than other EGFR-TKIs.[41-43] In patients with advanced disease, first-line osimertinib has been shown to be superior to gefitinib or erlotinib with respect to progression-free and overall survival, with efficacy in CNS metastases, including a 52% reduction in the risk of CNS progression or death.[18,20,21] In our trial, the well-established efficacy of osimertinib that has been observed in patients with advanced disease was observed in patients with resected disease. Unlike previous trials of EGFR-TKIs, the efficacy results showed a substantial reduction in the risk of disease recurrence.

Overall survival results were immature at the time of this interim analysis. The patients and investigators have continued to remain unaware of the trial-group assignments, and follow-up is ongoing in order to report a more mature assessment of overall survival.

A low frequency of dose modifications and discontinuations of osimertinib and no new

Table 2. Adverse Events.*

Adverse Event	Osimertinib (N=337)				Placebo (N=343)			
	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3
	number of patients (percent)							
Diarrhea	156 (46)	116 (34)	32 (9)	8 (2)	68 (20)	54 (16)	13 (4)	1 (<1)
Paronychia	85 (25)	31 (9)	50 (15)	3 (1)	5 (1)	3 (1)	2 (1)	0
Dry skin	79 (23)	75 (22)	3 (1)	1 (<1)	22 (6)	18 (5)	4 (1)	0
Pruritus	65 (19)	49 (15)	16 (5)	0	30 (9)	28 (8)	2 (1)	0
Cough	62 (18)	43 (13)	19 (6)	0	57 (17)	42 (12)	15 (4)	0
Stomatitis	59 (18)	35 (10)	18 (5)	6 (2)	14 (4)	10 (3)	4 (1)	0
Nasopharyngitis	47 (14)	30 (9)	17 (5)	0	35 (10)	25 (7)	10 (3)	0
Upper respiratory tract infection	45 (13)	24 (7)	19 (6)	2 (1)	35 (10)	19 (6)	16 (5)	0
Decreased appetite	44 (13)	29 (9)	13 (4)	2 (1)	13 (4)	9 (3)	4 (1)	0
Mouth ulceration	39 (12)	32 (9)	7 (2)	0	8 (2)	6 (2)	2 (1)	0
Dermatitis acneiform	37 (11)	29 (9)	8 (2)	0	16 (5)	12 (3)	4 (1)	0

* Listed are adverse events that were reported in at least 10% of the patients in either trial group, according to the maximum Common Terminology Criteria for Adverse Events grade and preferred term. The safety analyses included all the patients who received at least one dose of osimertinib or placebo (safety analysis set). None of the adverse events reported in at least 10% of the patients in either trial group were determined to be grade 4 or higher.

safety concerns were reported. All interstitial lung disease (grouped terms) events were mild or moderate in severity and were generally considered to be less clinically severe than those previously observed in patients with advanced disease, and all patients recovered. Furthermore, no notable differences between the trial groups were observed with respect to cardiac adverse events.

Future considerations for the ADAURA trial include subsequent treatment, longitudinal assessment of minimal residual disease, and acquired resistance mechanisms at relapse. The NeoADAURA (ClinicalTrials.gov number, NCT04351555) and LAURA (NCT03521154) trials are under way to investigate the efficacy and safety of neoadjuvant osimertinib in patients with *EGFR* mutation–positive resectable NSCLC and osimertinib after chemoradiation in stage III unresectable *EGFR* mutation–positive NSCLC, respectively.

In our international randomized trial, adjuvant osimertinib was associated with significant improvement in disease-free survival among patients with stage IB to IIIA *EGFR* mutation–positive NSCLC. Osimertinib as adjuvant therapy is an effective new treatment strategy for these patients after complete tumor resection.

Supported by AstraZeneca.

