The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 11, 2024 VOL. 390 NO. 14

Alectinib in Resected *ALK*-Positive Non–Small-Cell Lung Cancer

Yi-Long Wu, M.D., Rafal Dziadziuszko, M.D., Ph.D., Jin Seok Ahn, M.D., Ph.D., Fabrice Barlesi, M.D., Ph.D., Makoto Nishio, M.D., Ph.D., Dae Ho Lee, M.D., Ph.D., Jong-Seok Lee, M.D., Ph.D., Wenzhao Zhong, M.D., Ph.D., Hidehito Horinouchi, M.D., Ph.D., Weimin Mao, M.D., Ph.D., Maximilian Hochmair, M.D., Filippo de Marinis, M.D., M. Rita Migliorino, M.D., Igor Bondarenko, M.D., Ph.D., Shun Lu, M.D., Qun Wang, M.D., Tania Ochi Lohmann, Ph.D., Tingting Xu, M.D., Andres Cardona, M.Sc., Thorsten Ruf, M.D., Johannes Noe, Ph.D., and Benjamin J. Solomon, M.B., B.S., Ph.D., for the ALINA Investigators*

ABSTRACT

BACKGROUND

Platinum-based chemotherapy is the recommended adjuvant treatment for patients with resectable, *ALK*-positive non–small-cell lung cancer (NSCLC). Data on the efficacy and safety of adjuvant alectinib as compared with chemotherapy in patients with resected *ALK*-positive NSCLC are lacking.

METHODS

We conducted a global, phase 3, open-label, randomized trial in which patients with completely resected, *ALK*-positive NSCLC of stage IB (tumors ≥4 cm), II, or IIIA (as classified according to the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer and Union for International Cancer Control) were randomly assigned in a 1:1 ratio to receive oral alectinib (600 mg twice daily) for 24 months or intravenous platinum-based chemotherapy in four 21-day cycles. The primary end point was disease-free survival, tested hierarchically among patients with stage II or IIIA disease and then in the intention-to-treat population. Other end points included central nervous system (CNS) disease–free survival, overall survival, and safety.

RESULTS

In total, 257 patients were randomly assigned to receive alectinib (130 patients) or chemotherapy (127 patients). The percentage of patients alive and disease-free at 2 years was 93.8% in the alectinib group and 63.0% in the chemotherapy group among patients with stage II or IIIA disease (hazard ratio for disease recurrence or death, 0.24; 95% confidence interval [CI], 0.13 to 0.45; P<0.001) and 93.6% and 63.7%, respectively, in the intention-to-treat population (hazard ratio, 0.24; 95% CI, 0.13 to 0.43; P<0.001). Alectinib was associated with a clinically meaningful benefit with respect to CNS disease–free survival as compared with chemotherapy (hazard ratio for CNS disease recurrence or death, 0.22; 95% CI, 0.08 to 0.58). Data for overall survival were immature. No unexpected safety findings were observed.

CONCLUSIONS

Among patients with resected *ALK*-positive NSCLC of stage IB, II, or IIIA, adjuvant alectinib significantly improved disease-free survival as compared with platinum-based chemotherapy. (Funded by F. Hoffmann–La Roche; ALINA ClinicalTrials.gov number, NCT03456076.)

The authors' affiliations are listed in the Appendix. Dr. Wu can be contacted at wuyilong@gdph.org.cn or at the Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, 106 Zhongshan Er Lu, 510080 Guangzhou, China. Dr. Solomon can be contacted at ben.solomon@petermac.org or at the Department of Medical Oncology, Peter MacCallum Cancer Centre, 305 Grattan St., Melbourne, VIC 3000, Australia.

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

N Engl J Med 2024;390:1265-76.
DOI: 10.1056/NEJMoa2310532

CME

A Quick Take is available at NEJM.org

Approximately 50% of patients with non–small-cell lung cancer (NSCLC) receive a diagnosis with early-stage or locally advanced disease (stage I, II, or III).[1] For patients with resectable disease, the primary treatment is surgery, with adjuvant or neoadjuvant treatment where recommended.[2-4] Although the treatment landscape for early-stage NSCLC is rapidly evolving with the approval of cancer immunotherapy and targeted therapy regimens,[5-7] adjuvant targeted therapy in patients with resectable NSCLC harboring a rearrangement in the anaplastic lymphoma kinase (*ALK*) gene (*ALK*-positive NSCLC) warrants evaluation.[8]

Approximately 4 to 5% of patients with NSCLC have *ALK*-positive disease.[9-11] Patients with *ALK*-positive NSCLC are more likely to be younger, be nonsmokers, and receive a diagnosis with more advanced disease than those with *ALK*-negative NSCLC.[10,12,13] They are also at high risk for brain metastases, which are seen in up to 50 to 60% of patients.[14,15] Despite recent approvals for the treatment of resectable NSCLC, immunotherapy is generally not recommended in patients with *ALK*-positive disease because no clinical evidence has emerged that immunotherapy is beneficial in NSCLC with oncogenic driver alterations.[2-4,16-18]

The current recommended adjuvant treatment for patients with resected *ALK*-positive NSCLC is platinum-based combination chemotherapy.[2-4,19] However, adjuvant chemotherapy is associated with only modest improvements in patient outcomes (difference in survival as compared with observation, approximately 5 percentage points).[20] The risk of disease recurrence remains high (with the 5-year risk of recurrence or death ranging from 45% for stage IB disease to 76% for stage III disease),[20] and most cases of recurrence have metastatic spread.[21-26] Five-year survival ranges from 71% for stage IB disease to just 36% for stage IIIA disease.[27] Adjuvant chemotherapy is also associated with a high risk of adverse events,[28] with one meta-analysis showing that 66% of patients had grade 3 or 4 adverse events after treatment with adjuvant cisplatin-based chemotherapy.[20]