Dr. Wu reports receiving grant support and lecture fees from AstraZeneca, Bristol-Myers Squibb, Pfizer, and Roche and lecture fees from Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, and Sanofi; Dr. Tsuboi, receiving lecture fees from Johnson & Johnson Japan, Teijin Pharma, Taiho Pharma, and Medtronic Japan, grant support, paid to his institution, lecture fees, and advisory board fees from AstraZeneca and Merck Sharp & Dohme, grant support, paid to his institution, and lecture fees from Eli Lilly Japan, Bristol-Myers Squibb, and Ono Pharmaceutical, lecture fees and advisory board fees from Chugai Pharmaceutical, grant support, paid to his institution, from Boehringer Ingelheim Japan, and advisory board fees from Novartis; Dr. John, receiving advisory board fees and travel support from Roche, advisory board fees from Bristol-Myers Squibb, Merck, Ignyta, Takeda, Specialised Therapeutics, Pfizer, Boehringer Ingelheim, and Bayer, and advisory board fees, lecture fees, and travel support from AstraZeneca and Merck Sharp & Dohme; Dr. Grohe, receiving advisory fees and speakers bureau fees from AstraZeneca and Merck Sharp & Dohme and advisory fees, speakers bureau fees, and travel support from Boehringer Ingelheim; Dr. Majem, receiving grant support and advisory board fees from Bristol-Myers Squibb, consulting fees, advisory board fees, lecture fees, and travel support from Merck Sharp & Dohme, advisory board fees, lecture fees, and travel support from Boehringer Ingelheim, AstraZeneca, Roche, and Kyowa Kirin, lecture fees from Pierre Fabre and Bayer, and advisory board fees from Takeda; Dr. Goldman, receiving grant support from AbbVie and Bristol-Myers Squibb, grant support and speakers bureau fees from Merck, and grant support, consulting fees, and advisory board fees from AstraZeneca; Dr. Kato, receiving grant support, advisory board fees, and lecture fees

from AbbVie, Amgen, Eli Lilly, Merck Biopharma, and Pfizer, grant support, advisory board fees, lecture fees, and scientific committee fees from AstraZeneca, Chugai Pharmaceutical, and Merck Sharp & Dohme, grant support and lecture fees from Bristol-Myers Squibb, Novartis, and Taiho Pharmaceutical, grant support, lecture fees, and scientific committee fees from Ono Pharmaceutical, lecture fees from Boehringer Ingelheim, F. Hoffmann–La Roche, and Shionogi, lecture fees and scientific committee fees from Daiichi Sankyo, advisory board fees from Nippon Kayaku, scientific committee fees from Nitto Denko, Sumitomo Dainippon Pharma, and Takeda, and grant support from Astellas, Kyorin Pharmaceutical, Kyowa Kirin, and Regeneron Pharmaceuticals; Dr. Lu, receiving grant support, lecture fees, and consulting fees from AstraZeneca and Roche, grant support from Hutchison MediPharma, Bristol-Myers Squibb, and Heng Rui, lecture fees from Hansoh Pharmaceutical, and consulting fees from Boehringer Ingelheim, Hutchison MediPharma, Simcere Pharmaceutical, Zai Lab, and GenomiCare Biotechnology; Dr. de Marinis, receiving advisory fees from Roche, Bristol-Myers Squibb, and AstraZeneca and consulting fees from Merck Sharp & Dohme; Dr. Domine, receiving lecture fees and advisory board fees from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, and Roche; Dr. Shepherd, receiving advisory board fees and owning stock in AstraZeneca; Dr. Zeng, being employed by and owning stock in AstraZeneca; Ms. Hodge, being employed by and owning stock in AstraZeneca; Dr. Atasoy, being employed by AstraZeneca; Dr. Rukazenkov, being employed by and owning stock in AstraZeneca; and Dr. Herbst, receiving consulting fees from AbbVie, ARMO BioSciences, Biodesix, Genmab, Halozyme Therapeutics, Heat Biologics, Loxo Oncology, Mirati Therapeutics, Nektar, NextCure, Oncternal Therapeutics, Pfizer, Sanofi, Seattle Genetics, Shire, Spectrum Pharmaceuticals, Symphogen, Takeda, Tesaro, Tocagen, and WindMIL Therapeutics, grant support, advisory board fees, and consulting fees from AstraZeneca, advisory board fees from Bolt Biotherapeutics, Bristol-Myers Squibb, Cybrexa Therapeutics, I-Mab Biopharma, Immunocore, Infinity Pharmaceuticals, and Neon Therapeutics, grant support and consulting fees from Eli Lilly, Genentech–Roche, and Merck, data and safety monitoring committee fees from EMD Serono and Novartis, and board member fees from Junshi Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

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 and their families; all the trial site coordinators; Dakshayini Kulkarni, Ph.D., and Gianluca Laus, M.D., of the AstraZeneca ADAURA trial team for their contributions to the data analysis and study monitoring or oversight, respectively; the ADAURA independent data monitoring committee; and Natasha Learmond, B.Sc., of iMed Comms (an Ashfield Company, part of UDG Healthcare) for medical-writing support.