Targeted therapies that have shown efficacy and become established in the treatment of advanced oncogene-dependent NSCLC have the potential to improve outcomes in patients with resectable disease. In the phase 3 ADAURA trial, adjuvant osimertinib showed a significant benefit with respect to disease-free survival as compared with placebo among patients with epidermal growth factor receptor (*EGFR*) mutation–positive NSCLC of stage IB, II, or IIIA.[7] Recent data indicate that this large disease-free survival benefit can translate into an overall survival benefit.[29]

Alectinib is a potent oral ALK tyrosine kinase inhibitor (TKI) that has shown high levels of efficacy across three phase 3 trials involving patients with advanced *ALK*-positive NSCLC.[30-32] In the global phase 3 ALEX trial, patients with previously untreated advanced *ALK*-positive NSCLC who received alectinib had significantly longer progression-free survival than those who received crizotinib,[31] with improved 5-year overall survival.[33] Alectinib has also shown substantial activity in patients with central nervous system (CNS) disease.[15,34,35] Long-term treatment with alectinib has a safety profile that reflects mainly low-grade adverse events.[36] On the basis of these results, alectinib is a preferred first-line treatment in patients with advanced *ALK*-positive NSCLC.[2,4] These data in advanced NSCLC support investigation of alectinib in resected *ALK*-positive NSCLC to determine whether it can reduce the risk of disease recurrence, improve outcomes after surgery, and reduce the incidence of recurrence in the CNS.

We report results from the primary analysis of the randomized, open-label, phase 3 ALINA trial, which is investigating the efficacy and safety of adjuvant alectinib as compared with standard chemotherapy in patients with resected *ALK*-positive NSCLC. Follow-up is ongoing.

METHODS

TRIAL PATIENTS

Eligible patients were 18 years of age or older and had completely resected, histologically confirmed stage IB (tumors ≥4 cm), II, or IIIA NSCLC (as classified according to the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer and Union for International Cancer Control) and documented *ALK*-positive disease by a Food and Drug Administration–approved or European Conformity (CE)–marked test, either locally or centrally performed. Other criteria included eligibility for platinum-based chemo-

therapy, an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale in which higher scores reflect greater disability), and no previous systemic anticancer therapy. Full eligibility criteria are detailed in the trial protocol, available with the full text of this article at NEJM.org.

TRIAL DESIGN AND TREATMENT

ALINA is a global, phase 3, open-label, randomized trial (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Screening and randomization occurred 4 to 12 weeks after patients had undergone complete surgical resection (lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy). Eligible patients were randomly assigned in a 1:1 ratio to receive either oral alectinib at a dose of 600 mg twice daily or intravenous platinum-based chemotherapy in four 21-day cycles. Randomization was stratified according to disease stage (IB [≥4 cm] vs. II vs. IIIA) and race (Asian vs. non-Asian). Treatment with alectinib was given for 24 months or until the occurrence of disease recurrence, unacceptable toxic effects, or withdrawal of consent, whichever occurred first. Chemotherapy options were cisplatin at a dose of 75 mg per square meter of body-surface area on day 1 of each cycle, plus vinorelbine at a dose of 25 mg per square meter (on days 1 and 8), gemcitabine at a dose of 1250 mg per square meter (on days 1 and 8), or pemetrexed at a dose of 500 mg per square meter (on day 1), according to local prescribing information. In the event of cisplatin intolerance, carboplatin at an area under the curve of 5 or 6 mg per milliliter per minute was administered. A formal crossover design was not built into this trial. Subsequent treatment after disease recurrence was entirely at the discretion of the investigators.

TRIAL OVERSIGHT

The trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. An independent data monitoring committee evaluated data regularly during the trial. The protocol and subsequent amendments were approved by the institutional review board or ethics committee at each site. All the patients provided written informed consent.

F. Hoffmann–La Roche/Genentech sponsored the trial, provided the trial drugs, and collaborated with the academic authors on the collection, analysis, and interpretation of the data. All the authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol. Medical writing assistance, under the direction of the authors, was funded by F. Hoffmann–La Roche.

END POINTS AND ASSESSMENTS

The primary end point was disease-free survival, defined as the time from randomization to the first documented recurrence of disease or new primary NSCLC as determined by the investigator or to death from any cause. Secondary end points included overall survival and safety. Exploratory end points included CNS disease–free survival, defined as the time from randomization to the first documented recurrence of disease in the CNS or death from any cause.

Disease assessments were conducted at baseline and every 12 weeks for the first 2 years, every 24 weeks for years 3 through 5, and then annually until the occurrence of disease recurrence, death, loss to follow-up, withdrawal of consent, or trial termination by the sponsor, whichever occurred first. All disease assessments included magnetic resonance imaging (MRI) of the brain (or computed tomography of the brain if MRI was unavailable). The adverse-event reporting period lasted until 28 days after the last alectinib dose or chemotherapy cycle.

STATISTICAL ANALYSIS

Efficacy was assessed in the intention-to-treat population, defined as all the patients who underwent randomization, and in the subgroup of patients with stage II or IIIA NSCLC. The safety-evaluable population was defined as all the patients who underwent randomization and received any amount of trial drug.

Kaplan–Meier methods were used to estimate median disease-free survival and 2- and 3-year disease-free survival. Brookmeyer–Crowley methods and Greenwood's formula were used to construct 95% confidence intervals for medians and landmark rates, respectively. A stratified log-rank test was used to compare disease-free survival between treatment groups. To control the overall level of significance at a two-sided error rate of

0.05, disease-free survival was tested with the use of a prespecified hierarchical approach, first among patients with stage II or IIIA disease and then in the intention-to-treat population. Hazard ratios among patients with stage II or IIIA disease were estimated with the use of a stratified Cox regression model with race (Asian vs. non-Asian) as a stratification factor. For the intention-to-treat population, disease stage (IB [≥4 cm] vs. II vs. IIIA) was also a stratification factor.

The trial was designed to show superiority of alectinib as compared with chemotherapy with respect to disease-free survival, with 80% power to detect a target hazard ratio of 0.55 among patients with stage II or IIIA disease and 0.58 in the intention-to-treat population. This preplanned interim analysis was conducted when 67% of events (59 events) were observed among patients with stage II or IIIA disease.

Here we report the results of the preplanned interim analysis, conducted by an independent data monitoring committee. Additional statistical methods are provided in the Supplementary Appendix, and the statistical analysis plan is available with the protocol at NEJM.org.

RESULTS

PATIENTS AND TREATMENT

In total, 257 patients were enrolled from August 2018 through December 2021 at 113 sites across 26 countries: 130 patients received alectinib and 127 patients received chemotherapy (Fig. S2 and Table S1). The median time from surgery to randomization was 1.7 months. At the data-cutoff date (June 26, 2023), 20.3% of the patients in the alectinib group were receiving treatment.

The demographic and clinical characteristics of the patients at baseline were generally well balanced between the treatment groups (Table 1) and were broadly similar to the available demographic data in patients with *ALK*-positive NSCLC (Table S2); however, Black patients were underrepresented in the trial population. As compared with the chemotherapy group, the alectinib group had a higher percentage of female patients (57.7% vs. 46.5%) and patients who had never smoked (64.6% vs. 55.1%). No patients in the trial received neoadjuvant radiotherapy or postoperative radiotherapy.

EFFICACY

The median duration of follow-up for survival was 27.8 months (27.8 months in the alectinib group and 28.4 months in the chemotherapy group). At the data-cutoff date, approximately 18 months had passed since the last patient had undergone randomization.

A total of 231 patients had stage II or IIIA disease: 116 in the alectinib group and 115 in the chemotherapy group. Of these, 59 patients had disease recurrence or had died by the data-cutoff date: 14 in the alectinib group and 45 in the chemotherapy group. The disease-free survival among patients with stage II or IIIA disease at 2 years was 93.8% in the alectinib group and 63.0% in the chemotherapy group; the values at 3 years were 88.3% and 53.3%, respectively. The hazard ratio for disease recurrence or death was 0.24 (95% confidence interval [CI], 0.13 to 0.45; P<0.001), which corresponds to a 76% lower risk with adjuvant alectinib than with chemotherapy. Kaplan–Meier curves for disease-free survival show early and sustained separation between the alectinib group and the chemotherapy group (Fig. 1A).

The intention-to-treat population included 257 patients: 130 in the alectinib group and 127 in the chemotherapy group. Of these, 65 patients had disease recurrence or death: 15 in the alectinib group and 50 in the chemotherapy group. The disease-free survival in the intention-to-treat population at 2 years was 93.6% in the alectinib group and 63.7% in the chemotherapy group; the values at 3 years were 88.7% and 54.0%, respectively. The hazard ratio for disease recurrence or death in the alectinib group as compared with the chemotherapy group in the intention-to-treat population was 0.24 (95% CI, 0.13 to 0.43; P<0.001) (Fig. 1B).

The disease-free survival benefit from adjuvant alectinib as compared with chemotherapy was generally consistent across all subgroups (Fig. 2). This consistency was seen in subgroups defined according to disease stage (Fig. S3), race, sex, and smoking status.

Disease recurrence was observed in 15 patients (11.5%) in the alectinib group and 49 (38.6%) in the chemotherapy group. The most common site of recurrence was the brain, reported in 4 patients in the alectinib group and 14 in the chemotherapy group (Table S3). The hazard ratio for

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Alectinib (N=130)	Chemotherapy (N=127)
Age		
Median — yr	54	57
Distribution — no. (%)		
<65 yr	103 (79.2)	93 (73.2)
≥65 yr	27 (20.8)	34 (26.8)
Sex — no. (%)		
Female	75 (57.7)	59 (46.5)
Male	55 (42.3)	68 (53.5)
Race — no. (%)†		
Asian	72 (55.4)	71 (55.9)
Black	1 (0.8)	0
White	55 (42.3)	52 (40.9)
Unknown	2 (1.5)	4 (3.1)
ECOG performance-status score — no. (%)‡		
0	72 (55.4)	65 (51.2)
1	58 (44.6)	62 (48.8)
Smoking status — no. (%)		
Never smoked	84 (64.6)	70 (55.1)
Previous smoker	41 (31.5)	54 (42.5)
Current smoker	5 (3.8)	3 (2.4)
Disease stage at initial diagnosis — no. (%)§		
IB	14 (10.8)	12 (9.4)
II	47 (36.2)	45 (35.4)
IIIA	69 (53.1)	70 (55.1)
Regional lymph-node stage — no. (%)		
N0	21 (16.2)	18 (14.2)
N1	45 (34.6)	43 (33.9)
N2	64 (49.2)	66 (52.0)
Nodal assessment — no. (%)		
MLND	108 (83.1)	105 (82.7)
Lymph-node sampling	19 (14.6)	15 (11.8)
MLND and lymph-node sampling not performed¶	3 (2.3)	7 (5.5)
Histologic type — no. (%)		
Squamous	6 (4.6)	3 (2.4)
Nonsquamous	124 (95.4)	124 (97.6)
Surgical procedure for lung cancer — no. (%)		
Lobectomy	126 (96.9)	117 (92.1)
Sleeve lobectomy	0	1 (0.8)
Bilobectomy	2 (1.5)	5 (3.9)
Pneumonectomy	2 (1.5)	4 (3.1)

* The intention-to-treat population includes all the patients who underwent randomization. Percentages may not total 100 because of rounding. MLND denotes mediastinal lymph-node dissection.
† Race was reported by the patient.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
§ Disease staging was based on the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer and Union for International Cancer Control.
¶ An exception was granted for patients who had documented N2 disease in one nodal station or who had negative preoperative staging imaging (computed tomography and positron-emission tomography) in the mediastinum.