APPENDIX

The authors' affiliations are as follows: the Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, and Guangdong Academy of Medical Sciences, Guangzhou (Y.-L.W.), the Thoracic Surgery Department, National Cancer Center–National Clinical Research Center for Cancer–Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing (J.H.), and the Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai (S.L.) — all in China; the Department of Thoracic Surgery and Oncology, National Cancer Center Hospital East, Kashiwa (M.T.), and the Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama (T.K.) — both in Japan; the Department of Medical Oncology, Austin Health, Melbourne, VIC, Australia (T.J.); the Department of Respiratory Diseases, Evangelische Lungenklinik, Berlin (C.G.); the Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona (M.M.), and the Department of Oncology, Hospital Universitario Fundación Jiménez Díaz, Madrid (M.D.); the David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles (J.W.G.); the Center of Innovative Technologies and Oncology, N.N. Blokhin Russian Cancer Center, Russian Academy of Medical Sciences, Moscow (K.L.); the Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine (S.-W.K.), and the Precision Medicine Lung Cancer Center, Konkuk University Medical Center (K.-Y.L.) — both in Seoul, South Korea; the Department of Thoracic Surgery, Cho Ray Hospital, Ho Chi Minh City, Vietnam (H.-V.V.); the Division of Medical Oncology, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand (C.A.); the Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan (C.-J.Y.); the Division of Thoracic Oncology, European Institute of Oncology, IRCCS, Milan (F.M.), and Medical Oncology 2, Istituto Oncologico Veneto, IRCCS, Padua (L.B.) — both in Italy; the Department of Medical Oncology and Hematology, University Health Network, Princess Margaret Cancer Centre and the University of Toronto, Toronto (F.A.S.); Late Oncology Statistics, AstraZeneca, Gaithersburg, MD (L.Z.); Late Oncology Statistics (R.H.) and Oncology Research and Development (A.A., Y.R.), AstraZeneca, Cambridge, United Kingdom; and Section of Medical Oncology, Yale School of Medicine and Yale Cancer Center, New Haven, CT (R.S.H.).