CNS disease recurrence or death was 0.22 (95% CI, 0.08 to 0.58) in favor of alectinib (Fig. 3). After disease recurrence, at least one subsequent treatment was given to 13 patients in the alectinib group and 43 patients in the chemotherapy group (Table S4), most frequently alectinib (4 patients and 29 patients, respectively).

At the data-cutoff date, data for overall survival were immature, with a 2.3% event–patient ratio; six events (deaths) were included in the analysis of overall survival: two in the alectinib group and four in the chemotherapy group. An additional patient in the chemotherapy group died, but data for this patient were censored owing to incomplete date of death recorded.

SAFETY

The safety-evaluable population included 128 patients who received alectinib and 120 patients who received chemotherapy. The median duration of treatment for the safety-evaluable population was 23.9 months with alectinib and 2.1 months

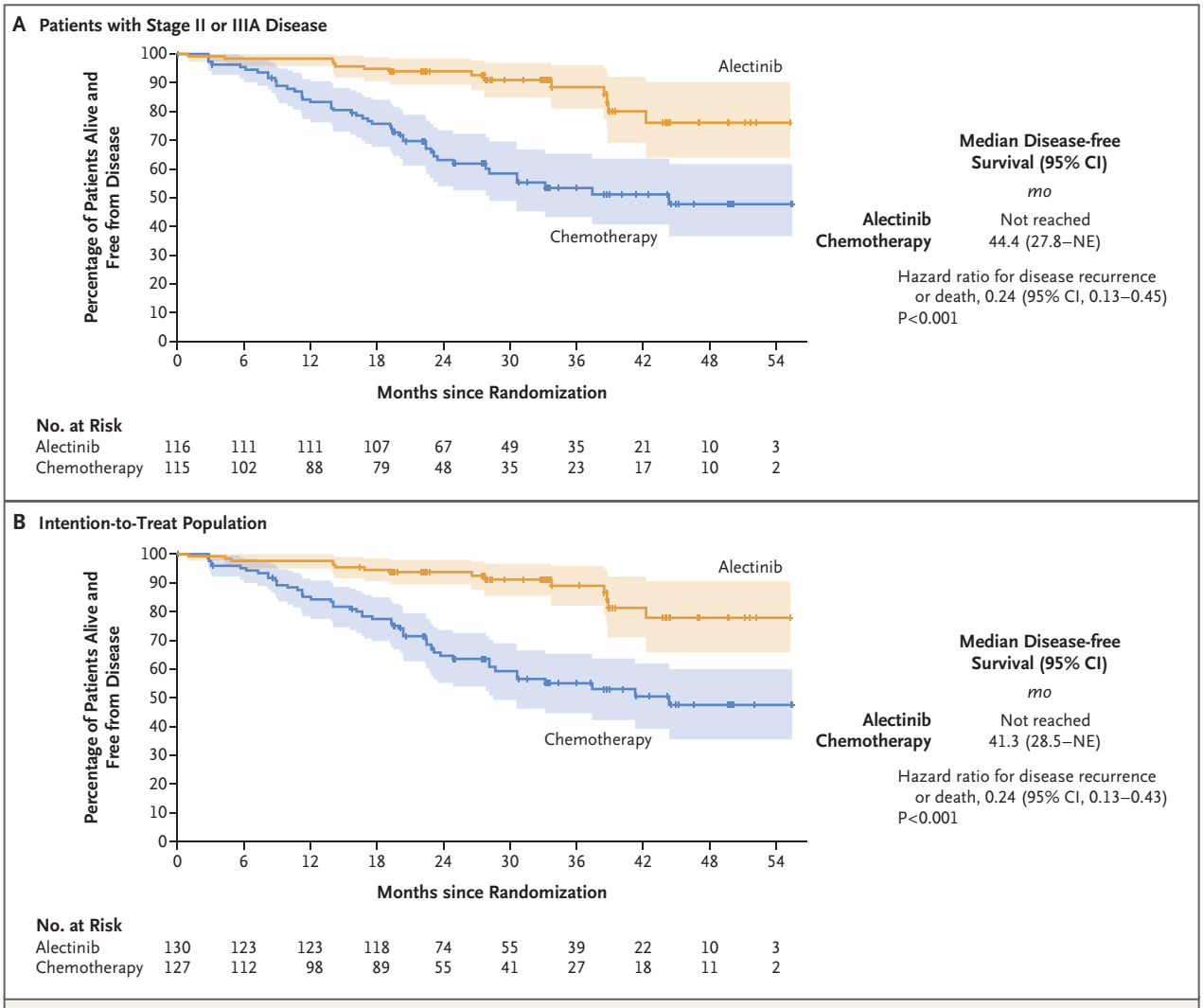

Figure 1. Disease-free Survival among Patients with Stage II or IIIA Disease and in the Intention-to-Treat Population.

The intention-to-treat population included patients with stage IB, II, or IIIA disease who had undergone randomization. Disease staging was based on the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer and Union for International Cancer Control (AJCC–UICC). The widths of the confidence intervals (indicated by shaded areas) have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Tick marks indicate censored data. NE denotes could not be estimated.

with chemotherapy. The median dose intensity was 99.4% and 100%, respectively.

At least one adverse event was reported by 98.4% of the patients in the alectinib group and 93.3% of those in the chemotherapy group (Table 2). The majority were grade 1 or 2 events. No grade 5 (fatal) adverse events were reported. The most commonly reported adverse events were increased creatine kinase levels (43.0%) and constipation (42.2%) in the alectinib group and nausea (72.5%) and decreased appetite (29.2%) in the chemotherapy group. Adverse events of any grade that were considered by the investigator to be related to treatment were reported in 93.8% of the patients in the alectinib group and 89.2% of those in the chemotherapy group; grade 3 or 4 treatment-related adverse events occurred in 18.0% and 27.5%, respectively.

Serious adverse events were reported in 17 patients (13.3%) in the alectinib group and 10 patients (8.3%) in the chemotherapy group (Table S5). All serious adverse events that were considered to be related to treatment with alectinib were resolved.

Adverse events that led to dose reduction were reported in 25.8% of the patients in the alectinib group and 10.0% of those in the chemotherapy group, and adverse events that led to dose interruption were reported in 27.3% and 18.3%, respectively. Adverse events that led to

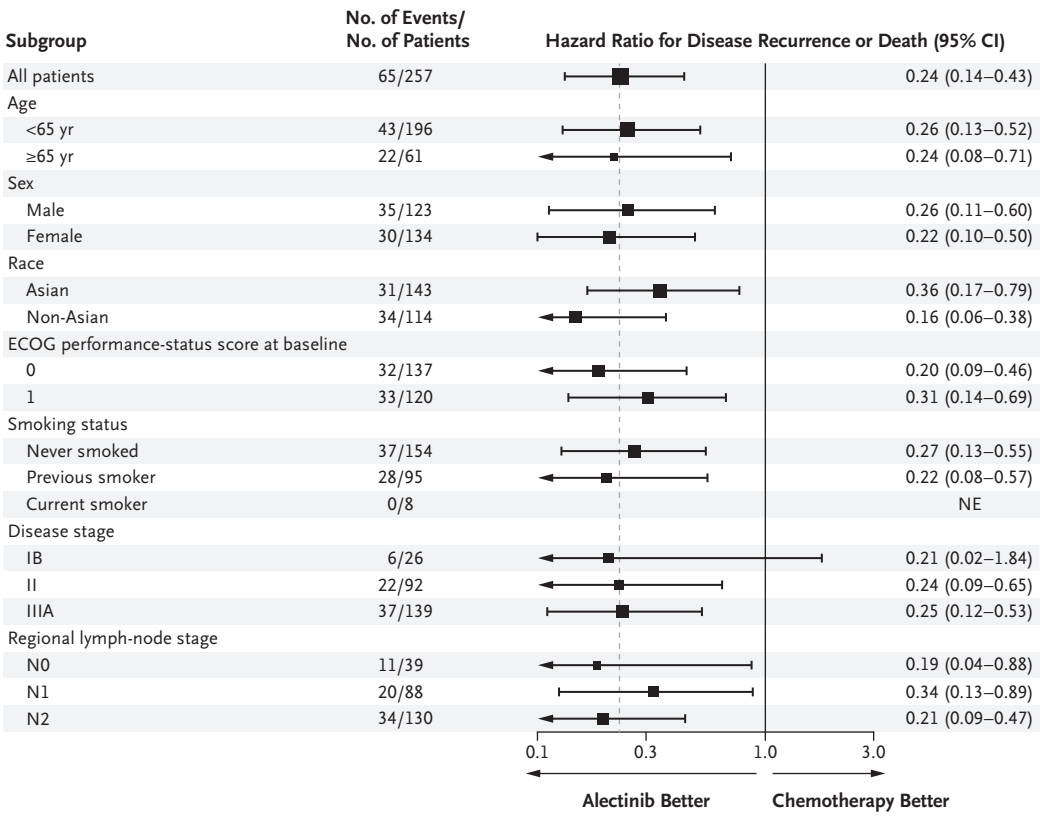

Figure 2. Subgroup Analysis of Disease-free Survival.

Race was reported by the patient. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. Disease staging was based on the seventh edition of the *Cancer Staging Manual* of the AJCC–UICC. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. The dashed line indicates the hazard ratio among all patients. The size of the boxes is proportional to the number of patients in the subgroup. Arrows indicate that the confidence interval extends past the graphed area.

dose discontinuation were reported in 5.5% of the patients in the alectinib group and 12.5% of those in the chemotherapy group.

DISCUSSION

In the phase 3, randomized ALINA trial, patients with resected *ALK*-positive NSCLC who received adjuvant alectinib had significantly longer disease-free survival than those who received the standard adjuvant platinum-based chemotherapy. The hazard ratio for disease recurrence or death was 0.24 among patients with stage II or IIIA NSCLC and in the intention-to-treat population, which corresponds to a 76% lower risk with adjuvant alectinib than with chemotherapy. The disease-free survival benefit was seen consistently across prespecified subgroups, including those defined according to disease stage, race, sex, and smoking status.

Disease-free survival is a well-established efficacy end point for trials of adjuvant therapy in resectable NSCLC. Most cases of recurrence after surgery are incurable, with metastatic spread and poor prognosis,[21-27,37] so improved disease-free survival with alectinib represents a meaningful benefit to patients. Recent data for adjuvant osimertinib in resected *EGFR*-positive NSCLC indicate the potential for a large disease-free survival benefit with a highly effective TKI to translate into an overall survival benefit in the adjuvant context.[29] In the ALINA trial, longer follow-up will be needed to better understand the effect of adjuvant alectinib on overall survival.