REFERENCES

1. Datta D, Lahiri B. Preoperative evaluation of patients undergoing lung resection surgery. Chest 2003;123:2096-103.
2. Cagle PT, Allen TC, Olsen RJ. Lung cancer biomarkers: present status and future developments. Arch Pathol Lab Med 2013;137:1191-8.
3. Le Chevalier T. Adjuvant chemotherapy for resectable non-small-cell lung cancer: where is it going? Ann Oncol 2010;21: Suppl 7:vii196-vii198.
4. Kris MG, Gaspar LE, Chaft JE, et al. Adjuvant systemic therapy and adjuvant radiation therapy for stage I to IIIA completely resected non-small-cell lung cancers: American Society of Clinical Oncology/Cancer Care Ontario clinical practice guideline update. J Clin Oncol 2017;35: 2960-74.
5. Pignon J-P, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.
6. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer 2007;7:169-81.
7. Sholl LM, Aisner DL, Varella-Garcia M, et al. Multi-institutional oncogenic driver mutation analysis in lung adenocarcinoma: the Lung Cancer Mutation Consortium experience. J Thorac Oncol 2015;10:768-77.
8. 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.
9. 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.
10. 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.
11. 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.
12. Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
13. Sequist LV, Yang JC-H, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
14. Cheng H, Li X-J, Wang X-J, et al. A meta-analysis of adjuvant EGFR-TKIs for patients with resected non-small cell lung cancer. Lung Cancer 2019;137:7-13.
15. Huang Q, Li J, Sun Y, Wang R, Cheng X, Chen H. Efficacy of EGFR tyrosine kinase inhibitors in the adjuvant treatment for operable non-small cell lung cancer by a meta-analysis. Chest 2016;149:1384-92.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. AJCC cancer staging manual. 7th ed. New York: Springer, 2010.
23. Wu Y-L, Herbst RS, Mann H, Rukazenkov Y, Marotti M, Tsuboi M. ADAURA: phase III, double-blind, randomized study of osimertinib versus placebo in EGFR mutation-positive early-stage NSCLC after complete surgical resection. Clin Lung Cancer 2018;19(4):e533-e536.
24. Kelly K, Altorki NK, Eberhardt WEE, et al. Adjuvant erlotinib versus placebo in patients with stage IB-IIIA non-small-cell lung cancer (RADIANT): a randomized, double-blind, phase III trial. J Clin Oncol 2015;33:4007-14.
25. Chouaid C, Danson S, Andreas S, et al. Adjuvant treatment patterns and outcomes in patients with stage IB-IIIA non-small cell lung cancer in France, Germany, and the United Kingdom based on the LuCaBIS burden of illness study. Lung Cancer 2018;124:310-6.
26. Buck PO, Saverno KR, Miller PJE, Arondekar B, Walker MS. Treatment patterns and health resource utilization among patients diagnosed with early stage resected non-small cell lung cancer at US community oncology practices. Clin Lung Cancer 2015;16:486-95.
27. Vansteenkiste JF, Cho BC, Vanakesa T, et al. Efficacy of the MAGE-A3 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small-cell lung cancer (MAGRIT): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2016; 17:822-35.
28. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719-27.
29. Kenmotsu H, Yamamoto N, Yamanaka T, et al. Randomized phase III study of pemetrexed plus cisplatin versus vinorelbine plus cisplatin for completely resected stage II to IIIA nonsquamous non-small-cell lung cancer. J Clin Oncol 2020;38: 2187-96.
30. Zhong WZ, Wang Q, Mao W-M, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncol 2018;19:139-48.
31. Yue D, Xu S, Wang Q, et al. Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIA EGFR mutation-positive non-small-cell lung cancer (EVAN): a randomised, open-label, phase 2 trial. Lancet Respir Med 2018;6:863-73.
32. Li N, Ou W, Ye X, et al. Pemetrexed-carboplatin adjuvant chemotherapy with or without gefitinib in resected stage IIIA-N2 non-small cell lung cancer harbouring EGFR mutations: a randomized, phase II study. Ann Surg Oncol 2014;21:2091-6.
33. 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.
34. Chang W-Y, Wu Y-L, Su P-L, Yang S-C, Lin C-C, Su W-C. The impact of EGFR mutations on the incidence and survival of stages I to III NSCLC patients with subsequent brain metastasis. PLoS One 2018; 13(2):e0192161.
35. Pennell NA, Neal JW, Chaft JE, et al. SELECT: a phase II trial of adjuvant erlotinib in patients with resected epidermal growth factor receptor-mutant non–small-cell lung cancer. J Clin Oncol 2019;37:97-104.
36. Wu Y-L, Zhong W, Wang Q, et al. CTONG1104: adjuvant gefitinib versus chemotherapy for resected N1-N2 NSCLC with EGFR mutation — final overall survival analysis of the randomized phase III trial 1 analysis of the randomized phase III trial. J Clin Oncol 2020;38:9005. abstract.
37. Xu S-T, Xi J-J, Zhong W-Z, et al. The unique spatial-temporal treatment failure patterns of adjuvant gefitinib therapy: a post hoc analysis of the ADJUVANT trial (CTONG 1104). J Thorac Oncol 2019;14: 503-12.
38. Oh BY, Shin H-T, Yun JW, et al. Intratumor heterogeneity inferred from targeted deep sequencing as a prognostic indicator. Sci Rep 2019;9:4542.
39. Wang Z, Cheng Y, An T, et al. Detection of EGFR mutations in plasma circulating tumour DNA as a selection criterion for first-line gefitinib treatment in patients with advanced lung adenocarcinoma (BENEFIT): a phase 2, single-arm, multicentre clinical trial. Lancet Respir Med 2018;6:681-90.
40. Shi P, Zhang S, Zhu L, et al. The third-generation EGFR inhibitor, osimertinib, promotes c-FLIP degradation, enhancing apoptosis including TRAIL-induced apoptosis in NSCLC cells with activating EGFR mutations. Transl Oncol 2019;12:705-13.
41. Ballard P, Yates JWT, Yang Z, et al. Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. Clin Cancer Res 2016;22:5130-40.
42. Vishwanathan K, Varrone A, Varnas K, et al. Osimertinib displays high brain exposure in healthy subjects with intact blood-brain barrier: a microdose positron emission tomography (PET) study with ^{11}C-labelled osimertinib. Cancer Res 2018;78:Suppl:CT013. abstract.
43. Colclough N, Ballard PG, Barton P, et al. Preclinical comparison of the blood brain barrier (BBB) permeability of osimertinib (AZD9291) with other irreversible next generation EGFR TKIs. Eur J Cancer 2016;69:Suppl 28:OF1-OF11.