Patients with *ALK*-positive NSCLC are at high risk for brain metastases, which are associated with poor prognosis and have a substantial effect on health-related quality of life.[14,38] In the ALINA trial, recurrence in the brain was observed in fewer patients in the alectinib group (4 [3.1%]) than in the chemotherapy group (14 [11.0%]). An exploratory analysis showed a clinically meaningful prolongation of CNS disease–free survival with alectinib. These early data suggest that adjuvant alectinib can prevent or delay CNS recurrence, findings consistent with the intracranial efficacy of alectinib in advanced NSCLC.[15,34,35]

The safety profile of adjuvant alectinib was consistent with that in previous reports in the context of advanced disease, with laboratory abnormalities and constipation being the most frequent adverse events, and no new safety concerns were identified.[30-32] Although treatment duration with adjuvant alectinib was much longer than with chemotherapy (median of 2 years vs. 2 months), similar numbers of adverse events

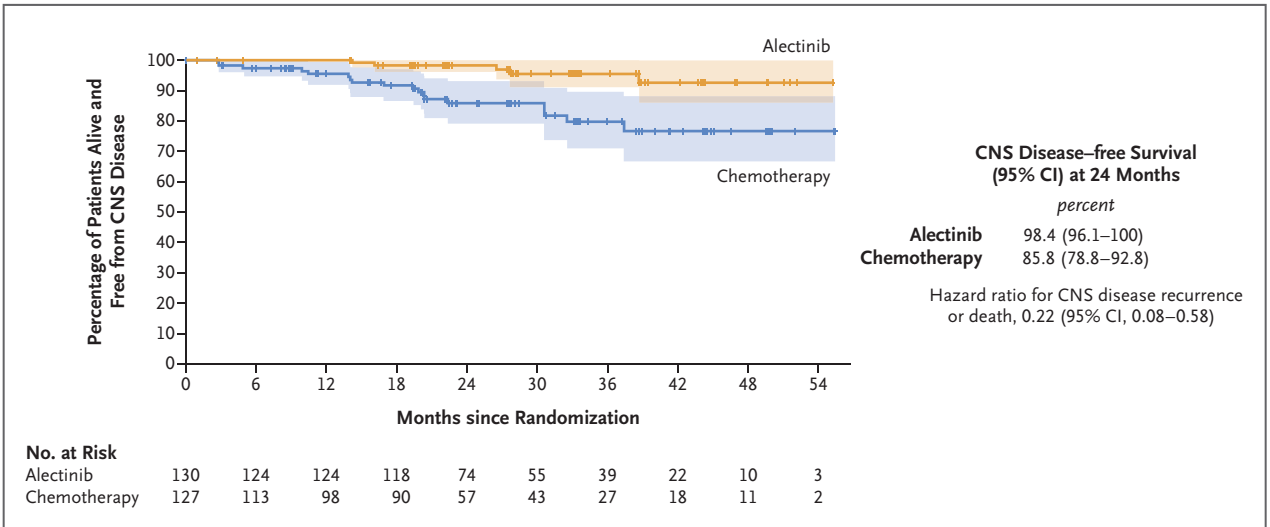

Figure 3. Central Nervous System (CNS) Disease–free Survival in the Intention-to-Treat Population.
The widths of the confidence intervals (indicated by shaded areas) have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Tick marks indicate censored data.

Table 2. Adverse Events Occurring in at Least 10% of Patients in Either Trial Group (Safety-Evaluable Population).*

Adverse Event	Alectinib (N=128)		Chemotherapy (N=120)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	126 (98.4)	38 (29.7)	112 (93.3)	37 (30.8)
Nausea	10 (7.8)	0	87 (72.5)	5 (4.2)
Creatine kinase increased	55 (43.0)	8 (6.2)	1 (0.8)	1 (0.8)
Constipation	54 (42.2)	1 (0.8)	30 (25.0)	1 (0.8)
Aspartate aminotransferase increased	53 (41.4)	1 (0.8)	6 (5.0)	0
Alanine aminotransferase increased	43 (33.6)	2 (1.6)	11 (9.2)	0
Blood bilirubin increased	43 (33.6)	2 (1.6)	1 (0.8)	0
Decreased appetite	7 (5.5)	0	35 (29.2)	1 (0.8)
Covid-19	37 (28.9)	0	1 (0.8)	0
Myalgia	36 (28.1)	1 (0.8)	2 (1.7)	0
Anemia	30 (23.4)	0	31 (25.8)	1 (0.8)
Vomiting	9 (7.0)	0	30 (25.0)	2 (1.7)
Alkaline phosphatase increased	32 (25.0)	0	4 (3.3)	0
White-cell count decreased	2 (1.6)	0	23 (19.2)	4 (3.3)
Neutrophil count decreased	3 (2.3)	0	21 (17.5)	12 (10.0)
Asthenia	14 (10.9)	0	19 (15.8)	3 (2.5)
Neutropenia	2 (1.6)	0	19 (15.8)	10 (8.3)
Creatinine increased	19 (14.8)	1 (0.8)	6 (5.0)	0
Cough	19 (14.8)	1 (0.8)	4 (3.3)	0
Fatigue	18 (14.1)	1 (0.8)	16 (13.3)	2 (1.7)
Rash	18 (14.1)	1 (0.8)	7 (5.8)	0
Malaise	6 (4.7)	0	16 (13.3)	0
Weight increased	17 (13.3)	1 (0.8)	1 (0.8)	0
Diarrhea	16 (12.5)	1 (0.8)	10 (8.3)	1 (0.8)
Headache	14 (10.9)	0	8 (6.7)	0
Dyspnea	13 (10.2)	1 (0.8)	3 (2.5)	0
Dysgeusia	13 (10.2)	0	3 (2.5)	0
Edema, peripheral	13 (10.2)	0	1 (0.8)	0

* The safety-evaluable population included patients who underwent randomization and received any amount of alectinib or chemotherapy. Adverse events are listed according to *Medical Dictionary for Regulatory Activities* preferred term. The median duration of treatment was 23.9 months in the alectinib group and 2.1 months in the chemotherapy group. No grade 5 events were observed. Multiple occurrences of the same adverse event in an individual patient are counted only once. Covid-19 denotes coronavirus disease 2019.

were observed in the two groups, and the percentage of patients who discontinued treatment owing to adverse events was lower with alectinib (5.5%) than with chemotherapy (12.5%). Long-term follow up will be needed to assess any potential long-term toxic effects of adjuvant alectinib.

Some aspects of the design of the ALINA trial differ from previous phase 3 trials of adjuvant targeted therapy.[7] An open-label trial design was used in order to make a head-to-head comparison between a chemotherapy-free regimen of 2 years of adjuvant oral alectinib and standard adjuvant intravenous chemotherapy, for which blinding would not be feasible. Chemotherapy-free regimens have potential benefits with respect to adverse-event profile, could allow chemotherapy to be reserved as a treatment option after disease recurrence, and may be preferred by patients and their families.[39] However, our trial does not address the potential additional usefulness of adding chemotherapy to alectinib. This approach could allow intensification of therapy in selected groups of patients and should be investigated in future clinical trials.

In the ALINA trial, the choice of treatment after disease recurrence was at the discretion of the investigators, because the trial did not have a formal crossover design. ALK TKIs were the most common systemic therapies after recurrence in both groups, the majority being second- and third-generation, CNS-penetrant ALK TKIs, including alectinib, brigatinib, and lorlatinib. These post-recurrence treatments are consistent with current clinical practice and global guidelines for advanced disease.[2-4]

The most effective timing and duration of adjuvant targeted therapy in resectable NSCLC has not yet been established. A 2-year treatment duration was chosen for the ALINA trial to balance the potential benefits of longer durations of adjuvant alectinib with limiting the burden of an extended treatment duration. A need remains for prospective trials to identify the most effective treatment duration of adjuvant targeted therapies in resectable NSCLC, which may differ for different patients depending on factors such as the molecular profile of tumors or the presence of minimal residual disease.[40,41] Future studies are planned to investigate a combination of chemotherapy and alectinib, as well as a longer duration of treatment with adjuvant alectinib.

The data from the ALINA trial reinforce the need for rapid biomarker testing for *ALK* alterations across all stages of NSCLC. *ALK* testing is well established in advanced NSCLC and is increasingly becoming standard in the context of early-stage disease.[2,4] Currently, biomarker testing for *ALK* alterations in resectable NSCLC is mainly performed to exclude patients from receiving immunotherapy, but routine *ALK* testing should also support identification of patients who are likely to benefit from adjuvant alectinib.

Adjuvant alectinib showed a significant benefit with respect to disease-free survival as compared with chemotherapy, as well as a mainly low-grade safety profile with few discontinuations due to adverse events. Adjuvant alectinib represents an important efficacious new treatment strategy for patients with resected *ALK*-positive NSCLC of stage IB, II, or IIIA.

Supported by F. Hoffmann–La Roche.

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, their families, trial investigators, clinical site staff, and the ALINA trial team past and present; and Sean R. Mills, Ph.D., of Ashfield MedComms, an Inizio company, for medical writing assistance with an earlier version of the manuscript.

APPENDIX

The authors' affiliations are as follows: the Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou (Y.-L.W., W.Z.), the Institute of Basic Medicine and Cancer, Chinese Academy of Sciences, Hangzhou (W.M.), and the Department of Medical Oncology, Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine (S.L.), the Department of Thoracic Surgery, Zhongshan Hospital, Fudan University (Q.W.), and the Department of Clinical Science, Roche (China) Holding (T.X.), Shanghai — all in China; the Department of Oncology and Radiotherapy and the Early Phase Clinical Trials Center, Medical University of Gdansk, Gdansk, Poland (R.D.); the Department of Hematology and Oncology, Samsung Medical Center (J.S.A.), and Asan Medical Center (D.H.L.), Seoul, and Seoul National University Bundang Hospital, Seongnam (J.-S.L.) — all in South Korea; the Department of Medical Oncology, International Center for Thoracic Cancers, Gustave Roussy, Villejuif, and Paris-Saclay University, Faculty of Medicine, Le Kremlin-Bicêtre — both in France (F.B.); the Cancer Institute Hospital, Japanese Foundation for Cancer Research (M.N.), and the Department of Thoracic Oncology, National Cancer Center Hospital (H.H.) — both in Tokyo; the Department of Respiratory and Critical Care Medicine, Karl Landsteiner

Institute of Lung Research and Pulmonary Oncology, Klinik Floridsdorf, Vienna (M.H.); the Thoracic Oncology Division, European Institute of Oncology, IRCCS, Milan (F.M.); the Pneumo-Oncology Unit, San Camillo Forlanini Hospital, Rome (M.R.M.); the Oncology and Medical Radiology Department, Dnipropetrovsk State Medical Academy, Dnipro, Ukraine (I.B.); PD Oncology (T.O.L.), Data and Statistical Sciences (A.C.), PD Safety Risk Management (T.R.), and Translational Medicine (J.N.), F. Hoffmann–La Roche, Basel, Switzerland; and the Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (B.J.S.).

REFERENCES

1. Waser N, Vo L, McKenna M, Penrod JR, Goring S. Real-world treatment patterns in resectable (stages I-III) non-small-cell lung cancer: a systematic literature review. Future Oncol 2022;18:1519-30.
2. National Comprehensive Cancer Network (NCCN). Non-small cell lung cancer, version 5.2023. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). 2023 (https://www.nccn.org).
3. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28: Suppl 4:iv1-iv21.
4. Remon J, Soria J-C, Peters S. Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy. Ann Oncol 2021;32:1637-42.
5. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet 2021;398:1344-57.
6. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med 2022;386:1973-85.
7. 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.
8. Loh J, Wijaya ST, Sooi K, Chia PL, Soo RA. Resectable non-small cell lung cancer: an evolving landscape. Transl Lung Cancer Res 2022;11:1241-6.
9. Tian H-X, Zhang X-C, Yang J-J, et al. Clinical characteristics and sequence complexity of anaplastic lymphoma kinase gene fusions in Chinese lung cancer patients. Lung Cancer 2017;114:90-5.
10. Chen MF, Chaft JE. Early-stage anaplastic lymphoma kinase (*ALK*)-positive lung cancer: a narrative review. Transl Lung Cancer Res 2023;12:337-45.
11. Barlesi F, Mazieres J, Merlio J-P, et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). Lancet 2016;387:1415-26.
12. Chaft JE, Dagogo-Jack I, Santini FC, et al. Clinical outcomes of patients with resected, early-stage ALK-positive lung cancer. Lung Cancer 2018;122:67-71.
13. Chevallier M, Borgeaud M, Addeo A, Friedlaender A. Oncogenic driver mutations in non-small cell lung cancer: past, present and future. World J Clin Oncol 2021;12:217-37.
14. Rangachari D, Yamaguchi N, VanderLaan PA, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer 2015;88:108-11.
15. Zou Z, Xing P, Hao X, et al. Intracranial efficacy of alectinib in ALK-positive NSCLC patients with CNS metastases — a multicenter retrospective study. BMC Med 2022;20:12.
16. Gainor JF, Shaw AT, Sequist LV, et al. EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer: a retrospective analysis. Clin Cancer Res 2016;22:4585-93.
17. Garassino MC, Cho B-C, Kim J-H, et al. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. Lancet Oncol 2018;19: 521-36.
18. Addeo A, Passaro A, Malapelle U, Banna GL, Subbiah V, Friedlaender A. Immunotherapy in non-small cell lung cancer harbouring driver mutations. Cancer Treat Rev 2021;96:102179.
19. 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.
20. 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.
21. Sugimura H, Nichols FC, Yang P, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. Ann Thorac Surg 2007;83:409-17.
22. Shimizu R, Kinoshita T, Sasaki N, et al. Clinicopathological factors related to recurrence patterns of resected non-small cell lung cancer. J Clin Med 2020;9:2473.
23. Taylor MD, Nagji AS, Bhamidipati CM, et al. Tumor recurrence after complete resection for non-small cell lung cancer. Ann Thorac Surg 2012;93:1813-20.
24. Consonni D, Pierobon M, Gail MH, et al. Lung cancer prognosis before and after recurrence in a population-based setting. J Natl Cancer Inst 2015;107(6):djv059.
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. Martin J, Ginsberg RJ, Venkatraman ES, et al. Long-term results of combined-modality therapy in resectable non-small-cell lung cancer. J Clin Oncol 2002;20: 1989-95.
27. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51.
28. Desage A-L, Bouleftour W, Tiffet O, Fournel P, Tissot C. Use of adjuvant chemotherapy in resected non-small cell lung cancer in real-life practice: a systematic review of literature. Transl Lung Cancer Res 2021;10:4643-65.
29. 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.
30. Zhou C, Kim S-W, Reungwetwattana T, et al. Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study. Lancet Respir Med 2019;7: 437-46.
31. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated *ALK*-positive non–small-cell lung cancer. N Engl J Med 2017;377:829-38.
32. Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet 2017;390:29-39.
33. Mok T, Camidge DR, Gadgeel SM, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced *ALK*-positive non-small-cell lung cancer in the ALEX study. Ann Oncol 2020;31:1056-64.
34. Gadgeel SM, Shaw AT, Govindan R, et al. Pooled analysis of CNS response to alectinib in two studies of pretreated patients with ALK-positive non-small-cell lung cancer. J Clin Oncol 2016;34:4079-85.
35. Gadgeel S, Peters S, Mok T, et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy

results from the ALEX study. Ann Oncol 2018;29:2214-22.
36. Dziadziuszko R, Peters S, Ruf T, et al. Clinical experience and management of adverse events in patients with advanced ALK-positive non-small-cell lung cancer receiving alectinib. ESMO Open 2022;7:100612.
37. Walsh GL, O'Connor M, Willis KM, et al. Is follow-up of lung cancer patients after resection medically indicated and cost-effective? Ann Thorac Surg 1995;60:1563-70.
38. Cella D, Wen PY, Ervin C, et al. Understanding the patient experience and treatment benefits in patients with non-small-cell lung cancer with brain metastasis. Cancer Med 2023;12:13637-48.
39. Wu Y-L, Zhou Q. Combination therapy for *EGFR*-mutated lung cancer. N Engl J Med 2023;389:2005-7.
40. Herbst RS, Wu Y-L, John T, et al. Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIA non-small-cell lung cancer: updated results from the phase III randomized ADAURA trial. J Clin Oncol 2023;41:1830-40.
41. Zhang J-T, Liu S-Y, Gao W, et al. Longitudinal undetectable molecular residual disease defines potentially cured population in localized non-small cell lung cancer. Cancer Discov 2022;12:1690-701.